Demyelination as a Rational Therapeutic Target for Ischemic or Traumatic Brain Injury

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Abstract

Previous research on stroke and traumatic brain injury (TBI) heavily emphasized pathological alterations in neuronal cells within gray matter. However, recent studies have highlighted the equal importance of white matter integrity in long-term recovery from these conditions. Demyelination is a major component of white matter injury and is characterized by loss of the myelin sheath and oligodendrocyte cell death. Demyelination contributes significantly to long-term sensorimotor and cognitive deficits because the adult brain only has limited capacity for oligodendrocyte regeneration and axonal remyelination. In the current review, we will provide an overview of the major causes of demyelination and oligodendrocyte cell death following acute brain injuries, and discuss the crosstalk between myelin, axons, microglia, and astrocytes during the process of demyelination. Recent discoveries of molecules that regulate the processes of remyelination may provide novel therapeutic targets to restore white matter integrity and improve long-term neurological recovery in stroke or TBI patients.

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Conflict of interest

None.

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Keywords

demyelination; oligodendrocyte; remyelination; cerebral ischemia; traumatic brain injury

1. Introduction

Stroke and traumatic brain injury (TBI) are worldwide public health and socioeconomic problems (Gillum et al., 2011; Roozenbeek et al., 2013). With recent improvements in emergency care, greater numbers of patients are able to survive after stroke or TBI than before. Unfortunately, most of these survivors still develop physical disabilities due to the lack of effective therapies to restrict and/or repair brain damage. Understanding the mechanisms underlying progressive brain damage after stroke or TBI is therefore imperative for the development of novel therapies that successfully improve long-term neurological functions.

The human brain consists of both gray matter and white matter. Gray matter mainly contains neuronal cell bodies and unmyelinated axons. Gray matter serves as an information processor for the central nervous system (CNS). White matter, on the other hand, is mainly composed of bundles of myelin-ensheathed axons, myelin-producing oligodendrocytes, and other glial cells. White matter plays an essential role in signal transmission and communication between different brain regions. Although previous research on brain injuries emphasized the pathological alterations in neuronal cells within gray matter, recent studies also highlight the importance of white matter integrity in long-term recovery after stroke and TBI (Matute et al., 2013; Pham et al., 2012; Semple et al., 2013). White matter injury is an integral component of most human stroke or TBI events and usually accounts for at least half of the lesion volume (Ho et al., 2005; Hulkower et al., 2013). Unfortunately, the adult brain has very limited capacity for white matter repair. Thus, unrepaired white matter injury disrupts sensorimotor function and elicits profound neurobehavioral and cognitive impairments (Desmond, 2002).

Demyelination, or loss of the myelin sheath, is a major pathological component of white matter injury and contributes significantly to long-term sensorimotor and cognitive deficits (Pantoni et al., 1996). Oligodendrocytes are the primary cells responsible for generating and maintaining the myelin sheath under normal conditions and for remyelination after axonal damage (Nave, 2010a). However, myelinating oligodendrocytes are highly vulnerable to ischemic or traumatic insults (Back et al., 2007; Petito et al., 1998) and the loss of oligodendrocytes is known to be a significant factor underlying demyelination after injury (Caprariello et al., 2012).

Herein, we will describe the major causes of demyelination and oligodendrocyte death following acute injury in the adult brain, and discuss the crosstalk between myelin, axons, microglia, and astrocytes. We will also describe the toxic sequelae of demyelination, and highlight potential therapeutic strategies to target demyelination and improve long-term neurological function recovery in stroke or TBI patients.

2. Molecular mechanisms underlying oligodendrocyte death and demyelination

Oligodendrocytes are highly sensitive to various stimuli, including oxidative stress (Husain and Juurlink, 1995), excitotoxicity (McDonald et al., 1998; Salter and Fern, 2005), and inflammation, all of which induce oligodendrocyte cell death and contribute to demyelination after stroke or TBI. Below we discuss the molecular mechanisms underlying oligodendrocyte cell death and demyelination.

2.1 Glutamate excitotoxicity

Glutamate toxicity is a major cause of cell death in oligodendrocytes and their progenitor cells in diverse CNS injuries (McDonald et al., 1998; Salter and Fern, 2005). Under conditions of energy breakdown, reversal of excitatory amino acid transporters (EAATs) may lead to unchecked extracellular glutamate release, which induces glutamate excitotoxicity through glutamate receptors on the surface of oligodendrocytes (Fern et al., 2014). Intracellular calcium overload from glutamate excitotoxicity is a significant cause of oligodendrocyte and myelin damage (Benarroch, 2009). Glutamate receptor overstimulation opens $\text{Na}^+/\text{Ca}^{2+}$ channels on oligodendrocytes, not only allowing the influx of calcium but also depolarizing the cell membrane (Tong et al., 2009). This membrane depolarization activates voltage-dependent Ca^{2+} channels, which could further increase intracellular Ca^{2+} levels. In addition, the decreased Na^+ gradient across the cell membrane caused by the glutamate surge may reduce the capacity of the Na^+ gradient-dependent antiporter to remove intracellular Ca^{2+} . In addition, Ca^{2+} can be released from its intracellular storage sites upon glutamate stimulation in oligodendrocytes. It has been reported that Ca^{2+} release from the endoplasmic reticulum through ryanodine receptors (RyRs) and from mitochondria through inositol triphosphate receptors (IP(3)Rs) is important for α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated excitotoxicity in oligodendrocytes (Ruiz et al., 2010). All of these mechanisms might contribute to the accumulation of cytosolic Ca^{2+} , which in turn can trigger oligodendrocyte toxicity (Benarroch, 2009).

There are three types of glutamate receptors on oligodendrocytes: AMPA, kainate, and N-methyl D-aspartate (NMDA) receptors (Butt, 2006; Salter and Fern, 2005). Glutamate receptors might be directly activated by glutamate released from damaged axons (Kukley et al., 2007; Ziskin et al., 2007). It has been shown that extracellular glutamate levels surge several hours after CNS injuries (Kolodziejczyk et al., 2010; Lai et al., 2014; Matute et al., 2006), leading to the over-activation of AMPA/kainate and NMDA receptors in the brain.

Previous studies have demonstrated that oligodendrocytes are highly vulnerable to AMPA/kainate receptor-mediated excitotoxicity (Alberdi et al., 2002). Blockade of this receptor reduces oligodendrocyte death *in vivo* (Tekkok and Goldberg, 2001) and *in vitro* (McDonald et al., 1998). Recent work further suggests that Zn^{2+} dysregulation is important in AMPA-induced excitotoxicity (Mato et al., 2013). The activation of AMPA receptors results in the cytosolic accumulation of Ca^{2+} , which in turn induces Zn^{2+} mobilization and accumulation in the cytosol (Mato et al., 2013). Excessive Zn^{2+} is known to activate ERK1/2 signal

transduction cascades and induce oligodendrocyte death in a poly[ADP]-ribose polymerase 1 (PARP-1)-dependent manner (Baxter et al., 2014; Domercq et al., 2013). NMDA receptors are expressed on the myelin sheath of oligodendrocyte processes and are similarly involved in oligodendrocyte cell death (Karadottir et al., 2005; Micu et al., 2006; Salter and Fern, 2005). Activation of these receptors leads to a drastic increase in ion concentrations (Benarroch, 2009; Butt, 2006; Salter and Fern, 2005; Song and Yu, 2014) and the disruption of myelin structure (Bakiri et al., 2008). Thus, excess glutamate released from damaged axons after CNS injuries may elicit calcium-induced excitotoxicity and zinc dysregulation in oligodendrocytes through AMPA and NMDA receptors.

2.2 Mitochondrial dysfunction and oxidative stress

Mitochondria are double membrane-bound organelles responsible for more than 80% of total ATP production within the cell. ATP production in mitochondria is achieved through the oxidative phosphorylation (OXPHOS) complexes embedded in the inner mitochondrial membrane. NADH and FADH₂ are produced through the tricarboxylic acid cycle in the matrix and are further oxidized by complexes I and II, respectively. The resulting electrons are passed through a series of electron carriers to the final electron acceptor, molecular oxygen. Furthermore, H⁺ ions are pumped into the intermembrane space to generate an electrochemical gradient across the inner membrane, thereby driving ATP synthesis (Newmeyer and Ferguson-Miller, 2003). In addition to serving as the power generator of the cell, mitochondria are intimately involved in apoptosis. Indeed, both anti-apoptotic and pro-apoptotic factors such as the Bcl-2 family members and caspases are closely associated with mitochondria (Chandra et al., 2004; Czabotar et al., 2014).

Mitochondrial dysfunction is implicated in the pathogenesis of various demyelinating disorders (Mahad et al., 2008; van Horssen et al., 2012). Damaged mitochondria have been shown accumulate in demyelinated axons and activated astrocytes after CNS insults. Under physiological conditions, the normal OXPHOS reaction produces reactive oxygen species (ROS) including superoxide (O₂⁻), hydroxyl radicals (OH), and hydrogen peroxide (H₂O₂) through complexes I and III. This ROS production is critical for redox signaling and integrating mitochondrial function with that of the whole cell (Murphy, 2009). The mitochondria-derived ROS can diffuse throughout the cell, thereby being reduced in concentration, and is usually removed by cytosolic antioxidant systems such as catalase, glutathione peroxidase, and thioredoxin peroxidase under normal, physiological conditions (Kong et al., 2014). However, excess ROS can be generated under stressful conditions, such as cyanide or rotenone poisoning, or during conditions of oxygen glucose deprivation (OGD), in which a lack of electron acceptors is especially harmful. Owing to their high energy demands, the abundance of iron, and low levels of molecular antioxidants, oligodendrocytes are highly sensitive to increased ROS (Juurlink, 1997; Shereen et al., 2011). Recent studies suggest that ischemia induces ROS production *in vivo* and *in vitro*, which leads to myelin loss and disruption of oligodendrocyte precursor cell (OPC) differentiation (Miyamoto et al., 2013). Furthermore, mitochondrial dysfunction may result in impaired Ca²⁺ regulation and axonal degeneration (Carvalho, 2013; Owens et al., 2013). When energy demands exceed the ATP-producing capacity of mitochondria, axons in injured regions become energy deficient, leading to intracellular Ca²⁺ influx and Ca²⁺

release from mitochondria (Kostic et al., 2013; Trapp and Stys, 2009). In addition, ATP signaling can directly trigger oligodendrocyte excitotoxicity by activation of Ca^{2+} -permeable purinergic P2X7 receptors (Matute, 2011). Mitochondrial injury has also been demonstrated to be involved in microglial release of pro-inflammatory cytokines (Lisak et al., 2009), many of which can induce oligodendrocyte damage, as described in the next section (section 2.3). Thus, oxidative stress and mitochondrial dysfunction are both critical players in the pathophysiology of demyelination.

2.3 Pro-inflammatory cytokines

Inflammatory cytokines are key mediators of pathological changes in demyelination disorders (Table 1). Cytokines such as tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , IL-2, and interferon- γ (IFN- γ), have all been repeatedly demonstrated to induce oligodendrocyte death (An et al., 2014; Curatolo et al., 1997; Li et al., 2008). For example, TNF- α has robust effects on oligodendrocyte cell lines. TNF- α inhibits OPC proliferation and differentiation, and induces oligodendrocyte apoptosis (Hovelmeyer et al., 2005; Pang et al., 2005). IFN- γ also produces concentration-dependent effects on oligodendrocyte cell lines. High levels of IFN- γ lead to oligodendrocyte apoptosis and demyelination, whereas low levels protect mature oligodendrocytes by maintaining OPCs in the cell cycle and mildly stressing the endoplasmic reticulum (Chew et al., 2005; Corbin et al., 1996; Lin et al., 2005). Furthermore, IL-6 enhances OPC differentiation and survival even in the presence of glutamate excitotoxicity (Pizzi et al., 2004; Valerio et al., 2002). Recent studies demonstrate that IL-17A exposure stimulates OPCs to differentiate and mature and participate in the inflammatory response (Rodgers et al., 2014). An improved understanding of inflammatory mechanisms underlying oligodendrocyte death and demyelination might lead to novel neuroprotective therapeutic approaches for stroke or TBI patients.

3. Crosstalk between oligodendrocytes and other white matter components

White matter consists of axons, myelin, oligodendrocytes, astrocytes, microglia, and capillaries. Accumulating evidence indicates that metabolite exchanges (cholesterol, glycogen, lactate, and N-acetyl-aspartate) between these components are important for the normal function of white matter tracts (Amaral et al., 2013; Saab et al., 2013). Understanding the interdependence of white matter components might help explain how pathological alterations expand through the nervous system across gray and white matter boundaries.

3.1 Axonal injury

In white matter tracts, axons are encapsulated by oligodendrocyte-generated myelin. The proliferation, migration, survival, and differentiation of oligodendrocytes require axon-derived signals (Bremer et al., 2010; Nave and Trapp, 2008). However, oligodendrocytes are also actively involved in sensing axonal energy needs and maintaining axonal integrity (Lappe-Siefke et al., 2003; Nave, 2010a). Once an axon has been demyelinated, its ability to transmit action potentials and its energy supply are severely impaired, and the exposed nerve fiber is highly susceptible to degeneration. Oligodendrocytes may support axonal survival and function through mechanisms independent of myelination (Funfschilling et al., 2012;

Morrison et al., 2013). For example, oligodendrocytes and their myelin processes deliver pyruvate or lactate to neurons, which is essential for normal axon integrity and function *in vivo* (Morrison et al., 2013; Nave, 2010b). Monocarboxylic acid transporters (MCTs), the most abundant lactate transporter in the CNS, are highly expressed on oligodendrocytes (Figure 1). The disruption of this transporter leads to blockade of the lactate shuttle from oligodendrocytes to axons and elicits axonal damage and neuron loss (Lee et al., 2012).

It is tempting to speculate that, during pathological conditions, energy may be gained by the breakdown of myelin lipids in oligodendrocyte peroxisomes (Kassmann, 2014). However, disruption of oligodendrocyte proteins such as proteolipid protein (PLP) (Al-Saktawi et al., 2003; Edgar et al., 2010) and 2',3'-cyclicnucleotide 3'-phosphodiesterase (CNP) (Lappe-Siefke et al., 2003) may contribute to severe disruption of axonal function and integrity. In short, oligodendrocyte damage invariably produces some degree of axonal demyelination and degeneration, and contributes to permanent neurological disabilities after stroke or TBI.

3.2 Astrocyte activation

In addition to direct energy support from oligodendrocytes to neurons, astrocytes may also be involved in supplying energy to axons. Astrocytes contact capillaries with their end feet and take up many metabolites from blood (Daneman, 2012) (Figure 1). Under physiological conditions, astrocytes, oligodendrocytes, and axons take up glucose from capillaries through glucose transporters (GLUTs). Damage to the axon or oligodendrocyte results in an increase in glutamate in the extracellular space, due to the reversal of glutamate transporters (Domercq et al., 2005) or the vesicular release of glutamate from unmyelinated axons (Ziskin et al., 2007). The excessive glutamate in white matter can, at least partly, be taken up by astrocytes. Glycolysis is known to occur within astrocytes, leading to the production of metabolites such as lactate. Lactate is then taken up as an energy substrate by axons and oligodendrocytes through MCTs and connexins (CXs) (Figure 1). This 'pan-glial' network of oligodendrocytes and astrocytes is the major regulator of glutamate homeostasis in the CNS (Matute et al., 2007) and also serves as a spatial potassium buffer, allowing water transport for the maintenance of ionic homeostasis (Menichella et al., 2006; Rash, 2010).

Oligodendrocyte death and axonal demyelination are invariably accompanied by the activation of astrocytes. Oligodendrocytes are interconnected not only with each other but also with astrocytes via gap junctions, allowing for intercellular transfer of small molecules (Orthmann-Murphy et al., 2007; Tress et al., 2012). Disruption of the coupling between astrocytes and oligodendrocytes has been shown to result in demyelination and motor impairments *in vivo* (Tress et al., 2012). When astrocytes are activated under stressful conditions, the use of astrocyte-released energy substrates may transiently support axon energy needs and partially compensate for loss of function. However, normal communication between astrocytes and oligodendrocytes through CXs is interrupted in pathological conditions, thereby resulting in oligodendrocyte death and subsequent demyelination. Activated astrocytes can also exacerbate oligodendrocyte cell death by reducing extracellular zinc concentrations, which then initiates NADPH oxidase activation within oligodendrocytes through stimulation of Ca^{2+} -permeable AMPA receptors (Johnstone et al., 2013). These results show that activated astrocytes exert both positive and

negative influences on oligodendrocyte pathophysiology, similar to the dual-faced nature of microglia discussed below.

3.3 Microglial activation

Microglia are resident immune cells within the CNS and play a central role in the initiation and propagation of inflammatory responses (Hu et al., 2014; Owens et al., 2013). They are present within all brain regions, including regions containing both gray and white matter. Microglia are rapidly activated and increase in numbers in response to CNS injuries. Activated microglia upregulate cell surface markers, which facilitates their migration to the site of the injury. Microglia demonstrate high levels of plasticity in their responses to CNS injuries (Kigerl et al., 2009; Perry et al., 2010). Remarkably, microglia play a dual-faced role in the progression of white matter injury after stroke or TBI (figure 2). On the one hand, microglia release ROS and pro-inflammatory cytokines such as TNF- α (Volpe, 2011), both of which are detrimental to neighboring oligodendrocytes. Activated microglia also produce glutamate (Takahashi et al., 2003), which exacerbates damage in oligodendrocytes and their progenitor cells following CNS insults (Kaur and Ling, 2009; Li et al., 2005; McTigue and Tripathi, 2008). On the other hand, activated microglia can also serve to resolve local inflammation, clear cellular debris, and provide protective factors to reduce oligodendrocyte injury or demyelination (Hanisch and Kettenmann, 2007; Wang et al., 2013). Recent studies have revealed that microglia assume different phenotypes with distinct destructive (M1-like phenotype) or protective (M2-like phenotype) functions at different stages after stroke or TBI (Figure 2) (Hu et al., 2015; Hu et al., 2012; Wang et al., 2013). Due to their pleiotropic functions, microglia may either accelerate or limit the spread of white matter pathology, depending on the context (Davalos et al., 2005; Miron et al., 2013; Wang et al., 2015). We have recently reviewed the differential roles of M1-like and M2-like microglia in oligodendrogenesis and white matter integrity (Hu et al., 2015). A deeper understanding of microglial activation will be critical for formulating effective therapeutic strategies for acute brain injuries.

4. The sequelae of demyelination

Myelination allows the rapid transfer of information that is needed for normal cognitive, emotional, and behavioral function (Deoni et al., 2011). Oligodendrocyte cell death and axonal demyelination lead to limited impulse propagation, and result in severe neurological dysfunction, including motor dysfunction, impaired cognitive abilities, psychiatric disorders, and neurodegeneration.

Motor dysfunction is the major neurological consequence of subcortical stroke and TBI and exhibits limited functional recovery. Magnetic resonance imaging (MRI) has revealed dynamic changes in white matter during complex sensorimotor tasks such as playing the piano, juggling, and abacus use (Bengtsson et al., 2005; Hu et al., 2011; Scholz et al., 2009). Intriguingly, recent studies suggest that learning a complex motor skill requires the generation of new oligodendrocytes and active myelination processes (Long and Corfas, 2014; McKenzie et al., 2014). Therefore, demyelination after stroke or TBI might result in catastrophic motor dysfunction.

Microglia, oligodendrocytes, and astrocytes are major sources of extracellular matrix components in late stages of memory consolidation (Babayan et al., 2012). Growing evidence supports several forms of activity-dependent signaling between axons and myelin-forming oligodendrocytes (Wake et al., 2011). Furthermore, recognition and spatial memory are impaired after corpus callosal injury *in vivo* (Kouhsar et al., 2011; Shibata et al., 2007; Yoshizaki et al., 2008). There is growing awareness that TBI is an important risk factor for neurodegenerative diseases (Daneshvar et al., 2011; Masel and DeWitt, 2010). For example, individuals with a history of TBI show an increased incidence of Alzheimer's disease (AD) (Guo et al., 2000; Jellinger et al., 2001; Plassman et al., 2000). A higher incidence of neurodegeneration is related to impaired white matter integrity in a subset of white matter tracts such as the parahippocampal white matter, caudal portions of the cingulum, the inferior fronto-occipital fasciculus, and posterior portions of the corpus callosum, all of which are related to episodic memory impairments in early AD (Bendlin et al., 2010; Douaud et al., 2011; Gold et al., 2012; Gold et al., 2010; Smith et al., 2010).

5. Potential therapeutic targets related to demyelination

Although the adult brain has limited capacity for full remyelination and white matter repair, remyelination is known to occur to some extent after CNS injuries, with the goal of ensheathing demyelinated axons with new myelin, reinstating saltatory conduction, and reducing functional deficits. The white matter regenerative processes may be categorized into OPC proliferation, OPC migration towards the demyelinated axons, OPC differentiation, and final maturation into functional oligodendrocytes (Franklin and Ffrench-Constant, 2008; Zhang et al., 2013). OPCs are continuously present in the normal adult brain and proliferate actively soon after ischemic injury (Chu et al., 2012). It is also possible that without this active OPC proliferation, there would be even worse white matter injury and catastrophic tissue necrosis. Furthermore, replenishment of oligodendrocytes by OPCs can be observed in peri-infarct areas after ischemia (Mandai et al., 1997). Unfortunately, our recent studies show that, despite active OPC proliferation, ischemic white matter demyelination showed little improvement over time (Chu et al., 2012). This failure of remyelination despite robust regeneration of OPCs has also been reported in perinatal hypoxia/ischemia brain injury, and may be attributed to a persistent arrest in preoligodendrocyte maturation (Segovia et al., 2008). Furthermore, aging is known to interfere with oligodendrocyte regeneration and axonal remyelination (Sim et al., 2002). Multiple factors may cause regenerative failure in the adult CNS, including the weakness of intrinsic growth capacities and the inhibitory extrinsic environment. When remyelination fails after CNS insults, axons remain naked and vulnerable to degeneration, leading to the progressive irreversible disabilities (Duncan et al., 2009; Franklin and Ffrench-Constant, 2008; Irvine and Blakemore, 2008). Therefore, interventions that promote the remyelination of axons are potentially promising strategies to improve white matter integrity and functional recovery after CNS injuries (Chen et al., 2014; McLaughlin and Gidday, 2013; Plemel et al., 2014). Below we will discuss potential therapeutic strategies targeting remyelination after injury.

5.1 Increasing the proliferation of oligodendrocyte progenitor cells

OPCs persist in the adult CNS (~5% of all neural cells) and continue to divide and differentiate into myelinating oligodendrocytes throughout life (Richardson et al., 2011; Rivers et al., 2008; Young et al., 2013). After white matter injury, OPCs rapidly proliferate and migrate to fill the demyelinated area, differentiate into mature oligodendrocytes, and restore myelin sheaths. Studies have shown that subventricular zone-derived progenitors contribute to myelin repair (Menn et al., 2006). Exogenous OPC transplantation has proven effective in initiating myelin formation after demyelination (Windrem et al., 2002; Windrem et al., 2008). However, transplanted mature oligodendrocytes fail to form myelin (Blakemore and Keirstead, 1999). Fibroblast growth factor 2 (FGF2) and epidermal growth factor (EGF) both enhance OPC generation in pathological conditions (Scafidi et al., 2014; Whittaker et al., 2012). Furthermore, neurotrophins such as BDNF, PDGF-A, and NT3 specifically stimulate OPC proliferation (Girard et al., 2005; McTigue et al., 1998; Murtie et al., 2005; Woodruff et al., 2004). Thus, exogenous delivery of these factors to promote OPC proliferation may boost white matter recovery.

5.2 Enhancing oligodendrocyte progenitor cell migration

OPCs remain motile and can migrate within the CNS. A recent study has shown that vascular remodeling after acute demyelination lesions favors the migration of neuroblasts from their original niche to the newly lesioned site (Cayre et al., 2013). Exercise and enriched environments have been shown to increase subventricular zone mitotic activity and subventricular zone-derived progenitor mobilization toward demyelinated lesions, thereby improving long-term functional recovery (Magalon et al., 2007). Several factors can specifically regulate OPC migration. Guidance cues such as Sema3F (Piaton et al., 2011; Syed et al., 2011), reelin (Courtes et al., 2011), and netrin 1 (Cayre et al., 2013) are involved in progenitor migration in the early phases of the regenerative process. In addition, chondroitin sulphate proteoglycan (CSPG), an extracellular matrix protein, is a negative regulator of myelin repair that limits OPC migration toward the lesion site and inhibits axonal regeneration (Siebert and Osterhout, 2011; Siebert et al., 2011). Therefore, treatment with the enzyme chondroitinase ABC (cABC), which removes the glycosaminoglycan side chains of CSPG, might reverse the inhibitory effects of CSPGs on OPC migration and enhance remyelination (Siebert and Osterhout, 2011; Siebert et al., 2011).

5.3 Promoting oligodendrocyte progenitor cell differentiation

Although an increase in OPC number is essential for recovery after CNS injury, it is not sufficient to induce remyelination by itself (Barres and Raff, 1999). Accumulating evidence emphasizes that the differentiation of OPCs into mature myelinating oligodendrocytes is essential for effective remyelination and recovery (Emery, 2010; Fancy et al., 2011; Miron et al., 2011). Promoting oligodendrocyte differentiation has therefore been proposed as a therapeutic strategy to enhance white matter repair. To this end, the molecules regulating OPC differentiation have received considerable attention. Several molecules, including fibronectins (Stoffels et al., 2013), LINGO-1 (Jepson et al., 2012; Mi et al., 2009; Mi et al., 2013), PSA-NCAM (Koutsoudaki et al., 2010) and the Wnt/ β -catenin/Tcf4 signaling pathway (See and Grinspan, 2009) have been shown to negatively regulate OPC

differentiation. In contrast, EGF, bFGF and PDGF α have been reported to promote OPC differentiation (El Waly et al., 2014; Karimi-Abdolrezaee et al., 2012). Therefore, reducing the differentiation inhibitors and/or boosting the differentiation promoting factors may improve white matter repair after stroke or TBI.

6. Conclusions

The past few decades have witnessed a significant increase in our knowledge about demyelination after stroke and TBI. For example, we now know that white matter injury accounts for up to half of the lesion volume in patients and leads to devastating neurological impairments (Edlow and Wu, 2012; Ho et al., 2005; Hulkower et al., 2013). Increasing numbers of molecules critical for the initiation, progression, or repair of demyelination have been identified and may serve as therapeutic targets to promote recovery after brain injuries. However, there are still many obstacles that hinder the development of clinically feasible therapies for demyelination. First, several molecules may possess dual roles in demyelination/remyelination processes. For example, proteoglycan CSPG, a major component of scar tissue known to hinder OPC migration and axonal regeneration, can induce the switch to a beneficial microglial M2 phenotype during acute phases of CNS injury (Rolls et al., 2008). For any strategies targeting these molecules, the treatment regimens will therefore have to be carefully designed to avoid unwanted side effects. Second, most of the demyelination-regulating molecules are not tissue or cell type specific, and the development of cell specific drug delivery systems will be essential. As the central role of demyelination becomes increasingly clear, further studies on ways to improve myelin integrity and protect both gray and white matter are warranted so that long-lasting functional recovery can finally be achieved in stroke and TBI victims.

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List of abbreviations

AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CNP	2',3'-cyclicnucleotide 3'-phosphodiesterase
CNS	central nervous system
EAAT	excitatory amino acid transporters
IFN	interferon
IL	interleukin
MCT	monocarboxylic acid transporter
NMDA	N-methyl D-aspartate

NO	nitric oxide
OGD	oxygen glucose deprivation
OPC	oligodendrocyte precursor cell
OXPHOS	oxidative phosphorylation
PARP	a poly[ADP]-ribose polymerase
PLP	proteolipid protein
ROS	reactive oxygen species
TBI	traumatic brain injury
TNF	tumor necrosis factor

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Highlights

- Demyelination contributes to long-term functional deficits after stroke or TBI
- Mechanisms of demyelination and oligodendrocyte death in acute brain injury
- Crosstalk between oligodendrocytes and other white matter components
- Potential therapeutic targets related to demyelination and remyelination

Figure 1. Astrocyte, oligodendrocyte, and axon interactions in white matter in normal or pathological settings

Under normal conditions, astrocytes take up glucose from capillaries through glucose transporters (GLUTs) and the subsequent glycolysis metabolites can be transmitted to axons and oligodendrocytes as energy sources by monocarboxylic acid transporters (MCTs) and connexins (CXs). However, when astrocytes are activated under stressful conditions, the normal CX-mediated communication between astrocytes and oligodendrocytes is interrupted, resulting in oligodendrocyte cell death and subsequent demyelination.

Figure 2. Microglial activation after stroke or TBI

After stroke or TBI, resting microglia are polarized toward the M1 or M2 phenotype. M1 microglia release multiple pro-inflammatory cytokines, leading to cell damage and exacerbate brain injury. However, M2 microglia secrete anti-inflammatory cytokines and growth factors, contributing to tissue repair.

Table 1

Effect of pro-inflammatory cytokines on oligodendrocyte line cells

Cytokine	Regulation	Function	References
TNF- α	TNFR1/JNK signaling, TIMP-3/caspase-3	induce oligodendrocyte apoptosis; delay myelination	(Deng et al., 2008; Deng et al., 2010; Hovelmeyer et al., 2005; Kim et al., 2011; Pang et al., 2005; Su et al., 2011; Wang et al., 2014; Yang et al., 2011)
	TNFR2/leukemia inhibitory factor (LIF), AMPK, oxidative stress	inhibit OPC proliferation and differentiation	(Bonora et al., 2014; Fischer et al., 2014; Kleinsimlinghaus et al., 2013; Maier et al., 2013)
IL-1 β	ciliary neurotrophic factor (CNTF)	induces the survival of oligodendrocytes	(Herx et al., 2000)
	glutamate excitotoxicity	promotes oligodendrocyte and OPC death	(Takahashi et al., 2003)
	MAPK signaling pathways	inhibit OPC proliferation, enhancing differentiation and survival	(Vela et al., 2002; Zhang et al., 2006)
IL-6	IL-6R	enhances OPC differentiation and survival	(Lara-Ramirez et al., 2008; Pizzi et al., 2004; Valerio et al., 2002)
IL-11	IL-11R	potentiates oligodendrocyte survival, maturation	(Zhang et al., 2006)
IL-17A	ERK1/2 signaling	promotes OPC differentiation	(Rodgers et al., 2014)
Interferon- γ	dendritic cell exosomes	maintain OPCs in the cell cycle, stress the endoplasmic reticulum, involved in remyelination	(Chew et al., 2005; Pusic et al., 2014)
	endoplasmic reticulum kinase	induces oligodendrocyte apoptosis	(Chew et al., 2005; Corbin et al., 1996; Lin et al., 2005)