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The axon-glia unit in white matter stroke: mechanisms of damage and recovery

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Abstract

Approximately one quarter of all strokes in humans occur in white matter, and the progressive nature of white matter lesions often results in severe physical and mental disability. Unlike cortical grey matter stroke, the pathology of white matter stroke revolves around disrupted connectivity and injured axons and glial cells, rather than neuronal cell bodies. Consequently, the mechanisms behind ischemic damage to white matter elements, the regenerative responses of glial cells and their signaling pathways, all differ significantly from those in grey matter. Development of effective therapies for white matter stroke would require an enhanced understanding of the complex cellular and molecular interactions within the white matter, leading to the identification of new therapeutic targets. This review will address the unique properties of the axon-glia unit during white matter stroke, describe the challenging process of promoting effective white matter repair, and discuss recently-identified signaling pathways which may hold potential targets for repair in this disease.

Keywords

White Matter; Stroke; Ischemia; Repair; Oligodendrocytes; Myelin

1. Introduction

Small vessel infarcts affecting brain white matter are an important clinical problem, accounting for up to 25% of all strokes (Arboix and Marti-Vilalta, 2009; Roger et al., 2012; Schneider et al., 2004). This percentage may grow in upcoming years due to the increasing prevalence of risk factors associated with small vessel disease, such as type II diabetes and metabolic syndrome (Bokura et al., 2008; Del Bene et al., 2013; Gouw et al., 2008). Many promising neuroprotective therapies for stroke failed the transition from animal studies to clinical trials, and a major reason for these failures may be the almost exclusive focus of preclinical studies on the neuroprotection of cerebral gray matter, with little attention to

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white matter tracts (Gladstone et al., 2002). A probable contributing factor is the predominant use of rodents in pre-clinical studies, whose white matter comprises only ~14% of total brain volume. Since white matter makes up to 50% of the volume in human brains, it is likely that the data from rodent studies misrepresents the relevance of white matter in human brain pathology (Matute, 2011; Zhang and Sejnowski, 2000). Although ischemic injuries in gray and white matter share some common characteristics, there are unique properties of stroke in white matter that are derived from the white matter elements: the axons, the oligodendrocytes that enwrap them in myelin, and fibrous astrocytes which interact with the former two. These, alongside microglia, progenitor cells and vasculature, form an intricate environment and a delicate homeostasis that is highly vulnerable to ischemic damage (Hamner et al., 2011; Matute et al., 2001; Matute, 2011; Pantoni et al., 1996; Stirling and Stys, 2010). Development of effective therapeutic strategies and identification of new targets for the treatment of white matter stroke (WMS) would require an enhanced understanding of the complex cellular and molecular architecture of white matter components. This article will review key mechanisms underlying the white matter response to ischemic WMS with focus on the axon-glia functional unit during stroke recovery.

2. The unique structure and function of brain white matter

The white matter is comprised primarily of axons and glial cells, and is devoid of neuronal cell bodies or their dendrites. Bundles of axons are topographically organized in white matter so that axons originating from specific regions form projections which occupy distinct parts of the white matter (Filley, 2010; Schmahmann et al., 2008). These tracts of axons enable rapid communication between non-adjacent brain regions as well as between peripheral and central areas.

The majority of white matter axons are enwrapped by oligodendrocytes which form segments of myelin sheaths around the axons. Myelin segments facilitate fast saltatory propagation of action potentials, and segregate the axonal membrane into defined regions: the *node* of Ranvier, where clusters of Na^+ channels “propel” the action potential along the axon (Huxley and Stampfli, 1949; Waxman and Swadlow, 1977), *paranode*, K^+ channel-rich *juxtaparanode*, and *internode* (Rios et al., 2003; Susuki and Rasband, 2008).

The lack of neuronal cell bodies and dendrites means there are no “classical” synapses in the white matter, but recent work demonstrates the existence of “axo-myelinic” synapses which involve vesicular transmitter release from axons, acting on receptors on the inner surface of the myelin sheath (Stys, 2011). Neurotransmitters released from unmyelinated white matter axons can also act on surrounding glia (Alix and Domingues, 2011). These types of signals are at the base of a bidirectional neuron-glia communication involving the secretion of endosome-derived vesicles by oligodendrocytes and their subsequent internalization by neurons through endocytosis (Fruhbeis et al., 2013). Whether this occurs in white matter is still unknown. Oligodendrocytes are also suggested to contribute to long-term axonal integrity by delivering products of aerobic glycolysis which are rapidly metabolized in axons (Funfschilling et al., 2012).

Additional important players in white matter homeostatic maintenance are fibrous astrocytes. The long processes of these cells run along axons and connect to blood vessels (Oberheim et al., 2009). White matter astrocytes are also an important source of energy, supplying axons with lactate converted from deposits of glycogen (Brown et al., 2003; Ransom and Fern, 1997). Astrocytic endfeet on brain capillaries are an important part of the blood–brain barrier (Abbott, 2005; Alvarez et al., 2013), and they also participate in regulating local microcirculation (Attwell et al., 2010; Gordon et al., 2008). In addition, astrocytic processes form contact with myelinated axons at the nodes of Ranvier, where they participate in "siphoning" of K^+ ions that accumulate following action potential generation (Kamasawa et al., 2005; Rash, 2010).

White matter microglia play an important role in neurodegeneration and inflammation. They are activated by cytokines, neurotransmitters and modulators, and can also synthesize and release many cytokines, chemokines, reactive oxygen radicals and neurotrophins which can be either injurious or beneficial to the surrounding axons and oligodendrocytes (Raivich and Banati, 2004).

The white matter components and the complex interactions among them create an optimal environment for fast transmission of signals along tracts of axons. However, the low blood flow and little collateral blood supply in deep white matter compared to gray matter make this intricate milieu highly susceptible to ischemic injuries (Iadecola et al., 2009; O'Sullivan et al., 2002), which disrupt white matter function with oftentimes devastating consequences.

3. White matter pathology in humans and WMS models

White matter "lacunar infarcts" in humans range in size up to 15 mm and often result in severe physical and mental disability including vascular dementia (Dufouil et al., 2009; Goldberg and Ransom, 2003), with an elevated mid-long-term risk of recurrence (Arboix and Marti-Vilalta, 2009; Norrving, 2008). Smaller white matter "micro-infarcts" with mean diameters between 0.2 and 1 mm are thought to have a similar ischemic origin and are even more common, appearing in a third of cognitively normal elderly patients (Smith et al., 2012). Infarcts in white matter are characterized by an irregular lesion bordered by reactive astrocytes and microglia/macrophages in older lesions, while acute lesions feature a necrotic encephalomalacic core (Bailey et al., 2012). The axons adjacent to white matter stroke show altered nodal structure and molecular disorganization that indicates a peri-infarct region of partial damage that radiates out from the infarct (Hinman et al., 2015)

In animals, transient focal ischemia achieved via injection of a vasoconstricting drug into white matter is thus far the closest model for human white matter lacunar infarcts. These injections produce focal white matter injury, with wide-scale axonal and oligodendrocyte damage (Hughes et al., 2003; Sozmen et al., 2009). In the striatum, these models were also shown to produce lesions with a peri-infarct penumbra region displaying axon pathology (Frost et al., 2006; Lecrux et al., 2008). In subcortical white matter, similar focal lesions evolve over time and features oligodendrocyte and axonal loss at the core, and a penumbra region displaying demyelination, inflammation and axonal degeneration which are in part age-dependent (Rosenzweig and Carmichael, 2013; Sozmen et al., 2009).

The sensitivity of different white matter elements to ischemia has been demonstrated in numerous models of cerebral artery occlusion. Swelling of white matter glia has been observed as early as 30 minutes after middle cerebral artery occlusion, followed by loss of oligodendrocytes (Irving et al., 1997; Pantoni et al., 1996), and axonal degeneration within 120 minutes of ischemia (Dewar and Dawson, 1997; Valeriani et al., 2000). Short transient ischemia was sufficient to cause widespread striatal white matter injury with extensive glial and axon pathology (Kubo et al., 2009).

The progressive damage to oligodendrocytes, myelin and axons observed in white matter stroke models and in human white matter stroke may be attributed to glutamate-mediated excitotoxicity and downstream molecular pathways. Glutamate, released from astrocytes during ischemia due to reversal of Na^+-dependent glutamate transporters, acts on ionotropic AMPA/kainate and NMDA receptors (Baltan et al., 2008; Micu et al., 2006; Tekkok et al., 2007). Prolonged activation of glutamate receptors in oligodendrocytes causes influx of Ca^{2+} and its accumulation within mitochondria, which prompts the production of radical oxygen species and activation of caspase-mediated cell death (Matute et al., 2006; Sanchez-Gomez et al., 2003). Oligodendrocytes are particularly sensitive to oxidative stress due to their low supplies of the cellular antioxidant glutathione, which is further depleted by excessive glutamate (Back et al., 1998; Thorburne and Juurlink, 1996).

A second source for the rise in cytosolic Ca^{2+} in oligodendrocytes is activation of metabotropic P2Y receptors and ionotropic P2X7 receptors by adenosine triphosphate (ATP) (James and Butt, 2001; Matute et al., 2007). ATP released from oligodendrocytes through pannexin hemichannels was shown to activate P2X7 receptors that cause oligodendrocyte death, myelin damage and axon dysfunction (Domercq et al., 2010). High levels of cytosolic Ca^{2+} were also shown to activate Ca^{2+}-dependent enzymes such as calpains and phospholipases, resulting in white matter degradation (Stys, 2004; Vosler et al., 2008). In addition to oligodendrocytes, P2X7 receptors can be found in white matter microglia, and their activation mediates inflammation that could further contribute to ischemic damage (Xiang and Burnstock, 2005).

The effects of ischemia on oligodendrocytes are directly relevant to axonal function. Documented changes in the ultrastructure of myelinated axons following ischemia and Ca^{2+} activation include splitting, retraction of myelin at paranodes and separation of the myelin lamellae, suggestive of loss of axoglial contact (Fu et al., 2009; Mclver et al., 2010). Other changes documented in mice as early as 3 days after mild cerebral hypoperfusion include a progressive reduction of paranodal neurofascin signal and a loss of septate-like junctions, increase in nodal length and changes in the spatial distribution of myelin-associated glycoproteins (Reimer et al., 2011).

Such changes in the axon-glia structure disrupt the spatial segregation of Na^+ and K^+ channels in the node and juxtaparanode areas. This segregation is critical to proper axonal conduction of action potentials and its perturbation has been suggested to contribute to many pathological conditions that involve failure of axonal function (Arroyo et al., 2002; Hinman et al., 2006; Rasband, 2011; Salzer et al., 2008). Studies in models of multiple sclerosis demonstrate that disrupted or less efficient axonal conductance may manifest as severely as

a complete loss of axonal function, due in most to the spatial and temporal summation requirements that are the hallmark of neuronal signaling; for a target neuron to reach threshold, several action potentials (from one or more axons) must arrive to its synaptic terminals within a narrow time window. Thus, even a small delay in conduction may equal a complete arrest of the signal downstream (Waxman et al., 1995). Many suggested repair strategies for white matter pathology, therefore, focus on restoring axonal function through oligodendrocytes and myelin repair.

4. Activity-dependent remyelination and oligodendrocyte response to white matter ischemia

While myelination is, at its core, a developmental process, the adult mammalian central nervous system (CNS) retains at least some capability of remyelination and regeneration following injury (Duncan et al., 2009; Franklin and Ffrench-Constant, 2008). In the case of white matter ischemia, demyelination and axonal degradation occur quickly in the ischemic core, yet gradual restoration of oligodendrocytes and remyelination have been observed in the peri-infarct area (Gregersen et al., 2001; Tanaka et al., 2003). An important feature of this process is oligodendrogenesis, which occurs following ischemia. This proliferative response of oligodendrocyte progenitor cells (OPC), peaks at 5–7 days after stroke induction and declines 14–28 days later (Iwai et al., 2010; Sozmen et al., 2009). However, this robust regenerative response appears to encounter a roadblock of OPC differentiation failure, which ultimately limits recovery after demyelination (Syed et al., 2008). A deeper understanding of this regenerative failure is crucial, since remyelination is key in preventing axonal degeneration (Irvine and Blakemore, 2008). Figure 1 offers a schematic overview of potentially successful repair vs. regenerative failure.

It is hypothesized that during regeneration there is recapitulation of many developmental processes. In the case of myelination, neuronal activity plays a crucial role during development. Suppressing neural activity during development reduces OPC proliferation and disrupts myelination (Barres and Raff, 1993; Demerens et al., 1996), while inducing neuronal activity via electrical stimulation promotes proliferation, survival and differentiation of oligodendrocytes, as well as axon myelination (Gary et al., 2012; Gibson et al., 2014; Ishibashi et al., 2006). In injured spinal cord, electrical activity was similarly demonstrated to promote OPC differentiation and remyelination, as well as improve locomotor recovery (Zhang et al., 2014).

The underlying mechanisms for this neuron-glia regulation are complex, and several known pathways and genes are discussed in the next section. A summarized view of these and other pathways is offered in Table 1. Some direct signals that have been identified include neurotransmitters such as glutamate and acetylcholine which are released from depolarized neurons and act on oligodendrocytes and OPC to modulate proliferation, migration, and differentiation (De Angelis et al., 2012; Gudz et al., 2006; Wake et al., 2011; Zonouzi et al., 2011).

Activity-dependent release of ATP enhances OPC differentiation and myelination (Ishibashi et al., 2006; Stevens et al., 2002). Oligodendrocytes express each of the different adenosine

receptor subtypes (Othman et al., 2003), and treatment of OPC in culture with adenosine promotes their maturation and migration through a A1 adenosine receptor-mediated pathway (Othman et al., 2003; Stevens et al., 2002).

Cyclic adenosine monophosphate (cAMP) may be another activity-dependent regulator of myelination. Electrical stimulation increases neuronal cAMP in vivo (Udina et al., 2008), and depolarized neurons affect myelin protein processing in oligodendrocytes in a cAMP-dependent manner (Trajkovic et al., 2006). In addition, elevating cAMP levels enhanced remyelination in a cuprizone demyelination model (Sun et al., 2012). Recently, cAMP was demonstrated to act as an activity-dependent pathway in neurons to promote myelination (Malone et al., 2013).

5. Molecular pathways involved in ischemic white matter damage and repair

Ischemia is associated with alterations in multiple biological processes and molecular pathways, and many proteins greatly affect repair processes in white matter. This section will address some of the recently identified molecular systems and their potential function in white matter regeneration. At present, the majority of findings come from commonly-used demyelination models rather than models of WMS, but it is likely that signals which play a role in these models are, to some extent, relevant to WMS pathology.

5.1 Extracellular Matrix related proteins

The extracellular matrix affects proliferation, survival, migration and differentiation of oligodendrocytes, as well as process extension and myelination (Sherman and Back, 2008). CNS damage leads to accumulation of several extracellular matrix components, particularly Chondroitin Sulfate Proteoglycans (CSPGs) and hyaluronan, in and around the injured area (Back et al., 2005; Galtrey and Fawcett, 2007). In white matter, high levels of CSPGs like aggrecan, neurocan and versican, as well as high molecular weight hyaluronan and one of its receptors, CD44, are found in active multiple sclerosis demyelinating lesions and neonatal white matter injury (Back et al., 2005; Buser et al., 2012; Sobel and Ahmed, 2001). In models of traumatic spinal cord injury and lysolecithin-induced demyelination, accumulation of CSPGs inhibits OPC migration and their maturation into myelinating oligodendrocytes, while clearance of CSPGs was correlated with remyelination (Karimi-Abdolrezaee et al., 2012; Lau et al., 2012; Siebert et al., 2011).

High molecular weight hyaluronan blocks OPC differentiation and maturation both in vitro and in vivo (Back et al., 2005; Dean et al., 2011; Marret et al., 1994; Sloane et al., 2010). It is digested to bioactive forms by the hyaluronidase PH20 which is highly expressed by OPC and reactive astrocytes in demyelinated lesions. Overexpression of PH20 inhibits oligodendrocyte differentiation in vitro and hyaluronan fragments generated by PH20 block remyelination in vivo (Preston et al., 2013). Similarly, overexpression of CD44 in myelinating oligodendrocytes induces progressive demyelination (Tuohy et al., 2004). In addition to CD44, hyaluronan inhibits OPC differentiation by acting through Toll-like receptor 2 (Sloane et al., 2010).

Dysregulation of matrix metalloproteinases (MMPs), a family of zinc endopeptidases which degrade extracellular matrix proteins, was also linked to damage and repair after stroke and other neurological diseases (Alvarez-Sabin et al., 2004; Anthony et al., 1997; Horstmann et al., 2003). MMPs, and especially MMP-2 and MMP-9, are known to break down myelin basic protein and myelin-associated glycoprotein (MAG), two major components of the myelin sheath (Chandler et al., 1995; Gijbels et al., 1993). Transient global ischemia increases activity of MMP-2 enzyme in reactive astrocytes in corpus callosum, with significant suppression of delayed myelin degradation apparent after treatment with the MMP inhibitor BB-94 (Walker and Rosenberg, 2010).

5.2 Wnt signaling

The Wnt/β-catenin pathway is involved in many developmental processes, one of which is oligodendrogenesis (Ortega et al., 2013). Canonical Wnt signaling through the intranuclear mediator Tcf, which is upregulated in OPC during white matter pathology, has been linked to impaired myelin repair after injury (Fancy et al., 2009). The binding of Wnt ligands to OPC promotes the stabilization of a β-catenin/Tcf/LEF complex and activation of downstream genes which, during instances of high activity, inhibit the differentiation and maturation of OPC into myelinating oligodendrocytes, ultimately leading to impaired myelination (Fancy et al., 2009; Fancy et al., 2014; Feigenson et al., 2009; Ye et al., 2009).

In spinal cord, Wnt and bone morphogenic protein (BMP) signaling pathways have overlapping temporal activity and a similar effect of inhibiting oligodendrocytes differentiation (Feigenson et al., 2011). Blocking BMP signaling prevents Wnt-mediated inhibition of oligodendrocyte differentiation, but not vice versa, suggesting that BMP signals act downstream from Wnt (Feigenson et al., 2011). BMP signaling is active in oligodendroglia and astrocytes within the demyelinated corpus callosum, and infusion of the BMP antagonist Noggin into the brains of mice during demyelination promoted mature oligodendrocyte regeneration and remyelination (Sabo et al., 2011).

Axin2 is a transcriptional target of active Wnt signaling that also serves to autoregulate and inhibit Wnt signaling by promoting β-catenin degradation (Jho et al., 2002; Lustig et al., 2002). Axin2 expression is upregulated in OPC in neonatal white matter injury and active multiple sclerosis lesions, and its deletion in mice delays OPC maturation and impairs remyelination following spinal cord demyelination injury (Fancy et al., 2011). Administration of an Axin2 stabilizer was found to be sufficient to promote myelination in cerebellar slice cultures after acute hypoxia and in demyelinated spinal cord (Fancy et al., 2011).

Adenomatous Polyposis Coli (APC) is another regulator of Wnt/β-catenin signaling (Miller et al., 2009; Nathke, 2006). APC is transiently expressed in oligodendrocytes during development and demyelination- induced regeneration. It was found to enhance proliferation and differentiation of OPCs in a cell- autonomous manner (Lang et al., 2013). Its deletion in oligodendroglial lineage cells revealed that APC regulates oligodendrocyte differentiation through β-catenin-independent, as well as β-catenin-dependent, mechanisms, with the β-catenin-independent mechanism involving cytoskeletal regulation (Lang et al., 2013).

Recent work has demonstrated a role for Hypoxia-inducible factors (HIFs) in Wnt7a/7b-mediated OPC regulation (Yuen et al., 2014). These factors act as transcriptional mediators of the cellular response to hypoxia (Majmundar et al., 2010; Semenza and Prabhakar, 2012). OPC HIF1/2α activity, triggered by hypoxia, inhibits myelination via autocrine Wnt7a/7b signaling, which also has a novel paracrine role in promoting Wnt-dependent vessel growth into developing postnatal white matter tracts. Loss of OPC-encoded HIF1/2α function inhibits angiogenesis in developing white matter, resulting in catastrophic loss of corpus callosum axons (Yuen et al., 2014). This possible interaction between OPC differentiation and angiogenesis is a promising research link in stroke, given the natural occurrence of angiogenesis in stroke tissue reorganization. It is possible that the HIF-Wnt7a/7b pathway is activated by decreased oxygen levels that are associated with ischemic white matter injury, and that it plays a role in modulating OPC and blood vessels in infarcted areas, but this has yet to be studied.

The SRY-box 17 (Sox17) transcription factor is a regulator of oligodendrocyte differentiation (Sohn et al., 2006), which was found to affect Wnt signaling at multiple levels, including Sox17-mediated proteasomal degradation of β-catenin (Chen et al., 2013; Chew et al., 2011). Enhanced Sox17 expression in oligodendrocytes was detected in active remyelinating lesions (Moll et al., 2013), and transgenic overexpression of Sox17 was shown to promotes oligodendrocyte differentiation and attenuate lysolecithin-induced demyelination (Ming et al., 2013).

5.3 Nogo related proteins

Myelin-associated inhibitory factors such as NogoA and MAG are among the most well-known factors that inhibit regeneration in the CNS (McKerracher et al., 1994; Schwab, 2010). These factors bind to the Nogo receptor 1 and 2 (NgR1, NgR2) which are expressed by neurons and glial cells (Huang et al., 2012; Hunt et al., 2002). NgR1 is well known to inhibit regeneration processes in multiple pathological conditions, but most studies have focused on its effects on axonal sprouting and regeneration (Harvey et al., 2009; Wahl et al., 2014; Yu et al., 2008). Much less is known about the effect of myelin inhibitory factors on remyelination and oligodendrocyte regeneration. This information is important in light of growing evidence showing that blocking NgR and its ligands improves the outcomes in demyelination models (Karnezis et al., 2004; Petratos et al., 2012; Yang et al., 2010). Recent reports have indicated that NogoA plays a direct role in regulating myelination in vitro and in an in vivo model of focal demyelination (Chong et al., 2012). Furthermore, blocking NgR1 significantly enhanced the remyelination process, recruitment of proliferating OPC to the lesion site, and functional recovery after demyelination in the optic nerve (Pourabdolhossein et al., 2014). The mechanism for NgR1-mediated inhibition of neurite outgrowth involves activation of RhoA and its downstream effector Rho kinase ROCK (Niederost et al., 2002), however, whether this mechanism also plays a role in the regulation of OPC and remyelination is still unknown.

LINGO-1 is a single transmembrane protein specifically expressed in CNS neurons and oligodendrocytes. It is an essential signaling co-receptor within the NgR1 complex, and has no known direct ligands (Mi et al., 2008). Reduced function of LINGO-1 in OPC promotes

differentiation and maturation in these cells, while overexpression of LINGO-1 inhibited these processes. Concordantly, increased myelination is present in LINGO-1 knockout animals (Lee et al., 2007; Mi et al., 2005; Zhao et al., 2007). An antagonist of LINGO-1 promoted remyelination and OPC differentiation in vivo after experimental demyelination (Mi et al., 2009). The mechanism for LINGO-1-mediated negative regulation of oligodendrocytes differentiation appears to involve self-association of the receptor in trans, as well as homophilic intercellular interactions (Jepson et al., 2012).

5.4 Positive regulators of repair and trophic factors

Several new positive regulators of white matter repair have emerged in recent years. The morphogen Sonic Hedgehog (Shh) controls the generation of oligodendrocytes during development and regulates their production in the adult white matter by inducing expression of the transcription factors Olig1 and Olig2 (Traiffort et al., 2010). Administration of Shh increases the number of OPC and premyelinating oligodendrocytes in the cerebral cortex and corpus callosum (Loulier et al., 2006), and an increase of Shh expression induces oligodendrogenesis and promotes recovery after chronic demyelination (Harsan et al., 2008). In a model of focal lysolecithin demyelination in mouse corpus callosum, Shh transcripts were upregulated in oligodendrocytes within the lesion but not in normal white matter, suggesting a broad reactivation of the Shh pathway. Adenovirus-mediated transfer of Shh into the lesioned brain attenuated the lesion extent and increased OPC maturation and differentiation, while blocking of Shh decreased OPC proliferation and differentiation, and prevented repair (Ferent et al., 2013).

Netrin-1 plays a role in axon guidance during development and contributes to white matter formation by influencing OPC proliferation, differentiation, and migration (Bradford et al., 2009; Tsai et al., 2006). The mechanism underlying the effect of Netrin-1 on OPC and oligodendrocytes involves signaling through the receptor Dcc, expressed by both cell types, and downstream inhibition of RhoA (Rajasekharan et al., 2009). Under pathological conditions, Netrin-1 inhibits inflammation and apoptosis, as well as promotes repair after ischemic stroke by increasing angiogenesis (Lu et al., 2012; Rosenberger et al., 2009; Sun et al., 2011). Overexpression of Netrin-1 increases proliferation and differentiation of OPC into mature oligodendrocytes, and promotes white matter remyelination and neurobehavioral outcomes after focal cerebral ischemia in mice (He et al., 2013).

Leukemia inhibitory factor (LIF) is a cytokine that exerts pleiotropic effects on cell survival (Metcalf, 2003). Intracerebral injections of LIF attenuate injury when administered after focal ischemia (Suzuki et al., 2005). LIF also promotes myelination by oligoderndrocytes when released by astrocytes in response to activity-dependent rise in ATP (Ishibashi et al., 2006). More recently, LIF effectively reduced infarct volume, reduced white matter injury and improved functional outcomes when administered to rats following permanent middle cerebral artery occlusion. The underlying mechanism for LIF-mediated white matter protection appears to involve activation of the Akt signaling pathway and antioxidation via inhibition of lactate dehydrogenase release from oligodendrocytes, reduction of superoxide dismutase activity and induction of peroxiredoxin 4 (Rowe et al., 2014).

6. Conclusion

Although white matter damage is an important part of many neurological disorders, and in particular white matter stroke, mechanisms of white matter damage and repair are relatively understudied compared to those in gray matter. The key to improving recovery, restoring function, and reducing long-term disability after white matter stroke lies in a better understanding of white matter biology and the changes that occur in different elements of the white matter following an ischemic insult. Signals transmitted between injured axons and glia, ionic imbalance, and downstream regulation of several genes and signaling pathways ultimately contribute to the complex pathology of white matter stroke. Animal studies have attempted to promote white matter repair and recovery in different models of white matter pathology, by identifying and manipulating specific factors, genes or signals involved in damage and repair processes. Considerable attention has been directed to preserving and restoring axonal integrity and conductance through remyelination, by targeting OPC and oligodendrocytes and promoting their differentiation. While some successes have been recorded, it is likely that an effective therapy for white matter stroke in humans would require a more comprehensive approach involving multiple targets.

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Abbreviations

WMS	White matter stroke
OPC	Oligodendrocyte progenitor cells

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Highlights

- Unique properties of stroke in white matter are derived from the main white matter components: axons and glia
- A limited regenerative response takes place in the peri-infarct area following white matter stroke
- Neuronal activity, trophic factors and positive regulators contribute to repair and remyelination

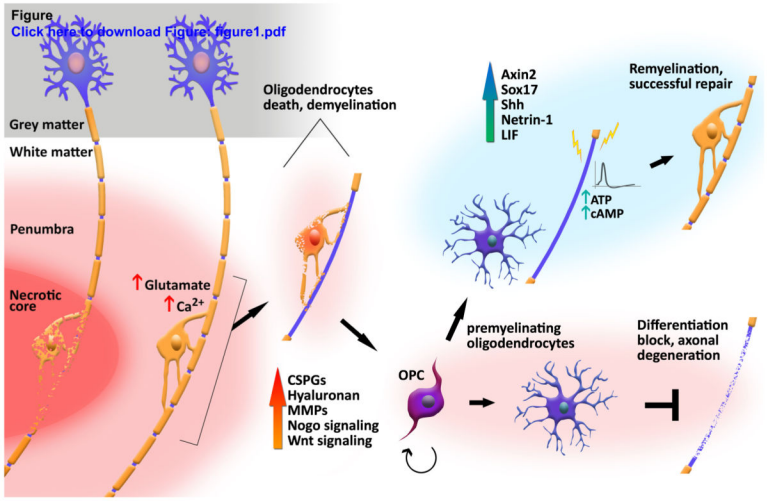

Figure 1. Damage and repair following white matter stroke

Complete loss of axons and glia in the necrotic ischemic core (left). Glutamate-mediated excitotoxicity and rising Ca^{2+} levels promote oligodendrocytes death and demyelination in the peri-infarct area. A regenerative response initiates with OPC proliferation, but inhibitory signals lead to a differentiation and maturation block. Vulnerable demyelinated axons may suffer secondary degeneration (bottom right). Alternatively, neuronal activity, trophic factors and positive regulators may contribute to oligodendrocytes maturation and successful remyelination (top right).

Table 1

Regulators of white matter damage and OPC regeneration, and their documented effects.

Pathway/protein	Mechanism/activity	Outcome/effect	Reference
Activity-dependent signals			
ATP	A1 adenosine receptor on oligodendrocytes	↑ OPC differentiation, maturation and migration	Othman et al., 2003 Stevens et al., 2002
cAMP	MEK-ERK pathway (?)	↑ T remyelination ↑ OPC maturation	Malone et al., 2013 Sun et al., 2012
ECM-related proteins			
CSPGs	Inhibitory GAG chains	↓ OPC differentiation, maturation and migration	Lau et al., 2012 Sherman and Back, 2008
hyaluronan	Digested by Hyaluronidase CD44, TLR2 signaling	↓ OPC differentiation, maturation ↑ progressive demyelination	Back et al., 2005 Sloane et al., 2010
MMPs	Degradation of MBP, MAG and ECM proteins	↑ T demyelination	Walker and Rosenberg, 2010
Wnt signaling			
Wnt/β-catenin	Nuclear β-catenin/tcf/LEF complex	↓ OPC differentiation, maturation	Fancy et al., 2009 Feigenson et al., 2009
Axin2	β-catenin degradation	↑ remyelination	Fancy et al., 2011
APC	β-catenin regulation cytoskeletal regulation	↑ OPC proliferation, differentiation	Lang et al., 2013
HIF	Autocrine Wnt7a/7b signaling	↓ developmental myelination ↑ White matter angiogenesis	Yuen et al., 2014
Sox17	β-catenin degradation	↑ oligodendrocyte differentiation	Ming et al., 2013
Nogo related proteins			
NogoA/NgR	RhoA(?), Rho kinase ROCK (?)	↓ remyelination, OPC recruitment	Pourabdolhossein et al., 2014 Niederost et al., 2002
LINGO-1	self-association, homophilic intercellular interactions	↓ OPC differentiation, maturation ↓ remyelination	Mi et al., 2009 Jepson et al., 2012
Additional regulators			
Shh	Induces Olig1 and Olig2 expression	↑ oligodendrogenesis ↑ OPC maturation, differentiation	Harsan et al., 2008 Ferent et al., 2013
Netrin-1	Signaling through Dcc, RhoA inhibition	↑ OPC proliferation, differentiation ↑ remyelination	Rajasekharan et al., 2009 He et al., 2013
LIF	Akt signaling, antioxidation	↓ white matter injury, infarct volume	Rowe et al., 2014