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Review

The role of cytokines in cytokine release syndrome (CRS) after CAR T cell therapy☆

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A B S T R A C T

Chimeric antigen receptor (CAR) T cell therapy has transformed the treatment landscape for hematological malignancies. However, cytokine release syndrome (CRS) remains a common and potentially severe toxicity, significantly affecting patient safety and requiring intensive clinical management. This review provides a focused synthesis on the role of cytokines in CRS after CAR T cell therapy, integrating recent mechanistic insights with clinical implications. We delineate the cellular and molecular pathways involving key cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), interferon γ (IFN-γ), tumor necrosis factor α (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF), describing their sources, downstream signaling events, and effects on target tissues. By bridging basic cytokine biology with clinical aspects and therapeutic strategies, this review aims to provide a comprehensive framework for understanding the role of cytokines in CRS pathophysiology, ultimately supporting the development of safer and more effective CAR T cell therapies.

1. Introduction

CAR T cell therapy has revolutionized the therapeutic landscape for patients with refractory and relapsed B cell cancers [1]. This form of therapy utilizes engineered T lymphocytes that express a synthetic receptor, combining antigen-recognition properties with T cell activation domains. Upon infusion, CAR T cells are activated through recognition of specific cancer antigens and selectively kill cells expressing these antigens via cytolytic mechanisms [2,3]. This offers new treatment options for cancer patients who have undergone various unsuccessful previous lines of therapy. Recent evidence even proposed to advance CAR T cell therapy up to second line for patients suffering from diffuse large B cell lymphoma based on phase 3 clinical trial data [4]. To date, seven CAR T cell products have received regulatory approval from the FDA: five targeting CD19 in B cell malignancies and two directed against B cell maturation antigen (BCMA) in multiple myeloma (Fig. 1) [5,6]. These therapies are capable of inducing high response rates in patient populations with otherwise limited treatment options [7]. While CAR T cell therapy demonstrates substantial clinical efficacy, it is also associated with severe systemic toxicities. One of the most common and serious adverse effects is CRS, which manifests in symptoms such as fever, hypotension, and respiratory failure, accompanied by elevated levels of cytokines including IL-6 and IFN-γ [8]. CRS is also known in the context of other immunotherapies, including bispecific antibodies and checkpoint inhibitors [9,10]. The syndrome is named after the associated surge of inflammatory cytokines secreted, in this case, not only by

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CAR T cells but also by subsequently activated monocytes and macrophages [6]. Clinical experience has revealed that immunosuppressive interventions can ameliorate this toxicity: corticosteroids provide broad suppression of inflammation, while the IL-6 receptor antagonist tocilizumab has emerged as a targeted and effective treatment that allows continued application of CAR T cell therapy [11]. Despite these advances in management, CRS remains one of the most frequent and potentially life-threatening toxicities associated with CAR T cell therapy. Management strategies of CRS have evolved substantially in recent years, but optimal approaches for prediction, prevention, and treatment are still being defined. This review will focus on the central role of cytokines in the pathogenesis of CRS, examining both clinical parameters and underlying molecular mechanisms, as well as and the current evidence guiding therapeutic intervention. In addition, we will discuss novel strategies under investigation to mitigate CRS without compromising CAR T cell efficacy, and highlight future directions for research.

2. Clinical manifestation of CRS

2.1. Incidence, definition and differentiation

CRS presents as an inflammatory syndrome characterized by a supraphysiologic immune response following certain immunotherapies such as CAR T cells. The incidence of CRS is highly dependent on the CAR T cell product used, the underlying malignancy, and a range of patient-specific factors including burden of disease and pretreatment serum inflammation markers [6]. Two landmark trials in relapsed/refractory B cell lymphoma showcased 58 to 93% of patients experiencing any grade and 22 to 13% of patients experiencing severe CRS (grade $\geq$ 3) in the ZUMA-1 and JULIET trial, respectively [8,12,13]. These high incidences reflect the need to address this adverse effect for future application of CAR T cell therapies, especially in earlier treatment lines. Notably, the most recently FDA-approved CAR T cell product, obecabtagene autoleucel, incorporates a “fast off-rate” CD19 binder to enable rapid antigen disengagement and employs split dosing rather than a single infusion to prevent side effects. In the FELIX study, this design translated into a markedly reduced incidence of severe CRS, with only 2.4% of patients experiencing grade $\geq$ 3 CRS, while maintaining high antitumor efficacy [5]. These findings demonstrate the feasibility and clinical impact of engineering strategies to attenuate CAR T-associated cytokine toxicities.

Clinically, CRS results from the release of high levels of cytokines into the circulation by activated immune cells, initiating a systemic inflammatory response. It is most commonly seen in CAR T cell therapy, but is also observed in other immunotherapies such as bispecific T-cell engagers, monoclonal antibody therapy and checkpoint inhibitors [9,10,14]. The onset of CRS usually occurs within 14 days of CAR T cell administration, with a medium onset time of 2–7 days [6,15,16]. Fever is deemed as the hallmark symptom of CRS [17]. Other clinical manifestations range from mild symptoms, such as fatigue, headache, rash, and myalgia, to severe, life-threatening conditions, including hypotension, vascular leakage, intravascular coagulation, and multi-organ failure requiring intensive care [14]. This broad spectrum of symptoms and severities has led to inconsistent definitions and grading, complicating comparisons of CRS incidence and severity across clinical studies. To address this, the American Society for Transplantation and Cellular Therapy (ASTCT) published consensus grading criteria in 2019, which have since become the standard for CRS assessment [17]. Although this grading system does not capture organ toxicities such as coagulopathy, reduced cardiac ejection fraction, hepatic or renal insufficiency, or electrolyte disturbances [6], it is widely adopted in clinical practice due to its simplicity and clarity. The ASTCT criteria use the three parameters fever, hypotension and hypoxia to define the grade of CRS, with fever being a requirement for classification as any grade of CRS [17]. The grading stages fever without hypotension or hypoxia (grade 1), fever with hypotension and/or hypoxia requiring minimal support and no vasopressors (grade 2), fever with hypotension requiring a vasopressor and/or hypoxia requiring support (grade 3) and fever with hypotension requiring multiple vasopressors and/or hypoxia requiring positive pressure ventilation (grade 4) [17].

One challenge consists in differentiating CRS symptoms from those of infection as the major other factor for non-relapse mortality [11,18].

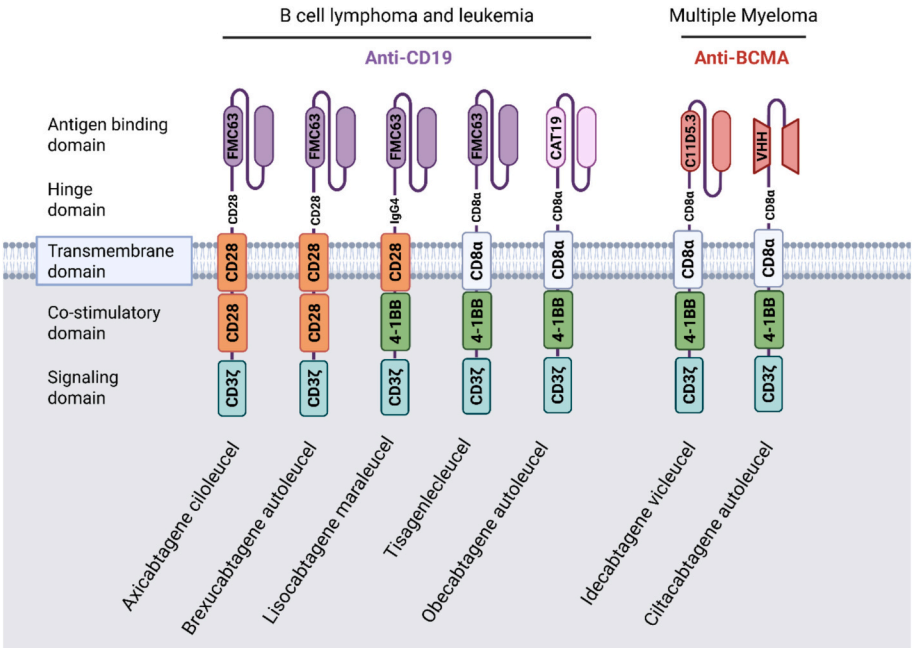

Fig. 1. Current FDA-approved CAR T cell therapies. As of now, seven CAR T cell therapies have received FDA approval. Five therapies target CD19 in B cell malignancies, while two target BCMA in multiple myeloma. In addition to their antigen specificity, these CAR T cell products differ in their hinge regions, transmembrane domains, costimulatory domains, and intracellular T cell activation domains. All currently FDA-approved CAR-T cell products are second-generation CARs, incorporating a single costimulatory domain (CD28 or 4-1BB) in addition to CD3ζ, which markedly enhances T-cell activation compared to first-generation CARs lacking costimulation. Figure created in BioRender.

To aid in this distinction, blood and urine cultures as well as imaging and laboratory parameters like procalcitonin should be assessed [11,19]. Furthermore, CRS must be distinguished from other CAR T cell-associated toxicities, such as immune effector cell-associated neurotoxicity syndrome (ICANS), which manifests primarily as neurological symptoms, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), which resembles a hyperinflammatory secondary hemophagocytic lymphohistiocytosis, and immune effector cell-associated haematotoxicity (ICAHT), which is defined by persistent cytopenias [6]. Although all of these toxicities are driven by cytokine dysregulation, they differ in clinical presentation and underlying mechanisms and can arise independently or in combination with CRS [6].

2.2. Biomarkers and prediction

Biomarkers and predictive models are crucial for anticipation and management of CRS in CAR T cell therapy. The central role of cytokines in the pathophysiology of CRS is reflected in elevated serum levels of various cytokines. Among these are CAR T derived IFN-γ, TNF-α, GM-CSF and IL-2, myeloid-derived IL-1, IL-6 and IL-10 and endothelium-derived monocyte CXCL8/IL-8, chemoattractant protein-1 (MCP-1/CCL2) and C-X-C motif chemokine ligand 9 and 10 (CXCL9/10) [1,11,20]. Acute phase proteins such as C-reactive protein (CRP) and ferritin are also frequently elevated, with higher concentrations correlating with increased CRS severity [14,21–23]. Furthermore, markers of vascular endothelial dysfunction, including angiopoietin-2 (Ang-2) and von-Willebrand-factor (vWF), are increased in severe CRS, and elevated pre-lymphodepletion levels of these proteins have been linked to subsequent development of CRS, highlighting the involvement of endothelial activation [23]. Changes in coagulation parameters, such as reduced platelet count, as well as elevated levels of lactate dehydrogenase (LDH) have also been reported in association with more severe CRS [22,23].

There are also clinical risk factors for CRS development, such as a higher burden of disease, which is consistently associated with increased CRS incidence and severity [23–25]. Other risk factors are higher CAR T cell doses [14,26], more intensive lymphodepleting regimens [23], elevated pretreatment serum inflammation markers [27,28] and low baseline platelet counts [23]. There is ongoing debate regarding the impact of CAR T costimulatory domains (CD28 vs. 4-1BB) on CRS risk and phenotype. Some studies report that CD28-based CARs exhibit distinct activation kinetics and cytokine production profiles, potentially resulting in a more rapid onset of CRS [12,22,29], whereas other studies suggest comparable patterns of severe CRS [30].

As a result of identification of these biomarkers and risk factors, several studies have tried to predict CRS occurrence or severity based on these findings. Among clinical prediction tools, the Endothelial Activation and Stress Index (EASIX) and its modified versions (m-EASIX, sEASIX), which integrate baseline blood creatinine, LDH, and platelet count (with m-EASIX using CRP), have demonstrated predictive value for severe CRS [31–33]. Other models focus on the use of CRS-specific cytokines and proteins and utilize early post-infusion cytokine levels, such as IFN-γ, soluble glycoprotein130 (sgp130) and Interleukin-1 Receptor Antagonist (IL-1RA), to forecast CRS risk [22]. Standard laboratory markers such as CRP and ferritin levels were associated, but not predictive, for CRS in these studies [22]. Notably, while markers such as tumor burden and CAR T cell dose are reliably associated with risk, the predictive value of cytokine profiles and standard laboratory markers varies considerably between studies and has not been consistently replicated in independent cohorts [21,22]. A possible explanation may reside in the substantial heterogeneity in how cytokines are measured and reported across clinical trials [34]. Overall, standardizing cytokine detection methods and reporting practices is essential not only to improve reliability of predictive biomarker analyses but also to enable pooling of data and validation of early-warning models for toxicity in CAR T cell therapies [34].

3. Cytokines in CRS – molecular and cellular mechanisms

3.1. CAR T-derived IFN-γ and TNF-α are involved in tumor cell death

The beginning of CRS is characterized by the release of proinflammatory cytokines from CAR T cells, which amplify cytotoxic activity and initiate downstream immune activation and local inflammation (Table 1). Upon recognition of specific tumor antigens, CAR T cells release IFN-γ and TNF-α, which can induce apoptosis and growth arrest in target tumor cells through engagement of their respective receptors. TNF-α can trigger caspase-dependent apoptosis via signaling through TNFR1-associated death domain (TRADD) and Fas-associated death domain (FADD) [35,36]. IFN-γ activates Janus kinase/Signal transducer and activator (JAK/STAT) signaling to upregulate pro-apoptotic genes, suppress cell cycle progression and enhance antigen presentation [37]. Additionally, CAR T cells also produce proinflammatory IL-2. This can induce JAK1/JAK3 signaling in activated T cells and NK cells via the IL-2-Rα/β/γc complex. This in turn induces STAT5 signaling, as well as phosphoinositide 3-kinase (PI3K), protein kinase B (AKT) and mitogen-activated protein kinase (MAPK) pathways, causing lymphocyte expansion and effector function. These processes lead to an increase of T cell numbers and total cytokine concentrations in the serum, thereby acting as a self-amplifying proinflammatory loop [38].

Next to proinflammatory cytokines, CAR T cells also release high amounts of cytotoxic molecules, including perforin and granzymes A and B[39]. Perforin forms pores in the plasma membrane of the target cell, facilitating the entry of granzymes into the cytoplasm [39]. Within the target cell, granzyme B activates caspase-3, which subsequently cleaves gasdermin E (GSDME), a pore-forming protein that is highly expressed in B-leukemic and other tumor cells, ultimately triggering pyroptosis [39]. Granzyme B can also cleave GSDME in a direct manner, while granzyme A is capable of directly cleaving and thereby activating gasdermin B (GSDMB) [40]. The activation of these gasdermin proteins allows insertion of their N-terminal domain into the cell membrane to form pores, causing extensive cellular swelling and the appearance of large membrane bubbles, ultimately resulting in cell lysis [39]. This leads to the release of LDH, proinflammatory factors, and danger-associated molecular patterns (DAMPs) such as adenosine 5′-triphosphate (ATP) and high-mobility group box 1 (HMGB1) into the extracellular space [39,41–43]. Unlike apoptosis, which is a non-inflammatory and caspase-dependent process, pyroptosis depends on the gasdermin protein family and is characterized by a strong inflammatory response [42,44].

3.2. Myeloid activation by DAMPs and CAR T-derived TNF-α, IFN-γ and GM-CSF

The release of DAMPs from pyroptotic tumor cells, together with the secretion of pro-inflammatory cytokines such as TNF-α, IFN-γ and GM-CSF by activated CAR T cells, leads to the activation of myeloid cells, especially macrophages, which subsequently act as key mediators of CRS (Fig. 2) [41]. HMGB1, released by pyroptotic tumor cells, binds to Toll-like receptors (TLR2 and TLR4) on macrophages, thereby activating the adaptor proteins myeloid differentiation primary-response 88 (MyD88) and TIR-domain-containing adaptor inducing IFN-β (TRIF, TICAM1), both involved in the innate immune response [39,41,45]. These adaptor proteins in turn activate MAPK and IκB kinase (IKK) signaling pathways, resulting in activation of the transcription factors nuclear factor κB (NF-κB) and activator protein 1 (AP-1) in the nucleus (Fig. 2) [39,41]. NF-κB and AP-1 play an important role in the regulation of cytokine secretion and induce the release of IL-1β and IL-6 from myeloid cells [39,41,45]. In addition, activation of TLR2 can induce secretion of soluble IL-6R (sIL-6R), further enhancing the proinflammatory effects of IL-6 [46]. The P2X7 receptor on macrophages

Table 1
Overview of cellular sources, target cells, signaling and effects of cytokines in CRS. Listed are predominant pathways, cells and effects that are driving the pathomechanisms in CRS. Cytokines are ordered after their main cellular source in CRS, from CAR T cells to myeloid cells to endothelial cells.

Cytokine	Main cellular source in CRS	Primary target cells	Core signaling	Principal effects in CRS	Ref.
IFN-γ	(CAR) T cells	Monocytes/macrophages, endothelial cells, various immune cells	JAK1/JAK2 ➔ STAT1	Myeloid and endothelial activation	[23,50,51]
TNF-α	(CAR) T cells, monocytes, macrophages	Monocytes/macrophages, endothelial cells	TRAF, MAPK ➔ NF-κB	Myeloid and endothelial activation	[54,56,78,79]
GM-CSF	(CAR) T cells	Monocytes/macrophages, neutrophils, microglia	JAK2 ➔ STAT5	Myeloid activation	[49,52,80,81]
IL-2	(CAR) T cells	T cells and NK cells	JAK1/JAK3 ➔ STAT5	T cell proliferation	[38]
IL-1	Monocytes, macrophages	T cells, endothelial cells	MyD88-IRAK-TRAF ➔ NF-κB/MAPK	Myeloid activation, fever, hypotension	[26,58,59,62]
IL-6	Monocytes, macrophages, endothelial cells	Endothelium via sIL-6R/gp130, hepatocytes and leukocytes via mIL-6R/gp130	JAK-STAT ➔ VEGF, IL-8, MCP-1, PAI-1	Vascular permeability, hypotension, coagulopathy	[26,62–65]
IL-10	Monocytes, macrophages	Myeloid cells and T cells	JAK1/TYK2 ➔ STAT3	Compensating, anti-inflammatory	[73,74]
CXCL9, CXCL10	Myeloid and stromal cells	T cells and NK cells	CXCR3 ➔ PI3K/Akt, MAPK	T cell trafficking	[77]
CXCL-8/IL-8	Endothelial cells, myeloid cells	Neutrophils and endothelium	CXCR1/2 ➔ PI3K/Akt, MAPK	Neutrophil and monocyte recruitment	[68,75]
CCL2/MCP-1	Endothelial cells, myeloid cells	Monocytes	CCR2 ➔ PI3K/Akt, MAPK, Rho GTPase	Monocyte recruitment	[68,76]

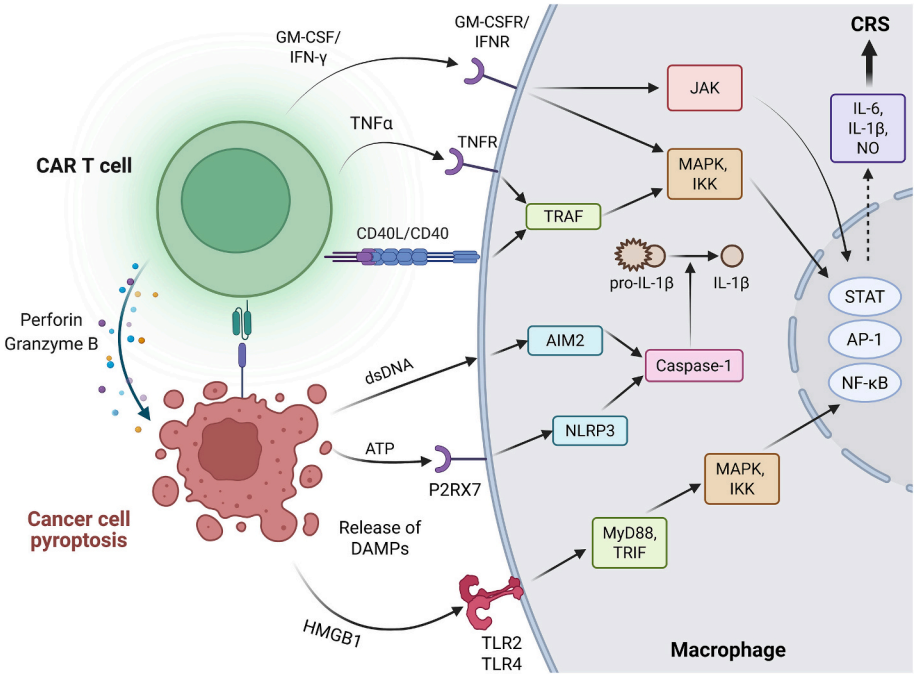

Fig. 2. Macrophage activation in CRS. CAR T cells release cytokines such as GM-CSF, IFN-γ and TNF-α that bind corresponding receptors on macrophage surfaces. This drives downstream MAPK, IKK and JAK signaling cascades, leading to activation of STATs, AP-1 and NF-κB in the nucleus, causing secretion of proinflammatory mediators. CD40L/CD40 interaction between CAR T cells and macrophages also initiates MAPK, IKK pathways. DAMPs released from tumor cells via pyroptosis cause MAPK, IKK signaling and inflammasome activation, leading to caspase-mediated cleavage of IL-1β. Figure created in BioRender.

recognizes ATP and triggers activation of NOD-, LRR-, and NLR family pyrin domain containing 3 (NLRP3), which in turn recruits apoptosis-associated speck-like protein (ASC) and pro-caspase 1 [43]. These proteins assemble to form the NLRP3 inflammasome, which maturates caspase 1, enabling cleavage of pro-IL-1β to its active form, IL-1β (Fig. 2) [41,43]. As part of a feed-forward loop, caspase 1 can also activate gasdermin D (GSDMD), resulting in macrophage pyroptosis and release of additional DAMPs, which in turn amplifies macrophage activation [41,43]. Another DAMP released during tumor cell pyroptosis is double-stranded DNA (dsDNA), which is phagocytosed by macrophages and activates the absent in melanoma 2 (AIM2) inflammasome. This occurs via the formation of an AIM2/ASC-pro-caspase 1 complex, which can also facilitate caspase 1-dependent maturation of IL-1β [47].

In addition to the release of DAMPs during tumor cell pyroptosis, macrophages are directly activated by cytokines secreted by activated CAR T cells, including TNF-α, GM-CSF and IFN-γ (Fig. 2). These cytokines induce macrophage polarization toward an M1 phenotype, which is characterized by increased production of nitric oxide (NO) via inducible nitric oxide synthase (iNOS), as well as elevated secretion of pro-inflammatory cytokines such as IL-6, IL-12, IL-23 and TNF-α [48,49]. IFN-γ activates macrophages through the JAK-STAT signaling pathway [48]. Upon IFN-γ binding, the IFN-γR1 and IFN-γR2 receptor subunits dimerize, promoting autophosphorylation of JAK1 and JAK2 [50]. This event recruits and phosphorylates STAT1, which then homodimerizes and translocates to the nucleus to regulate interferon-stimulated genes (ISGs) that promote a pro-inflammatory M1

phenotype in macrophages [51]. A similar mechanism operates for GM-CSF, which signals via the JAK2-STAT5 signaling pathway [48]. Binding of GM-CSF to its receptor subunits (GM-CSFRα and GM-CSFRβ) forms a dodecameric ligand–receptor complex that facilitates JAK2-dependent phosphorylation and homodimerization of STAT5 [52]. These STAT5 homodimers drive transcription of M1-associated genes and promote the release of inflammatory cytokines, including TNF-α, IL-6, IL-12 and IL-23 [49]. In addition, GM-CSF signaling engages NF-κB pathway, as well as PI3K/Akt and MAPK/ERK pathways in macrophages [49,53]. TNF-α modulates macrophage proliferation, apoptosis, and inflammation via its receptors, TNFR1 and TNFR2, which both activate NF-κB and MAPK signaling pathways [48]. Engagement of TNFR1 recruits adaptor proteins such as TRADD, FADD, TNF-receptor-associated factor 2 (TRAF2), and serine/threonine kinase receptor-interacting protein 1 (RIP1), leading to the activation of the IKK complex and nuclear translocation of NF-κB, which in turn upregulates pro-inflammatory gene expression [48,54,55]. TRAF2 further activates c-Jun N-terminal kinase (JNK) and p38 MAPK, while RIP1 can activate IKK via MAP3K7, contributing to macrophage inflammation, survival, and the maintenance of the M1 phenotype [56]. The TNFR2-mediated pathway, in addition to activating classical NF-κB and MAPK signaling pathways engaged by TNFR1, uniquely engages the alternative p52-RelB NF-κB pathway and initiates additional MAPK phosphorylation, further promoting a pro-inflammatory macrophage phenotype and the production of inflammatory mediators. Beyond these cytokine-mediated mechanisms, CD40L/CD40 interaction between CAR T cells and macrophages also induce a pro-inflammatory response [48]. CD40, a member of the TNF-receptor superfamily, recruits TRAF adaptor proteins (TRAF2, 3, 5, and 6) upon ligand binding, thereby activating NF-κB and MAPK signaling pathways (Fig. 2) [36,57].

3.3. *Myeloid-derived IL-1 and IL-6 mediate endothelial dysfunction and systematic inflammation*

The activation of myeloid cells causes a secondary cytokine surge in CRS development. This surge is dominated by myeloid-derived IL-1 and IL-6, which disrupt endothelial integrity and drive the clinical manifestations of capillary leak, hypotension, and multi-organ dysfunction.

IL-1 is a pleiotropic cytokine, with both pro-inflammatory and anti-inflammatory properties, that plays a key role in CRS development [1,58]. The main producers of IL-1 in the context of CRS are macrophages and monocytes [1]. Its receptor, IL-1R1, is ubiquitously expressed and, upon ligand binding, recruits the adaptor protein MyD88, leading to the assembly of interleukin-1 receptor-associated protein kinase 4 (IRAK4) [59]. This results in oligomerization of TRAF6 and recruitment of MAPK signaling components, ultimately activating the transcription factors NF-κB and AP-1 in the nucleus [59]. Activation of this pathway induces production of additional pro-inflammatory cytokines, such as IL-6, as well as chemokines that promote maturation and recruitment of immune cells. Because IL-1R1 is widely expressed on different cell types, the downstream effects of IL-1 signaling target not only myeloid cells, but also endothelial cells and neurovascular cells [60]. This explains the important role that IL-1 plays in both CRS and ICANS as the second major CAR T cell-associated toxicity. Ultimately, IL-1 signaling leads to increased production of pro-inflammatory factors by myeloid cells and contributes to increased vascular permeability and leakiness, thereby exacerbating effects of other key driver cytokines of CRS such as IL-6, IFN-γ, and GM-CSF.

The second myeloid-derived cytokine with a central role as a mediator of systemic hyperinflammation in CRS is IL-6 [1]. Its signaling on endothelial cells leads to vascular leakage (Fig. 3), which is responsible for many of the more severe symptoms associated with the condition [41]. IL-6 is produced by multiple cell types, including activated CAR T cells, monocytes, macrophages, dendritic cells, endothelial cells and B cells, with myeloid cells being the main producer in CRS settings [61,62]. IL-6 can bind either the membrane-bound IL-6 receptor (mIL-6R, classical cis-signaling) or the soluble IL-6 receptor (sIL-6R, trans-signaling), in both cases forming a complex with the signal transducer glycoprotein 130 (gp130) [63,64]. This interaction leads to downstream JAKs phosphorylating and thereby activating the transcription factor STAT3 [63]. STAT3 then induces expression of genes involved in acute phase response and immune cell activation. The membrane-bound version of the IL-6R is mainly found on hepatocytes and immune cells, whereas gp130 is ubiquitously expressed [41]. In cells lacking mIL-6R, signaling is mediated by trans-signaling via sIL-6R, which forms a complex with IL-6, leading to dimerization of gp130 on the cell membrane, triggering the downstream signaling cascade [63]. This mechanism of signaling broadens the range of cells responsive to IL-6 and enables a local danger response, as sIL-6R can be released by monocytes, macrophages and neutrophils. This acts as paracrine amplifier of IL-6 signaling and promotes inflammatory activation of surrounding stromal tissues [64,65]. In CRS, activated macrophages release high amounts of sIL-6R, thereby triggering the JAK(JAK1/JAK2/TYK2)-STAT3 axis in endothelial cells. In addition, IL-6 activates PI3K/AKT and MAPK pathways, which contribute to endothelial survival, proliferation, and the acquisition of a pro-inflammatory phenotype [64,66].

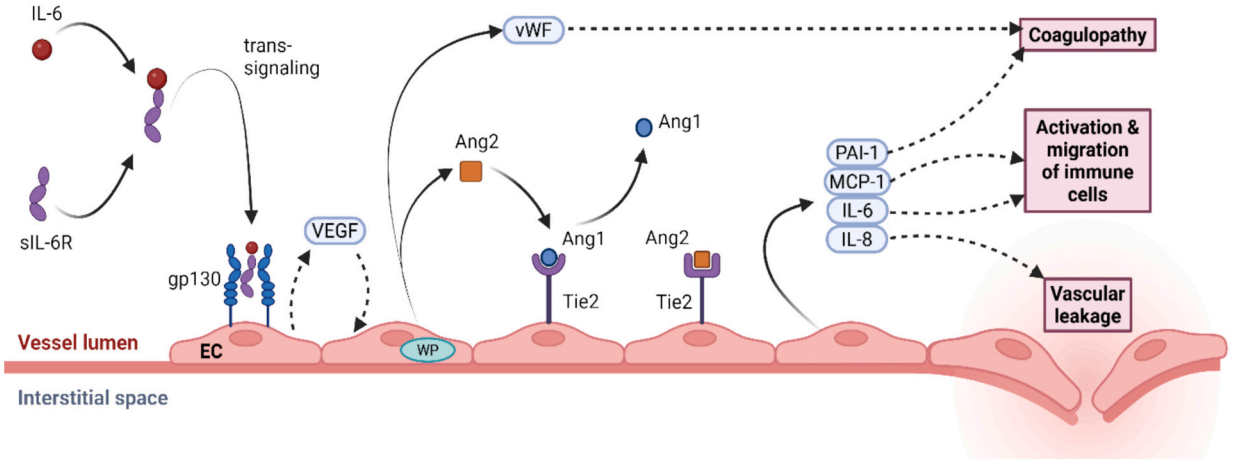

Fig. 3. Endothelial activation by trans-signaling of IL-6. sIL-6R forms a complex with IL-6 secreted by activated macrophages. gp130 on the endothelial cell (EC) surface binds the sIL-6R-IL6 complex, initiating secretion of VEGF, thereby causing Weibel-Palate-bodies (WPs) to secrete Ang2 and vWF. Ang2 replaces Ang1 in the Tie2 receptor, causing ECs to secrete PAI-1, MCP-1, IL-6 and IL-8, ultimately causing coagulopathy, activation and migration of immune cells and vascular leakage. Figure created in BioRender.

These signaling cascades prompt endothelial cells to secrete proinflammatory factors such as vascular endothelial growth factor (VEGF), IL-8, IL-6, monocyte chemoattractant protein-1 (MCP-1) and plasminogen activator inhibitor-1 (PAI-1) [66–68]. This leads to junctional disorganization and increased vascular permeability. Inflammatory cues such as VEGF, thrombin and catecholamines promote the release of angiopoietin-2 (Ang-2) and von-Willebrand-factor (vWF) from endothelial cell Weibel–Palade (WP) bodies, inhibiting angiopoietin-1 receptor (TEK tyrosin kinase, Tie2) signaling and further destabilizing the endothelial barrier (Fig. 3) [69–71]. These mechanisms collectively cause hypotension, vascular leakage, coagulopathy and organ dysfunction in the patient [41,72]. In addition to these processes caused by myeloid-derived cytokines, vascular activation is further enhanced by the signaling of CAR T-derived TNF-α and IFN-γ on endothelial cells [72].

All of these proinflammatory processes are to some extent mediated by another relevant cytokine, which is IL-10. This acts as a regulatory, anti-inflammatory cytokine that is produced by monocytes and macrophages during CRS. It binds to IL10-R1/IL-10R2 receptors on myeloid cells, inducing JAK1/tyrosine kinase 2 (TYK2) signaling and downstream activation of STAT3 [73,74]. IL-10 thereby suppresses proinflammatory cytokine production and is elevated in the serum of CRS patients alongside pro-inflammatory cytokines.

3.4. Endothelium- and myeloid-derived chemokines drive recruitment of further immune cells

As the inflammatory cascade progresses, activated endothelium emerges as a source of chemokines that guide immune cell infiltration, thereby amplifying local tissue inflammation and sustaining the cytokine network. This includes CXCL8/IL-8, CCL2/MCP-1, CXCL9 and CXCL10. CXCL8 is produced mainly by endothelial cells and binds to CXCR1 and CXCR2 receptors on neutrophils and endothelial cells. It causes GPCR-mediated chemotaxis, activation and degranulation, leading to neutrophil recruitment and thereby driving tissue inflammation and vascular leakage in CRS [75]. CCL2/MCP-1 is produced by endothelial and myeloid cells and recruits monocytes via C—C chemokine receptor type 2 (CCR2), facilitating monocyte extravasation and amplifying macrophage-mediated cytokine production [76]. CXCL9 and CXCL10 are produced by myeloid and stromal cells in response to IFN-γ and are frequently elevated in the serum profiles of CRS patients. These chemokines induce chemotaxis of activated T and NK cells, reinforcing IFN-γ-dominated circuits and T cell trafficking [77].

4. Therapeutic interventions

4.1. Clinically established intervention strategies

As CRS has been observed as a side effect of CAR T cell therapy from early clinical studies onwards, there has been continuous interest in how this toxicity can be mitigated and treated. Current clinical management relies primarily on IL-6 blockade, often in combination with systemic corticosteroids [8,82]. Tocilizumab, an anti-IL-6-receptor monoclonal antibody, is considered the first-line pharmacological therapy for moderate to severe CRS (≥ grade 2) according to current consensus guidelines [6]. Its half-life is concentration dependent, and the FDA prescribing information reports an effective steady-state half-life of up to 13 days at the doses used for CRS treatment. It can be redosed at relatively short intervals of at least 8 h and has been shown to reduce systemic inflammation without impairing CAR T cell expansion or antitumor efficacy [83,84]. After administration, IL-6 levels rise transiently due to receptor blockade inhibiting receptor-mediated clearance [15]. This may increase the risk of associated neurological toxicities such as ICANS, although data on whether this actually occurs are inconsistent [85,86]. There have also been studies investigating whether prophylactic tocilizumab administration would be able to prevent CRS, rather than treating already established toxicity. These trials have administered tocilizumab at lower grades of CRS and shown that this regimen was effectively preventing the development of severe toxicities [84,87,88]. If treatment with tocilizumab is insufficient, corticosteroids such as dexamethasone or methylprednisolone are used as second-line therapy, providing broad suppression of inflammatory responses [82]. The impact of corticosteroids on therapy efficacy remains a matter of debate, due to concerns about steroid-mediated impairment of T cell proliferation and persistence. Some retrospective studies have found an association between corticosteroid use and shorter progression-free and overall survival [89], while others have not observed any negative impact on CAR T cell therapy [84,90–92]. The effect, if any, appears to depend on the dosage and duration of corticosteroid treatment, with short-term use posing less risk for interference with therapeutic efficacy [89]. Consequently, clinical practice favors the lowest effective dose and the shortest possible duration, with escalation only when clinically necessary and prompt tapering once toxicity is controlled. For CRS that is refractory to tocilizumab and corticosteroids, third line treatment is based on the use of anakinra, a recombinant IL-1 receptor antagonist, blocking the pro-inflammatory IL-1 signaling axis [8]. This approach has been shown to mitigate both CRS and ICANS, with a favorable safety profile and no evidence of negative impact on CAR T cell efficacy [93].

4.2. Emerging cytokine-targeting strategies

In addition to established therapeutic interventions, several emerging strategies for treatment of CRS are under investigation (Fig. 4). Many of these approaches focus on targeting cytokines, as these are the main mediators of CRS. Complementary to IL-6 receptor blockade with tocilizumab, the IL-6 ligand can be neutralized directly using siltuximab, a monoclonal antibody. Siltuximab has demonstrated efficacy in controlling CRS and has shown comparable rates of intensive care unit transfer to tocilizumab-based protocols, making it a valid alternative [94,95]. Ongoing phase 2 clinical trials are evaluating this strategy further (NCT07106671, NCT04975555). Another path involves targeting IFN-γ with the monoclonal antibody emapalumab. Since IFN-γ plays a role in macrophage activation, neutralization of this signaling pathway has been shown to mitigate CRS by reducing the pro-inflammatory environment in preclinical and clinical studies [96–98]. Importantly, data from humanized mouse models indicate that IFN-γ inhibition does not impair efficacy of anti-CD19 CAR T cells, suggesting that this can be a mitigation strategy that does not compromise therapeutic success [96]. It should be noted, however, that studies in solid tumor settings indicate that IFN-γ blockade can negatively impact CAR T cell therapy efficacy there [98]. GM-CSF is another cytokine targeted for therapeutic purposes. The monoclonal antibody lenzilumab effectively neutralizes GM-CSF, mitigating both CRS and neurotoxicity by reduction of myeloid cell infiltration and decreasing levels of proinflammatory myeloid-related cytokines and chemokines such as MCP-1, IL-6, IL-8, CXCL10, TNF-α and IL-1RA [80,99]. Interestingly, is has been shown in a xenograft model, that anti-CD19 CAR T cells demonstrate enhanced proliferation and tumor control after GM-CSF neutralization with lenzilumab [80]. Cytokine targeting can also be achieved with fusion proteins, such as the TNF-α inhibitor etanercept, which has shown efficacy in small cohorts, with no reported adverse effects or alteration of BCMA-targeted CAR T cell therapy response [79]. Similar effects have been observed with the TNF-α inhibitor adalimumab [78]. Lastly, there are emerging concepts that address the global cytokine surge in CRS using extracorporeal cytokine adsorption, for example with Cytosorb®. This strategy has been reported to be successful in a single case of treatment-refractory CRS [100] and a clinical trial is currently ongoing to evaluate its application in severe CRS (NCT04048434).

4.3. Other strategies for management and prevention of CRS

Beyond direct cytokine inhibition, current research on CRS

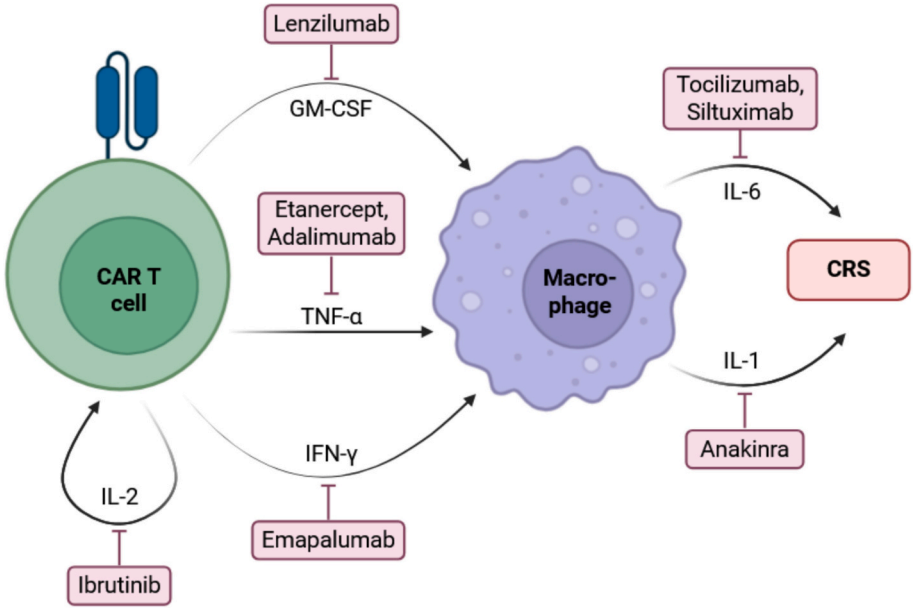

Fig. 4. Therapeutic strategies for CRS targeting different cytokines. Overview of clinically established and novel strategies for treatment of CRS by targeting different cytokines involved in the pathogenesis. Tocilizumab and siltuximab are shown together as inhibitors of the IL-6 axis, in detail they are inhibiting the corresponding receptor and ligand, respectively. Figure created in BioRender.

prevention and management encompasses a diverse array of strategies, including pharmacological interventions that target intracellular signaling pathways or transcriptional regulators, as well as advanced synthetic biology approaches, each aiming to modulate CAR T cell activity and the inflammatory response through distinct mechanisms. One of the most prominent approaches revolves around the use of different tyrosine kinase inhibitors, which affect signaling pathways downstream of T cell activation and thereby interfere with the production of proinflammatory cytokines. The most notable among these are the small molecule inhibitors dasatinib, ruxolinitib and ibrutinib. Dasatinib interrupts CAR signaling by inhibition of Lymphocyte-specific protein tyrosine kinase (Lck) and downstream CD3ζ/ZAP70 phosphorylation, thereby acting as an reversible off-switch for CAR T cells [101]. Ruxolitinib inhibits JAK1/2 in T cells, broadly blocking downstream JAK-STAT signaling that leads to production of proinflammatory cytokines [102,103]. Ibrutinib targets IL-2-inducible tyrosine kinase (ITK), thereby enhancing CAR T cell efficacy while simultaneously mitigating the risk of severe CRS [104–106]. Preclinical studies have demonstrated that these substances are able to potently, and sometimes even reversibly, inhibit key pathways required for CAR T cell activation and cytokine production, resulting in lower levels of proinflammatory cytokines and controlling CRS in mouse models [101,102,105]. These studies have been followed by clinical evidence supporting the safety and efficacy of these tyrosine kinase inhibitors for CRS prevention and management [103,104,107]. Another pharmacological approach involves inhibition of cyclin-dependent kinase 7 (CDK7) [108]. In preclinical studies, the covalent inhibitor THZ1 was shown to suppress the activity of super-enhancers that are regulating the expression of inflammatory genes in activated macrophages. In the context of CRS, this mainly affected the transcription factor STAT1 and the production of IL-1. Targeting these pathways alleviated CRS without impairing antitumor effects in mice [108]. The mitochondrial uncoupler BAM15 may also improve antitumor efficacy of CAR T cells, while reducing secretion of proinflammatory cytokines such as IL-6 and TNF-α [109].

A different, non-pharmacological strategy for the prevention and mitigation of CRS lays in synthetic biology solutions. Extensive research is ongoing on the development of concepts such as safety switches and tunable CARs. These approaches aim to control CAR activation by external substances or enable substance-controlled "off-switches" within CAR T cells, for example by introducing caspase 9 fusion proteins [110,111]. Other approaches include knockouts of key molecules in CAR T cells that are involved in the pathogenesis of CRS, such as CD40L or GM-CSF [112]. An elegant method of CAR T cell engineering addresses CRS by developing CAR T cells that are themselves able to neutralize proinflammatory cytokines. One example involves the expression of a non-signaling, membrane-bound IL-6 receptor on CAR T cells, enabling them to remove IL-6 from the microenvironment without compromising their cytotoxicity or proliferative capacity in mice [113]. Recent clinical case reports have demonstrated promise when CAR T cells were engineered to secrete anti-IL-6 scFv and IL-1 receptor antagonist, supporting this as a feasible and safe strategy for future clinical application [114].

5. Conclusions

CRS remains a major challenge in the clinical use of CAR T cell therapy, driven by a complex network of cytokines. Despite growing knowledge of the molecular and cellular mechanisms underlying CRS, many questions remain regarding optimal risk prediction, early biomarkers, and targeted interventions. As CAR T cell therapies are rapidly expanding from the field of hematological malignancies into new indications such as solid tumors and autoimmune diseases, the clinical presentation and underlying biology of CRS may further diversify, necessitating continual adaptation of diagnostic and management strategies. Future research should therefore focus on unraveling context-specific mechanisms of CRS, refining prediction and diagnostics, and developing a wider variety of approaches for intervention. The ongoing integration of mechanistic discoveries and clinical evidence will be critical to improving outcomes and safety as CAR T cell therapies continue to advance.

CRediT authorship contribution statement

Kathrin Gabriel: Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization. **Lucie Heinzerling:** Writing – review & editing. **Louisa von Baumgarten:** Writing – review & editing. **Marion Subklewe:** Writing – review & editing. **Sebastian Kobold:** Writing – review & editing, Writing – original draft,

Visualization, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Informed consent

All authors approve the manuscript for publication.

Declaration of competing interest

K.G. declares no competing interests. L.H. has received honoraria from BMS, Immunocore Ireland, Merck, Novartis and Therakos. L.H. is involved in clinical studies of Agenus, AstraZeneca, BMS, Huya Bioscience International, Immunocore Limited, IO Biotech, Merck, PamGene International, Pfizer, Pierre Fabre, Regeneron, Replimune and Sol-Gel Technologies. L.v.B. has received Consulting/Scientific Advisory Board honoraria from Merck and Servier. M.S. has received research support from Amgen, BMS/Celgene, Miltenyi, Molecular Partners, Roche and Seagen. M.S. has received an educational grant by BMS/Celgene, Gilead/Kite, Johnson & Johnson, Novartis, Roche and Takeda. M.S. has received honoraria from AbbVie, Crossbow, Debiopharm, Gilead/Kite, Interuis, Johnson & Johnson, Molecular Partners, Novartis and Otsuka. M.S. has received travel support from AbbVie, Amgen, Molecular Partners, Pierre Fabre and Roche. S.K. has received honoraria from Plectonic, Regeneron, TCR2 Inc., Miltenyi, Galapagos, Cymab, Novartis, BMS and GSK. S. K. is an inventor of several patents in the field of immuno-oncology. S. K. received license fees from TCR2 Inc. and Carina Biotech. S.K. received research support from TCR2 Inc., Tabby Therapeutics, Catalym GmbH, Plectonic GmbH and Arcus Bioscience.

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