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1 Title page

2 **Pathways involved in remyelination after cerebral ischemia**

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Abstract

Brain ischemia, also known as ischemic stroke, occurs when there is a lack of blood supply into the brain. When an ischemic insult appears, both neurons and glial cells can react in several ways that will determine the severity and prognosis. This high heterogeneity of responses has been a major obstacle in developing effective treatments or preventive methods for stroke. Although white matter pathophysiology has not been deeply assessed in stroke, its remodelling can greatly influence the clinical outcome and the disability degree. Oligodendrocytes, the unique cell type implied in CNS myelination, are sensible to ischemic damage. Loss of myelin sheaths can compromise axon survival, so new Oligodendrocyte Precursor Cells are required to restore the brain function. Stroke can, therefore, enhance oligodendrogenesis to regenerate those new oligodendrocytes that will ensheath the damaged axons. Given that myelination is a highly complex process that requires coordination of multiple pathways such as Sonic Hedgehog, RTKs or Wnt/ β -catenin, we will analyse new research highlighting their importance after brain ischemia. In addition, oligodendrocytes are not isolated cells inside the brain, but rather form part of a dynamic environment of interactions between neurons and glial cells. For this reason, we will put some context into how microglia and astrocytes react against stroke and influence oligodendrogenesis to highlight the relevance of remyelination in the ischemic brain. This will help to guide future studies to develop treatments focused on potentiating the ability of the brain to repair damage.

Keywords: Cerebral ischemia, Stroke, Oligodendrocyte, Oligodendrocyte Precursor Cell, Remyelination

1. Introduction

The term stroke refers to a phenomenon in which abnormal flow of blood into the brain causes cell death. According to World Health Organization, stroke is a leading cause of long-term disability and mortality after ischaemic heart disease, with more than 15 million people suffering an episode of stroke annually. Thus, 5 million people have been estimated to die and other 5 million are left permanently disabled worldwide. The probabilities of suffering a stroke are greatly influenced (~ 90 %) by risks attributed to modifiable factors such as high blood pressure, obesity or smoking related to air pollution [1,2]. Although the causes of brain ischemia are heterogenous and not fully understood (30-40% are considered cryptogenic), the restriction of blood supply produces a lack of oxygen and nutrients needed for cellular metabolism, as well as accumulation of waste products [3,4]. If this scenario is sustained over a period of time, the clinical outcome will worsen due to blood-brain barrier (BBB) dysfunction, vasogenic brain edema and neuronal death [5,6].

Brain ischemia has attracted the attention of multiple research groups who have put efforts to elucidate what cellular and molecular processes are taking place in the ischemic brain and how to stop it or prevent it. To accomplish this challenge, scientists have developed numerous animal models, each with its own strengths and limitations to reproduce the heterogeneous nature of stroke. From all of them, middle cerebral artery occlusion (MCAO) in rodents has been widely studied to produce focal cerebral ischemia [7], as it mimics a localized occlusion of a cerebral artery either by an embolus or local thrombosis [8,9]. Using both human samples and MCAO models, scientists have been able to describe two areas surrounding the vessel occlusion: the ischemic core and the penumbra. The ischemic core covers the area directly affected by the occlusion and it is where neuronal death mostly occurs. It is usually located in the caudate/putamen and the parietal cortex and its size is proportional to the occlusion time. Second, the penumbra surrounds the ischemic core, where neuronal damage of varying degree can be found but most importantly, where there is potential for functional recovery (Figure 1).

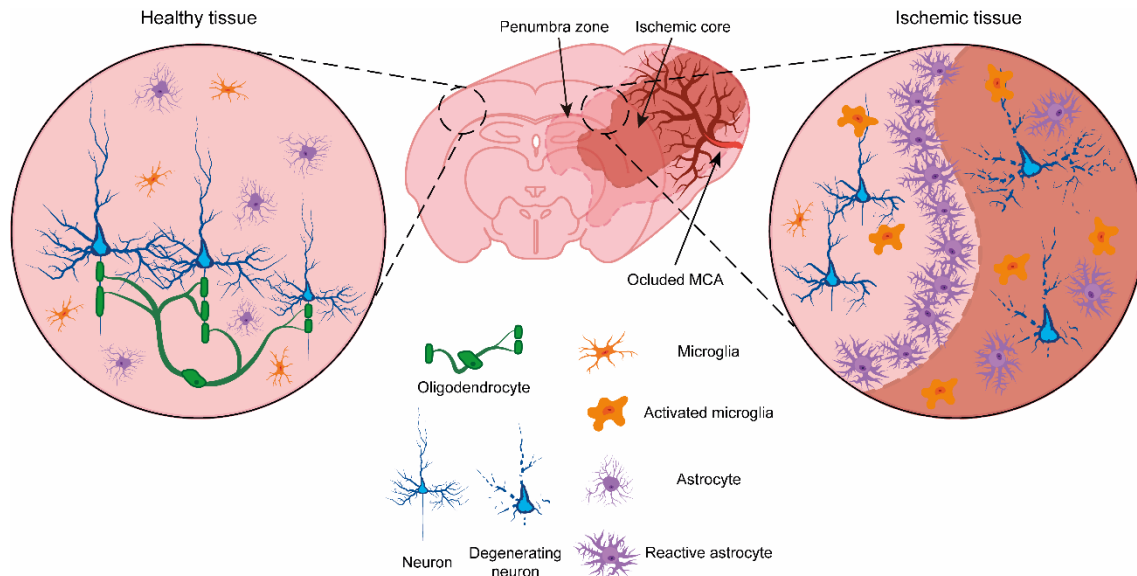


Figure 1. Schematic representation of MCAO brain ischemia model. In a physiological situation (left), healthy neurons (blue) are covered by oligodendrocytes (green). Astrocytes (violet) and microglia (orange) have resting morphologies. When middle cerebral artery (MCA) is occluded (right), we can distinguish two zones: the ischemic core, where we can find degenerating neurons, and the penumbra zone, with slightly damaged neurons. Oligodendrocytes are affected by the ischemic insult and myelin is lost. Activated microglia adopt ameboid morphologies around neurons and modulate the inflammatory response. Reactive astrocytes accumulate around the ischemic core to form the glial scar and phagocyte cellular debris to prevent further extension of the damage.

From a cellular point of view, neurons are energetically demanding cells that require vast amounts of oxygen and nutrients to work properly. The brain uses 20% of all oxygen consumed by the body although it only constitutes 2 % of its mass. Without a constant supply of oxygen and energy, like in stroke, neuronal function is compromised [10]. When an artery is obstructed, oxygen and nutrient supplies are largely blocked, which induces a sequence of harmful processes known as the “ischemic cascade”[11]. The cascade is triggered mainly by the lack of ATP due to the oxygen deficit. Without energy, neurons in the ischemic core are unable to maintain a proper transmembrane gradient, which in turn induces depolarization. Released glutamate cannot be

83 taken up by either neurons or astrocytes, leading to excessive activation of glutamate receptors
84 like N-Methyl-D-Aspartate Receptor (NMDAR) that allow the entrance of Ca^{2+} [12], which
85 trigger more glutamate release, and the cycle repeats. Excess calcium enhances the generation of
86 reactive oxygen species (ROS) and triggers apoptotic and necrotic events [13]. Neurons in the
87 ischemic core die from swelling and disruption of their plasma membrane, which derives in
88 neuroinflammation [14,15]. In the penumbra, cells are still metabolically active even though they
89 receive no electric signals from the ischemic core. Since they receive deleterious signals from the
90 dead neurons of the ischemic core, they will die unless they get rescued [12,16]. One essential
91 component that contributes to neuronal survival is myelin [17,18], which is produced by
92 Oligodendrocytes (OLs) in the Central Nervous System (CNS) [19–22]. Myelin sheaths will
93 speed up action potential transmission, reduce neuronal energetic requirements and provide
94 metabolic support to neurons. [23–27]. In fact, loss of myelin is considered an important factor
95 that worsens the prognosis of ischemic stroke and other pathologies [28–30].

96 In stroke, both OLs and Oligodendrocyte Progenitor Cells (OPCs) are also affected [31–34].
97 During the ischemic cascade, glutamate receptors expressed by OLs are overactivated, leading to
98 excitotoxicity [35,36]. In addition, inflammatory cytokines released by activated microglia and
99 macrophages contribute to OL death: $\text{IFN-}\gamma$ leads to OL demyelination and apoptosis [37] while
100 Tumor Necrosis Factor- α (TNF- α) also inhibits the proliferation and differentiation of OPCs [38–
101 40]. In addition, rodent models of MCAO show lower staining against myelin basic protein
102 (MBP) and a decrease in the number of OLs [41,42]. After stroke, brain repair mechanisms will
103 try to restore the lost connections. Sprouting axons must be adequately isolated by new myelin
104 sheaths, which cannot be formed by injured OLs. In the adult brain, OPC niches can be found in
105 the corpus callosum, the striatum and the cortex [43], all of them derived from Neural Progenitor
106 Cells (NPCs) found in the sub-ventricular zone (SVZ) of the lateral ventricles [44–47]. Recent
107 studies have described that OPCs can be generated and mobilized in response to ischemic insults
108 [48]. In fact, brain ischemia induces oligodendrogenesis in order to create new mature OLs from

OPCs [49]. Preclinical studies show that enhancement of endogenous oligodendrogenesis in ischemic brain reduces neurological deficits and improves general outcome [50,51].

In this review, we will focus on the repercussions of stroke in myelin and how remyelination could be achieved by promoting different signaling pathways. In addition, we will summarize the role of each glial cell after ischemic stroke to modulate remyelination.

2. Pathways involved in myelination: Sonic Hedgehog, Receptor-Tyrosine Kinases (RTKs) and Wnt pathway.

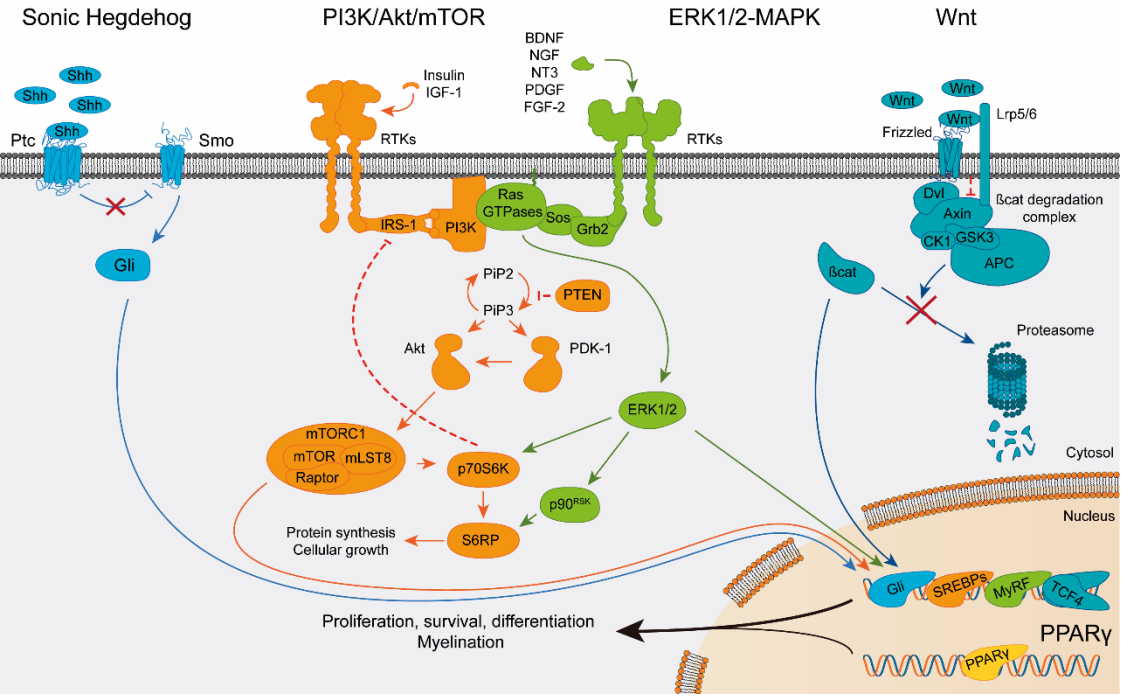


Figure 2. Schematic diagram of Shh, PI3K/Akt/mTOR, ERK1/2-MAPK, Wnt/β-catenin and PPARγ signaling pathways. Key elements of each pathway are shown when each route is active.

Arrowheads indicate positive interactions while bars show inhibitory signals. Shh: Sonic Hedgehog, Ptc: Patched, Smo: Smoothed, Gli: Glioma-associated oncogene family. BDNF: brain-derived neurotrophic factor, NGF: nerve growth factor, NT3: neurotrophin 3, RTKs: receptors tyrosine kinase, IRS-1: insulin receptor substrate 1, PI3K: phosphoinositide-3 kinase, PIP2: phosphatidylinositol (4,5)-biphosphate, PIP3: phosphatidylinositol (3,4,5)-triphosphate, PTEN: phosphatase and tensin homolog, PDK-1: 3-phosphoinositide-dependent protein kinase, Akt: protein kinase B, mTOR: mammalian target of rapamycin, mLST8: target of rapamycin complex subunit LST8, Raptor: regulatory associated protein of mTOR, p70S6K: Ribosomal

protein S6 kinase beta-1, S6RP: Ribosomal protein S6, SREBPs: Sterol regulatory element-binding proteins. PDGF: platelet-derived growth factor, FGF-2: fibroblast growth factor 2, Grb2: growth factor receptor-bound protein 2, Sos: son of sevenless, ERK1/2: extracellular signal-regulated kinases 1 and 2, p90RSK: p90 ribosomal S6 kinase, MyRF: Myelin Regulatory Factor. Lrp5/6: Lipoprotein receptor-related proteins 5/6, Dvl: disheveled, GSK3: glycogen synthase kinase 3, CK1: casein kinase 1, APC: adenomatous polyposis coli, β -cat: β -catenin, TCF4: transcription factor 4, PPAR γ : peroxisome proliferator-activated receptor γ .

2.1 Sonic Hedgehog

The Sonic Hedgehog (Shh) pathway was discovered more than 30 years ago and has been established as a regulator of OL and myelin production [52,53]. When the pathway is off, the 12-pass transmembrane protein Patched (Ptc) acts inhibiting Smoothened (Smo), a G-protein coupled receptor. Hedgehog proteins binding to Ptc suppress its inhibition over Smo, which transduces the signaling cascade via the transcription factors of the Glioma-associated oncogene (Gli) family [54]. Parallely, Smo can act in a Gli-independent manner, known as the “non-canonical” route [55] (Figure 2). Shh was discovered to be both sufficient and necessary for the expression of the Oligodendrocyte Transcription Factors 1 (Olig1) and 2 (Olig2), which are indeed markers of the OL lineage. Zebrafish lacking Smo exhibited an almost complete lack of OLs due to absence of Shh signaling [56,57]. Diverse demyelination models have shown Shh implication in myelin repair: Shh promoted proliferation and differentiation of OPCs [58] while Smo inhibition aggravated demyelinating phenotype [59]. In addition, it is worth noting that transient Gli1 transcription was observed in oligodendroglial cells during the step of OPC differentiation [58]. Regarding contribution of Shh in oligodendrogenesis after brain ischemia, stroke upregulated Shh in NPCs from the SVZ [60,61]. Administration of cerebrolysin, a mix of neurotrophic peptides that activate Shh, enhanced neurological outcome by increasing oligodendrogenesis. Furthermore, inhibition of Shh with cyclopamine abolished the effects of cerebrolysin, proving the importance of Shh in recovery after brain ischemia [62]. Still, not only the canonical Shh

pathway is important in myelin repair. Blockade of Gli1 in NPCs preferentially fated them towards oligodendroglial lineage in a context of high Shh signaling [63]. In addition, cuprizone-induced demyelination, recruited Gli1⁺ NSCs to the corpus callosum, where they were preferentially differentiated into OLs concomitantly with Gli1 downregulation [64]. In the same model, activation of Smo by microinjection of a Smo agonist into the corpus callosum increased cell proliferation and enhanced remyelination [54,64]. All the data above strongly suggest a role for Shh pathway in remyelination after ischemic stroke.

2.2 Receptor-tyrosine kinases (RTKs)

Many tyrosine kinase receptors (RTKs) have a role in the regulation of OPC differentiation, myelination and remyelination. They can be activated by a variety of growth factors, like Insulin/IGF-1, brain-derived neurotrophic factor (BDNF), platelet-derived growth factor (PDGF), fibroblast growth factor-2 (FGF-2) and neurotrophins. Upon stimulation, they can trigger activation of several signaling pathways, such as phosphatidyl inositol-3-phosphate kinase (PI3K) class I /Akt/ mechanistic target of rapamycin (mTOR) and Ras/Mitogen-Activated Protein Kinases (MAPK).

The PI3K/Akt/mTOR pathway is well described for its role in the regulation of OPC differentiation, myelination and remyelination [65,66]. PI3K/Akt/mTOR pathway starts at the cell surface, where a variety of growth factors like Insulin/IGF-1, brain-derived neurotrophic factor (BDNF) or neurotrophin 3 (NT3) bind tyrosine kinase receptors that activate PI3K-Class I. This lipid kinase catalyzes the conversion of phosphatidylinositol (4,5)-biphosphate (PIP₂) to generate phosphatidylinositol (3,4,5)-triphosphate (PIP₃). 3-phosphoinositide-dependent kinase 1 (PDK1) and Akt are then bound to the membrane and activated, allowing further transduction of the signal by the multiple effectors of Akt. In myelination, Akt principal target is mTORC1, which in turn mediates protein and lipid biosynthesis (Figure 2). Use of either constitutively active models of Akt or knockdowns of phosphatase and tension homolog (PTEN) lead to discover a pathological increase in myelin sheath thickness and myelin proteins levels [67,68]. Akt downstream effector, mTOR, is key for a proper myelin development as well [69,70]. Inhibition of mTOR with

rapamycin reduced the expression of myelin proteins and generated a phenotype of hypomyelination. These effects were mediated in part because mTOR is also a regulator of lipid biosynthesis via the sterol regulatory element-binding proteins (SREBPs) [71].

Another related pathway to RTKs is the Ras/MAPK pathway. As a general rule, RTK activation phosphorylate and stimulate proteins such as Grb2 and SOS 1/2. This RTK-Grb2-SOS activation stimulates GTP binding to Ras proteins, which trigger the MAPK/extracellular signal-related kinases 1 and 2 (Erk1/2) through the Raf-MEK complex [72]. It is important to remember that Ras has a direct interaction with PI3K class I, which make both pathways directly intermixed [73,74].

Erk1/2-MAPK signaling is crucial for oligodendroglial development, proliferation, survival, differentiation and myelination [65,75]. Once active, Erk1/2 are translocated to the nucleus to regulate the expression of the master transcriptional regulator of critical myelin genes MyRF (Figure 2) [76]. Lack of Erk1/2 resulted in significant hypomyelination, while overexpression of some proteins of the pathway derived in hypertrophic myelin sheaths and upregulated expression of myelin proteins [77]. Both pathways PI3K-Akt and Ras/MAPK exhibit similar phenotypes when altered because there is an active crosstalk between them through proteins like insulin receptor substrate 1 (IRS-1) or ribosomal protein S6 kinase beta-1 (p70S6K). For instance, p70S6K can inhibit IRS-1 as a negative feedback loop against overactivation [78,79]. On the other hand, relevant members of the Ras family in OLs are R-Ras1 and R-Ras2. Mice lacking R-Ras1/2 showed lower levels of Akt and ERK signaling together with an hypomyelinating phenotype and axonal degeneration [80,81]. PI3K/Akt/mTOR and Erk1/2-MAPK cooperation in myelination has been extensively studied [82], however few studies have showed their potential role after stroke. In a rat model of MCAO, phospho-Akt levels rise followed by an increase in phospho-ERK, but only after reperfusion [83]. In addition, use of Bisperoxovanadium (BpV), a PTEN inhibitor, increased phospho-Akt and phospho-ERK1/2 levels, which was associated with a neuroprotective effect [84]. Treatment with WIN55, 212-2, a cannabinoid, resulted in enhanced OPC proliferation and remyelination in ischemic lesions by activation of ERK1/2 [85]. Interestingly, an *in vitro*

study pointed out that following ischemic insult, Thymosin beta 4 can guide NPCs from the SVZ to differentiate towards the oligodendroglia lineage [86]. In addition, enhanced proliferation of NPCs from the SVZ was observed [87] together with increased OPC proliferation and OL differentiation after ischemia through MAPK dependent mechanisms [88].

2.3 *Wnt pathway*

The wingless integration site (Wnt) intracellular β -catenin signaling cascade is a negative regulator of OPC differentiation, myelination and remyelination [65,66]. Canonical Wnt pathway starts with the extracellular binding of Wnt proteins to Frizzled receptors at the cell surface. The activated receptor is then able to bind and repress the β -catenin degradation complex, formed by adenomatous polyposis coli (APC), Axin, glycogen synthase kinase 3B (GSK-3B) and casein kinase 1 (CK1). The activation of the Wnt complex allows β -catenin to stop being degraded and enter the nucleus to activate gene expression by interacting with intranuclear T-cell factors/lymphoid enhancers factors (TCF/LEF) (Figure 2) [89]. The first studies that connected myelination with this pathway were performed in mice using dominant-active forms of β -catenin [90,91]. These mice showed a severe hypomyelination phenotype, displaying lower myelin protein levels, a decrease in myelin sheath thickness and lower numbers of mature OLs. Another study found increased levels of OPCs after addition of Wnt3a, which corroborated the inhibitory role of this pathway on myelination [92]. In addition to the Wnt canonical signaling, non-canonical pathways also exist: tissue inhibitor of metalloproteinase (TIMP)-1 is both a metalloproteinase inhibitor and a trophic factor that enhances myelination and remyelination through Akt activation, which directly promotes β -catenin signaling in OPCs [93]. However, role of Wnt in ischemic OLs has not been exhaustively studied. Some studies point out that Wnt signals released from OPCs may be important to protect and restore the blood-brain barrier after ischemic insults [94] while others suggested that oligodendroglia stimulates angiogenesis by releasing vascular-endothelial growth factor (VEGF) in a Wnt-independent manner [95].

Downstream the pathway, early studies suggested that Transcription Factor 7-like 2 (TCF7L2, also known as TCF4) expression was correlated with immature OLs [90]. However, later on was

described that a proper balance of expression between TCF712, β -catenin and other members of the pathway is essential to regulate OL lineage development [66,96–98]. Indeed, TCF712 may have additional roles independent of β -catenin signaling: new studies have pointed out that TCF712 expression was upregulated in a specific point of OL maturation, just after OLs became mature [99]. Supporting these observations, two more research groups later stated that TCF712 binds different partners depending on the developmental stage. In an immature state, TCF712 can be found bound to β -catenin to repress differentiation. However, upon differentiation signals, TCF712 switches partners with Kaiso (also known as ZBTB33), a corepressor that facilitates repression of differentiation inhibitors. In addition, a recent study described that TCF712 directly binds to a regulatory region of BMP4 to inhibit its expression, as BMPs are negative regulators of OL differentiation [100,101]. In later phases, TCF712 associates with Sox10 to accomplish a successful maturation and remains active in fully mature OLs, although at lower levels [98,102].

3. Additional key elements in oligodendrogenesis

Apart from the traditional signaling pathways involved in OL differentiation and myelination, additional elements have been found to participate in OL proliferation and maturation after brain injury. Among them, Peroxisome proliferator-activated receptor γ (PPAR γ) or microRNAs (miRNAs) may be an interesting target for future therapies.

PPAR γ is a transcription factor that regulates the expression of a wide variety of genes, many of them with high relevance in stroke [31]. If brain injury occurs, PPAR γ is a master gatekeeper of cytoprotective responses [103]. Mice lacking PPAR γ exhibited greater brain damage and oxidative stress after MCAO [104], which was recovered by administration of PPAR γ agonists prior to or after stroke [31,105]. Using these kinds of agonists less loss of white matter integrity was reported after MCAO [105,106]. Although this effect was partly due to enhanced microglial M2 polarization [105], PPAR γ activation in NSCs can guide them towards oligodendroglial differentiation [107,108] and contribute to OPC differentiation in both developmental [109] and post-injury myelination [105] (Figure 2). It is thought that PPAR γ beneficial effects may be due to its importance in lipid metabolism, reduction of oxidative stress vulnerability and enhancement

of mitochondrial function during OL process formation [109–111]. However, negative effects of PPAR γ agonists in OPCs have also been described depending on the context of OPC stage [31] and need to be further addressed.

Other key elements in OL differentiation are microRNAs (miRNAs). miRNAs are small non-coding RNA molecules of approximately 20 nucleotides long. Their function is to suppress protein translation by binding to the 3'-untranslated region of mRNAs in a specific manner. Growing evidence indicates that miRNAs are important for a proper CNS development, with roles in neuronal and glial differentiation, synaptic plasticity and general homeostasis [112]. First reports linking miRNAs to OLs came from experiments where Dicer, an essential element for miRNA biogenesis, was conditionally ablated in Olig2⁺ or in proteolipid protein (PLP)⁺ lineage cells [113–115]. In both cases, Dicer suppression led to a reduction in the myelination degree. Studies on miRNA expression profiles revealed that miR-219 and miR-338 promoted OL differentiation by repressing genes such as PDGFR α , Sox6, Zfp238, FoxJ3 and Hes5. However, miRNAs may have dual roles in regulating OL differentiation. Some miRNAs, like miR-145-5p, prevent OPC differentiation by repressing the myelin regulator MyRF while at the same time enhance OPC proliferation [116]. In the context of cerebral ischemia, miRNAs such as miR17-92, miR-146a, miR-9 or miR-200b, may play a role in OLs fate. Repression of miR17-92 cluster, a group of seven miRNAs, produced decreased proliferation of progenitor cells within the SVZ after stroke, while upregulation of this cluster had the opposite effect [61]. Indeed, it is worth noting that miR17-92 effects may be mediated by crosstalk with the Shh pathway [61]. In the same way, *in situ* hybridization experiments reported that miR-146a was considerably upregulated in the SVZ and corpus callosum of MCAO rat models. When miR146-a was overexpressed in primary cultured NPCs or OPCs, the result was an increased generation of O4⁺ OPCs or enhanced expression of myelin proteins, respectively [117]. This data strongly suggested that miR-146a plays an active role in stroke-induced oligodendrogenesis. On the other hand, miR-9 and miR-200b were considerably downregulated in white matter after ischemic injury, but their overexpression suppressed OPC differentiation [118]. Another study later reported that the

mentioned effects of Thymosin beta 4 on promoting oligodendrogenesis after MCAO were partially mediated by upregulation of miR-200b levels [119]. So, further studies need to be conducted in order to fully understand the potential that miRNAs may have as a therapeutic approach after stroke.

4. Role of Microglia and Astrocytes in cerebral ischemia

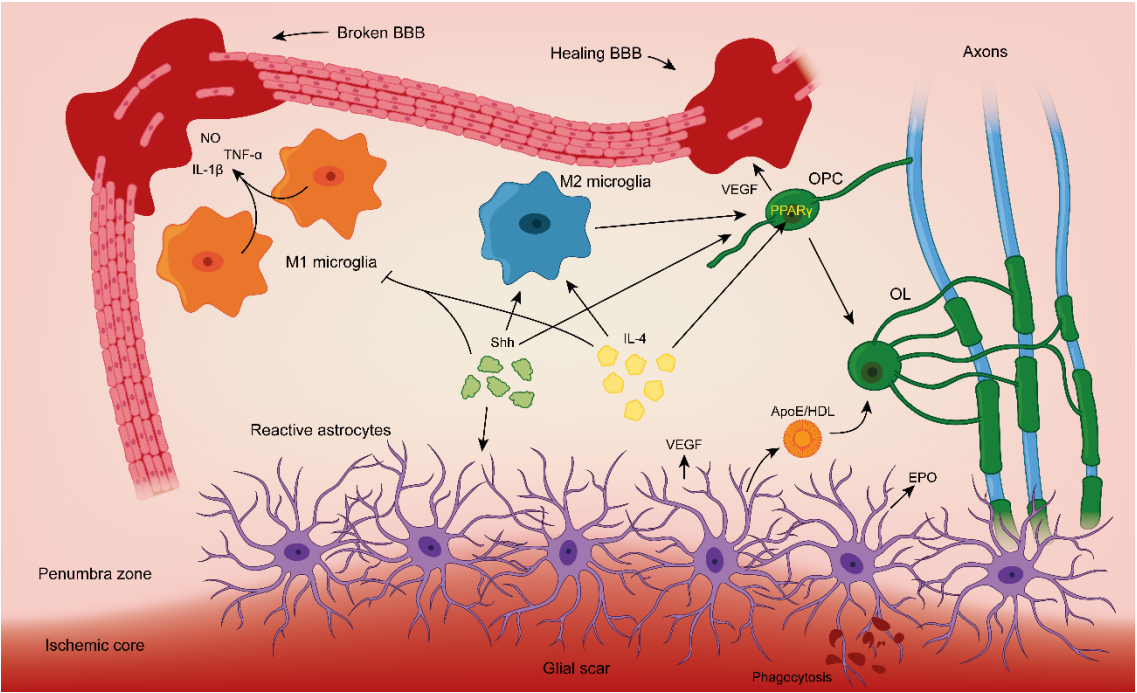


Figure 3. Schematic illustration of novel intercellular interactions in response to brain ischemia. Upon ischemic damage, a variety of signals is released to the medium. M1 microglia releases pro-inflammatory signals like nitric oxide (NO), tumoral necrosis factor α (TNF- α) or interleukin-1 β (IL-1 β) and disrupt the blood-brain barrier (BBB). These effects are mediated by NF- κ B. M2 microglia promotes repair mechanisms and Oligodendrocyte Precursor Cell (OPC) proliferation. OPCs release vascular endothelial growth factor (VEGF) to promote angiogenesis and repair the BBB. In addition, they will differentiate into mature Oligodendrocytes (OL) to ensheath damaged axons. Reactive astrocytes participate in the process by generating the glial scar to confine the ischemic core. They also provide OLs with cholesterol via Apolipoprotein E (ApoE)/ High-density lipoproteins (HDL) for myelin biogenesis and release regulatory factors like VEGF and erythropoietin (EPO). Sonic hedgehog (Shh) signals modulate glial scar

formation, direct microglia towards M2 phenotype and promoting OPC proliferation. Interleukin-4 (IL-4) also guide M2 differentiation and OPC proliferation via PPAR γ .

Understanding intracellular pathways inside oligodendroglial cells is important to know what mechanisms drive OL regeneration and maturation after stroke, but OLs are not isolated cells in the brain. Instead, there are a lot of extracellular interactions between healthy and damaged glial cells and neurons that modulate not only oligodendrogenesis but how the brain will recover from the ischemic insult.

When the ischemic cascade, or any brain injury, takes place, astrocytes and microglia activate and react triggering a stereotypic mechanism known as *reactive gliosis* [120,121]. Activated microglia and reactive astrocytes accumulate around the ischemic core, mainly in the penumbra zone. This process is followed by the release of chemokines and cytokines to regulate the inflammatory process [122]. Depending on the extent and duration of the ischemic insult, the array of secreted molecules can exacerbate the damage or as emerging studies are showing, try to repair the neuronal function [15]. Indeed, there are situations in which, if the ischemic insult is mild enough, the brain acquires a state of tolerance against further ischemic damage, mainly mediated by astrocytic and microglial adaptations [123]. These findings bring new questions about the role of glial cells within the brain and open the window for new therapies that could be focused on potentiating this self-protection phenomenon.

4.1 Microglia

Microglia are considered the immune cells of the nervous system [124] because of their ability to react to various insults, such as ischemic stroke. After an ischemic lesion, resident microglia are the first cell type to activate, migrate and proliferate in response to the chemokines released in the injury area. Clinical studies demonstrated that microglial activation is present in the brain during the acute [125] and the recovery phase after ischemic stroke [126]. In transient MCAO models, in which the lesion only lasts for a few hours after reperfusion, the number of microglial cells

gradually increases over time [122] as revealed by the increased expression of Ionized calcium-binding adapter molecule 1 (Iba-1), a specific marker of microglial population. Another way to detect microglia activation are morphological changes: resting microglia has ramified processes to be in contact with their surroundings. When they are activated, they adopt a rounded morphology with large bodies and shorter dendritic arbors [127]. Transformed microglia can release a diverse range of molecules, some of which are cytotoxic and pro-inflammatory, like cytokines or ROS, while others can be neuroprotective, such as BDNF or IGF-1 [128].

Some studies have pointed out that inhibition of microglial activation enhances recovery after ischemia, while the injury resulting from ischemic insult was augmented in the presence of microglia [129,130]. Oxidative stress is considered a key contributor to the early phase of damage: high levels of ROS affect endothelial cell function and activates microglia, both of which contribute to BBB disruption after ischemia [131]. Microglia processes towards blood vessels could be observed by two-photon imaging 72 h after MCAO [132] (Figure 3). In addition, Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- κ B), which is a ubiquitously expressed complex that controls transcription of DNA in response to stress, was up-regulated in microglia after cerebral ischemia. Even though NF- κ B activation in OLs seems to be relevant to protect them against damage [133], microglial activation of NF- κ B could promote transcription of matrix metalloproteinases, which are essential in the BBB disruption [134]. Co-immunostaining revealed that Iba-1⁺ microglia co-localized with CD31⁺/Gu1⁺/caveolin-1⁺/claudin-5⁺/podocalyxin⁺ blood vessels, indicating that activated microglia phagocytosed endothelial cells to contribute to BBB disruption. On the other hand, inhibition of microglia activation using CX3CR1 ko mice or minocycline greatly increased blood vessel integrity [135–137]. These studies suggested that microglia activation could induce BBB disruption after brain ischemia through disintegration of blood vessels in the penumbra [128]. This type of harmful response is usually carried out by microglia that underwent differentiation into the *M1* (classical) phenotype. M1 microglia is similar to macrophages, as they are specialized in secreting pro-inflammatory molecules such as interleukin 1 β (IL-1 β), interleukin 6 (IL-6), nitric oxide (NO) or

TNF- α , antigen-presenting capacity and immune-potentiating abilities [124,138] (Figure 3). On the contrary, M2 microglia is neuroprotective, anti-inflammatory and regenerative. Studies have shown that, under ischemic conditions, M2 microglia is an early response to damage that can clean cellular debris and limit brain damage. Anti-inflammatory phenotype is achieved by expression of cytokines such as interleukin 10 (IL-10), Tissue Growth Factor β (TGF- β), interleukin 4 (IL-4), IL-13 or IGF-1 that control inflammation and promote tissue repair [128]. In addition, expression of Arginase-1 instead of NO synthase helps to switch from production of NO to synthesis of ornithine and polyamines that will be used for the regeneration of collagen and extracellular matrix synthesis [138]. However, we still do not know which molecules or events direct microglia towards M1 or M2 polarization. It seems like it is partially dependent on different pathophysiological conditions and can be influenced by the time and severity of injury, age or microenvironment circumstances [128,139]. Interestingly, new studies showed that mild brain damage, like a brief period of global ischemia or hypoxic conditions, could activate microglia in a way that protects the brain for further damage if an ischemic stroke occurs [140].

Furthermore, microglia have shown an important role in oligodendrogenesis processes after ischemia, both M1 and M2 phenotypes have demonstrated to be relevant regarding new generation of OLs [128]. Inhibition of M1 microglia activation with minocycline seems to reduce OL/OPC damage under ischemic conditions [141]. In a rat model of chronic cerebral ischemia, increased loss of OLs was coupled with activated microglia releasing TNF- α [142–144]. On the other hand, M2 microglia seems to be way more beneficial. Culture of OPCs with medium from M2 conditioned microglia enhanced OL differentiation and maturation [145]. In this same study, the use of a mouse model of multiple sclerosis showed that depletion of M2 microglia impaired OPC differentiation and blocked any possible remyelination [145]. This phenomenon could be important in physiological conditions, as activation of microglia in the SVZ of neonatal rats was found to be essential in OPCs generation [146]. A study found that IL-4 is an important mediator of these beneficial effects. It is an anti-inflammatory cytokine produced by injured neurons after stroke that polarizes microglia towards M2 phenotype [147]. IL-4 deficiency exacerbates brain

damage and worsens the stroke outcome in MCAO models while intranasal delivery of IL-4 nanoparticles improved white matter integrity after stroke [148]. This same study found increased proliferation of OPCs and differentiation into mature OLs after IL-4 treatment. Interestingly, these OPCs expressed the IL-4 receptor, which tells us that this effect seems to be both dependent and independent of microglia. Oligodendroglial PPAR- γ , which we explained earlier, resulted to be the downstream effector of IL-4 signaling. This was described after seeing that knocking down OPC-PPAR- γ completely abolished IL-4 enhanced oligodendrogenesis after stroke [106] (Figure 3).

4.2 Astrocytes

Even though microglia are the first glial cells to respond to ischemic stimulus, increased expression of glial fibrillary acidic protein (GFAP) around the ischemic lesion indicates the presence of activated astrocytes [149]. The role of astrocytes has been controversial because many studies have described detrimental roles for astrocytes in addressing brain ischemia for their ability to secrete inflammatory factors, including NO [120]. In contrast, other studies have demonstrated that reactive astrocytes are essential to minimize damage after stroke. This discrepancy is because activated astrocytes migrate and proliferate around the penumbra zone to confine the ischemic core and inhibit its expansion. This process generates the glial scar (Figure 3), a phenomenon that protects the brain from further damage by restoring the physical and chemical integrity of the CNS at the cost of losing potential for recovery. [150]. In this sense, reactive astrocytes are interconnected by molecules like connexins, channel-forming proteins that allow cell-cell communication through the cytoplasm. These connections generate a dense network that allow astrocytes to buffer and redistribute harmful molecules. However, connexins can also have detrimental roles, as diffusion of glutamate or ATP through these channels can enhance damage under ischemic, inflammatory or neurodegenerative conditions [151]. Specifically, in vivo studies have shown that specific deletion of astrocytic connexins enhances tissue recovery after damage: knocking-out connexin43 in astrocytes reduces glial activation and enhances OL maturation and remyelination after demyelination [152]. However, inhibition of

connexins could also affect physiological processes, so future therapies based on pharmacological modulation of connexins require further studies.

In addition, some studies suggest new neuroprotective roles of astrocytes regarding ischemic tolerance [153]. A mild non-lethal ischemic episode can produce resistance to a subsequent more severe ischemic insult [140]. Upon this challenging situation, astrocytes start to upregulate glutamate transporters to prevent glutamate excitotoxicity from dying neurons [154,155][155]. They also produce a wide variety of neuroprotective molecules such as erythropoietin (EPO), VEGF and adhesion molecules and aquaporins with the aim to preserve neurons and brain function [156–159]. On the other hand, inhibition of reactive astrocytes made ischemic tolerance impossible to achieve. In addition, rapid clearance of cellular debris after brain injuries is vital to restore brain function. It has been shown that astrocytes can participate in phagocytic processes (even under physiological conditions) [160]. This data shows that endogenous remodeling mechanisms are also important after stroke or cerebral ischemia.

Interestingly, one way by which astrocytes can modulate oligodendrogenesis is through cholesterol: apart from being a risk factor in developing stroke, cholesterol is a major source of myelin and a limiting-step in myelin membrane biogenesis [161,162] (Figure 3). In addition, disturbances in cholesterol metabolism have been described in patients with myelin alterations such as multiple sclerosis [163]. Apolipoprotein E (ApoE) is the most abundant apolipoprotein in the brain. It helps to solubilize phospholipids and cholesterol and stabilizes high-density lipoproteins (HDL) vesicles. ATP-binding cassette transporter A1 (ABCA1) is a reverse cholesterol transporter critical for the formation of these vesicles in the brain [164]. However, plasma cholesterol cannot be taken up by the brain [165], so it is synthesized by the astrocytes and delivered to the rest of cells via the ABCA1/ApoE/HDL signaling axis. Even though OLs can synthesize cholesterol, *ABCA1*^{-/-} mice showed decreased myelin density and OL numbers during developmental myelination [166]. After ischemic stroke, *ABCA1*^{-/-} mice also had impaired oligodendrogenesis and lower levels of ApoE and HDL in the remaining OPCs [164]. This phenotype was related to decreased white matter remodeling and a worse functional outcome

439 from 3 to 21 days after stroke induction. On the other hand, supplementation with human ApoE
440 or HDL had beneficial effects on the corpus callosum and reversed the demyelination phenotype
441 [164,167,168]. In conclusion, beneficial or detrimental roles of astrocytes may depend on the
442 severity of ischemic insults, although age and environment related processes cannot be discarded
443 to affect astrocytic functions. Modulating reactive astrocytes responses may be crucial to control
444 ischemic damage in the brain.

Concluding remarks

During brain ischemia, a wide array of mechanisms are triggered by the brain. Some of them are beneficial and try to restore the damage done, while others compromise the recovery from the disease. This repair system involves neurons, astrocytes, microglia and OLs. Myelin loss after ischemic stroke needs new OPCs to differentiate into myelinating OLs that will restore the myelin sheaths. In this review, we focused in oligodendrogenesis and myelin regeneration after stroke, which are two extremely complex processes that require multiple and coordinated signaling pathways. We also assessed how the environment around the ischemic zone and other glial cells participate in the modulation of the ischemic process and remyelination. Future work will help to better understand the mechanisms that orchestrate remyelination following ischemic insults to generate treatments focused on enhancing oligodendrogenesis.

456 **Abbreviations**

457 ABCA-1: ATP-binding cassette transporter A1

458 APC: adenomatous polyposis coli

459 ApoE: Apolipoprotein E

460 BBB: Blood-Brain Barrier

461 BDNF: Brain-derived Neurotrophic Factor

462 BMPs: Bone Morphogenetic Proteins

463 BMP4: Bone Morphogenetic Protein-4

464 Bpv: Bisperoxovanadium

465 CK1: Casein Kinase 1

466 CNS: Central Nervous System

467 CX3CR1: CX3C chemokine receptor 1 / fractalkine receptor

468 EPO: erythropoietin

469 Erk1/2: Extracellular signal-related kinases 1/2

470 FGF-2: Fibroblast Growth Factor-2

471 GFAP: Glial Fibrillary Acidic Protein

472 Gli: Glioma-associated oncogene

473 GSK-3B: Glycogen Synthase Kinase 3B

474 HDL: High-density Lipoproteins

475 Iba-1: Ionized calcium-binding adapter molecule 1

476 IGF-1: Insulin Growth Factor

477 IL-1 β : Interleukin-1 β

478 IL-4: Interleukin-4

479 IL-6: Interleukin-6

480 IL-10: Interleukin-10

481 IL-13: Interleukin-13

482 IRS-1: Insulin Receptor Substrate-1

483 LEF: Lymphoid Enhancer Factors

484 MAPK: Mitogen-Activated Protein Kinases

485 MBP: Myelin Basic Protein

486 MCAO: Middle Cerebral Artery Occlusion

487 miRNAs: microRNAs

488 mTOR: mechanistic/mammalian Target Of Rapamycin

489 MyRF: Myelin Regulatory Factor

490 NF- κ B: Nuclear Factor kappa-light-chain-enhancer of activated B cells

491 NMDAR: N-Methyl-D-Aspartate Receptor

492 NO: Nitric Oxide

493 NPCs: Neural Progenitor Cells

494 NT3: Neurotrophin 3

495 Olig1/2: Oligodendrocyte Transcription Factors 1/2

496 OLs: Oligodendrocytes

497 OPCs: Oligodendrocyte Progenitor Cells

498 PDGF(R): Platelet-derived Growth Factor (Receptor)

499 PDK1: 3-phosphoinositide-dependent Kinase

500 PIP2: Phosphatidylinositol (4,5)-biphosphate

501 PIP3: Phosphatidylinositol (3,4,5)-triphosphate

502 PI3K: Phosphatidyl inositol-3-phosphate Kinase

503 PLP: Proteolipid Protein

504 PPAR γ : Peroxisome Proliferator-activated Receptor γ

505 P70S6K: Protein S6 Kinase beta-1

506 Ptc: Patched

507 PTEN: Phosphatase and Tensin homolog

508 ROS: Reactive Oxygen Species

509 RTKs: Receptor Tyrosine Kinases

510 Shh: Sonic Hedgehog

511 Smo: Smoothened

512 SREBPs: Sterol Regulatory Element-binding proteins

513 SVZ: Sub-Ventricular Zone

514 TCF: T-cell Factors / Transcription Factors

515 TCF4: Transcription Factor 4

516 TCF7l2: Transcription Factor7-like 2

517 TGF- β : Tissue Growth Factor β

518 TIMP-1: Tissue Inhibitor of Metalloproteinase-1

- 519 TNF- α : Tumor Necrosis Factor α
- 520 VEGF: Vascular-endothelial Growth Factor
- 521 Wnt: Wingless integration site

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Figure Legends

Figure 1. Schematic representation of MCAO brain ischemia model. In a physiological situation (left), healthy neurons (blue) are covered by oligodendrocytes (green). Astrocytes (violet) and microglia (orange) have resting morphologies. When middle cerebral artery (MCA) is occluded (right), we can distinguish two zones: the ischemic core, where we can find degenerating neurons, and the penumbra zone, with slightly damaged neurons. Oligodendrocytes are affected by the ischemic insult and myelin is lost. Activated microglia adopt amoeboid morphologies around neurons and modulate the inflammatory response. Reactive astrocytes accumulate around the ischemic core to form the glial scar and phagocytose cellular debris to prevent further extension of the damage.

Figure 2. Schematic diagram of Shh, PI3K/Akt/mTOR, ERK1/2-MAPK, Wnt/ β -catenin and PPAR γ signaling pathways. Key elements of each pathway are shown when each route is active. Arrowheads indicate positive interactions while bars show inhibitory signals. Shh: Sonic Hedgehog, Ptc: Patched, Smo: Smoothened, Gli: Glioma-associated oncogene family. BDNF: brain-derived neurotrophic factor, NGF: nerve growth factor, NT3: neurotrophin 3, RTKs: receptors tyrosine kinase, IRS-1: insulin receptor substrate 1, PI3K: phosphoinositide-3 kinase, PIP2: phosphatidylinositol (4,5)-biphosphate, PIP3: phosphatidylinositol (3,4,5)-triphosphate, PTEN: phosphatase and tensin homolog, PDK-1: 3-phosphoinositide-dependent protein kinase, Akt: protein kinase B, mTOR: mammalian target of rapamycin, mLST8: target of rapamycin complex subunit LST8, Raptor: regulatory associated protein of mTOR, p70S6K: Ribosomal protein S6 kinase beta-1, S6RP: Ribosomal protein S6, SREBPs: Sterol regulatory element-binding proteins. PDGF: platelet-derived growth factor, FGF-2: fibroblast growth factor 2, Grb2: growth factor receptor-bound protein 2, Sos: son of sevenless, ERK1/2: extracellular signal-regulated kinases 1 and 2, p90RSK: p90 ribosomal S6 kinase, MyRF: Myelin Regulatory Factor. Lrp5/6: Lipoprotein receptor-related proteins 5/6, Dvl: disheveled, GSK3: glycogen synthase kinase 3, CK1: casein kinase 1, APC: adenomatous polyposis coli, β -cat: β -catenin, TCF4: transcription factor 4, PPAR γ : peroxisome proliferator-activated receptor γ .

Figure 3. Schematic illustration of novel intercellular interactions in response to brain ischemia. Upon ischemic damage, a variety of signals is released to the medium. M1 microglia releases pro-inflammatory signals like nitric oxide (NO), tumoral necrosis factor α (TNF- α) or interleukin-1 β (IL-1 β) and disrupt the blood-brain barrier (BBB). These effects are mediated by NF- κ B. M2 microglia promotes repair mechanisms and Oligodendrocyte Precursor Cell (OPC) proliferation. OPCs release vascular endothelial growth factor (VEGF) to promote angiogenesis and repair the BBB. In addition, they will differentiate into mature Oligodendrocytes (OL) to ensheath damaged axons. Reactive astrocytes participate in the process by generating the glial scar to confine the ischemic core. They also provide OLs with cholesterol via Apolipoprotein E (ApoE)/ High-density lipoproteins (HDL) for myelin biogenesis and release regulatory factors like VEGF and erythropoietin (EPO). Sonic hedgehog (Shh) signals modulate glial scar formation, direct microglia towards M2 phenotype and promoting OPC proliferation. Interleukin-4 (IL-4) also guide M2 differentiation and OPC proliferation via PPAR γ .