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Müller cells trophism and pathology as the next therapeutic targets for retinal diseases

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ABSTRACT

Müller cells are a crucial retinal cell type involved in multiple regulatory processes and functions that are essential for retinal health and functionality. Acting as structural and functional support for retinal neurons and photoreceptors, Müller cells produce growth factors, regulate ion and fluid homeostasis, and facilitate neuronal signaling. They play a pivotal role in retinal morphogenesis and cell differentiation, significantly contributing to macular development.

Due to their radial morphology and unique cytoskeletal organization, Müller cells act as optical fibers, efficiently channeling photons directly to the photoreceptors. In response to retinal damage, Müller cells undergo specific gene expression and functional changes that serve as a first line of defense for neurons, but can also lead to unwarranted cell dysfunction, contributing to cell death and neurodegeneration. In some species, Müller cells can reactivate their developmental program, promoting retinal regeneration and plasticity—a remarkable ability that holds promising therapeutic potential if harnessed in mammals.

The crucial and multifaceted roles of Müller cells—that we propose to collectively call "Müller cells trophism"—highlight the necessity of maintaining their functionality. Dysfunction of Müller cells, termed "Müller cells pathology," has been associated with a plethora of retinal diseases, including age-related macular degeneration, diabetic retinopathy, vitreomacular disorders, macular telangiectasia, and inherited retinal dystrophies.

In this review, we outline how even subtle disruptions in Müller cells trophism can drive the pathological cascade of Müller cells pathology, emphasizing the need for targeted therapies to preserve retinal health and prevent disease progression.

1. Introduction

Müller cells are a specific type of retinal glial cell found in the vertebrate retina, including mammals. Müller cells play a variety of critical roles in maintaining retinal homeostasis and supporting retinal function (Fig. 1). For this reason, the maintenance of Müller cell

functionality, namely Müller cells trophism, is of primary importance to guarantee the proper structural and functional retinal homeostasis.

Not surprisingly, an increasing number of studies indicate that Müller cells are significantly involved in various retinal disorders, making these cells valuable as both diagnostic biomarkers and potential therapeutic targets.

This review discusses how the involvement of Müller cells in retinal

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List of abbreviations		IRDs	Inherited Retinal Dystrophies
		LDH	Lactate Dehydrogenase
AAV	Adeno-Associated Virus	LDLs	Low-Density Lipoproteins
AMD	Age-related Macular Degeneration	LIF	Leukemia Inhibitory Factor
AQP4	Aquaporin 4	LRP-1	Lipoprotein Receptor-related Protein 1
Asics	Acid-sensing ion channels	MacTel-2	2 Macular Telangiectasia type 2
ATP	Adenosine Triphosphate	MCP-1	Monocyte Chemoattractant Protein-1
BBB	Blood-Brain Barrier	MCT	Monocarboxylate Transporters
bHLH	Basic helix-loop-helix	MMPs	Matrix Metalloproteinases
BRB	Blood-Retinal Barrier	NFI	Nuclear Factor I
COX-2	Cyclooxygenase-2	OCT	Optical Coherence Tomography
CRALBP	Cellular retinaldeheyde binding protein	ORT	Outer Retinal Tubulations
DME	Diabetic Macular Edema	ONL	Outer Nuclear Layer
DR	Diabetic Retinopathy	OPL	Outer Plexiform Layer
DG	Days of Gestation	Р	Postnatal day
EAATs	Excitatory Amino Acid Transporters	PEDF	Pigment Epithelium-derived Factor
ELM	External Limiting Membrane	RGR	Retinal G-protein-coupled Receptor
EGF	Epidermal Growth Factor	RLBP1	Retinaldehyde-binding Protein 1
EPPK1	Epiplakin	ROS	Reactive Oxygen Species
ERM	Epiretinal Membrane	RPCs	Retinal Progenitor Cells
GCL:	Ganglion Cell Layer	RPE	Retinal Pigment Epithelium
GFAP	Glial Fibrillary Acidic Protein	SER	Smooth Endoplasmic Reticulum
HDLs	High-Density Lipoproteins	TNF	Tumor Necrosis Factor
HIF	Hypoxia-Inducible Factor	TRAP	Translating Ribosome Affinity Purification
HMGCR	Hydroxymethylglutaryl-Coa Reductase	TRP	Transient Receptor Potential
ILM	Inner Limiting Membrane	TRPV	Transient Receptor Potential channels of the vanilloid type
INL	Inner Nuclear Layer	VEGF	Vascular Endothelial Growth Factor
IPL	Inner Plexiform Layer		

diseases can be structural, functional, or both, depending on the pathological features of each condition. The complexity and heterogeneity of Müller cell involvement make it difficult to attribute their damage to few pathogenetic elements and/or effects. Therefore, we proposed the term "Müller cells pathology" to emphasize that the involvement of Müller cells in retinal diseases is multifaceted and requires more extensive research.

The primary objective of this review is to compile and synthesize the current knowledge on the physiological functions and pathogenetic roles of Müller cells. By offering an updated overview, we seek to stimulate new multidisciplinary research on this intriguing retinal cell type. Moreover, we highlight the importance of preserving Müller cells trophism and the role of Müller cells pathology in the pathogenesis of retinal diseases.

2. Müller cells: conducting the finale of retinal development

During retinal neurogenesis, all cell types arise from a common pool of retinal progenitor cells (RPCs; Marquardt and Gruss, 2002; Turner and Cepko, 1987). RPCs constitute a highly dynamic cell population that undergoes extensive gene expression changes throughout development, driven by multiple transcription factor cascades in distinct combinatorial patterns through interactions with Notch signaling. RPCs can be categorized into two subtypes-early and late RPCs-each with distinct potential to generate specific retinal cell types. Retinal ganglion cells are the first to differentiate, arising from early RPCs (Prasov and Glaser, 2012), which also give rise to cones, horizontal cells, and amacrine cells (Sapkota et al., 2014; Inoue et al., 2010). In contrast, late-stage progenitors generate rods, bipolar cells, and, as the last retinal cell type to differentiate, Müller cells (Cepko, 2014; Tworig and Feller, 2022). In the mouse retina, Müller glia is generated between postnatal day (P) P0 and P10, well after all neuronal cell types have differentiated and after the initial formation of the plexiform layers (Bassett and Wallace, 2012; Tworig and Feller, 2022).

While the exact molecular mechanisms regulating Müller cell differentiation from late retinal progenitor cells are not fully elucidated, numerous studies have identified the gene expression changes and regulatory networks essential for effective Müller cell differentiation (Lyu et al., 2021; Eastlake et al., 2021). Generally, Notch signaling engages crucial transcription factors to regulate glial and neuronal differentiation, sustaining RPC proliferation when active and facilitating neurogenesis upon downregulation (Dorsky et al., 1997; Bao and Cepko, 1997).

More specifically, Notch signaling promotes gliogenesis through the basic helix-loop-helix (bHLH) superfamily of Hes and Hey effectors and by interacting with various other gene regulatory networks (reviewed in (Engler et al., 2018; Hu and Zou, 2022; Weber et al., 2014)). For instance, in the mouse retina, Notch effectors such as Hes5, Hes1, and Hesr2 promote gliogenesis at the expense of neuronal fate, inducing Müller cells differentiation (Furukawa et al., 2000; Hojo et al., 2000; Satow et al., 2001). Notch signaling also modulates the transcription of the group E high-mobility-group-domain family of transcription factors (i.e., Sox8, Sox9, and Sox10) during glial development (Stolt et al., 2002; Stolt et al., 2003; reviewed in Vogel and Wegner, 2021). Consequently, in the murine retina, these factors are expressed in late retinal progenitor cells (RPCs) and subsequently solely in Müller cells. The downregulation of either Sox8 or Sox9 leads to impaired development of Müller cells and an increased generation of rod photoreceptors (Muto et al., 2009), indicating potential redundancy in their roles. Sox9 is prominently expressed in multipotent Sox2+ mouse RPCs during embryonic development, but its expression diminishes as RPCs cease proliferation and differentiate into neurons, while it continues to be specifically expressed in postmitotic Müller cells (Poche et al., 2008). Although the function of Sox9 in facilitating Müller cell differentiation is well-established, it remains unclear whether Sox8 is expressed by Sox2+ cells, suggesting that Sox8 and Sox9 may delineate distinct subpopulations of Müller cells.

The LIM homeodomain transcription factor Lhx2 is crucial for Müller

cell development, overseeing progenitor proliferation, terminal differentiation, and the expression of Müller cell-specific markers. Lhx2 functions as a transcriptional regulator of Notch signaling components by activating specific Notch receptors, primarily Notch1, and Notch ligands, including Dll1 and Dll3 (de Melo et al., 2016). It additionally governs Notch-independent elements of retinal gliogenesis by directly modulating the expression of gliogenic transcription factors including Hes1, Hes5, Sox8, and Rax (de Melo et al., 2016). The conditional ablation of Lhx2 results in the downregulation of late differentiation markers such as P27Kip1, glutamine synthetase, Sox9, and genes associated with the Notch pathway, alongside the attenuation of Notch signaling (de Melo et al., 2016).

Another key molecular pathway implicated in Müller cell generation is BMP signaling. The temporary activation of BMP-Smad1/5/8 signaling in Müller glia from postnatal day 5 to postnatal day 9 is crucial for maintaining their glial phenotype during retinal development (Ueki et al., 2015a,b,c). This activation markedly enhances glial gene expression while suppressing the neural transcription factor Otx2 (Ueki Progress in Retinal and Eye Research 106 (2025) 101357

et al., 2015a,b,c). Inhibition of BMP signaling adversely affects Müller cell development, resulting in permanent alterations to retinal morphology and compromised retinal function.

Müller cell proliferation has been documented in response to epidermal growth factor (EGF) stimulation in multiple species (Close et al., 2006; Lillien, 1995). Despite the ambiguity surrounding the molecular mechanisms, EGF stimulation in P12 mouse retinas activates PI3K/AKT signaling, which in turn induces BMP/Smad1/5/8 activation, facilitating Müller glia proliferation (Ueki and Reh, 2013).

Single-cell RNA sequencing identified Nuclear Factor I (NFI) a/b/x transcription factors as candidates for the temporal regulation of retinal development (Clark et al., 2019). These transcription factors are recognized for their role in astrocyte specification in both murine and human models (Tchieu et al., 2019). Loss-of-function experiments in the postnatal mouse retina for these NFI factors resulted in enhanced neurogenesis at the cost of Müller glia, accompanied by significant alterations in retinal morphology (Hoang et al., 2020; Lyu et al., 2021).

MicroRNAs also regulate Müller glia differentiation and homeostasis.

Light guidance			M vitreous
Water transport and homeostasis		Basal endfeet	NFL
Regulation of the extra- cellular space volume			GCL
Neurotransmitter clearance and recycling	Peri pr	synaptic ocesses	
Gliotransmission modulates information processing			IPL
Maintenance of the tissue immune homeostasis			
Metabolic support and waste collection		velate sheats	INI
Regulation of retinal blood flow			
Maintenance of the inner	Peri pr	synaptic ocesses	OPL
blood-retinal barrier Regulation of pH		velate sheats	01
Neuroprotection and secretion of neurotrophins			ONL
Structural organization of the retina			OLM
Regeneration of visual pigment	n n	Apical nicrovilli	PRS

Fig. 1. Anatomy of a prototypic Müller cell (in black) and main functions (see text for detailed explanations). ILM, inner limiting membrane; NFL, nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; OLM, outer limiting membrane; PRS, photoreceptor segments.

Initial evidence derived from studies indicating that the inactivation of Dicer, an RNaseIII enzyme crucial for microRNA biogenesis, results in modified retinal development, impacting cell survival, differentiation, and progenitor proliferation across various species (Damiani et al., 2008). The conditional ablation of Dicer regulated by late RPC-specific genes (i.e., Pax6 (Georgi and Reh, 2010) or Dickkopf 3 (Iida et al., 2011)) resulted in diminished progenitor proliferation in transgenic lines, culminating in a reduced number of late-born neurons, such as rods, bipolar cells, and Müller cells (Georgi and Reh, 2010). La Torre et al. identified three miRNAs (let-7, miR-125, and miR-9) that facilitate the transition from early to late retinal progenitor cells (RPCs) (La Torre et al., 2013). The inhibition of these microRNAs resulted in phenotypes similar to Dicer conditional knockouts, characterized by an increase in the number of ganglion cells, horizontal cells, and photoreceptors. A subsequent study demonstrated that let-7 promotes the differentiation of late-born neurons and Müller cells by inhibiting HMCa2, a DNA-binding protein that sustains self-renewal in retinal progenitor cells (Xia and Ahmad, 2016). A Müller cell-specific Dicer knockout, induced in differentiated postnatal Müller cells (at P11-14 in mice), reveals that miRNA is essential not only for establishing but also for maintaining the homeostasis of the Müller cell compartment (Wohl et al., 2017).

Müller cell maturation at the functional level extends beyond molecular changes described so far and coincides with the retina's overall functional development, reaching full maturity between P15 and P21 in rodents (Bringmann et al., 2013; Wurm et al., 2006; Pannicke et al., 2002). Their maturation is linked to synaptic refinement processes that occur during the first postnatal weeks in the rodent retina (Bassett and Wallace, 2012; Tworig and Feller, 2022), specifically involving the formation of synaptic connections within the inner and outer plexiform layers (Bassett and Wallace, 2012). During this time, Müller cells extend their processes to ensheathe synapses and help organize a functional retinal network, a process that is partially dependent on sensory input (Wurm et al., 2006). During this phase, Müller cells regulate osmotic and ionic balance through inwardly rectifying K+ (Kir) channels and aquaporins, with a developmental increase in Kir channel expression associated with improved volume regulation under anisoosmotic conditions. Immature glial cells (up to P15) swell under hypotonic stress, but mature cells cease to swell unless Kir channels are blocked, highlighting their key role in volume homeostasis, a process that can be delayed by visual deprivation (Wurm et al., 2006). In line with these data, the purine receptors P2Y1 and P2Y4, which regulate calcium responses and contribute to volume regulation in Müller cells, are implicated in retinal differentiation and cell signaling (Wurm et al., 2009a,b). Specifically, P2Y1 is active in Müller cells from P5 and P2Y4 from P20, suggesting their roles in these developmental processes (Wurm et al., 2009a,b).

2.1. Müller cells: architects of foveal morphogenesis and vascular regulation

The fovea centralis distinct intricacies to retinal development. This specialized retinal area, measuring approximately 1.5 mm in the central retina, is particularly vulnerable to numerous retinal disorders and is unique to primates, including humans. The fovea contains an avascular depression primarily made up of long- and medium-wavelength cone photoreceptors, with a lesser quantity of short-wavelength cones and no rods (Curcio et al., 1990). The initial indication of Müller cell participation in foveal development appears at 54 days of gestation (DG) (fetal weeks [FWKs] 7-8), when the inaugural Müller cell marker, RLBP1, becomes identifiable in the central retina-particularly in an area preceding the prospective fovea (Wohlschlegel, 2023). Enhanced clarity; eliminated redundancy. By 59 DG (FWKs 8), supplementary Müller cell markers, such as SOX9 and VSX2, are expressed, indicating progressive differentiation in this retinal subregion. Enhanced coherence and lucidity. The mitotic marker PHH3 is lacking in the prefoveal region, indicating that Müller cell differentiation corresponds with the final stages of retinal development seen in other species. Subsequently, at 150 DG (FWKs 21), enhanced expression of Müller cell markers, including SOX9 and VSX2, indicates ongoing maturation in this area (Wohlschlegel et al., 2023).

During the maturation of the human fovea, which occurs prior to the development of the peripheral retina (Hendrickson et al., 2006), Müller cells serve as a structural and metabolic framework, facilitating the centrifugal movement of inner retinal neurons (Provis et al., 1985; 2013). This displacement ultimately creates the distinctive pit-like morphology of the fovea (Bringmann et al., 2018). By gestational weeks 14-15, mitotic activity in the fovea and the adjacent 0.5 mm ceases, signifying the completion of retinal cell generation in this area, while the peripheral retina continues to generate cells beyond 24 weeks gestation (Provis et al., 1985). Research on monkey retina corroborates this central-to-peripheral developmental pattern, indicating that Müller cells are the final cells to differentiate, as noted in rodents (La Vail et al., 1991). Furthermore, in the rod-free zone delineating the prospective fovea, late progenitors fail to produce rods, likely owing to the lack of NR2E3, a transcription factor critical for rod development (Bumsted O'Brien et al., 2004).

The development of the foveal pit is intricately linked to the lack of retinal blood vessels, as the foveal pit does not develop in vascularized regions (reviewed in Bringmann et al., 2018). This is apparent in individuals with foveal hypoplasia, characterized by the absence of a foveal avascular zone (FAZ) (Walsh and Goldberg, 2007; Querques et al., 2008). Müller and ganglion cells probably contribute to the inhibition of vessel ingrowth by producing antiangiogenic factors, including pigment epithelium-derived growth factor and brain natriuretic peptide (Kozulin et al., 2010). The role of ganglion cells in the formation of the foveal avascular zone (FAZ) is contentious, as anencephalic neonates, devoid of central retinal ganglion cells, are capable of developing a shallow foveal pit and FAZ (Hendrickson et al., 2006). Macular pigment, particularly the xanthophyll carotenoids lutein and zeaxanthin, is present in the fetal retina by gestational week 17 and may also play a role in inhibiting vascularization. Despite lutein exhibiting antiangiogenic properties in experimental models, its direct involvement in foveal development remains uncertain (Gariano, 2010). Confocal resonance Raman microscopy demonstrates that lutein is widely dispersed throughout the adult macula, whereas zeaxanthin is predominantly localized in the foveal center, especially within Müller cells (Li et al., 2020, 2024). Collectively, these data indicate that a specialized subset of Müller cells may be essential in facilitating proper macular development.

3. Retinal cytoarchitecture and Müller cell morphology

Cytoarchitecture refers to the pattern of distribution of cell bodies and processes in the tissue (Nieuwenhuys and Broere, 2020; Vogt, 1903). The vertebrate neural retina resembles the cytoarchitectonic structure of the archicortex with three nuclear layers (like the hippocampus and dentate gyrus), but with two distinct synaptic layers in between (reviewed in (Hoon et al., 2014)). The three nuclear layers contain (i) photoreceptors in the outer nuclear layer (ONL), which convert light into electrical signals; (ii) horizontal/bipolar/amacrine neurons in the inner nuclear layer (INL), which act as relay neurons; and (iii) displaced amacrine and ganglion cells in the ganglion cell layer, (GCL) while the latter cells of this layer project to the brain (Fig. 2A). Synaptic connections among retinal neurons occur in two intermediate layers: (i) the outer plexiform layer (OPL), located between the ONL and the INL, where synapses are formed between photoreceptors and bipolar/horizontal cells, and (ii) the inner plexiform layer (IPL), located between the INL and the GCL, where synapses connect bipolar cells and ganglion/amacrine cells. Non-neuronal cells (including astrocytes, microglia, retinal vasculature cells (endothelial cells and pericytes), and Müller cells) are also part of this structure. The neuroretina is shielded from light reflection on the photoreceptor side by the retinal pigment epithelium (RPE) (reviewed in (Somasundaran et al., 2020)) and the choroid, which harbors endothelial cells, pericytes, fibroblasts, mast



(caption on next page)

Fig. 2. Hypothesis of region-dependent Müller cells' contribution to the cone visual cycle on basis of anatomical features, molecular profiles and existing literature. Adaptation of Müller cells' morphology to the special needs of the macular retina resulting in z-shaped, elongated Müller cells only contacting cone photoreceptors, but no rods. (A) Sections through central macular (foveal) human donor retina and through the outer border of the macula, where the z-shape of Müller cells is still present, but the ganglion cells are only stacked in 2–3 layers instead of 6–8 as in the foveal area. Müller cells are delineated by staining for vimentin (VIM) as established marker, but specifically label for RDH10. Note that RDH10 staining is more intense in Müller cells of the macular periphery. Scale bars, 50 µm. (B) Cell type-specific profiles for proteins detected by a cell type-specific LC-MS/MS approach and known to be key for the visual cycle from Müller cells, neurons and R PE isolated from human donor eyes. Data are retrieved from the resource data of our recently published study Kaplan et al., (2023). Bars represent mean ± SEM. Each dot represents a biological replicate. One-way Anova was performed with Dunnett's multiple comparision and only significances for comparisions with respective Müller cells populations are plotted (following the respective color code). *P < 0.05; **P < 0.01; $\forall P < 0.01; \forall \forall \forall V = 0.001, (C)$ Scheme of how the contribution of Müller cells to the cone visual cycle might differ depending on the retinal area, as deduced from the expression profiles of the relevant proteins involved.

cells, and melanocytes (reviewed in (Ferrara et al., 2021; Nickla and Wallman, 2010)).

The structure of the vertebrate retina differs among species, with the neuroretina of humans, some nonhuman primates and few other vertebrate species (e.g., some birds, fish, or chamelids) being divided into two distinct anatomical, functional, and transcriptional regions (Hahn et al., 2023; Peng et al., 2019; Yew et al., 2012): (i) the retinal periphery, which is mainly populated by rod photoreceptors and is characterized by low spatial acuity, making it crucial for night vision and some aspects of motion detection, and (ii) the macular region, located along the optical axis, which contains cone photoreceptors, especially in its center (the *fovea centralis*), and is therefore responsible for the high visual acuity necessary for activities such as face recognition or reading in humans. The foveal subregion is exclusive to primates (Bringmann et al., 2018; Peng et al., 2019). Retinal cell types, in both peripheral and macular regions, can be classified according to morphology, function (reviewed in (Hoon et al., 2014; Masland, 2012)), and molecular signatures (reviewed in (Diacou et al., 2022; Hahn et al., 2023; Li et al., 2017; Voigt et al., 2021; Ying et al., 2021; Kaplan et al., 2023; Zauhar et al., 2022a, b). These categories are further broken down into distinct subsets of cell types through expression analysese at the single-cell level (Hahn et al., 2023; Peng et al., 2019).

Given the retinal developmental processes described in the coming chapters, each Müller cell forms the "core" of a columnar functional unit of clonally and functionally related groups of neurons (Fig. 2A). The composition of these units, i.e. how many neurons associate with "their" Müller cell, varies depending on the retinal region (Reichenbach and Bringmann, 2020) as does the morphology of Müller cells. In the fovea, where visual acuity is paramount, one Müller cell serves a single photoreceptor, reflecting the complexity and specialization of Müller cell connections in this area (Reichenbach & Bringmann, 2010, 2020). As the distance from the fovea increases, a single Müller cell serves an increasing number of photoreceptors, resulting in less specialized functional units towards the retinal periphery. Consequently, the Müller cells/photoreceptor ratio is 1:1 in the fovea and decreases progressively with increasing distance from the retinal center (Burris et al., 2002).

Generally, the Müller cell prototype spans the whole thickness of the neuroretina (Fig. 1), from the external limiting membrane (ELM) to the internal limiting membrane (ILM), engaging in close relationships with blood vessels, astrocytes, and neurons (Fig. 1; Müller, 1851; Distler and Dreher, 1996, Reichenbach and Bringmann, 2010). The perikarya of Müller cells are in the INL. From there, they extend an inner stem process to the GCL, and another stem process that connects the OPL and ONL (Reichenbach & Bringmann, 2010, 2020).

From these stem processes, Müller cells extend myriads of specialized side processes that allow them to form functional connections with astrocytes, amacrine cells, bipolar cells, ganglion cells, horizontal cells, and photoreceptors. Additionally, Müller cells project to intraretinal capillaries, contributing to the formation and regulation of the inner BRB (Tout et al., 1993; Shen et al., 2012; Wang et al., 2022a,b). These intricate connections form the anatomical basis for the multiple functions performed by Müller cells.

The structure of Müller cells in the macula is noticeably different from their structure in the peripheral retina. In the macular region, Müller cells take on a distinct Z-shaped form (Fig. 2A). Their outer stem processes align with Henle's fibers (i.e., the slanted extensions of photoreceptor axons radiating centrifugally from the fovea centralis). This unique arrangement places the Müller cell bodies in the laterally displaced INL, while their inner stem processes extend through the unusually thick IPL, GCL, and NFL that make up the macular rim. (Bringmann et al., 2018; Reichenbach and Bringmann, 2020; Kar et al., 2024) (Fig. 2A). The fovea centralis contains a sparse population of very peculiar Müller cells whose soma and inner stem processes are located at the base of the foveal pit. Their precise morphology and functional roles, however, remain to be fully elucidated (Bringmann et al., 2018; Reichenbach and Bringmann, 2020; Kar et al., 2024).

4. Multiple domains, multiple functions: the versatility of Müller cells

Müller cells are the predominant macroglial cells of the vertebrate retina, with densities exceeding 30,000 cells/mm² in the foveal and parafoveal regions and progressively decreasing to 6000 cells/mm² in the far peripheral retina of the Macaca mulatta (rhesus monkey) (Distler and Dreher, 1996). The foveal region contains the highest concentration of Müller cells, where they form a densely packed central Müller cell bouquet, so that each cone has its own private Müller cell (Bringmann et al., 2018). A minor population of macroglial cells in the retina is represented by astrocytes, which are confined to vascularized regions of the retina, where they play a role in establishing and maintaining the blood-retinal barrier at the level of the inner vascular plexus. In contrast, Müller cells are found in all vertebrate retinae, with a widespread distribution across the retinal layers (Distler and Dreher, 1996). They support the integrity of the retinal blood barrier, especially in vessels of the intermediate and deep vascular plexus. Upon specific ablation of Müller cells in mice, a clear disorganization of intraretinal blood vessels was observed (Shen et al., 2012; Chung et al., 2013).

Research undertaken in the 1980s and 1990s meticulously examined the morphology of Müller cells through a combination of impregnation methods, electron microscopy, and immunohistochemistry across diverse vertebrate species, including mammals (Drager et al., 1984; Dreher et al., 1992; Reichenbach et al., 1989; Reichenbach and Wohlrab, 1986; Robinson and Dreher, 1990). Recent advancements in genetic techniques have greatly enhanced these observations, providing novel insights into the diverse structure-function relationships of Müller cells with other retinal components in adults (Wang et al., 2017) and during development (Charlton-Perkins et al., 2019). Additionally, specialized 3D image analysis toolkits have been created to conduct quantitative assessments of the characteristic cellular morphology of Müller cells (Kugler et al., 2023). Müller cells exhibit a characteristic bipolar structure in the radial direction, mirroring the morphology of their precursor cells, the radial glia. They extend from the ELM to the ILM, facilitating the development of these membranes via specialized cell-cell adhesion complexes (Müller, 1851; Reichenbach and Bringmann, 2020). The perykaria of Müller cells are centrally positioned within the inner nuclear layer (INL), from which an inner and outer stem process extend to encompass most of the retinal thickness. Müller cells transverse the retina, acquiring unique morpho-functional specializations in each

retinal layer, which allows them to perform multiple distinct functions, as detailed below.

4.1. ELM domain: selectively permeable barrier, survival signaling Hub, and visual pigment regeneration

At the ELM, which can be clearly visualized by optical coherence tomography (OCT), Müller cells exhibit distinct junctional complexes in the retinal periphery compared to the foveal region. Müller cells of the peripheral retina are connected to each other through homotypic adherens junctions, while they form unique heterotypic junctions when connected to photoreceptors. These latter junctions display an organization of the actin cytoskeleton characteristic of adherens junctions on the glial side, while the photoreceptor side displays tight junction-like structures and components, creating a hybrid adherens-tight junction (Omri et al., 2010). In the fovea, the junctional complexes between Müller cells and photoreceptors at the ELM resemble small desmosomes, featuring dense, intermediate filament-rich membrane thickenings. Additionally, Müller cells extend projections between the outer segments of cones to form hybrid adherens-tight junctions with photoreceptors beneath these glial extensions (Omri et al., 2010). Similar hybrid junctions were also observed between auditory hair cells and supporting cells in the inner ear (Nunes et al., 2006). Heterotypic adhesion structures, due to their tight junction components, are believed to form a semipermeable barrier for solute diffusion in both sensory organs. Regarding the retina, studies in various species have shown that the ELM indeed serves as a semipermeable barrier for protein diffusion (Bunt-Milam et al., 1985; Marmor, 1990), and its disruption compromises visual acuity (Ito et al., 2013).

These cell-cell junctions are also discussed as signaling hubs for pathways that critically regulate morphogenesis and tissue homeostasis, with adherens junction signaling acting mainly through the Wnt/β-catenin pathway (reviewed in (Hayat et al., 2022; Liu et al., 2022)) and the tight junction signaling through a variety of cell survival, migration, and proliferation pathways (reviewed in (Martin, 2014)). In the whole retina, the Wnt/β-catenin pathway in Müller cells plays a role in regulating retinal angiogenesis during development and disease (reviewed in (Drenser, 2016)) and, in the adult, in activating a protective neuronal response in damaged retinas (reviewed in (Kassumeh et al., 2021)), mainly through the downstream activation of Leukemia Inhibitory Factor (LIF)-mediated signaling (Boesl et al., 2020; Kassumeh et al., 2020). It is plausible to hypothesize that the activation of the Wnt/β-catenin pathway at the ELM could modulate both neoangiogenesis and neuronal protection in retinal pathologies affecting the inner retinal layers. This potential modulation could be mediated by the paracrine diffusion of cytokines and growth factors related to this signaling pathway. In addition, tight junctions in retinal neurons are likely involved in cell differentiation and synaptic maturation, similar to their roles in brain neurons (Tikiyani and Babu, 2019). These processes may rely on specialized proteins, such as the angiomotin family, which serve as scaffolds for organizing synaptic proteins (Wigerius et al., 2020), and the ephrin family, which act as hubs for signal transduction (Henderson and Dalva, 2018).

Besides forming junctional complexes, the fine microvillous processes that Müller cells extend across the ELM, toward the photoreceptor outer segments, may play a critical role in supporting photoreceptor transduction activity. Notably, during daylight, the photoreceptors' demand for 11-cis-retinal, the essential visual chromophore, typically exceeds the supply provided by the retinal pigment epithelium (RPE) through the classical retinoid recycling pathway, which depends on the activity of retinoid isomerase (RPE65) (Choi et al., 2021). This shortfall is compensated by an alternative regeneration pathway for 11-cis-retinal, dependent on the retinal G-protein-coupled receptor (RGR) photoisomerase (Choi et al., 2021), which is expressed in both the RPE and Müller cells (Tworak et al., 2023). Intriguingly, RGR's role in chromophore recycling under continuous illumination conditions significantly impacts the subsequent dark adaptation of cone photoreceptors (Tworak et al., 2023).

Consistent with this concept, RGR is predominantly expressed in Müller cells (and RPE) of the macula in the human retina, which primarily interact with cones, in contrast to cells from peripheral regions where rods are more prevalent (Fig. 2B). Determining whether RPE or Müller cells are more pivotal in chromophore regeneration in the human retina, especially in the macula, remains a challenge (Fig. 2C). RGR interacts with other proteins, such as RDH10 (Morshedian et al., 2019) and RDH5 (Chen et al., 2001), which exhibit unique regional expression patterns in Müller cells and retinal pigment epithelium (RPE). Notably, RDH10 exhibits the highest expression in the retinal pigment epithelium of the macula, while its expression peaks in Müller cells of the perimacular retina. Likewise, cellular retinaldehyde binding protein (CRALBP), which serves as a transporter for 11-cis-retinal, is predominantly expressed in perimacular Müller cells, with reduced expression in macular and peripheral Müller cells. CRALBP, functioning as a transporter for 11-cis-retinal, is predominantly expressed in perimacular Müller cells, with reduced expression in macular and peripheral Müller cells (Ikeda et al., 2019). The unique spatial expression pattern of proteins associated with the visual cycle in Müller cells and retinal pigment epithelium (RPE) may arise from the proximity of the central cones in the foveola to the RPE. In contrast, outside the foveola, where rods predominate and possess significantly longer outer segments, cone outer segments are situated farther from the RPE and rely more heavily on Müller cell support (Fig. 2C).

4.2. Müller cell domains in the plexiform layers: support and modulation of neuronal metabolism and synaptic activity

As they traverse the synaptic layers of the retina (i.e., OPL and IPL), Müller cells extend fine horizontal processes, which make multiple contacts with the synaptic network (Fig. 1). This reflects specific functions they serve in these layers, including the metabolic support of synaptic activity, maintenance of the ion and fluid homeostasis of the neuropil, the recycling of neurotransmitters, and modulation of neuronal information processing via gliotransmission.

4.2.1. Metabolic support for retinal neurons

Intense neuronal activity in the retina, mainly triggered by glutamate, induces neuronal swelling and compensatory glial morphological changes, primarily mediated by AMPA-kainate receptor activity (Uckermann et al., 2004a,b). These changes, which involve active regulation of extracellular volume by Müller cells, are energy demanding and demonstrate that Müller cells play a key role in preventing neuronal hyperexcitation, strongly suggesting a metabolic coupling between Müller cells and retinal neurons.

Given these high metabolic demands, glucose serves as the primary fuel for the adult brain and acts as its major oxidative substrate (reviewed in (Dienel, 2019)). The main storage form of glucose in many cells is glycogen. In the brain, glycogen is predominantly synthesized and accumulated by astrocytes (Caltaldo and Broadwell, 1986). Similarly, in the retina, glycogen is mainly localized in Müller cells (Kuwabara and Cogan, 1961), along with critical enzymes for its synthesis (i.e., glycogen synthase and its regulatory partner, glycogen synthase kinase 3b (GSK3b) (Perezleon et al., 2013)) and degradation (i. e., the brain isoform of glycogen phosphorylase (Pfeiffer-Guglielmi et al., 2005)). More recently, lactate-the end product of both the aerobic (by the Warburg effect) and anaerobic glycolytic pathways (reviewed in (Rajala and Rajala, 2023))-has been identified as a new metabolic player, which can supplement or even replace glucose in neurons and glia under specific physiological and pathological conditions (e.g. during recovery from hypoxia) (reviewed in (Schurr, 2014)). Similarly in the retina, lactate plays a crucial role in metabolic pathways, cellular signaling, and gene regulation (reviewed in (Rajala and Rajala, 2023; Kocherlakota et al., 2024)). The LDHA and LDHB genes encode the tetrameric enzyme lactate dehydrogenase (LDH): LDHA homotetramers primarily convert pyruvate to lactate using NADH as a cofactor, whereas LDHB predominantly catalyzes the conversion of lactate to pyruvate with NAD as a cofactor (reviewed in (Rajala and Rajala, 2023)). Using Translating Ribosome Affinity Purification (TRAP) technology, it has been shown that photoreceptors express the more efficient isoform, LDHA, while LDHB is mainly used by the RPE, Müller cells, and retinal ganglion cells (Rajala et al., 2023). Lactate produced by photoreceptors is transported into the RPE and Müller cells via a family of bidirectional proton-linked carriers known as monocarboxylate transporters (MCT) (Halestrap, 2013). Within these cells, lactate is converted to pyruvate, fueling mitochondrial adenosine triphosphate (ATP) production (Chertov et al., 2011).

Additionally, Müller cells independently produce lactate, which is believed to be released through MCTs toward retinal ganglion cells, where it supplements their energy needs (Winkler et al., 2004a, 2004b; Vohra et al., 2018). In both Müller cells and ganglion cells, lactate serves as a preferred energy substrate over glucose, with lactate-dependent ATP production being crucial for promoting ganglion cell survival during periods of high metabolic demand (Vohra et al., 2019). Müller cells independently produce lactate, which is believed to be released through monocarboxylate transporters (MCTs) toward retinal ganglion cells, supplementing their energy needs (Winkler et al., 2004a, 2004b; Vohra et al., 2018). In both Müller cells and ganglion cells, lactate serves as a preferred energy substrate over glucose, with lactate-dependent ATP production being crucial for promoting ganglion cell survival during periods of high metabolic demand (Vohra et al., 2019). Müller cells produce lactate aerobically and anaerobically at high rates (Winkler et al., 2004a, 2004b). This observation led Winkler and colleagues to hypothesize that mitochondria in retinal neurons primarily utilize lactate produced by Müller cells rather than glucose (Winkler et al., 2004a, 2004b). However, this hypothesis has been challenged by evidence showing retinal neurons preferentially metabolize glucose when its supply is adequate (Winkler et al., 2003a, 2004b; Chertov et al., 2011; Hass et al., 2024). Recently, this understanding has evolved even further with the proposal of metabolic uncoupling between glycolysis and oxidative phosphorylation through mechanisms such as the Cori cycle, the Cahill cycle and the mini-Krebs cycle (Chen et al., 2024). Furthermore, the ability of Müller cells to significantly increase anaerobic glycolysis rates and utilize lactate for their metabolic demands contributes to their enhanced resistance to ischemia or hypoglycemia compared to retinal neurons (Winkler et al., 2000, 2003b). It is noteworthy that Müller cells in vascularized retinas have higher glycogen stores and a more extensive mitochondrial network than those in non-vascularized retinas, attributed to the greater oxygen availability in the former tissues (reviewed in (Toft-Kehler et al., 2018)).

Müller cells release purines mainly through connexin (43) hemichannels (Xu et al., 2022; Brückner et al., 2012; Voigt et al., 2015; Wagner et al., 2017; Birol et al., 2007). This release is triggered by various signals, including the activation of metabotropic glutamate receptors and osmotic membrane stretching (reviewed in (Reichenbach and Bringmann, 2016; Ventura et al., 2019)). ATP, once released, primarily acts through two classes of P2 receptors: G protein-coupled receptors (P2Y and ligand-gated ion channels (P2X) (reviewed in (Fletcher, 2020; Sanderson et al., 2014; Wurm et al., 2011). Alternatively, ATP is converted by ectoenzymes into adenosine, which exerts its effects via four distinct adenosine receptor subtypes - i.e. A1, A2a, A2b, and A3 receptor - all of which are G protein-coupled receptors (Schulte and Fredholm, 2003). In the retina, Müller cells release ATP into the inner plexiform layer, where it is mainly converted to adenosine. Adenosine then activates A1 adenosine receptors on retinal ganglion cells, inhibiting their synaptic activity and providing a protective effect against phototoxicity (Newman, 2003). However, during potent stimulation of metabotropic glutamate receptors, such as in cases of glutamate excitotoxicity, Müller cells can release large amounts of ATP (Loiola and Ventura, 2011; Wagner et al., 2017). In vitro studies have shown that this massive ATP release can kill retinal ganglion cells via activation of their P2X7 receptor, suggesting that reactive Müller cells could contribute to retinal ganglion cell death by this mechanism (Xue et al., 2016). Thus, Müller cells can play a dual role in the retina through purine signaling, depending on the level of ATP release: small amounts of ATP are converted to adenosine, which has a protective effect, while massive ATP release can be cytotoxic.

Exposure of cultured Müller cells to high glucose levels leads to reduced mitochondrial activity, increased mitochondrial fragmentation, and decreased extracellular acidification rate, along with cytochrome *c* release and apoptosis (Tien et al., 2017). The high glucose-induced decrease in mitochondrial connexin 43 (mtCx43) levels is known to promote mitochondrial fragmentation, cytochrome c release, and apoptosis in retinal endothelial cells (Trudeau et al., 2012). This mechanism likely operates in Müller cells as well, given that the downregulation of mtCx43 is a widespread process that links reduced mtCx43 channel activity to altered mitochondrial morphology and cytochrome c release (Roy et al., 2019). Conversely, counteracting the high glucose-induced decrease in mtCx43 levels has been shown to protect against apoptosis (Sankaramoorthy and Roy, 2021). These findings suggest that in diseased states, such as diabetic retinopathy, Müller cells may experience mitochondrial stress and damage. Mitochondrial dysfunction can lead to Müller cell impairment, compromising their protective role against glutamate excitotoxicity in the retina and resulting in neuronal death, particularly affecting retinal ganglion cells. Consistent with this assumption, functional deficits in Müller cells, such as impaired ability to counteract hyposmotic stress, have been observed in rodent models of diabetic retinopathy (Krügel et al., 2011; Pfaller et al., 2024). Blockade of mitochondrial oxidative stress with perindopril or inhibition of the mitochondrial permeability transition with cyclosporin A or minocycline effectively reduced swelling (Krügel et al., 2011), while hyposmotic stress and glutamine overload impaired mitochondrial fitness (Karl et al., 2011).

When neurotransmitters are released, protons (H+ ions) are also released into the synaptic cleft, and glial cells may add additional protons to the extracellular space (reviewed in (Soto et al., 2018)). Acid-sensing ion channels (ASICs) detect these protons and are present in many neurons, including photoreceptors and retinal ganglion cells across species (Liu et al., 2014; Vina et al., 2015; Lilley et al., 2004). Key questions remain about whether these protons induce specific signaling events and, if so, whether this signaling is confined to synaptic regions or serves as a broader modulator of neuronal excitability. ATP, potentially via an autocrine loop, triggers Müller cells to release H+ ions, leading to extracellular acidification (Tchernookova et al., 2018). In salamanders, this ATP-driven H+ flux is evident in the OPL, where photoreceptors synapse with bipolar neurons, and in the IPL, where bipolar and amacrine cells transmit signals to ganglion cells (Tchernookova et al., 2018). Remarkably, this ATP-induced extracellular acidification is highly conserved across diverse species, including in cultured Müller cells derived from human retinas (Tchernookova et al., 2018).

The retina has high lipid demands due to its intense membrane trafficking, which includes extensive phagocytosis of photoreceptor outer segments and intense synaptic activity. However, our understanding of membrane synthesis and recycling in the retina remains to be fully elucidated, especially for the contribution of glial cells to this event. Recently, attention has focused on Müller cellsthe cholesterol metabolism of Müller cells, including de novo synthesis and the import of cholesterol from external sources, such as lipoproteins. Cholesterol plays a critical role in neurogenesis and synaptogenesis (Mesa et al., 2024; Pfrieger, 2003; Mauch et al., 2001), with age-related declines in cholesterol levels potentially leading to synaptic loss and reduced synaptic plasticity, which may contribute to neurodegeneration (reviewed in (Shin et al., 2024)). Maintaining cholesterol homeostasis in neuronal plasma membranes is crucial for proper brain function, as disruptions in cholesterol balance are linked to several neurodegenerative disorders, such as Alzheimer's, Parkinson's, and Huntington's diseases (reviewed

in (Shin et al., 2024)). While the blood-brain barrier (BBB), and likely the inner BRB due to their similar structure, are largely impermeable to plasma lipoproteins (Bjorkhem and Meaney, 2004; Chobanian and Hollander, 1962), the outer BRB at the RPE allows their passage, with low-density lipoproteins (LDLs) being more efficient than high-density lipoproteins (HDLs) in crossing it (Tserentsoodol et al., 2006a, 2006b). The uptake of LDLs into RPE cells is mediated by specific receptors, including LDL-R, SR-BI and II, and cluster differentiation 36 (CD-36) (Fliesler and Anderson, 1983; Tserentsoodol et al., 2006a, 2006b; Harrison, 2019). Müller glia express low-density lipoprotein receptor-related protein 1 (LRP-1), which, upon activation, regulates functions such as cell proliferation, migration, differentiation, gliosis, glucose homeostasis, and survival of these and surrounding cells (Safina et al., 2016; Sanchez and Chiabrando, 2022). Thus, uptake by Müller cells might happen via their perivascular processes in the inner retina or via their microvilli reaching into the subretinal space. Additionally, increasing evidence suggests that Müller cells may represent the main hub in cholesterol biosynthesis and signalling in the retina (Fig. 3A): (i) Müller cells show strong expression of 3-hydroxy-3-methylglutaryl-CoA synthase 1 (HMGCS1), en enzyme that catalyzes the condensation of acetyl-CoA with acetoacetyl-CoA to form HMG-CoA (Fig. 3B); (ii) although not detected in our human Müller cell data, others have found strong expression of hydroxymethylglutaryl-CoA reductase (HMGCR) in rat Müller cells (Fliesler and Bretillon, 2010; Leger-Charnay et al., 2019) which generates mevalonic acid from HMG-CoA, the rate-limiting step in cholesterol synthesis; (iii) Müller glia express key components of the cholesterol transport machinery (e.g., TSPO, ApoE and ABCA1) and regulators of cholesterol metabolism (SREBP2 and LXR β) (Fig. 3; Mages et al., 2019; Leger-Charnay et al., 2019); (iv) Müller cells can sharply adjust their cholesterol metabolism in response to 24(S)-hydroxycholesterol (Leger-Charnay et al., 2019), an oxysterol synthesized by neurons to eliminate cholesterol, which also has neuroprotective effects in the retina (Ishikawa et al., 2016, 2018); (v) cholesterol levels ultimately influence how Müller cells interpret stimuli from the surrounding extracellular matrix and neurons, thereby contributing to retinal homeostasis (Lakk et al., 2017; Prieto-López et al., 2024).

4.2.2. Retinal ion and water homeostasis

Astroglia regulate ion concentrations in the neuropil by adjusting membrane permeability through various ion channels, a process crucial for maintaining a proper, fine-tuned neurotransmitter release (reviewed in (Verkhratsky et al., 2019)). These ion channels include voltage-dependent channels (such as K^+ , Ca^{2+} , and Na^+ channels, with K^+ channels being dominant), ligand-gated ion channels (such as NMDA receptor channels), and Transient Receptor Potential (TRP) channels (reviewed in (Verkhratsky et al., 2019)). The expression of similar channels in Müller cells suggests that they may perform comparable regulatory functions in retinal health and disease, including channels belonging to the Kir family (Kofuji et al., 2000, 2002), tandem-pore (TASK) channels (Skatchkov et al., 2006) and calcium-dependant K



Fig. 3. Cholesterol transport and biosynthesis pathways in Müller cells. (A) Scheme of the interplay of select transporters and enzymes for cholesterol uptake/ release and de novo biosynthesis potentially active in Müller cells. (B) Protein expression for genes involved in cholesterol pathways as indicated in (A), plotted according to profiles determined by cell type-specific LC-MS/MS analysis for Müller cells, neurons, and RPE isolated from human donor eyes. This is based on the resource data in our recently published study (Kaplan et al., 2023). Bars represent mean \pm SEM. Each dot represents a biological replicate. One-way Anova was performed with Dunnett's multiple comparision and only significances for comparisions with respective Müller cells populations are plotted (following the respective color code). *P < 0.05; **P < 0.01; $\mathbf{\nabla} P < 0.05$; $\mathbf{\nabla} P < 0.01$; $\mathbf{\nabla} \mathbf{\nabla} P < 0.001$. (D) Scheme of how the contribution of Müller cells to the cone visual cycle might differ depending on the retinal area, as deduced from the expression profiles of the relevant proteins involved.

channels (Bringmann et al., 1997). Moreover, AOP4 with Kir4.1 proteins also colocalize in the perivascular space (Nagelhus et al., 1999). Given their prominent role in the Müller cell-mediated retinal ion and water homeostasis, this chapter is specifically focused on the roles of Kir4.1 potassium, aquaporin 4 (AQP4) water channel and mechanosensitive TRP channels, while referring readers to other reviews for insights into the functions of additional ion channels relevant for these cells' function (Ochoa-de la Paz and Gulias-Canizo, 2022; Pannicke et al., 2017). Genetic studies in mice have shown that most of the K^+ conductance in Müller cells is mainly due to a single inward-rectifying potassium channel, Kir4.1 (Kofuji et al., 2000). Although Müller cells express a variety of other Kir channel subunits, their specific functions remain largely unexplored (Gao et al., 2018). Notably, Kir4.1 channels are weakly rectifying, allowing both inward and outward K⁺ currents, depending on the electrical and K⁺ concentration gradients across the cell membrane (Shuck et al., 1997). Kir4.1 is primarily found in Müller glial perivascular processes and endfeet adjacent to the inner limiting membrane and its subcellular localization is critically improtant for its proper function (Connors and Kofuji, 2006). Retinal K⁺ buffering is accomplished through three concurrent mechanisms: the Na⁺/K⁺ ATPase activity, passive co-transport with other ions by transporters, and the function of the Kir4.1 channel (Gao et al., 2018). Although many retinal disorders affect K⁺ permeability, this occurs primarily through mislocalization and reduced expression of Kir4.1 (Pannicke et al., 2014), without apparently altering the other players of retinal K⁺ buffering like Kir2.1 (Iandiev et al., 2006). This selective reduction in Kir4.1 expression leads to decreased hyperpolarization of Müller cells, impairing their function and exacerbating disease. Reduced Kir4.1 expression has been observed in conditions such as reperfusion after retinal ischemia, diabetic retinopathy, in late stages of inherited retinal dystrophy, retinal detachment, and glaucoma (reviewed in (Li et al., 2021; Gao et al., 2018; Beverley and Pattnaik, 2022).

Kir4.1 acts in concert with AQP4, a water channel highly expressed in Müller cells, as demonstrated by several studies in rodent and human retinas. These proteins are organized in orthogonal arrays by large protein complexes, including dystrophin-associated proteins (DAPs), which coordinate interactions with the matrixof basement membranes (e.g., the ILM), the glial cytoskeleton, and Müller cell membranes. This arrangement tethers Kir4.1 and AQP4 to critical glial microdomains, such as perivascular processes and basal endfeet (Nagelhus et al., 1998, 1999; Fort et al., 2008; Derouiche et al., 2012; Grosche et al., 2012; Rao et al., 2019). Disruption of this protein machinery—whether due to the deletion of a major basement membrane component like laminins (Hirrlinger et al., 2011), the Dp71 dystrophin gene product (Dalloz et al., 2003) or components of the glial cytoskeleton such as the intermediate filaments vimentin and GFAP-leads to the mislocalization of Kir4.1 and AQP4 and concomitant dysfunction of glial homeostasis. Conversely, rescue experiments, such as the re-expression of Dp71, restore the typical localization of these proteins (Vacca et al., 2016). This strong functional interaction is further supported by evidence showing that decreased Kir4.1 expression in retinal edema correlates with altered AQP4 expression or localization under various conditions, including hypobaric hypoxia (Han et al., 2024), suppression of glutamine synthetase activity by DL-alpha aminoadipic acid (Xie et al., 2023), in rodent models of diabetic retinopathy (Iandiev et al., 2007; Wang et al., 2021) as well is in detached human donor retinas (Grosche et al., 2012). These findings strongly imply that AQP4 and Kir4.1 cooperate to mediate the permeability of Müller cell membranes to water and potassium, thereby controlling this important function of Müller cells-the maintenance of retinal ion and water homeostasis, which, when dysregulated, plays a fundamental role in the formation of retinal edema (Reichenbach et al., 2007).

The role of Kir4.1 in Müller cell volume regulation is complemented by a glutamatergic-purinergic signaling cascade (Reichenbach and Bringmann, 2013; Pannicke et al., 2014; Lipp et al., 2009; Wurm et al., 2009, 2010; Slezak et al., 2012), which activates alternative cation channels, such as tandem pore potassium channels (Skatchkov et al., 2006), and partially unknown anion channels (Fig. 4). Multiple regulatory signaling molecules and homeostatic modulators, including growth factors like VEGF (Wurm et al., 2008a), HB-EGF (Weuste et al., 2006), NGF (Garcia et al., 2014); erythropoietin (Krügel et al., 2010), BDNF and endothelin 1/2 via FGF2 (Behl et al., 2016; Vogler et al., 2016), osteopontin and NGF via VEGF (Wahl et al., 2013); glucocortiocoids (Wurm et al., 2008b) or even neurosteroids especially progesterone (Neumann et al., 2010), further fine-tune Müller cell volume regulation (summarized in Fig. 4). Since efficient Müller cell volume regulation is most likely a major prerequisite for maintaining retinal ion and fluid homeostasis, it is therefore tightly regulated by a complex network of pathways that dynamically adapt to the tissue's activity state and stress conditions.

TRP channels have emerged as a significant area of interest in astroglia research, particularly for their role in Ca²⁺ signaling triggered by purinergic, glutamatergic, and mechanical stimulation (reviewed in Sawamura et al., 2017; Verkhratsky et al., 2019). Similarly, Müller cells express a variety of TRP channels with diverse functions. TRPC1 and TRPC7 were the first TRP channels identified in murine Müller cells, acting as essential co-receptors for proper activation of metabotropic muscarinic receptor-induced Ca^{2+} inward currents (Thebault et al., 2005). Later, TRP channels of the vanilloid family (TRPVs), specifically the osmo- and mechanotransducers TRPV1 and TRPV4, were identified in Müller cells. Activation of these channels leads to elevated intracellular Ca²⁺ levels, which can trigger extracellular signal-regulated kinase, upregulation of transcription factor c-Fos, and basic FGF expression within a few minutes to hours (Lindqvist et al., 2010). Activation of these channels can trigger Ca²⁺-dependent proapoptotic signaling pathways, induce osmotic changes that alter cell volume (Martinez-Garcia et al., 2013; Ryskamp et al., 2011, 2014; Toft-Bertelsen et al., 2019), and potentially influence the aforementioned glutamatergic-purinergic volume regulatory cascade. This suggests that TRPVs also play a role in responding to pathological increases in intraocular pressure and edema. A study by Pereiro and colleagues showed that the activation of TRPV4 is associated with Müller cells gliosis induced by the increased intracellular Ca²⁺ concentration (Pereiro et al., 2024). Moreover, also the localization of TRPV4 showed a clinical role, resulting its expression in peripheral Müller cells associated with greater susceptible to high intraocular pressure than central Müller cells (Pereiro et al., 2024).

Furthermore, a recent study uncovered a significant interplay between TRP channels and cholesterol in Müller cells: cholesterol supplementation enhances TRPV4-mediated responses, while cholesterol depletion reduces them (Lakk et al., 2018). Additionally, in a murine ischemia-reperfusion model, ischemia significantly increased TRPM7 expression in Müller cells, correlating with decreased retinal responsiveness to light and reactive gliosis (Martinez-Gil et al., 2023). These latter findings highlight TRPM7 as a potential therapeutic target for ischemia-related retinal conditions.

These key features of Müller cells highlight their crucial role in regulating the intra- and extracellular water distribution in retinal tissue. This function is vital because, like the brain parenchyma-where astrocytes perform a similar role-the retina lacks lymphatic vessels. In the brain, this astrocyte-mediated drainage has been termed the "glymphatic system" (Iliff et al., 2012; Hablitz and Nedergaard, 2021). Recently, it has been suggested that similar mechanism operate in the retina demonstrating that labeled human amyloid-beta peptide (h)A β is transported by axons of retinal ganglion cells and along the perivenous space in the optic nerve after intravitreal delivery (Delle et al., 2024). Deletion of AQP4 significantly reduces retinal hA_β penetration and clearance along the optic nerve, indicating that ocular glymphatic clearance is facilitated by AOP4 expression in retinal Müller glia and pre-laminar astrocytes. Additionally, Delle and Nedergaard's data imply that translaminar pressure is the main driving force for ocular glymphatic clearance, as physiological intraocular pressure exceeds



Müller cell

Fig. 4. Schematic overview of signaling pathways that fine-tune Müller cell volume regulation. Triamcinolone and anti-VEGF therapies were included to illustrate how they might interact with this complex signaling machinery. Compounds initiating the alternative, Kir4.1-independent volume regulatory cascade in Müller cells are highlighted in green. Pathways that converge to stimulate exocytotic glutamate release are shown in purple. HB-EGF, heparin-binding EGF-like growth factor; VEGF, vascular endothelial growth factor; FGF2, fibroblast growth factor 2 (basic); RTK, receptor tyrosine kinase; NPRA, atrial natriuretic peptide receptor A; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; TRPV1/4, transient receptor potential cation channel subfamily V member 1/4; PLC, phospholipase C; PKC, protein kinase C; NTPDase2 (alias CD39), ectonucleoside triphosphate diphosphohydrolase 2; mGLUR1/6, metabotropic glutamate receptor 1/6; P2Y1R, purinergic receptor P2Y1; A1, adenosine A1 receptor.

intracranial pressure. Although the precise role of Müller cells in intraretinal glymphatic clearance has yet to be systematically investigated, it is evident that deficits in their ion and water homeostasis functions contribute to intra- and extracellular retinal edema, leading to severe consequences for neuronal function and survival (reviewed in Reichenbach et al., 2007; Reichenbach and Bringmann, 2020; Lai et al.,

2023).

Importantly, Müller cells are also responsible for extracellular pH regulation. This function is mediated in these cells by carbonic anhydrase II, an enzyme that facilitates the removal of carbon dioxide and the regulation of bicarbonate and proton concentrations, thus maintaining extracellular pH balance (Newman, 1996). Recent evidence highlights

an additional mechanism of pH regulation involving ATP-mediated proton flux. A study by Tchernookova et al. (2018) demonstrated that extracellular ATP induces significant extracellular acidification via Na⁺/H⁺ exchange in Müller cells: ATP stimulation results in dose-dependent H⁺ efflux from Müller cells, mediated primarily by P2Y receptors and intracellular calcium release. The ATP-induced proton flux was substantially reduced when extracellular sodium was replaced by choline or when Na⁺/H⁺ exchange was pharmacologically inhibited with agents such as amiloride, cariporide, and zoniporide. This mechanism likely plays a critical role in modulating synaptic activity, as small alterations in extracellular acidity profoundly impact neurotransmitter release (reviewed in Sinning and Hübner, 2013) and synaptic vesicle recycling (reviewed in Du et al., 2014). Collectively, these findings reveal that Müller cells regulate extracellular pH through multiple pathways, with ATP-activated Na⁺/H⁺ exchange being a key contributor to pH homeostasis and neuronal signaling (Tchernookova et al., 2018).

4.2.3. Clearance of neurotransmitters

The extracellular concentration of glutamate, the primary excitatory neurotransmitter in the central nervous system, including the retina, is tightly controlled and kept at low levels. This regulation is crucial for maintaining an optimal signal-to-noise ratio in synaptic communication, ensuring that neuronal signaling remains precise and effective. Recent live cell imaging studies on the murine hippocampal neuropil have revealed that the short-range spread of glutamate is more extensive than previously thought, even at the level of single quantum release (Matthews et al., 2022). This study also demonstrates that multivesicular release could coactivate adjacent synapses if not restricted by the robust glutamate buffering action of glial cells through specific neurotransmitter transporters. To ensure precise and sustained synaptic transmission, this buffering action is likely to be particularly important in regions of nervous tissue with high synaptic density and continuous activity, such as the plexiform layers of the retina, where photoreceptors release glutamate continuously in darkness.

Keeping glutamate levels low not only prevents background noise from disturbing or even disrupting neural signals but also protects neurons from excessive stimulation. High levels of extracellular glutamate can cause overactivation of glutamate receptors, particularly NMDA and AMPA receptors (reviewed in (Iovino et al., 2020; Neves et al., 2023)). Excessive receptor activation can lead to "excitotoxicity," a pathological process characterized by a massive influx of calcium ions (Ca^{2+}) into cells primarily mediated by the glutamate-NMDAR pathway (reviewed in (Shen et al., 2022)). This calcium overload initiates a cascade of harmful intracellular events, including the activation of enzymes that degrade cellular components, increase production of reactive oxygen species, induce mitochondrial dysfunction (reviewed in (Angelova and Abramov, 2024; Montal, 1998)), and ultimately, trigger cell death by apoptotic and non-apoptotic pathways, including necroptosis and parthenatos (Yuan and Ofengeim, 2024; Zhang et al., 2024a).

Neurons and glial cells express a family of Na⁺-driven Excitatory Amino Acid Transporters (EAATs), specifically EAAT1-5, which help maintain low extracellular glutamate concentrations (reviewed in (Andersen et al., 2021; Neves et al., 2023; Shen et al., 2022)). While EAAT3 (also known as EAAC1) is primarily found in neurons, EAAT1 (GLAST) and EAAT2 (GLT-1) are mainly expressed in glial cells (Majumdar, 2023; Rothstein et al., 1994). In the retina, EAAT1 is exclusively present in Müller cells, EAAT2 is expressed by Müller cells and photoreceptors (Rauen et al., 1996; Ayten et al., 2024), whereas EAAT3 is undetectable in cell type-specific proteome profiling via LC/MS mass spectrometry in mice and is present at extremely low levels in the human retina. Interestingly, inactivation of the GLAST (EAAT1) gene does not completely prevent Müller cells from taking up glutamate (Sarthy et al., 2005), possibly due to compensatory mechanisms by other transporters such as GLT-1 (EAAT2). However, GLAST-deficient mice exhibit increased susceptibility to retinal damage following ischemic events, with near-complete loss of cells in the INL and thinning of IPL, OPL, and nerve fiber layer (Harada et al., 1998). In GLT-1 mutant mice, similar degenerative changes are observed, though they are less severe than those described in GLAST knockout mice (Harada et al., 1998). This is in line with our proteome data that show much higher GLAST than GLT-1 expression levels in murine (~26-fold) and human Müller cells (~155-fold in cells isolated from the macula, ~105-fold in peripheral Müller cells) (Fig. 4). Reanalysrs of single cell RNA-seq data sets from murine and human retinas confirm this expression pattern.

Once taken up by Müller cells, glutamate is rapidly converted to glutamine by the glia-specific enzyme glutamine synthetase (Bringmann et al., 2009a, 2009b, 2013). As a result, overall glutamate levels in Müller cells are kept low by the action of glutamine synthetase. Glutamine is then provided to neurons for resynthesis of glutamate—thus, glutamate levels in neurons are comparatively high, facilitating its packaging for synaptic release. Notably, similar synergistic mechanisms between retinal neurons and Müller cells for transmitter uptake and recycling may also apply to γ -aminobutyric acid (GABA), since Müller cells express high-affinity transporters for this neurotransmitter, facilitating its uptake and contributing to the regulation of inhibitory neurotransmission in the retina (reviewed in Bringmann et al., 2013).

4.2.4. Gliotransmission

Gliotransmission refers to the process by which glial cells release chemical signals, known as gliotransmitters, to communicate with neurons and other glial cells. Traditionally, the definition of gliotransmitters has been limited to neurotransmitters such as glutamate, ATP, and D-serine released by Ca²⁺-triggered exocytosis (reviewed in (Savtchouk and Volterra, 2018)). However, we propose broadening the definition to include any chemical signals exchanged between glia and neurons, including cytokines. In contrast to traditional synaptic transmission, gliotransmission-under this broader definition-can operate on a similarly fast, but also on a slower timescale, ranging from a few milliseconds to hundreds or even several minutes, and influences a wide array of cellular functions beyond synaptic activity, including metabolic and functional responses of recipient cells. This approach enables a more inclusive framework for future research, recognizing both fast, neurotransmitter-like actions and slower, modulatory processes as integral components of glial communication. Notably, the occurrence of neurotransmitter-mediated gliotransmission during normal synaptic activity remains controversial (reviewed in (Fiacco and McCarthy, 2018)). Under the expanded definition, gliotransmission appears more likely to occur in response to pathological conditions (reviewed in (Baraibar et al., 2024; Lei et al., 2024)).

In the retina, gliotransmission, which originates from Müller cells, influences various functions such as neuronal excitability, ion balance, synaptic plasticity, and blood vessel responses. However, studies in mouse models have shown that when gliotransmission is blocked by inhibiting the release of intracellular calcium in astrocytes, it does not cause noticeable changes in the structure or function of the nervous system under normal conditions (Agarwal et al., 2017; Fiacco et al., 2007; Srinivasan et al., 2015). Similarly, when gliotransmission, such as glutamate release via Ca²⁺ dependent exocytosis, is prevented in Müller glia by cell type-specific disruption of SNARE proteins, no significant morphofunctional defects of the retina are observed (Slezak et al., 2012). However, when non-physiological or pathological conditions are mimicked, the scenario changes: Blocking SNARE-mediated exocytosis in Müller cells interferes with their ability to regulate their volume and prevents neuronal swelling caused by the release of glial glutamate (Slezak et al., 2012). Moreover, neuronal function and survival are enhanced in the postischemic retina (Wagner et al., 2017). This suggests that under stress conditions, glutamate released from Müller cells via vesicular release is detrimental and contributes to neuronal hyperexcitation.

A recent in-depth analysis of the proteome and secretome of primary

Müller cell cultures after stimulation with pro-inflammatory cytokines (INFy, TNFa), anti-inflammatory cytokines (IL-4, IL-6, IL-10), and growth factors (Vascular Endothelial Growth Factor (VEGF), TGFβ1-3) revealed significant and distinct responses (Schmalen et al., 2021a,b). On the secretome side, stimulation with pro-inflammatory cytokines and growth factors led to the release of pro-inflammatory cytokines and proteins involved in extracellular matrix organization. These findings highlight the activation of pathways related to the "humoral immune response" and "immune system processes," with a notable increase in the secretion of complement proteins (Schmalen et al., 2021a,b). The secretome analysis confirms and extends previous observations that Müller cells are a central source of retinal cytokines, particularly under pathological conditions like gliotic scar formation (Eastlake et al., 2016). On the proteomic side, cytokine and growth factor stimulation significantly impacted pathways related to mitochondrial function, resulting in mitochondrial dysfunction with increased production of reactive oxygen species (ROS) and reduced oxidative phosphorylation. Additionally, protection pathways—including caveolarand clathrin-mediated endocytosis, phagosome formation, ubiquitylation, and neuroinflammation-were notably regulated (Schmalen et al., 2021a.b).

Similarly, our studies on mouse (Demais et al., 2022) and human retina (Kaplan et al., 2023) strongly implicate that many of the aforementioned compounds-chemokines, cytokines, complement components, and proteins that shape and form the extracellular matrix-are released by Müller cells via small extracellular vesicles (sEVs; ~50-150 nm in size). Cell type-specific expression analysis unequivocally identified Müller cells as the major cell type of the retina expressing know markers of sEVs. The (patho-)physiological relevance of this route of communication of Müller cells with retinal neurons, microglia, vascular cells, or RPE has not been studied systematically yet. We have recently initiated an in-depth analysis of the molecular and functional adaptations of Müller cells to their environment, with a particular emphasis on their role in sEVs-mediated communication. Proteomic comparisons of cone (macular)- and rod-rich (peripheral) retinae in humans and mice revealed distinct Müller cell expression profiles linked to extracellular matrix and cell adhesion pathways, with epiplakin (EPPK1) and CD9, an established sEVs marker, highly enriched in macular Müller cells. Functional studies showed that EPPK1 knockout in the human Müller cell line MIO-M1 disrupted cellular mechanics, altering traction forces the cells employ on ECM, cell shape, size, and filopodia (Kaplan et al., 2023). Additionally, immunohistochemical, electron microscopic, and molecular analyses in adult mice demonstrated that Müller cells release distinct sEVs from their endfeet and microvilli. These glial EVs incorporate VAMP5, a Müller cell-specific SNARE protein responsive to ischemia, and differ from neuronal secretomes (Demais et al., 2022). These findings highlight exocytosis-mediated communication, particularly through sEVs, as a critical mediator of Müller cell interactions and adaptations to the specific needs of surrounding cells/tissues. This is especially true in the human retina with its peculiar specialization between the macular and peripheral retina. Moreover, the overall picture suggests that in pathological conditions, cell-cell communication reshapes Müller cells function and signaling, activating either protective or destructive responses that dramatically influence the overall retinal response to disease.

4.2.5. Neuroprotection through secreted trophic factors

Aligning with what has been discussed in section 4.2.4, Müller cells are highly active secretory cells. It is well established that they release multiple neurotrophic factors and antioxidants (extensively reviewed in Vecino et al., 2016; Eastlake et al., 2020). These include glial cell line-derived growth factor (GDNF)(Del Río et al., 2011), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF)(Seki et al., 2005), pigment epithelium-derived factor (PEDF) (Unterlauft et al., 2012), VEGF (Wurm et al., 2008a; Foxton et al., 2013; Zwanzig et al., 2021), interleukin-6 (IL-6) family members IL-6 (Yoshida et al., 2001; Sauter and Brandt, 2016) and leukemia inhibitory factor (LIF)(Pannicke et al., 2018), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4),(García et al., 2003). Proteomic analyses have also identified osteopontin and basigin as neuroprotective proteins secreted by Müller cells (Ruzafa et al., 2018). Given this vast array of neuroprotective secreted factors and their effects on retinal cell types are complex, we refer readers to comprehensive reviews on their neuroprotective roles (e.g. Vecino et al., 2016; Eastlake et al., 2020), and will highlight only a few key examples in the following sections.

Given that Müller cells express receptors for most if not all af these molecules, for sure one mode of their action is to diretly promote Müller glial homeostasis functions through autocrine signaling-indirectly supporting neuronal function (Fig. 4) (Harada et al., 2002; Wurm et al., 2008a; Garcia et al., 2014; Behl et al., 2016; Vogler et al., 2016). However, substantial evidence indicates that these factors are also critical for the survival of retinal neurons and for promoting neurite regeneration under both physiological and stress conditions, acting directly on neurons through paracrine mechanisms (García et al., 2002; Ruzafa and Vecino, 2015). Müller cells and their secreted factors support the survival of organoid-derived RGC-like cells, enhance neurite outgrowth, and may contribute to neuronal maturation. (Pereiro et al., 2020a,b). Additionally, GDNF, produced by and also acting directly on Müller cells in an autocrine fashion (Hauck et al., 2006), serves as a critical protective agent for retinal photoreceptors via a paracrine mode of action (Del Río et al., 2011). LIF is a cytokine involved in neuroprotection and regulation of reactive gliosis in the nervous system. In the retina, LIF is primarily expressed by Müller cells, while its receptor is expressed by Müller cells, but also by microglia and retinal neurons (Pannicke et al., 2018). Studies in LIF-deficient mice show reduced expression of GFAP, indicating impaired gliosis during retinal degeneration (Pannicke et al., 2018).

To exploit this neuroprotective potential of Müller cells, their application in animal models of glaucoma has been explored. Intravitreal transplantation of human Müller glia resulted in improved retinal function, primarily through the secretion of neuroprotective factors rather than direct integration into the host retina (Singhal et al., 2012). Notably, Müller glia isolated from retinal organoids derived from human induced pluripotent stem cells (hiPSCs) were able to partially restore visual function in rats with NMDA-induced retinal ganglion cell loss, highlighting their potential as a cell source for the treatment of retinal degenerative diseases (Eastlake et al., 2019).

These studies highlight the therapeutic potential of modulating the release of trophic factors by Müller glia in retinal diseases. However, further research is needed to fully understand their capabilities, especially in the pathologically stressed retina.

4.2.6. Müller glia and blood-retinal barrier

The close association of Müller cells with intraretinal blood vessels, combined with their release of cytokines that influence the integrity of the BRB, represents another key function. When exposed to oxygen deficiency in vitro, Müller cells activate the hypoxia-inducible factor (HIF) pathway, which induces the expression of Angiopoietin-like 4 and VEGF (Babapoor-Farrokhran et al., 2015; Xin et al., 2013). Angiopoietin-like 4 is a multifunctional cytokine involved in regulating lipid metabolism, angiogenesis, and vascular permeability, loosening the BRB (reviewed in (Fernandez-Hernando and Suarez, 2020)). VEGF is one of the most critical factors in the formation of new blood vessels (reviewed in (Ahmad and Nawaz, 2022)), and its activity can disrupt the endothelial permeability by activating the removal of tight-junction proteins by phosphorylation/ubiquitylation (Li et al., 2019; Murakami et al., 2009, 2012). Notably, Angiopoietin-like 4 and VEGF may act synergistically on the destabilization of the BRB, resulting in an accumulation of fluid, ultimately leading to the development of macular edema (Sodhi et al., 2019). Several cytokines regulate VEGF synthesis in the nervous tissue and retina (reviewed by (Ferreira et al., 2023; Zhang et al., 2024b)). For instance, IL-6, secreted by retinal vascular endothelial cells, and IL-8, released by both endothelial and glial cells, stimulate VEGF expression or its signaling transactivation (Coughlin et al., 2019; Nakahara et al., 2003; Petreaca et al., 2007). Conversely, Pigment Epithelium-derived Factor (PEDF), secreted by RPE, Müller cells and retinal capillary endothelial cells, acts as an angiogenic inhibitor (Araujo et al., 2021) and antagonizes VEGF by preventing receptor binding, thus reducing VEGF's effects (Zhang et al., 2006).

Despite the extensively studied role of VEGF in (neo-)angiogenesis, which is underpinned by the success of anti-VEGF therapies for wet agerelated macular degeneration and diabetic macular edema, VEGF also has crucial benefits for Müller cell homeostasis. It supports key glial functions such as maintaining the retinal ion and volume balance. Notably, under stress conditions that lead to a diminished function of Kir4.1 potassium channels, VEGF plays a pivotal role in restoring Müller cell volume regulation, triggering a complex glutamatergic-purinergic signaling cascade (Wurm et al., 2008a and 2008b; Fig. 4)-a vital process for sustaining tissue homeostasis and ensuring the proper function of inner retinal neurons (Pannicke et al., 2014). Indeed, our cell type-specific proteome analysis identified Müller cells of the human retina to express high levels of VEGF receptor 2 (KDR; note that vascular cells and microglia were not analyzed), while VEGFR1 (FLT1), which seems to primarily act as a decoy receptor for VEGFR2 ligands (Uemura et al., 2021), is present in Müller cells, neurons, and RPE, but at rather low levels. A single injection of bevacicumab (anti-VEGF antibody) in healthy pig eyes did not lead to negative effects on the expression of Müller cell homeostasis genes; instead, the aforementioned Kir4.1 potassium channel was slightly upregulated (Iandiev et al., 2011a,b). However, this study focusing on the effects of anti-VEGF therapy was performed in healthy eves. As mentioned before, VEGF seems especially important for Müller cells when they switch into a gliotic state that includes Kir4.1 down- and GFAP-upregulation. Henceforth, systematic studies are needed to assess the potential unintended effects of excessively efficient suppression of retinal VEGF signaling—such as through the permanent expression of VEGF traps via gene therapy-on Müller cell survival. This is particularly important given reports that VEGF functions as a survival factor for both Müller cells (Saint-Geniez et al., 2008) and retinal neurons (Nishijima et al., 2007; Kim and D'Amore, 2012). Since VEGF's Müller cell-protective effects-particularly in cell volume regulation—can also be stimulated by alternative factors such as HB-EGF, BDNF, FGF2, neurosteroids, glucocorticoids, and others (Fig. 4), combining anti-VEGF therapies with compounds targeting these pathways shows significant potential. Studies have demonstrated that Müller cell loss can lead to vascular abnormalities, including BRB breakdown (Shen et al., 2022; Shen et al., 2012; Shen et al., 2014). Therefore, a combined therapeutic approach could preserve Müller cell function while enhancing vascular integrity. Such strategies may simultaneously reduce retinal edema, support Müller cell survival, and stabilize the BRB, ultimately promoting overall retinal health more effectively.

Other potentially interesting but less studied angiogenetic cytokines of the retina that may contribute to loosening the BRB are monocyte chemoattractant protein-1 (MCP-1), released by photoreceptors (Tonade et al., 2017) and Müller glia (Eastlake et al., 2016), and prostaglandins, secreted by Müller cells (reviewed in (Zhang et al., 2024b)). MCP-1 directly increases retinal endothelial cell permeability in vitro via changes in claudin expression (Tonade et al., 2017). Conversely, inhibiting MCP-1 expression, along with other cytokines, using the histone deacetylase inhibitor ITF2357 dramatically improves the impermeability of the outer BRB (Lim et al., 2024). Prostaglandins also play a role in BRB regulation. Early expression of cyclooxygenase-2 (COX-2) in Müller cells after an ischemic event suggested that prostaglandin release from these cells might contribute to BRB breakdown. However, blocking prostaglandin signaling with the selective COX-2 inhibitor SC-58236 failed to prevent BRB breakdown, though it did reduce microglia activation and protect ganglion retinal neurons (Ju et al., 2003). Prostaglandins are derived from arachidonic acid, which is

converted by fatty acid cyclo-oxygenase into prostaglandin H2, leading to further production of prostanoids like PGD2, PGE2, PGF2 α , PGI2 (prostacyclin), and thromboxane A2. More recent work using two specific agonists of the prostaglandin receptors—i.e., the PGE2 receptor 2 agonist omidenepag and the F prostanoid receptors agonist latanoprost acid—showed that co-activation of these two specific prostaglandins signaling pathways enhances inner BRB functioning at early stages but promotes inner BRB breakdown at later stages (Nakamura et al., 2023). Additionally, omidenepag, either at high concentrations or in combination with latanoprost, causes transient dysfunction of the outer BRB, although the molecular mechanisms behind these effects on the BRB are not fully understood, aside from a reduction in tight junction protein expression (Nakamura et al., 2023).

Indeed, these cells enhance the integrity of the inner BRB by secreting factors such as PEDF, thrombospondin-1, and glial cell linederived neurotrophic factor (Eichler et al., 2004a, 2004b; Nishikiori et al., 2007). Moreover, Müller cells regulate BRB permeability, being a major source of VEGF and tumor necrosis factor (TNF) (Aiello et al., 1995; Eichler et al., 2004a, 2004b; Noda et al., 2005). In particular, VEGF and TNF increase vascular permeability. This can be also increased by Müller cells by producing matrix metalloproteinases, which are able to degrade endothelial tight junctions' proteins (Behzadian et al., 2001; Noda et al., 2005; Giebel et al., 2005). By this way, Müller cells modulate the vascular growth in physiologic conditions. Moreover, Müller cells also play an angiostatic effect mediated by the release of soluble antiangiogenic factors such as PEDF in pathologic conditions (Eichler et al., 2004a, 2004b).

4.3. The endfeet domain of Müller glia and the ILM: beyond the vitreoretinal interaction

Müller cells terminate on the inner side of the retina with peculiar funnel-shaped endfeet that attach to the basement membrane known as the ILM (Retzius, 1871). These endfeet are precisely aligned, creating a continuous boundary that separates nerve fibers from the ILM, without any gaps that would expose the axons of ganglion cells directly to the vitreous (Cohen, 1961). In the adult eye, the ILM acts like a dual-sided adhesive tape that anchors the endfeet of Müller cells and thereby the entire retina to the vitreous body (Peynshaert et al., 2019; Reichenbach and Bringmann, 2020). This basement membrane also likely contributes to maintaining the alignment of the endfeet along the optic axis (Peynshaert et al., 2019), a critical requirement for optimizing light transmission from Müller cells to photoreceptors, as discussed later.

At the ultrastructural level, the ILM resembles a typical basement membrane, with a lamina densa sandwiched between an external and an internal lamina lucida (Cohen, 1961). Its overall thickness varies across different regions of the retina, being thickest in the peripheral macular region and thinnest at the fovea, near the optic disc, and at the retinal periphery, as shown by various morphological studies (Fine, 1961; Foos, 1972; Henrich et al., 2012). Studies using atomic force microscopy have shown that the native hydrated ILM is significantly thicker and stiffer on the retinal side compared to the vitreal side, a property not captured by other morphological techniques, which measure ILM thickness after dehydration (Henrich et al., 2012).

The primary components of the ILM are consistent with those of a typical basal lamina, including collagen type IV, laminin, nidogen, and proteoglycans as the most abundant proteins (Kleinman et al., 1982). Laminin is more concentrated in the external lamina rara, while collagen type IV is more uniformly distributed throughout the ILM (Halfter et al., 2013). Proteomic analyses, using LC-MS/MS, have revealed both qualitative and quantitative differences in the ILM compared to other basement membranes in the body, suggesting a unique compositional profile (Balasubramani et al., 2010). However, the full physiological and pathological implications of these findings remain unclear.

During eye development, morphological studies have shown that many of the proteins forming the inner limiting membrane (ILM) are synthesized in the lens and ciliary body (Dong et al., 2002). These proteins are secreted into the vitreous body, which acts as a reservoir for the subsequent deposition of ILM components (Halfter et al., 2008). However, there is also strong evidence that Müller cells play a central role in ILM formation, particularly during the first two years of life (Ponsioen et al., 2008a; Sebag, 1992). Although direct data on the fetal human ILM are lacking, studies on chick embryonic ILM suggest it is primarily composed of laminins and nidogens, with collagen IV playing only a minor role (Balasubramani et al., 2010). Notably, after birth, the inner limiting membrane (ILM) continues to grow throughout life, expanding from approximately 70 nm in fetal stages to several microns in older individuals (Candiello et al., 2010; Stepp and Menko, 2021). This age-related growth is accompanied by a slight reduction in laminin and a marked increase in collagen IV and agrin deposition, ultimately resulting in an adult ILM composed of over 50 % collagen IV—reflecting a transition from a laminin-rich to a collagen IV-dominant basement membrane (Candiello et al., 2010; Stepp and Menko, 2021). Both cultured and isolated Müller cells from intact retinas have been shown to synthesize collagen and agrin, underscoring their key role in ILM growth and maintenance (Grosche et al., 2016; Ponsioen et al., 2008b; Kaplan et al., 2023). This compositional shift is likely driven by the extremely slow turnover of collagen, which has a half-life ranging from 11 to 100 years (Maroudas et al., 1992; Verzijl et al., 2000, 2001; Bishop et al., 2003), and/or by the sustained, low-level secretion of basement membrane proteins by Müller cells, particularly in the macular region (Stepp and Menko, 2021; Kaplan et al., 2023; Pietro-Lopez et al., 2024). The importance of Müller cells for shaping the ILM composistion is underscored by the observation that ILM formation is impaired in conditions involving dystrophic Müller cells (Kellner et al., 1998). Interestingly, despite the aforementioned ongoing deposition of ILM components throughout adulthood, the ILM does not regenerate following surgical peeling, as demonstrated in early clinical studies using ILM dye labeling and longitudinal imaging (Li et al., 2008; Nakamura et al., 2003; Piven and Moisseiev, 2010). The failure of regeneration may be due to the incomplete secretion of essential basement membrane components—such as laminin and collagen IV—by Müller cells, as revealed by single-cell transcriptomic and proteomic analyses (Roesch et al., 2008; Kaplan et al., 2023).

The molecular adhesion of the ILM to both the vitreous body and the retina has been investigated due to its implications for vitreous detachment. Electron microscopy studies have shown that this adhesion is mediated by distinct molecular complexes on either side of the ILM. On the vitreal side, collagen type IV fibers extend from the internal lamina rara to the vitreous cortex, creating a loose connection between the ILM and the vitreous body (Bu et al., 2015). On the retinal side, dystroglycan, together with $\beta 1$ integrins from the Müller cells plasmalemma, binds to laminin-1 in the external lamina rara of the ILM, forming mechanically strong, atypical focal adhesion junctions (Brem et al., 1994; Claudepierre et al., 1999; Clements et al., 2017). Conditional inactivation of dystroglycan in murine Müller cells reveals that this glycoprotein is crucial for maintaining ILM integrity by preventing retinal neurons from migrating into the vitreous, while also regulating neuronal migration, axon guidance, and dendritic stratification within the inner retina (Clements et al., 2017), confirming earlier in vitro findings (Mehes et al., 2005). Similarly, conditional inactivation of $\beta 1$ integrin in the mouse retina, by disrupting CAS signaling, causes ganglion cells to fail in responding to the laminin-rich ILM, resulting in ectopic neuronal clusters that fail to organize into the typical single-cell layer of the ganglion cell layer (Riccomagno et al., 2014). Interestingly, and somewhat unexpectedly, mice mutants with impaired laminin-1 exhibit additional defects in retinal vascular development, characterized by persistent fetal vasculature, the absence of a primary retinal vascular plexus, and the presence of proliferative vitreoretinopathy, while also phenocopying previously observed defects in ganglion cell organization in dystroglycan and b1 integrin mutants (Edwards et al., 2011). Notably, in macular hole repair, peeling surgery typically

involves the mechanical removal of the internal layer(s) of the ILM to avoid damaging the nerve fiber layer and potentially stimulate axonal regrowth into the vitreous (Steel et al., 2015).

Like other basement membranes, the ILM acts as a molecular sieve with a particle exclusion limit that was calculated to be around 75 kDa in molecular weight or 2.5–4.9 nm in hydrodynamic radius, meaning it restricts the diffusion of molecules larger than those sizes (Hutton-Smith et al., 2017; Jackson et al., 2003). Increasing the ILM's exclusion limit—thereby enhancing its permeability—holds significant clinical potential for improving the effectiveness of intravitreal drug delivery and gene therapy for retinal treatments. Various methods have been explored to modulate ILM permeability, including mild enzymatic digestion with proteases or glycosidases (reviewed in (Zhang and Johnson, 2021)), surgical ILM peeling (Teo et al., 2018), and sub-ILM injections of vectors (Gamlin et al., 2019), though none of these methods have yet seen widespread application.

In summary, the ILM is essential for retinal development and longterm integrity, making it a key target for research aimed at enhancing retinal therapies through permeability modulation. Müller cells are crucial in regulating ILM stability, permeability, and overall function.

5. Müller cells shape the retinal immune homeostasis

Microglial cells, the macrophages of the CNS and retina, play a pivotal role in retinal immune responses, often acting as first responders to tissue damage and pathological changes (Lu et al., 2011a, 2011b; Mages et al., 2019; Paolicelli et al., 2022; Zhang et al., 2006). Effective immune responses, however, depend on the complex interaction between microglia and Müller cells, which enhance microglial activity through feedback loops and contribute significantly to retinal immune modulation (Di Pierdomenico et al., 2020; Mages et al., 2019; Wang et al., 2011). Müller cells express receptors for several cytokines, such as interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α), which are secreted by microglia (Natoli et al., 2017; Kaczmarek-Hajek et al., 2018; Todd et al., 2019). In response, Müller cells can release cytokines such as interleukin-6 (IL-6) or IL-8, further influencing immune activity, including that of microglia (Liu et al., 2014, 2015; Schmalen et al., 2021a,b; Yoshida et al., 2001). This molecular interaction positions Müller glia as central regulators, balancing pro-inflammatory and anti-inflammatory mediators to foster protective inflammation (Krishnan and Chatterjee, 2012). For example, in situations of tissue stress, Müller cells increase the secretion of neuroprotective factors, including glial cell-derived neurotrophic factor (GDNF), leukemia inhibitory factor (LIF), and diazepam binding inhibitor (DBI) (Demais et al., 2022; Mages et al., 2019; Wang et al., 2011). DBI, identified as the putative endogenous ligand for the translocator protein 18 kDa (TSPO), is expressed by Müller cells. TSPO expression becomes markedly upregulated in reactive microglia, and its stimulation by exogenous ligands like XBD173 has shown neuroprotective effects in retinal pathology models (Hector et al., 2024; Mages et al., 2019; Scholz et al., 2015).

Additionally, Müller cells play a significant role in the complement system, an essential component bridging innate and adaptive immunity. They produce and secrete key complement cascade proteins, including the central component C3 (Pauly et al., 2019; Zauhar et al., 2022a,b). Activation of the complement cascade can lead to cell opsonization, formation of membrane attack complexes, and release of anaphylatoxins such as C3a and C5a. (Tabor et al., 2023). At the same time, Müller cells are also a major intraretinal source of complement factor H, which can suppress the activity of the complement system, e.g. by preventing excessive cleavage of C3 (Pauly et al., 2019; Zauhar et al., 2022a,b). Microglia are the only retinal cells expressing substantial levels of receptors for opsonins such as C3a and C5a, which are generated during complement activation (Pauly et al., 2019; Zauhar et al., 2022a,b). Consequently, the secretion of C3 by Müller cells can facilitate microglial functions such as synaptic pruning, a process dependent on complement signaling and integral to sculpting retinal circuitry during development but potentially also during adulthood and disease (Schafer et al., 2012; Stevens et al., 2007; Stevens and Johnson, 2021).

The close spatial and functional association of microglia with Müller cell processes in the plexiform layers of the retina underscores the critical role of their interaction in maintaining retinal immune homeostasis (Wang et al., 2011). Müller cells, spanning the entire retinal structure, may play a pathfinding role, directing microglia to sites of lesion. This chemoattractive capability may be linked to the upregulation of chemokines such as CCL2, as demonstrated in models of retinal light-induced damage (Rutar et al., 2011). In vitro studies also suggest that Müller cells might serve as an adhesive scaffold, aiding microglial migration through altered cell-cell physical interactions (Tassi et al., 2006).

Beyond their roles in signaling and scaffolding, Müller cells are capable of phagocytosing cellular debris, such as dead photoreceptors or shed photoreceptor discs (Francke et al., 2001; Long et al., 1986; Sakami et al., 2019). There is also evidence suggesting that Müller cells might act as atypical antigen-presenting cells, potentially influencing alloreactive naïve or memory T cell activity (Mano et al., 1991; Schmalen et al., 2021a,b). This potential is particularly intriguing given the recent identification of regulatory T cells as critical players in maintaining retinal homeostasis during aging and preventing age-related neurodegeneration (Conedera et al., 2023; Llorián-Salvador et al., 2024).

In summary, the multifaceted interplay between Müller cells and microglia, mediated through cytokines, chemokines, complement, and physical interactions, highlights their cooperative role in retinal immune regulation. These interactions are essential for ensuring coordinated responses to injury and maintaining retinal health, underscoring the importance of these cells in immune and neuroprotective mechanisms within the retina.

6. Müller glia as living optical fibers: enabling optimal retinal light transmission and novel non-invasive diagnostic tools

The retina has an inverted structure relative to the direction of incoming light, with photoreceptors located in its outermost layer. As a result, light must traverse multiple layers of irregularly shaped, randomly oriented cell processes—phase objects that inherently scatter light—before reaching the photoreceptors. (Snyder, 1975). This should result in blurred vision. In humans and non-human primates, the fovea—the central region of the retina—mitigates these optical challenges by forming a shallow, saucer-shaped depression. This structure radially displaces inner retinal neurons, such as bipolar neurons, amacrine cells, and ganglion cells, significantly reducing the number of cellular layers light must pass through. As a result, light reaches the photoreceptors almost directly after passing through the vitreous humor.

How does visual acuity work in the absence of a fovea, as seen in most mammals, including typical preclinical model organisms like mice, rats, rabbits, and pigs? A seminal study by Franze et al. (2007) elegantly demonstrated that Müller cells function as optical fibers in the guinea pig retina, channeling light from their endfeet directly to the outer segments of photoreceptors, where photons are detected and transduced into synaptic signals. Using confocal microscopy on whole-mount retinas, they compared transmission versus reflection images and observed tubular structures that transmitted significantly more light than the surrounding tissue. Intense backscattering was observed in retinal layers proximal to the photoreceptors, except within these tubes. These structures matched the spatial pattern and diameters of columnar Müller cells, previously identified using vital dyes in retinal whole mounts (Uckermann et al., 2004a,b). Additionally, the funnel-like structures seen in reflection mode resembled Müller cell endfeet, and morphological markers confirmed their identity as Müller cells (Franze et al., 2007). In a follow-up study, Agte et al. (2011) confirmed these findings and further demonstrated that each Müller cell channels light signals to its corresponding cone photoreceptor, suggesting that high

spatiotemporal resolution is achieved by this dedicated light-guiding system. Müller cells also optimize the signal-to-noise ratio, enhancing visual and contrast sensitivities (Labin and Ribak, 2010; Agte et al., 2011, 2018). Labin et al. (2014) showed that Müller cells concentrate green-red light onto cones while directing blue-purple light onto nearby rods, a function maximized at the parafoveal region, where the Müller cell-to-photoreceptor ratio is 1:1, before decreasing toward the retinal periphery.

In line with these findings, Zueva et al. (2014) demonstrated that Müller cell endfeet in the fovea capture light and channel it directly to individual cone photoreceptors. This light-capturing capability is further enhanced by the increased density of Müller cell endfeet in the foveal pit, which optimizes photon capture and transfer efficiency, albeit the Z-shaped arrangement of Müller cells in this region (Zueva et al., 2014).

More recently, Makarov and colleagues systematically investigated the structural features of the optical fiber system represented by Müller cells in the bird fovea to identify its cellular components and physical constraints. Crystallins are the main proteins responsible for lens transparency (reviewed in (Taylan Sekeroglu and Utine, 2021)) and mutations in lens intermediate filament proteins also lead to lens opacity (Alizadeh et al., 2002, 2003; Oka et al., 2008). Building on this understanding, it was found that intermediate filaments surrounded by αA-crystallins form nano-optical channels that efficiently conduct photons in Müller cells (Zayas-Santiago et al., 2018; Zueva et al., 2016). The spectral selectivity of these nanostructures has been precisely determined, revealing that a set of intermediate filaments with different geometries, as observed in Müller cells, can provide light transmission over the entire visible spectrum with very high efficiency and high contrast (Khmelinskii et al., 2017; Khmelinskii and Makarov, 2019a). Quantum confinement within these nanostructures facilitates exciton-based light energy transfer between the inner and outer limiting membranes, virtually eliminating light scattering and preserving contrast (Khmelinskii and Makarov, 2019b; Makarov et al., 2017). Studies on porcine retina intermediate filaments confirmed exceptional light and electrical conductivity, supporting this quantum mechanism (Khmelinskii and Makarov, 2019b).

Overall, these findings underscore the critical role of Müller cells in minimizing light scattering, enhancing contrast sensitivity, and efficiently transferring photon energy to photoreceptors—an essential function for optimizing vision.

These very peculiar optical characteristics of Müller cells, which are assumed to optimize retinal light passage, avoiding reflection and scattering, has been used to isolate and quantify Müller cells in vivo, non-invasively, starting from OCT images (Arrigo et al., 2020). In particular, we developed an algorithm to isolate and segment the transretinal, non-reflective, vertical signal from OCT scans, and the output was compared with histologic data. We were able to provide a good non-invasive estimate of extrafoveal Müller cells in human eyes (Arrigo et al., 2020). Conversely, it was not possible to reconstruct macular Müller cells because (i) their z-shape morphology makes the proper isolation of the signal challenging and (ii) because the small diameter of the Müller cell stem processes, especially in the macula, is below the resolution limits of state-of-the-art OCT devices (Arrigo et al., 2020). Despite these challenges, our study may mark an initial step toward developing a novel diagnostic pipeline: the in vivo assessment of glial cell status, with potential applications in both retinal and neurological diseases.

7. The role of Müller cells in retinal diseases

Having outlined many of the important Müller cell functions critical to retinal health, understanding the role of Müller cells in retinal disorders associated with characterisitic changes of these glial functions has meaningful diagnostic and therapeutic implications. In this section, we discuss the role of Müller cells in the major retinal diseases.

7.1. Müller cells in normal aging and in age-related macular degeneration

The aging human retina progressively accumulates damage from oxidative stress and lipid peroxidation due to the gradual downregulation and diminished efficacy of defense mechanisms that protect the tissue from sustained high exposure to these stressors. Müller cells are affected by age-related changes, which goes along with a progressive reduction of their functionality (Fig. 5A). Specifically, an age-dependent accumulation of smooth endoplasmic reticulum (SER) and of glial intermediate filaments has been described (Reichenbach and Bringmann, 2010a,b). The SER is fundamental to support the detoxification of harmful aldehydes degraded from lipid peroxides (Gaschler and Stockwell, 2017). Thus, the initial accumulation can be considered as an attempt of the cells to counteract age-related oxidative stress, while a progressive reduction of this key glial function with advanced aging very likely has toxic effects on retinal neurons (Nag et al., 2011). Additionally, accumulation of degenerated axonal remnants and lipofuscin in Müller cells has been described in aging retinae with detrimental effects on their phagocytic activity (Sparrow and Boulton, 2005). In general, there appears to be a clear correlation between advancing age and the extent of Müller cell gliosis. While mild gliosis does not affect the protective and homeostatic function of Müller cells, severe gliotic changes are associated with a decline in Müller cell function, leading to Müller cell swelling, increased oxidative stress with direct damage to Müller cell mitochondria and reduced energy production (Paasche et al., 2000; Toft-Kehler et al., 2017), neuronal and photoreceptor damage, and ultimately cell death (Gao and Hollyfield, 1992; Nag et al., 2011).

Alterations in Müller cell function have been strongly implicated in the pathogenesis of AMD, both in neovascular (Fig. 5B–C) and atrophic (Fig. 5D–E'') complications. It can be hypothesized that all of the processes occurring in Müller cells of the aging retina are accelerated in agerelated macular degeneration (AMD), thereby promoting the progression of retinal degeneration. Some of these changes may be driven by an overly active complement system and the pro-inflammatory environment that are characteristic of the AMD pathogenesis (Enzbrenner et al., 2021), especially since Müller cells themselves are a main source of complement components (Pauly et al., 2019; Zauhar et al., 2022a,b) (Fig. 5).

Using the power of scRNA sequencing (scRNA-seq) of the human retina, Menon et al. (2019) analyzed the activity patterns of 585 genes near 34 AMD risk loci identified by gene association studies and found that most of these genes were associated with Müller glia and astrocytes. Müller cells expressed increased levels of AMD-associated genes, such as VEGFA, COL4A3, TIMP3, C3, CFI, APOE and HTRA1 compared to the other retinal cell types (Menon et al., 2019; Yan et al., 2020; Zauhar et al., 2022a,b) (Fig. 5 A). Using a systems biology approach that integrated RNA sequencing (RNA-seq) and DNA methylation microarrays from bulk macular retinal pigment epithelium (RPE)/choroid of clinically phenotyped normal and AMD donor eyes, along with single-nucleus RNA-seq and single-nucleus ATAC-seq from the retina, RPE, and choroid of AMD and control donors, Orozco et al. (2023) identified a distinct "AMD Müller state" in Müller cells, distinct from their normal or classical gliotic state. This suggests that Müller cells undergo very specific molecular changes in AMD. Interestingly, this study implicates WNT signal regulators such as FRZB and TLE2 as potential drivers of Müller cell changes in AMD pathology.

Upregulation of GFAP—a classic marker of Müller cell gliosis—has been clearly associated with AMD progression, particularly at sites of drusen formation (Wu et al., 2003). Moreover, Müller cells showed an increased expression of the drusen components clusterin (CLU) and crystallin alpha B (CRYAB) in AMD samples (Umeda et al., 2005; Crabb et al., 2002). CLU is a known substrate of the protease HTRA1, a strong candidate gene implicated in the onset and progression of AMD (Tom et al., 2020; Thee et al., 2022). CRYAB, a widely expressed small heat shock protein, is abundant in soft drusen associated with AMD (Crabb et al., 2002). Müller cells also appear to modulate IL-1 family member activity, even under physiological conditions, contributing to antigen presentation and immune regulation within the neuroretina (Roberge et al., 1988). In the context of AMD, increased IL-1 β production by retinal microglia and macrophages may stimulate chemokine expression in both Müller and RPE cells, thereby promoting retinal degeneration (Natoli et al., 2017). Consequently, targeting IL-1 β has emerged as a potential therapeutic strategy for AMD (Natoli et al., 2017).

Müller cell gliosis, morphological remodeling, and even migration has been described in areas of RPE atrophy, photoreceptor loss, and macular neovascularization. However, it remains unclear what is the excat contribution of Müller cells to the different stages of AMD (Wu et al., 2003a,b; Edwards et al., 2017; Palko et al., 2022). Recently, the formation of outer retinal tubulation (ORT), often interpreted as photoreceptor remnants, were described in AMD. Detailing the different stages of this imaging biomarker imply is association with advanced stages of AMD (Arrigo et al., 2021a,b). The ELM, a structure formed by apical Müller cell processes in association with photoreceptors, changes first as a result of photoreceptor damage followed by RPE damage. Apical Müller cell membranes envelop degenerating photoreceptors and RPE cells, resulting in ORT formation (Arrigo et al., 2021a,b). Based on the above, we can hypothesize that the formation of ORT is the result of an incomplete, defective phagocytic activity of Müller cells, which is not able to completely remove the cellular remnants and thus generate ORT. This assumption is further supported by the evidence that Müller cells in AMD strongly interact with microglia to engage in phagocytic activity of AMD-related debris (Edwards et al., 2016; Wang and Wong, 2014). In addition, it is possible to assume that the pro-angiogenic activity of Müller cells, exerted through the production of many factors, first of all VEGF, has a role in the onset and progression of AMD-related macular neovascularization when becoming aberrant (Bai et al., 2009).

Taken together, these findings suggest that the role of Müller cells in AMD pathology is far more complex than previously thought and warrants further functional validation. However, they also emphasize the critical importance of investigating Müller cells to advance the development of novel, targeted therapies for AMD.

7.2. Müller cells in diabetic retinopathy

Pathomechanisms of diabetic retinopathy (DR) involve the activation of pro-inflammatory pathways that disrupt the metabolic and homeostatic tissue balance. As central components of the neurovascular unit, Müller cells play a pivotal role in DR pathology. Their functional changes are largely driven by hyperglycemia-induced gliosis and the accumulation of advanced glycation endproducts (Curtis et al., 2011). Gliotic activation of Müller cells in DR is evident from increased GFAP expression (Mizutani et al., 1998; Rungger-Brändle et al., 2000) and leads to altered release of several growth factors, chemokine, and pro-inflammatory cytokines.

Hyperglycemia triggers the production of several pro-inflammatory cytokines, including IL-1 β , IL-6, and TNF- α , which contribute to retinal ganglion cell death. Notably, inhibition of these cytokines by dexamethasone confers protection to retinal ganglion cells, though not to Müller cells, in vitro (Pereiro et al., 2018). In other in vitro studies, Müller cells were shown to secrete elevated levels of VEGF, PEDF, interleukins, TNF- α and C-C Motif Chemokine Ligand 2 (CCL2) (Mu et al., 2009; Wang et al., 2010; Lei et al., 2011; Liu et al., 2015; Yu et al., 2015; Zhou et al., 2017), along with other DR-related mediators, such as FGF, IGF-1, TGF- β , IL-1 β , IL-6, and interferon- γ (Rezzola et al., 2021; Peng et al., 2022; Actis Dato et al., 2021; Wang et al., 2020).

As in AMD, it is likely that Müller cells contribute to the dysregulated complement cascade observed in DR (Huang et al., 2018; Mandava et al., 2020; Shahulhameed et al., 2020). They produce and secrete key components of the alternative and classical pathways, as well as the complement C3 (Pauly et al., 2019; Zauhar et al., 2022a,b). Thus, Müller cells are able to induce and enhance microgliosis, as microglia are the



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Fig. 5. The role of Müller cells in AMD. (A) Schematic overview of a selected pathways driven by Müller cells that affect the progression of AMD. (B–C) Multimodal retinal imaging in neovascular age-related macular degeneration. Multicolor (B) and blue-light autofluorescence (B') images show diffuse macular alterations with perifoveal atrophic areas. OCT (B") shows the presence of a macular neovascularization mainly localized in the sub-RPE space. Outer retinal atrophy and choroidal hypertransmission are also visible. (C) OCT angiography confirms the presence of an extensive neovascular network. (D-D") Multimodal retinal imaging in atrophic age-related macular degeneration. Multicolor (D) and blue-light autofluorescence (D') images show diffuse atrophic areas involving the macular region. OCT (D") confirms the presence of a region of complete outer retinal atrophy. (E-E") The one-year follow-up shows the progression of the atrophic alterations, well detected by multicolor (E), blue-light autofluorescence (E') and OCT (E") images.

major retinal cell population expressing receptors for complement activation products. This Müller cell-microglial interaction is therefore likely to be a route by which neuroinflammation unfolds in DR.

Another mechanism by which Müller cells may initiate and propagate inflammatory signals in DR is through enhanced release of ATP, as this activates P2X7 purinoceptors, which are abundantly expressed by microglia (Kaczmarek-Hajek et al., 2018). In response, microglia amplify neuroinflammation and retinal damage, releasing TNFalpha and IL-1beta (Abcouwer, 2017). Indeed, notably, the latter has emerged as a prominent pro-inflammatory cytokine associated with DR (Yoshida et al., 2001; Li et al., 2008; Coughlin et al., 2024), being significantly upregulated in the vitreous and serum of DR patients. These may activate Müller cells, thus triggering the activation of retinal endothelial inflammation, which is a major occurrence in diabetes-related complications (Ramos and Penn, 2020). Recent findings indicate that the IL-1β/IL-1 receptor (IL-1R1) axis plays a key role in driving inflammation and retinal damage via a feedback mechanism that sustains caspase-1 activity in diabetic mouse retinas and in human Müller cells under hyperglycemic stress, ultimately promoting cell death (Feenstra et al., 2013; Coughlin et al., 2024). Notably, in the human Müller cell model, these effects were prevented by treatment with an IL-1 receptor antagonist, highlighting the therapeutic potential of targeting the IL-1β/IL-1R1 signaling pathway to reduce inflammation and protect against retinal degeneration in diabetic retinopathy.

Another fundamental Müller cell-mediated pro-inflammatory mechanism involves the interaction between CD40 and TNF receptorassociated factor 6 (TRAF6). Triggerd by increasing concentrations of glycation products, advanced end this activates the CD40-PLCy1-ATP-P2X7-proinflammatory cytokine pathway, promoting the release of pro-inflammatory mediators and the activation of the microglia/macrophages (Portillo et al., 2022, 2024). Additionally, accelerated retinal infiltration of Th22 cells activates Müller cells via the Act1/TRAF6 pathway, leading to upregulated IL-22 production. This exacerbates inflammation and contributes to the disruption of intraretinal vascular integrity (Wang et al., 2022).

The intercellular communication between Müller glia, endothelial cells and pericytes is impaired in DR. One underlying reason for this is a reduced expression of connexin 43 by Müller cells, which destabilizes glial intercellular communication and promotes cell death (Muto et al., 2014; Danesh-Meyer et al., 2016). As the severity of DR increases, so does the rate of Müller cell death. This in turn accelerates the breakdown of retinal homeostasis (Vincent and Mohr, 2007; Yego et al., 2009). Müller cell loss in DR also results in a lack of neuroprotective mediators, such as brain derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) driving subsequent neurodegernation (Fu et al., 2015). Finall, the formation of retinal microaneurysms and vascular remodeling have been associated with the absence of Müller cells (Hori and Mukai, 1980; Shen et al., 2012). Consistent with this, Müller cell changes leading to neurodegeneration in DR have been shown to precede microvascular remodeling (Hammes, 2018; Sohn et al., 2016).

It has been demonstrated that metabolic dysregulation and mitochondrial dysfunction in Müller cells significantly impacts their homeostatic functions e.g. the maintenance of the retinal ion and volume homeostasis (Krügel et al., 2011; Pannicke et al., 2006; Pfaller et al., 2024; Reichenbach et al., 2007). One of the Müller cell functions undergoing dysregulation is the regulation of glutamate levels. In DR rats, it was demonstrated glutamate accumulation in the retina with

decreased activity of glutamine synthetase leading to reduced conversion of glutamate to glutamine (Lieth et al., 1998, 2000; Li and Puro, 2002), and increased glutamate-mediated neurotoxicity (Ambati et al., 1997). Moreover, Müller cells in DR showed reduced activity of Kir4.1 channel, leading to the loss of potassium and cell volume regulation (Bringmann et al., 2002; Pannicke et al., 2006; Krügel et al., 2011). Moreover, the oxidative stress is known to be increased in DR. Müller cells contribute to the dysregulation of the polyol pathway, leading to decreased concentration of NADPH and NAD+, which are required to restore the concentration of glutathione (Barnett et al., 1986; Pfaller et al., 2024). If glutathione levels decrease, the polyol pathway is overactive with consequentl increased of oxidative stress (Behl et al., 2016). In addition, the excessive sorbitol produced by the polyol pathway has a direct toxic effect on retinal cells (Brownlee, 2005; Gabbay, 1973). In addition, the presence of high level of glucose was associated with reduced production of energy by Müller cells. Indeed, high glucose caused mitochondrial morphology changes and dysfunction, promoting Müller cells apoptosis (Tien et al., 2017).

A common DR complication is diabetic macular edema (DME) (Fig. 6). The progressive intraretinal fluid accumulation is mainly driven by the combined activity of inflammation and dysregulation of the inner BRB. In DME, Müller glial Kir4.1 channels, but not Kir2.1, are downregulated, leading to continued potassium uptake within Müller cells but inefficient release into the intraretinal capillaries (Pannicke et al., 2004, 2006; Reichenbach et al., 2007; Pfaller et al., 2024). As a result, Müller cells swell and lose their ability to efficiently remove fluid from the extracellular space. Concurrently, the aquaporin-mediated water transport is changing as evidenced by the overexpression of AQP4. In the end, the Müller cell-driven retinal drainage system is disrupted by the combined dysregulation of Kir4.1 and AQP4 (Rao et al., 2019; Ruiz-Ederra et al., 2007; Kida et al., 2017). Other aquaporins, such as AQP6, AQP7 and AQP1, have been found to be expressed in Müller cells (Tran et al., 2013; Iandiev et al., 2011a,b). However, their role in DR pathogenesis remains to be addressed. Currently, there is a consensus in the literature that loss of Kir4.1-AOP4 coupling is as a milestone in the DME pathogenesis (Nagelhus et al., 1999; Ruiz-Ederra et al., 2007; Goodyear et al., 2009).

Another factor contributing to DME onset originating from Müller cells is VEGF. It is implicated both in increasing exudative and transudative phenomena, and in the neovascular complication that characterizes the proliferative stage of DR (Wang et al., 2015). VEGF acts together with pro-inflammatory cytokines and interleukins to increase vascular permeability. Moreover, the overexpression of intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and monocyte chemotactic protein 1 (MCP-1 alias CCL2) in Müller cells also promote the leukocytes migration and adhesion to the intraretinal capillaries wall, disrupting the permeability of intraretinal vascular network (Taghavi et al., 2019). Vascular permeability is also increased by the TNF- α produced by microglia and Müller cells, which induces a damage of the endothelial tight junctions through the $\text{PKC}\zeta/\text{NF-}\kappa\text{B}$ pathway, reducing the expression of ZO-1 and claudin-5 proteins (Aveleira et al., 2010; Kaczmarek-Hajek et al., 2018; Schmalen et al., 2021a,b).

Müller cell changes are not only part of the DME pathology, but they are mediate the tissue response to intravitreal treatments. A recent OCT biomarker for DME, foveal eversion, indicates that DME may occur with or without sparing of the foveal depression (Arrigo et al., 2021a,b). Foveal eversion is considered a sign of more severe Müller cell



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Fig. 6. Müller cells in diabetic retinopathy (DR). (A) Schematic overview on the role of Müller cells in the onset and progression of DR. (B-E") Multimodal retinal imaging in diabetic macular edema. (B-B") The first case is characterized by altered foveal reflex secondary to DME, as shown by multicolor (B) and blue-light autofluorescence (B'). OCT (B") shows the sparing of the foveal depression together with hard exudates and hyperreflective foci. (C-C") The second case shows similar characteristics looking at the multicolor (C) and blue-light autofluorescence (C') images. However, OCT (C") shows the presence of a DME with a foveal eversion type 1a, characterized by the presence of a central thick column corresponding to partially spared Müller cells. (D-D") The third case shows in multicolor (D) and blue-light autofluorescence (D') images, corresponds to a DME with type 1b foveal eversion on OCT (D"), characterized by the presence of thin vertical columns, associated with the reduced Müller cells sparing. (E-E") The last case, shows in multicolor (E) and blue-light autofluorescence (E') images, corresponds to a DME with type 2 foveal eversion on OCT (E"), showing no signs of vertical columns. This is the sign of a stronger Müller cells damage and higher risk of DME persistence.

impairment, as their death leads to the loss of foveal structural support (Arrigo et al., 2021a,b). Accordingly, the presence of foveal eversion has been linked to higher DME persistence and poorer response to intravitreal treatments (Arrigo et al., 2021a,b). In a subsequent study, foveal eversion was categorized into three patterns based on the presence of intraretinal vertical columns: pattern 1a (thick columns), pattern 1b (thin columns), and pattern 2 (absence of columns) (Arrigo et al., 2022). The presence of the intraretinal vertical columns has been interpreted as a sign of better surivial of Müller cells, associated also with a better response to intravitreal treatments and better visual outcome than in the case of pattern 2 of foveal eversion has been confirmed to be associated with the best response to treatment and potentially better visual outcome (Arrigo et al., 2022).

In light of all these findings, the search for tools to improve Müller glial homeostasis functions in the context of DR could be a game changer for the development of long-term efficient treatment options in DR, as they would interfere with early steps in the progression of the pathology, i.e. the remodeling of the neurovascular unit.

7.3. Müller cells in vitreomacular disorders

Müller cells, which play a key role in maintaining the structural organization of the retina, are also likely to be involved in the pathogenesis of vitreomacular disorders (Fig. 7). This spectrum of pathologies typically go along with a disruption of the fragile retinal architecture of the foveal region. We have already discussed the role of Müller cells in foveal maturation, cells migration and in the maintenance of the physiologic morphology of the macular region. Bringmann and colleagues have provided an excellent description of changes associated with different vitreomacular disorders (Bringmann et al., 2021). Regarding the development of a macular pucker, the authors described the



Fig. 7. The spectrum of vitreomacular disorders. The first case is characterized by a small central alteration, as shown by multicolor (A) and blue-light autofluorescence (B) images. This corresponds to a macular pseudo-hole, namely a deformation of the foveal profile, with spared retinal layers on OCT (C). The second case shows a central hole both in multicolor (D) and blue-light autofluorescence (E) images. OCT (F) shows the presence of a full thickness macular hole. The third case is characterized by normal fundus appearance (G) and a small defect on blue-light autofluorescence image (H). OCT (I) shows the presence of a focal vitre-omacular traction. The last case is characterized by diffuse alterations both in multicolor (J) and blue-light autofluorescence (K) images. Both images show the typical tractional signs. OCT (K) confirms the presence of an epiretinal membrane causing the complete deformation of the foveal profile (macular pucker).

stretching of the central Müller cell buquet and the foveola, with or without the formation of intraretinal cysts. The onset and progression of an epiretinal membrane (ERM) formation may further increase the thickening of and tractiol forces on the foveola, leading to foveal erniation and the development of macular pucker (Bringmann et al., 2021). Disappearance of the foveal pit may be due to either thickening of the foveolar Müller cells, as observed in vitreomacular traction, or thinning, as in macular pseudohole (Bringmann et al., 2021). The Müller cell gliosis described for these pathologies appears to contribute to the formation of the ERM and the same pro-inflammatory mediators described in the previous sections accelerate this process (Bringmann and Wiedemann, 2009). For example, extracellular matrix remodeling is mediated by the expression of matrix metalloproteinases (MMPs) by Müller cells (Limb et al., 2002). In addition, other Müller cell-related factors that regulate proliferative and anti-proliferative pathways leading to vitreoretinal disease include α 2-macroglobulin, apolipoprotein E, and neuropeptide Y (Hollborn et al., 2004; Milenkovic et al., 2004, 2005; Cantó Soler et al., 2002). The pathogenic mechanisms leading to a dysfunctional foveal glial scaffold are highly complex. They encompass processes such as Müller cell deformation, gliosis, proliferation, and the release of various mediators, as discussed in other sections of this review. Given the intricate nature of Müller cell involvement in tractional macular disorders, detailed descriptions are beyond the scope of this review. For further in-depth exploration, we refer readers to the comprehensive work of Bringmann et al. (2022).

7.4. Müller cells in macular teleangectasia

Macular telangiectasia type 2 (MacTel-2) is a late-onset, idiopathic macular degeneration confined to the central retina. It begins with macular pigment alterations, progressing to photoreceptor distress and potential macular edema (Fig. 8A) (Leung et al., 2018). Vascular anomalies include dilated retinal capillaries and telangiectatic vessels, with blood-retina barrier breakdown causing macular leakage on fluorescein angiography (Clemons et al., 2010) (Fig. 8B–B'''), consistent with findings that Müller cell depletion results in loss of homeostatic mechanisms governing macular pigment metabolism and vascular stability (Powner et al., 2010, 2013). High-throughput multi-resolution electron microscopy revealed mitochondrial structural changes in all retinal cell types except the RPE inside the MacTel zone (Zucker et al., 2024). Where Müller glial cells are lost, microglial cells accumulate in the Henle fiber layer, ensheathing Henle fiber similarly to Müller cells.

There is a body of evidence that serine and glycine deficiency is part of the pathology as patients typically present with low blood serine and glycine levels (Scerri et al., 2017; Bonelli et al., 2021a; Lia et al., 2023) – notably, a metabolic signature that MacTel-2 patients share in part with DR patients (Green et al., 2023; Clemons et al., 2013). Serine, a non-essential amino acid, is obtained from the bloodstream or synthesized from glucose via the glycolytic intermediate 3-phosphoglycerate (3 PG). It interconverts with glycine (see Fig. 8 for details) and plays a vital role in maintaining retinal tissue integrity. Beyond its incorporation into proteins, free serine is crucial for synthesizing cysteine, glycine, methionine, and sphingolipids (Mattaini et al., 2016). Reflecting its importance in retinal health, mice kept on a serine- and glycine-restricted diet for several months exhibit an age-dependent decline in retinal function (Gantner et al., 2019).

Under low-serine conditions, serine palmitoyltransferase (SPT) increasingly incorporates alanine into sphingolipids, producing deoxysphingolipids that lack the hydroxyl group essential for complex sphingolipid synthesis and degradation. Accordingly, deoxysphingolipid levels inversely correlate with serine levels (Gantner et al., 2019; Green et al., 2023; Lim et al., 2024). These toxic lipids induce photoreceptor cell death in retinal organoids by impairing mitochondrial function, autophagy, and protein folding (Rosarda et al., 2023). Although Müller cells exhibit strong resistance to oxidative stress due to their high glutathione production via glutathione synthetase (Fig. 8C and D), serine depletion compromises this defense as it is essential for generating cysteine and glycine—along with glutamate, the main precursors of glutathione. Therefore, serine and/or glycine deficiency may lead to glutathione depletion, increasing susceptibility of Müller cells and in turn also neighbouring neurons to oxidative damage. This could result in enhanced lipid peroxidation and mitochondrial dysfunction ultimately resulting in cell death (Fig. 8C).

It is worth of mention that the study of lipids distribution within the retina, including phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol (PI), provided lipid signature for retinal ganglion cells and Müller cells (Pereiro et al., 2020a,b). In particular, the expression of these lipids resulted different for these two cytotypes, resulting much more expressed in retinal ganglion cells, thus providing potential fingerprints for these cells (Pereiro et al., 2020a,b). Since these lipids are involved in different cell activities, the lipidomic changes might provide new insights on the implications of lipids in retinal diseases, also identifying new potential therapeutic targets (Pereiro et al., 2020a,b).

Interestingly, some MacTel-2 patients harbor pathogenic variants in SPTLC1, encoding an SPT subunit (Bonelli et al., 2021b; Gantner et al., 2019). Our cell type-specific proteome analysis of normal donor retina confirms high, specific SPTLC1 expression in Müller cells (Fig. 7D). Other MacTel-2-associated variants identified by Bonelli et al. Bonelli et al. (2021) were strongly enriched in Müller cell proteomes including PGHDH, for whose locus at 1p12 strongest association was found by GWAS, and PSPH (Fig. 7D). Both enzymes are key for serine synthesis from the intermediated of glycolysis - 3-phosphoglycerate (3 PG). Additionally, CERS4, a ceramide synthase selective for long-chain (C18-C20) lipids (Ben-David et al., 2011), was identified by GWAS and shows strong Müller cell expression, particularly in the macula. Notably, SPTLC1 and CERS4 even show a region-dependent enhanced expression in macular Müller cell. Notably, CERS4 dysfunction has been linked to cone-rod dystrophy (Bertrand et al., 2021) and photoreceptor degeneration in Cers4 knockout mice (Brüggen et al., 2016).

Together, these data strongly suggest a genetic component in MacTel-2 (and potentially related pathologies), directly impacting Müller cell-specific genes and functions. Given the fovea's heightened susceptibility to tissue stress, dysfunctional Müller cells accelerate degeneration in this peculiar retinal region.

7.5. Müller cells in inherited retinal dystrophies

Inherited retinal dystrophies (IRDs) represent a heterogeneous group of genetically determined disorders having the primary localization of the anomaly at the level of the RPE/photoreceptors complex. However, as discussed in section 7.4, this perspective must expand, as advances in cell type-specific expression analysis are revealing an increasing number of mutations in Müller cell-specific genes. Emerging evidence underscores the significant role of Müller cells in IRD pathogenesis.

An example already known for a while is the autosomal recessive form of retinitis pigmentosa caused by pathogenic variants of the gene encoding CRALBP. It is characterized by a major involvement of RPE cells and Müller cells - the two cell types exclusively expressing this protein in the retinal microenvironment (Maw et al., 1997). Moreover, it has been speculated that the production of many neuroprotective growth factors by Müller cells is important also in IRDs to promote the survival of retinal neurons and photoreceptors (Bringmann et al., 2006). This is particularly significant because photoreceptors lack receptors for many neurotrophic factors, unlike Müller cells (Kirsch et al., 1997; Wahlin et al., 2000, 2001). As a result, the anti-apoptotic stimulus is mediated through direct Müller cell activation. A recent study in a mouse model of retinitis pigmentosa demonstrated that Müller cells respond to the downregulation of survival genes in photoreceptors by upregulating these same genes, likely enhancing metabolic support and reducing cell death (Tomita et al., 2021).

Also mutations in CRB1 and CRB2 provide a clear example of genetic



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Fig. 8. Müller cell related changes in MacTel-2. (A – B") Multimodal retinal imaging in macular teleangectasia type 2. Multicolor (A) and blue-light autofluorescence (A') images show the presence of diffuse alterations localized in the temporal side of the macula. OCT (A") shows the presence of intraretinal fluid. Fluorescein angiography reveals dilated capillaries in the early phase (B), followed by late leakage (B'). OCT angiography shows an almost preserved superficial capillary plexus (B"), and dilated capillaries in the temporal side of the deep capillary plexus (B"). (C) Scheme of putative serine and glycine metabolism in Müller cells with a selected set of downstream pathways affected. Genes for which SNPs associated with MacTel-2 have been identified by GWAS are highlighted in dark red (Bonelli et al., 2021 (Commun Biol) & Lim et al., Cell Metabolism). (D) Cell type-specific protein expression profiles across distinct retinal regions of genes involved in the transport and metabolism of serine and glycine, and gluthathione synthetase as a key enzyme to promote the production of the cell's main protection against oxidative stress - gluthathione. Information on the donors and the initial experiment can be found in our corresponding research paper by Kaplan et al. (2023), which also includes the proteomic resource data. Mean values (each dot represents a biological replicate) \pm SEM are plotted from distinct retinal regions as indicated by the color code. One-way Anova was performed with Dunnett's multiple comparision and only significances for comparisions with respective Müller cells populations are plotted (following the respective color code). *P < 0.05; ***** P < 0.01; **v** P < 0.001.

alterations in Müller cells leading to IRDs. These genes encode for proteins localized in outer Müller cell processes forming the ELM and in interacting photoreceptor membranes at the ELM. Mutations in CRB1 or CRB2 cause early onset forms of retinitis pigmentosa or Leber congenital amaurosis (LCA). A mouse model demonstrated that Müller cell-specific loss of CRB2 exacerbates CRB1-associated RP, accelerating its progression toward an LCA-like phenotype (Quinn et al., 2019). An example of the retinal structure of a RP patient is shown in Fig. 9A. In addition, Müller cell disorganization has been also described in canine RPE65 model of Leber congenital amaurosis (Hernández et al., 2010).

Often Müller cell gliosis and ultimately impairment of their homeostiatic functions may often also represent a secondary effect in response to primary RPE/photoreceptors complex damage. Like in many pathologies, first signs of gliosis are an upregulation of GFAP and CD44 (Ayten et al., 2024). Using CD44 knockout bread on a Pde6b^{STOP/STOP} RP mouse model showed that loss of CD44 accelerates photoreceptor degeneration, reduces retinal function, and increases inflammation, likely due to downregulated glutamate transporter SLC1A2 and impaired glutamate homeostasis. These findings suggest that the initial upregulation of CD44 indeed is protective and promotes glutamate uptake in Müller cells, supporting photoreceptor survival and retinal function (Ayten et al., 2024).

However, persistent Müller cell gliosis in IRDs at some point also contributes to disease progression. For instance, macular edema is a complication affecting 25-50 % of RP cases (Hartong et al., 2006), but has an unclear pathogenesis (Hartong et al., 2006). Hypotheses include BRB breakdown, RPE pump dysfunction, autoimmune mechanisms, vitreous traction, but could also be due to an impaired homeostasis function of overactive gliotic Müller cells (Strong et al., 2017). Indeed, a recent multimodal retinal imaging study supports a central role for Müller cells in RP-associated macular edema (Arrigo et al., 2023a,b). Excluding patients with vitreoretinal anomalies, the authors reported that retinitis pigmentosa eyes with macular edema were characterized by (I) nonsignificant reduction in visual acuity, (II) nonsignificant worsening of the disorder over time, and (III) better intraretinal vascular status, with respect to eyes without macular edema (Arrigo et al., 2023a, b). Based on the absence of clear signs of inflammation and the primary involvement of the INL, where the Müller cell bodies are located, the authors proposed a Müller cell impairment as the underlying cause for macular edema formation in retinitis pigmentosa (Arrigo et al., 2023a, b). This could also explain the poor response to current treatments, which primarily target exudative/transudative mechanisms or RPE dysfunction rather than restoring Müller cell-mediated retinal fluid homeostasis (Arrigo et al., 2023a,b).

While Müller cells are not directly implicated in the pathogenesis of Stargardt disease, ELM thickening observed on structural OCT suggests a gliotic response (Lee et al., 2020) (Fig. 8B). In contrast, among IRDs, choroideremia likely exhibits the earliest and most pronounced Müller cell involvement. (Fig. 9B). Early stages of the disease are marked by diffuse retinal thickening due to Müller cell swelling (Jacobson et al., 2006). The spectrum of Müller cell alterations in choroideremia is highly heterogeneous, encompassing extensive remodeling and gliosis (MacDonald et al., 2009). This has been further highlighted by OCT assessments of ELM changes, which identified three distinct retinal

regions—the partially preserved islet, atrophic retina, and an intermediate transition zone—offering valuable insights for optimizing gene therapy administration (Arrigo et al., 2023a,b, Fig. 9C).

Additionally, Müller cell remodeling and reactivity have been histologically documented in Best vitelliform macular dystrophy (Fig. 9D) (Bonilha et al., 2020). Then, as Müller cells become even more atrophic, there is subsequent atrophy of the outer retina and choroid (Jacobson et al., 2006; MacDonald et al., 2009).

To our knowledge, there is a scarce data on the involvement of Müller cells in other IRDs. However, based on the findings described above, it can be assumed that Müller cell reactivity, gliosis and remodeling occur in response to the degenerative mechanisms that characterise IRDs, irrespective of the pathogenic variants.

8. Retinal Müller cells as future therapeutic target

8.1. Müller cells as target cell for gene therapeutic approaches

Müller cells are an interesting therapeutic target because, in addition to correcting a potential Müller cell-specific disease gene, regenerative and neuroprotective mechanisms can be stimulated. Gene therapeutic approaches using lentiviral and adeno-associated viral (AAV) vectors have been explored to enhance the production of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) (Di Polo et al., 1998; Gauthier et al., 2005), ciliary neurotrophic factor (CNTF; Liang et al., 2001), glial cell line-derived neurotrophic factor (GDNF, Dalkara et al., 2011). As another example, expression of a truncated version of complement factor F - a complement component that attenuates complement activation - in Müller cells using an AAV-vectored gene therapy approach has shown promising results in reducing complement-associated retinal degeneration in a preclinical mouse model (Biber et al., 2024).

Among various therapeutic approaches, intravitreal administration of glucocorticoids such as triamcinolone acetonide (TA) has been effective in reducing cytotoxic edema in DR (Brooks et al., 2004). Notably, treating Müller cell-ablated mouse models with TA, a selective glucocorticoid receptor agonist, mitigates effects like photoreceptor degeneration, vascular leakage, and neovascularization, all typical of DR as well (Shen et al., 2014). TA's effectiveness in reducing vascular leakage, inhibiting VEGF secretion (Itakura et al., 2006), and preventing Müller cell swelling underscores (Wurm et al., 2008a) the therapeutic potential glucocorticoid receptor agonists in DR. This effect of TA seems to be primarily mediated through acting on the glucocorticoid receptor (GR) that in the retina is expressed predominantly in Müller cells (Gallina et al., 2014; Pfaller et al., 2024). However, probably due to persistently high blood corticosteroid levels that trigger a negative feedback loop, GR expression in Müller cells of the diabetic retina in a mouse model is downregulated (Pfaller et al., 2024). As an increase in systemically circulating corticosteroids has also been described in DR patients (Chiodini et al., 2007; Nakao and Yokoyama, 1976), a similar aberrant regulation of GR in the retina may limit the efficacy of intravitreal corticosteroids in the treatment of DR. In a gene therapeutic approach applied to a DR mouse model, a beneficial effect of overexpressing GR exclusively in Müller cells (instead of injecting more of its



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ligand) was demonstrated (Pfaller et al., 2024), suggesting a possible new therapeutic concept for DR therapy. Such an approach would also avoid the unwarranted common side effects of GR agonists, currently rather used as second-line treatment because of rather common side effects like cataract and ocular hypertension (Taloni et al., 2023). Also another gene therapy approach based on the overexpression of cellular retinaldehyde binding protein (RLBP1), a Müller cell protein that acts as a soluble retinoid carrier essential for proper photoreceptor function in the visual cycle, has shown impressive beneficial effects on neuronal function and survival in a preclinical study (Niu et al., 2021).

Such a disease-gene independent approaches, like a gene therapy targeting the complement cascade or Müller cell gliosis regulation via **Fig. 9. Multimodal retinal imaging of multiple forms of inherited retinal disorders (IRDs).** (A) Ultrawide field pseudocolor image of a RP patient shows the presence of optic disc pallor, attenuated retinal vessels and diffuse pigment accumulations. (A') The ultrawide field autofluorescence image of that same patient shows extensive atrophy with only the partial sparing of the posterior pole. (A'') OCT highlights the centripetal disappearance of outer retinal photoreceptors bands, together with the presence of intraretinal cysts. (B) Ultrawide field pseudocolor image of a Stargardt patient shows the presence of yellowish accumulations, together with central macular atrophy. (B') The ultrawide field autofluorescence image of that same patient clearly visualizes the presence of hypoautofluorescent and hypeautofluorescent lipofuscin accumulations (flecks), also better delineating the extension of macular atrophy. (B'') Its presence is confirmed by OCT showing the centrifugal disappearance of outer retinal photoreceptors bands. (C) Ultrawide field pseudocolor image of an choroideremia patient shows the presence of diffuse rod-cone atrophic changes, with only the partial sparing of a central isle, better visualized by ultrawide field autofluorescence images of a partially preserved foveal region in that patient, together with an evident choroidal thinning. (D) The color fundus and (D') the blue-light autofluorescence images of a patient suffering from Best vitelliform macular dystrophy illustrates a pseudo-hypopion stage, characterized by the gravitational distribution of the vitelliform material. The vertical OCT line (D'') confirms the presence of hyperreflective vitelliform material on the inferior side and a serous subretinal accumulation in the superior side, with signs of photoreceptors bands elongation.

GR, go beyond the possibilities of conventional gene therapy correcting specific disease causative genes, as it could reach a spectrum as broad as that of anti-VEGF therapy for the treatment of retinal vascular dysfunction. Given that the complement system (and potentially also Müller glial GR) is dysregulated in most RDs including AMD, DR and RP, such therapeutic strategies could be a productive and cost-effective approach to counteract vision loss in millions of people.

8.2. Müller glia and cell therapies to treat retinal degeneration

Neuronal cell death is a hallmark of retinal degenerative diseases that lead to irreversible vision loss. Despite therapeutic advances, disease progression cannot always be halted. Recent research on Müller cells, which have stem cell properties, has sparked interest in their potential for retinal regeneration. Although Müller glia with stem cell potential fail to integrate into the retina when transplanted, they have been shown to partially restore visual function by releasing neuroprotective factors that support damaged neurons. Advances in pluripotent stem cell technology have made it possible to derive Müller cells from retinal organoids, offering new therapeutic possibilities. For further details, we would refer the reader to the comprehensive review by Eastlake et al. (2021).

Müller cells likely play a crucial role in the integration of transplanted cells, including photoreceptors, a promising therapeutic approach for photoreceptor degeneration. However, the success of such transplants depends on addressing several key challenges in preclinical studies, such as determining the optimal timing for transplantation-especially given the extensive retinal remodeling in latestage disease-and understanding the role of Müller cells in this process (Reh, 2016). In degenerative conditions, Müller cells often form a glial scar that can hinder successful cell integration. However, in a study where human photoreceptors purified from retinal organoids were transplanted into the subretinal space of cone photoreceptor function loss 1 (Cpfl1) mice, Gasparini et al. (2022) found that instead of forming a glial barrier, Müller cells extended into the graft and established adherens junctions between mouse and human cells, resembling an outer limiting membrane. This interaction supported donor-host integration, promoting photoreceptor polarization, maturation, and functional development. Notably, such integration did not occur when transplanted cells remained isolated in the subretinal space and did not interact with Müller cells as closely. These findings underscore the critical role of Müller cells in facilitating structural organization and connectivity, ultimately enhancing the success of transplanted human photoreceptors in a partially degenerated retina. The processes required to establish this beneficial interaction between Müller cells and transplants are not yet understood and require intensive investigation to advance this exciting field of research.

8.3. Müller glia in retinal repair and plasticity: current and potential future roles

Stimulating Müller cell proliferation to generate regenerative neuronal progenitors has been an area of interest, with evidence

demonstrating that newly formed neurons in response to retinal injury originate from proliferating Müller cells (Braisted et al., 1994; Fausett and Goldman, 2006; Kassen et al., 2007; Bernardos et al., 2007; Ramachandran et al., 2010). In various species Müller cells can regenerate both glial cells and neurons (Das et al., 2006; Giannelli et al., 2011; Lawrence et al., 2007; Zhao et al., 2014). In non-mammalian vertebrates, retinal injury induces partial (as in birds (Fischer and Reh, 2001)) or extended neuronal regeneration (as in teleost fishes (Fausett and Goldman, 2006)). Müller cells play a crucial role in this process: by upregulating the proneural transcription factor Achaete-Scute Complex-Like 1 (ASCL1), Müller cells trigger a signaling cascade that prompts their dedifferentiation into retinal progenitor-like cells (RPCs) that proliferate and generate offspring, that differentiate into functional neurons, ultimately restoring visual function (Fausett et al., 2008). Notably, knocking down ASCL1 in zebrafish prevents Müller cells from initiating this regeneration pathway (Fausett et al., 2008). Unlike in the aforementioned species with regenerative potential, mammalian Müller cells do not upregulate ASCL1 expression following retinal injury and are unable to differentiate into RPCs (Pollak et al., 2013). Instead, Müller cell gliosis, which involves cell hypertrophy, increased expression of type III intermediate filaments, particularly glial fibrillary acidic protein (GFAP) and vimentin, leads to scarring (Hippert et al., 2021), along with cell proliferation and migration in very severe forms of degeneration (Lewis et al., 1995, 2010). This glial scar fills gaps left by dying neurons, but may also inhibit neuronal cell migration, axonal regrowth, and limit endogenous regeneration (reviewed in (Bringmann and Wiedemann, 2012; Reichenbach and Bringmann, 2020; Silver and Miller, 2004)).

Interestingly, overexpression of ASCL1 in mouse (Pollak et al., 2013; Ueki et al., 2015a,b,c) and human Müller cells (Wohlschlegel et al., 2023) induces a RPC phenotype, akin to the response seen in injured fish retinas. However, despite this reprogramming, Müller cells produce only a limited number of functional neurons both in mouse cell culture and in vivo (Jorstad et al., 2017; Pollak et al., 2013; Ueki et al., 2015a,b,c). Even human Müller cells can be reprogrammed by delivering ASCL1 alone or in combination with other transcription factors (ATOH1 and NEUROD1) via lentiviral vectors to generate new neurons even in cell cultures (Wohlschlegel et al., 2023), but also in fetal and adult 3D tissue cultures (Wohlschlegel et al., 2025). Notably, in mouse cultures, these ASCL1-reprogrammed Müller cells primarily differentiate into bipolar or amacrine-like cells (Jorstad et al., 2017, 2020), while in human Müller cells cultures, they retain the progenitor-like stage (Wohlschlegel et al., 2023). In addition to overexpressing factors that promote the formation of RPCs, suppressing inhibitory pathways can significantly enhance reprogramming efficacy. For instance, Le et al. (2024) found that Notch signaling and NFI factors act in parallel to inhibit the neurogenic potential of mammalian Müller glia. By disrupting Rbpj or Notch1/2, they successfully reprogrammed mature Müller glial cells into bipolar- and amacrine-like neurons. Additionally, combined loss of Rbpj and Nfia/b/x led to the conversion of nearly all Müller glia into neurons. Furthermore, promoting Müller glial proliferation through dominant-active Yap overexpression enhanced neurogenesis in both Rbpj- and Nfia/b/x/Rbpj-deficient Müller glia.

Comparing RPCs, immature, and mature Müller cells, revealed that epigenetic changes during Müller cell maturation reduce neurogenic gene expression and chromatin accessibility, limiting reprogramming efficiency (VandenBosch et al., 2020). Müller cell reprogramming involves metabolic and signaling pathways that can be triggered by a growing number of genetic and epigenetic regulators (Xiao et al., 2023). Achaete-scute homolog 1 (ASCL1) is a core transcription factor involved in Müller cells transformation into retinal progenitors (RPCs; Löffler et al., 2015; Ueki et al., 2015a,b,c; Elsaeidi et al., 2018). Polypyrimidine tract-binding protein 1 (PTBP1), an essential factor for neuronal growth and differentiation (Oberstrass et al., 2005), has been used to convert Müller cells into retinal ganglion cells (Zhou et al., 2020). Additionally, the Wnt/ β -catenin signaling pathway has been shown to stimulate Müller cell proliferation and reprogramming, leading to photoreceptor formation (Yao et al., 2016, 2018). The Notch pathway plays a critical role in determining the injury-response threshold of Müller cells and activating their repair mechanisms (Fausett and Goldman, 2006; Wan and Goldman, 2016). Müller cell reprogramming is also influenced by the Yes-associated protein (YAP), which, when activated, is linked to Müller cell activation (Hamon et al., 2019; Rueda et al., 2019). Other factors promoting Müller cell reprogramming are IGF-1 (Fischer et al., 2002), Sonic hedgehog (Shh; Wan et al., 2007), glutamate (Takeda et al., 2008), ciliary neurotrophic factor (CNTF; Kassen et al., 2009), fibroblast growth factor (FGF; Fischer et al., 2009), heat shock proteins (Qin et al., 2009), glycogen synthase kinase-3β (Ramachandran et al., 2011), heparin-binding epidermal-like growth factor (HB-EGF; Wan et al., 2012), STAT3 (Nelson et al., 2012), TNFa (Nelson et al., 2013), BMP–SMAD and EGF (Ueki and Reh, 2013), TGF-β (Lee et al., 2020), Jak-STAT (Jorstad et al., 2020), and many others. These factors represent promising therapeutic targets for future treatments, including gene therapy and Müller cell transplantation (Pellissier et al., 2014; Devoldere et al., 2019; Eastlake et al., 2021).

Most of the current studies on stimulating the regenerative potential of Müller cells focus on models of retinal degeneration. However, others showed that Müller cell plasticity and generation of neurons by Müller cells can also be triggerd by specific mediators depending on the animal model investigated. These approaches include the subretinal delivery of subtoxic doses of glutamate (Takeda et al., 2008) or the stimulation of Wnt and Notch signaling pathways (Del Debbio et al., 2010). Recently it has been shown that small extracellular vesicles (sEVs) derived from retinal progenitor cells isolated from human embryonic stem cell-derived retinal organoids can modulate the fate of Müller cells after subretinal transplantation into RCS rats. These sEVs delay photoreceptor degeneration, protect retinal function, and are taken up by the rat Müller cells, where they inhibit gliosis and promote dedifferentiation. Mechanistically, the sEVs likely regulate Müller cell fate through miRNA-mediated downregulation of NFIB transcription factors (Huang et al., 2024).

As an alternative to stimulating the regenerative capacity of Müller cells, the therapeutic effect can be achieved by inhibiting specific, potentially harmful Müller cell responses. In a model of retinopathy of prematurity, microparticles derived from apoptotic human T lymphocytes have been used to suppress the pro-angiogenic signature of Müller cells in response to hypoxia, which favours retinal neovascularization (Cai et al., 2021). These microparticles were internalized by Müller cells, interfering with the production of VEGF.

In fact, microRNAs seem to be strongly involved in regulating Müller cell functions including their gliotic activation or repair processes that require their dedifferentiation into retinal progenitor cells (García-García et al., 2020) To investigate the role of microRNAs, Dicer1, an essential endoribonuclease for miRNA maturation, was selectively deleted in Müller cells (Wohl et al., 2017). This loss led to abnormal Müller cell migration within one month, progressing to large Müller cell aggregations and severe retinal architectural disruption by six months. The most upregulated gene was the proteoglycan Brevican (Bcan), regulated by miR-9, whose overexpression partially rescued the

Müller cell phenotype. Furthermore, Müller cells from RP patients showed increased Bcan immunoreactivity at aggregation sites, linking microRNA dysregulation to retinal remodeling in inherited retinal diseases (IRD).

In line with this strong effect of the absence of miRNAs on Müller cell fate, Wohl et al. (2019) demonstrated substantial differences in miRNA expression between Müller glia and retinal progenitor cells (RPCs), contributing to their distinct neurogenic potential. Overexpression of miR-25 and miR-124, or inhibition of let-7, induced Ascl1 expression and reprogrammed approximately 40 % of mature Müller cells into a neuronal/RPC-like phenotype, suggesting that miRNA manipulation could be a promising strategy for retinal regeneration.

Targeting miRNAs in Müller cells may also offer a novel treatment approach. For example, Kang et al. (2021) found that in reactive Müller glia after retinal light damage, most miRNAs were downregulated, with miR-124 being one of the few that increased. The gene expression changes in reactive Müller cells were similar to those observed in Müller cells lacking Dicer, indicating that miRNAs play a crucial role in the Müller glial stress response, and manipulating these miRNAs could help reduce gliosis. Supporting this, Li et al. (2019) showed that repression of miR-21 reduced Müller cell gliosis and promoted retinal neuron survival (Li et al., 2019). Similarly, the inhibition of miR-423-5p, up-regulated in the plasma, but also in the retina in a rat model of DR, has been associated with improvements of the retinal vascular integrity in DR (Liu et al., 2023). MiR-29 showed protective effects, reducing Müller cell activation in response to tissue stress induced by intravitreal injection of hydroxyeicosatetraenoic acid (HETE). In consequence, 12pro-inflammatory and oxidative pathways were dampened (Moustafa et al., 2024). Another example is miR-340-5p. Its overexpression reduced bone morphogenetic protein-4 (BMP4)-induced Müller cell gliosis in a model of DR - again with a consequent reduction in inflammation and DR progression (Wu et al., 2022). In contrast miR-9-3p overexpression in Müller cells in DR was associated with increased angiogenesis due to the phosphorylation and internalization of VEGFR2 independently from the presence of exogenous VEGF-A (Liu et al., 2021). Many other microRNAs are associated with Müller cells activity. Their study can potentially pave the way for novel therapeutic strategies to be applied in retinal disorders (Lamb et al., 2024).

Overall, the concept of endogenous self-repair by regenerating neurons from Müller cells with innate stem cell potential has been studied extensively for over three decades. As discussed by select examples in this chapter, the molecular mechanisms required to overcome the genetic barriers to retinal regeneration in mammals are highly complex and not yet fully understood. However, this approach holds great promise as a therapeutic strategy for patients with advanced retinal degeneration where preservative treatments are no longer effective. In addition, it may offer advantages over retinal transplantation by reducing challenges such as immune rejection and integration into the retinal circuitry (Thomas et al., 2006; Demb and Singer, 2015).

9. Müller cells trophism and pathology: final remarks and conclusions

This review examines the critical role of Müller cells in the health and disease of the retina and attempts to integrate, in particular, studies actually performed on the human retina to allow the best possible conclusions regarding the relevance of these findings for patients. As key regulators of retinal metabolism and homeostasis, their dysfunction, whether directly due to a pathogenic gene variant in a Müller cellspecific gene or indirectly due to overactive gliosis, contributes to the pathogenesis of many, if not all, retinal diseases. Pushed by recent advancements in cell type-specific and even single-cell expression analysis, we are increasingly uncovering primary Müller cell pathologies (e.g., MacTel-2 and potentially cone-rod dystrophy linked to CERS4 mutations) that remained undetected for years due to the limitations of bulk expression profiling, which failed to distinguish Müller cell-specific

signatures.

For these reasons, when assessing retinal functionality and health, we should always consider Müller cells trophism as the milestone of retinal homeostasis preservation. Similarly, when speaking about retinal diseases, we should always consider Müller cells pathology as a major element promoting the progression of the disease and the onset of complications. The deep understanding of Müller cell-related mediators and pathways provides the basis for the development of new therapeutic strategies centered on Müller cells. They may be stimulated to produce growth and protective factors. These cells can be stimulated to produce protective factors and reprogrammed to promote retinal repair, neuronal recovery, and photoreceptor regeneration.

Current treatments for exudative retinopathies mainly target single pathological mediators, such as VEGF and inflammation. Nextgeneration drugs, like aflibercept (targeting VEGF and placental growth factor) and faricimab (targeting VEGF and angiotensin-2), employ dual inhibition. However, exudative retinal disorders involve complex mechanisms, including fluid dysregulation and multiple mediators. Approaching treatment from the Müller cell perspective may enhance disease control, retinal fluid stabilization, and overall cell health.

Atrophic retinopathies currently largely lack approved treatments. While gene therapy has shown promise for some IRDs, only a few IRD subtypes are viable candidates, and therapy primarily halts degeneration without restoring lost tissue. Similarly, potential treatments for atrophic AMD, such as complement inhibitors (e.g., pegcetacoplan), may slow progression with moderat impact on patients' quality of life.

For both exudative and atrophic retinopathies, reprogramming Müller cells to produce growth factors or even regenerate retinal neurons and photoreceptors could significantly alter disease progression and prognosis. This approach may also circumvent challenges associated with retinal transplantation, such as immune rejection and integration into retinal-brain circuitry.

In summary, Müller cells are central to the structure and metabolism of the human retina and play a critical role in both homeostasis and disease. Their dysfunction, through homeostatic dysregulation and reactive gliosis, contributes to retinal pathology and drives or even initiates disease progression. However, their therapeutic potential is immense, as outlined in the various sections of this review. Therefore, more approaches to preserve "Müllerotrophism" need to be developed and "Mülleropathy" should be a key consideration in both diagnosis and treatment strategies.

CRediT authorship contribution statement

Alessandro Arrigo: Writing - original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation. Ottavio Cremona: Writing - original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Emanuela Aragona: Writing - review & editing, Methodology, Formal analysis, Data curation, Conceptualization. Filippo Casoni: Writing - review & editing, Methodology, Investigation, Formal analysis, Data curation. Giacomo Consalez: Writing - review & editing, Investigation, Formal analysis, Data curation. Rüya Merve Dogru: Writing - review & editing, Investigation, Formal analysis, Data curation. Stefanie M. Hauck: Writing - review & editing, Investigation, Formal analysis, Data curation. Alessio Antropoli: Writing - review & editing, Formal analysis, Data curation. Lorenzo Bianco: Writing - review & editing, Formal analysis, Data curation. Maurizio Battaglia Parodi: Writing - review & editing, Formal analysis, Data curation. Francesco Bandello: Writing - review & editing, Formal analysis, Data curation. Antje Grosche: Writing original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Data will be made available on request.

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