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# The role of moonlighting proteins in neurogenesis

Florencia Merino[1,2,3] and Magdalena Götz[1,2,4]

The complexity of the mammalian brain must arise from a comparably small number of genes. Proteins with moonlighting functions, i.e. entirely different functions in different compartments or cell types, contribute to multiply functional diversity. Here we review examples of such proteins with moonlighting functions during neurogenesis and in neuronal maturation. These range from cytoskeletal proteins acting as transcriptional regulators or synaptic proteins or exon junction proteins binding to and regulating the cytoskeleton to immediate early gene transcription factors regulating lipid metabolism in the endoplasmic reticulum. We further discuss how proteins with such moonlighting functions contribute to the heterogeneity of organelles shaping cell-type diversity in the brain.

**Addresses**
[1] Division of Physiological Genomics, Biomedical Center, Ludwig-Maximilians-Universität, Planegg-Martinsried, Germany
[2] Institute of Stem Cell Research, Helmholtz Center Munich, Planegg-Martinsried, Germany
[3] Graduate School of Systemic Neuroscience, Ludwig-Maximilians-Universität, Planegg-Martinsried, Germany
[4] SYNERGY, Excellence Cluster of Systems Neurology, Ludwig-Maximilians-Universität, Planegg-Martinsried, Germany

Corresponding author: Götz, Magdalena (magdalena.goetz@helmholtz-munich.de)

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## Introduction

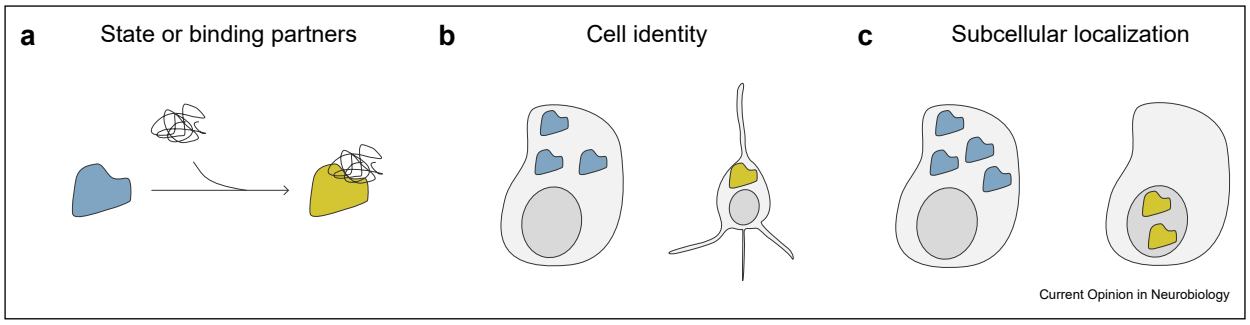
The brain is the organ with the most stunning heterogeneity of cell types, prompting the fascinating question of how this diversity is generated during development. Intriguingly, humans and the nematode *C. elegans* possess a similar number of protein-coding genes (approximately 20,000) [1,2], yet differ profoundly in nervous system complexity. Alternative splicing, post-translational processing as well as gene duplications and rearrangements are some mechanisms by which a single gene can produce multiple proteins with distinct functions. But even proteins with identical amino acid sequences i.e. a single polypeptide chain can have more than one function. This is known as protein moonlighting [3]. Moonlighting proteins act through distinct molecular mechanisms to produce at least two distinct functions that depend on their state i.e. oligomeric state, posttranslation modification or binding partner (Figure 1a), the cell type (Figure 1b) and/or their subcellular localization [3,4] (Figure 1c). Importantly, this does not mean that proteins that can operate in different locations or use different substrates are defined as moonlighting proteins, but in a strict definition, a protein would only be moonlighting if the different locations or interactions result in distinct biological mechanisms and/or functions [5].

As other gene-sharing mechanisms, protein moonlighting increases the functional diversity of the genome. It has been proposed as an energy-efficient way of doing so, being more cost-effective to perform two functions with a single protein than to produce two separate proteins [4]. Additionally, the repurposing of an already translated protein for a different function in response to physiological demands can save time by eliminating the need for new transcription and translation. Such efficiency may contribute to its evolutionary advantages. Notably, higher functional genome diversity is positively associated with organismal complexity [6], with gene-sharing events becoming more prevalent over the course of evolution [7]. Mechanisms regulating the functional diversity of proteins contribute to the development and specialization of organs, with the brain standing out for its unique cellular diversity [8] and its developmentally dynamic alternative splicing [9]. In this review, we discuss how moonlighting proteins influence neural development giving specific examples, while also highlighting their broader significance in cellular crosstalk and cell-type diversity.

### Moonlighting proteins in neurogenesis

In the developing mammalian cerebral cortex, neural stem cells (NSCs) reside at the ventricular zone, where they maintain apical-basal polarity and form adherens junctions (AJs) at their apical domain [10]. These junctions are crucial for maintaining the structural integrity of the ventricular surface and regulating neurogenesis [11]. A very well-known regulator of this process is also one of the most studied cases of

**Figure 1**



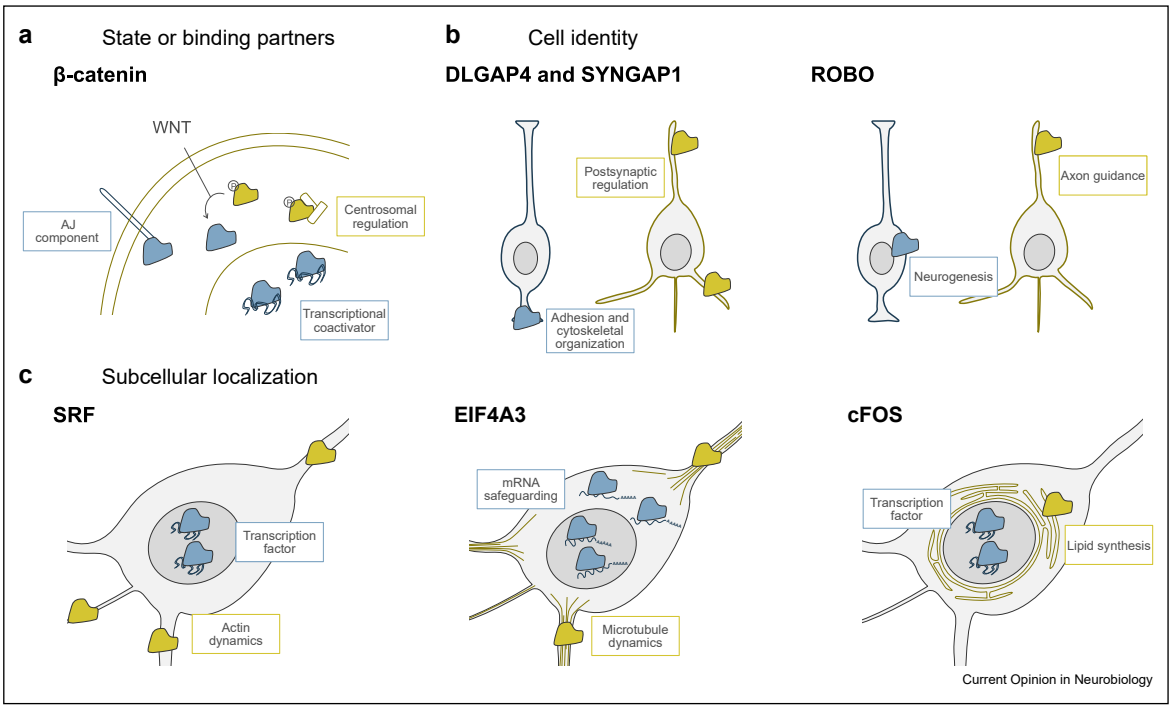

**Moonlighting protein's functional regulations.**
The function of moonlighting proteins may depend on their state and/or association with other compounds **(a)**, cell identity **(b)** and/or their subcellular localization **(c)**. Different colors represent different functions carried out by the same protein.

multifunctional proteins in neurogenesis: β-catenin [12]. As part of the canonical WNT signaling pathway, upon its activation, β-catenin is de-phosphorylated and released from the 'destruction complex' (composed of the scaffolding protein Axin, the regulator protein APC, and the kinases GSK3 and CK1) [12]. This results in its accumulation in the cytosol and further translocation into the nucleus where it acts as a transcriptional coactivator [12] (Figure 2a). In addition, β-catenin is a well-studied regulator of cell adhesion as component of AJs [13] (Figure 2a). Non-phosphorylated β-catenin binds to cadherins and α-catenin, coupling the adhesion molecules with the actin cytoskeleton [14]. The cadherin-β-catenin association is essential for AJs assembly, with its impairment resulting in NSCs detachment and complete disorganization of the neural tissue [15]. Interestingly, cadherin-β-catenin coupling prevents the association of non-phosphorylated β-catenin with the destruction complex, allowing the protein to escape its degradation [16]. This is possible as non-phosphorylated β-catenin associates with cadherins at the endoplasmic reticulum (ER), after which they translocate to the cell membrane [17]. Phosphorylated β-catenin has also been found to be enriched at the centrosome (Figure 2a), where it is presumably less susceptible to degradation [18]. By engineering a non-phosphorylatable version of β-catenin, thus a loss-of-function of phosphorylated β-catenin, defects in centrosome maintenance, microtubule dynamics, and spindle orientation of NSCs were identified, consistent with a role at the centrosome regulating cell polarity [18]. Overall, this well-studied case is an example of how a protein, in both its phosphorylated and unphosphorylated form, can contribute to the integration and regulation of diverse signaling pathways and biological processes within the cell.

More recently, proteins that have been traditionally categorized as 'synaptic', such as the proteins DLGAP4 and SYNGAP1 present at the postsynaptic density of excitatory synapses, have also been found as regulators of NSC's polarity, enriched in their apical domain in the developing cortex [19,20] (Figure 2b). This novel localization is of particular interest given their association with neurodevelopmental disorders [19,20]**.** Using loss and gain of function mouse models, DLGAP4 was found to regulate AJs and the actin cytoskeleton at the ventricular surface of the brain, affecting the cleavage plane of NSCs and thereby reducing neurogenesis and impairing neuronal migration [19]. These processes are affected when introducing DLGAP4 mutation found in patients, suggesting that this novel, non-synaptic role of DLGAP4 may contribute to the disease phenotype [19]. Notably, SYNGAP1 has also been found to regulate cytoskeletal remodeling in the apical domain of NSCs, affecting the angle of division and their basal process [20]. Using cortical organoids derived from patients induced pluripotent stem cells, they found that SYNGAP1 haploinsufficiency leads to premature neurogenesis together with alterations in neuronal positioning in the cortical-like structures [20]. These examples demonstrate how unbiased studies across different cell types and developmental stages can reveal the impact of proteins typically associated with other specific functions on early brain development, suggesting their involvement in neurodevelopmental disorders through alternative mechanisms.

Among cell-type dependent moonlighting proteins, Robo receptors also play diverse roles in cortical development. These receptors are best known for their classical role in post-mitotic neurons, where they regulate axon guidance by cytoskeletal rearrangements [21–24]. In the presence of the secreted protein Slit, Robo transduces intracellular signaling cascades which result in the regulation of the Rho family small GTPases impacting actin rearrangements [25]. In addition, Slit-Robo interaction leads to the association of the

**Figure 2**




**Moonlighting proteins in neurogenesis and neuronal maturation.**
Examples of moonlighting proteins in neurogenesis and neuronal maturation. Their functions can be regulated by their state and/or binding partners as the case of β-catenin regulated by phosphorylation **(a)**, cell identity as for DLGAP4, SYNGAP1, and ROBO receptors having different functions in neural stem cells and neurons **(b)**, and/or their subcellular localization **(c)**. The latter includes SRF, regulating transcription and the actin cytoskeleton *in situ*; MAP1B, regulating both microtubule's stability and gene regulation in neural stem cells; EIF4A3, safeguarding mRNA as part of the exon junction complex and regulating microtubule's polymerization and stability in neurons; and cFOS, which in addition to its most studied role as an immediate early gene, it can also activate lipid synthesis in the endoplasmic reticulum of neurons. Different colors represent different functions carried out by the specified protein.

receptor with N-cadherin and the kinase Abelson (Abl), which results in the phosphorylation of β-catenin, weakening AJs [24]. Both the regulation of the cytoskeleton and cell adhesion result in the repulsion of the growing axon in the presence of Slit proteins [24]. In agreement, transgenic mice lacking both Robo1 and Robo2 (the two most expressed Robo family members in the developing forebrain) display axon guidance defects, affecting the development of corticofugal, thalamocortical, and corticocortical connections [21]. However, in addition to axonal growth abnormalities, researchers observed that the embryonic brains of the double knockout mice were significantly smaller compared with wild-type controls [26]. This phenotype, combined with the expression of Robo in the germinal zones of the developing cortex, prompted researchers to explore their function in neural stem and progenitor cells. Interestingly, Robo receptors were found to promote the self-renewal of NSCs by acting synergically with the Notch signaling pathway, a well-established regulator of NSC maintenance [26] (Figure 2b). Furthermore, Robo receptors regulate neurogenesis mode, with high Robo1 and Robo2 levels promoting direct neurogenesis i.e. direct neuronal production from NSCs, bypassing intermediate progenitors [27]. Interestingly, this effect is mediated by Delta-like 1 (Dll1), a canonical ligand of Notch1, which subsequently results in the upregulation of the Notch-associated protein Jagged [27]. While these two mechanisms of Robo receptors can also impact other cell types [24], they illustrate how a multifunctional protein can regulate the different aspects of cortical development—such as neurogenesis and neuronal connectivity —by their function in alternative cellular pathways.

As seen with β-catenin, the subcellular localization of moonlighting proteins contributes to their distinct functions. Indeed, this is also the case for serum response factor (SRF), a transcription factor known for integrating cellular conditions (such as serum and growth factor stimulation or actin dynamics changes) with gene expression. Different yet interconnected pathways regulate SRF transcriptional activity [28], which result in its diverse roles in neurodevelopment ranging from NSC fate [29] to neuronal polarization [30] and plasticity [31]. One of such pathways involves the cytosolic to nuclear shuttling of the SRF cofactors and actin-binding proteins myocardin-related

transcription factors (MRTFs) upon actin polymerization [32]. Once in the nucleus, MRTFs associate with SRF to activate the expression of actin cytoskeleton genes such as actin isoforms and actin-binding proteins [32]. Interestingly, beyond its nuclear functions, SRF has also been found to directly regulate the actin cytoskeleton in the cytosol, particularly after axonal injury. Following injury, SRF undergoes a relocalization from the nucleus to the cytoplasm, where it accumulates in neurites and growth cones [33] (Figure 2c). Expressing an engineered SRF lacking its nuclear localization signal highlights the function of cytosolic SRF in promoting nerve regeneration, regulating neurite growth and branching [33]. Interestingly, cytoplasmic SRF has a negligible effect on the expression of its canonical target genes, yet it modulates the actin cytoskeleton increasing F-actin abundance, potentially through the actin-severing protein cofilin [33]. Thus, SRF can positively regulate actin polymerization through two distinct mechanisms. While the extent to which these mechanisms cooperate remains to be explored, they may represent responses that operate on different time scales, contributing to the modulation of the cytoskeleton in both rapid yet limited (involving protein modulation) and a broader (involving new protein production) manner.

## Moonlighting functions contributing to heterogeneity of organelles

Moonlighting proteins normally active in splicing in the nucleus have recently been identified in large numbers also at the centrosome [34]. This is particularly striking as indeed the top category of centrosomal proteins differing between cells, even closely related such as NSCs and neurons, are RNA-binding proteins with many of them involved in splicing [34]. These were e.g. exon junction proteins discussed below, or the PRPF6 complex, a ubiquitous protein complex normally localized in splicing speckles [34]. Importantly, this novel centrosome interactome allowed to prioritize gene mutations found in neurodevelopmental diseases, such as periventricular heterotopia (PH), where some cells remain aberrantly at the ventricle. Having found a mutation of the ubiquitous PRPF6 protein in PH patients prompted the question how a ubiquitous protein when mutated brings about this brain-specific phenotype only. Here the moonlighting function at the centrosome is important, because the PRPF6 mutation not only could replicate the hallmarks of PH in the mouse but also suggested that it brings some of its splicing targets to the centrosome. A critical target for the PH phenotype with some cells remaining at the ventricle is the kinase SADA encoded by the gene *Brsk2*. This is lacking a critical exon when PRPF6 is mutated, and reintroduction of this critical exon rescues the PH phenotype. Importantly, SADA phosphorylates MAPs, and MT stability and regulation is critical for delamination of cells from the ventricle [35]. Thus, PRPF6 is involved in regulating splicing in the nucleus and in regulating MT stability by *Brsk2* (and probably others) RNA localization at the centrosome.

As mentioned above, many other proteins involved in splicing were found at the centrosome, such as the exon junction proteins, including EIF4A3. EIF4A3's function at the centrosome has not yet been elucidated in detail, but its moonlighting function at the cytoskeleton, which can also be considered as an organelle [36], has been. The canonical role of EIF4A3 as a core component of the exon junction complex (EJC) is to safeguard mRNA throughout its life cycle [37]. EIF4A3's role has mainly been studied in NSCs, partially because of its high abundance in this cell type and the microcephaly phenotype observed in the cortical conditional knockout mice [38,39], where it inhibits neurogenesis through its EJC and RNA association [38]. However, recent work showed that EIF4A3 also binds to microtubules [40] (Figure 2c). EIF4A3 binding to microtubules is independent of the EJC and RNA, and it regulates their polymerization and stability, ultimately affecting neuronal polarization and axonal growth [40]. This function may also explain its presence at the centrosome, even though it was still present at the centrosome when MTs were depolymerized by Nocodazole [34]. Interestingly, a competition between MT and EJC binding was observed [40], providing a molecular link between both subcellular processes.

Conversely, we recently discovered a moonlighting role of an MT-associated protein (MAP1B) in the nucleus. MAP1Bs canonical role is regulating MT and actin cytoskeleton in neurons, where its levels are highest [41–44]. However, in NSCs it is also in the nucleus, where we have recently identified its role in regulating transcription and thereby influencing NSC fate (Merino, F. & Götz, M., unpublished). Interestingly, MAP1B promotes neurogenesis and differentiation in the cytoplasm, demonstrating how a protein not only exerts different functions in different compartments, but also can have opposite effects depending on its subcellular localization. Strikingly, the novel function of MAP1B seems also involved in the disease phenotype as many PH patients with MAP1B mutations have been identified [45–48]. Thus, subcellular localization can define different functions affecting brain development.

The examples above illustrate how moonlighting proteins affect organelle composition and function during neurogenesis. We next move to a few examples of moonlighting proteins at later stages, in neuronal maturation.

## Moonlighting proteins in neuronal maturation

As the last step of this process, neurons undergo maturation, which includes becoming electrically

active, i.e. being able to receive and transmit electrical signals, along with its associated molecular and morphological changes [49]. In this context, a very well-studied group of regulators are immediate early genes (IEG) such as cFOS, which represent the first wave of genes whose expression levels are regulated by neuronal activity [50]. Interestingly, only recently, researchers found that the IEG cFOS also acts in the ER of neurons (Figure 2c), where it activates lipid synthesis [51]. Using truncated cFOS isoforms to separate the two functions driven by cFOS, the authors have shown that the novel function of cFOS as a lipid synthesis activator is fundamental for proper cortical development [51]. While this IEG has a moonlighting function in metabolism, a centromere protein (CENP-A) has recently been identified to also have IEG functions in neurons (A. Stankovic & S. Jessberger, unpublished data). Knock-down of CENP-A led to impaired expression of other IEGs such as cFOS and ARC, ultimately resulting in learning deficits associated with hippocampal function in mice. Thus, a centromere protein has a moonlighting function as IEG, and IEGs can exert other moonlighting functions. Clearly, also in neural development, proteins are multipurpose and multiply their functions in different compartments, with distinct interactors and in different cell-type contexts. Thus, further moonlighting functions will likely be discovered and help us understand development, cell diversification, and disease.

## Outlook

Generally, increasing the numbers and functions of moonlighting proteins open a fascinating avenue for understanding cellular and developmental complexity. Proteins such as PRPF6 and EIF4A3, which were initially thought of functioning exclusively in RNA metabolism, are now identified as players at the centrosome and cytoskeleton [34,40] or IEGs act at the ER-regulating metabolism [38]. This reclassification reflects a broader shift in our understanding of protein functionality, where single genes were historically studied associated with a unique biological function [4]. However, it is likely that multifunctional proteins would not be exceptions, but rather the rule the more we learn about proteins in different contexts. This prompts the hypothesis that moonlighting functions not only add another level of cellular complexity, but that this is necessary to generate and differentiate the repertoire of diverse cell types present in complex organisms. Unbiased subcellular proteomics [34,52] and identification of proteome trafficking [53] represent great opportunities to unravel the extent of proteins shuttling between compartments unbiasedly within different cell types, that can now be generated in large numbers from many species, including humans. This allows not only an unbiased view of multiple and distinct protein localizations in the same or different cell types, but also to explore this phenomenon in different species casting an eye on this in evolution.

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## Declaration of competing interest

The authors declare no conflict of interest.

## Data availability

No data was used for the research described in the article.

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