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Review

Mechanisms of demyelination and remyelination in the young and aged brain following white matter stroke

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ABSTRACT

Subcortical white matter stroke (WMS) accounts for 25% of all incidences of stroke and results in severe motor and cognitive disability. WMS stands as the second leading cause of dementia and is immensely prevalent in older adults. In a startlingly statistic, a majority of human beings will present WMS by 80 years of age. Early ischemic lesions produced by WMS are asymptomatic and termed “silent strokes”. WMS is, however, progressive with both the size of the lesions and their distribution, increasing as patients age. Pathological analyses in both postmortem human tissue samples and mouse models of WMS demonstrate myelin degeneration as a chief hallmark of WMS. This suggests that the development of rehabilitative strategies in human WMS will necessitate an understanding of the pathophysiology of demyelination and remyelination following ischemic injury. This review will address our current understanding of WMS from human imaging studies, the development of rodent models of WMS, the mechanistic underpinning of myelin degeneration following WMS as well as remyelination dynamics in the adult brain.

1. White matter plays a critical role in CNS function

White matter is composed of a dense array of myelinated and unmyelinated axonal tracts that emerge from a variety of projection neurons across the central nervous system. In the central nervous system, white matter tracts serve varying functions. For example, the optic nerve allows for the propagation of visual input through axons of retinal ganglion cells into the thalamus and midbrain. The internal capsule carries myelinated fibers from the motor cortex to the spinal cord and is critical for movement. The corpus callosum, which is located just ventral to the cortex, stands as the largest white matter tract in the brain and serves as a primary interhemispheric commissure allowing for the integration of sensorimotor and cognitive information (Patel et al., 2013). Of the roughly 20 million axons that compose the corpus callosum, a majority form homotopic connections with homologous regions of the brain in the opposite hemisphere while a minority form heterotopic connections with various other cortical regions (Bloom and Hynd, 2005; Hofer and Frahm, 2006; Patel et al., 2013). Indeed, it is the corpus callosum that allows for rapid communication between both hemispheres of the brain. The corpus callosum is also a major site for white matter disease. It is the major locus of damage in subcortical white matter stroke or vascular dementia (DeCarli et al., 2005). Damage to the corpus callosum is a predictor of both multiple sclerosis (MS) lesions on MRI and predicts cognitive decline due to MS progression (Group, 2002). Due to its large size in the mouse, the corpus callosum functions as a primary target for injury in rodent models of white matter stroke (WMS). As such, the focus of this review will be the corpus callosum, its dysfunction after WMS and experimental models of remyelination in this white matter tract. However, the basic principles underlying myelin biology are likely applicable in all white matter tracts of the central nervous system.

Myelin is a multi-lamellar extension of membrane from the oligodendrocyte – or Schwann cells in the peripheral nervous system – which wraps around the axon (Rasband and Peles, 2016) Myelin serves a variety of functions in the brain. Mylein insulates the axon by increasing resistance and decreasing the capacitance of the axolemma allowing for fast, saltatory conduction with ion exchange largely at nodes of Ranvier – 1μm gaps situated in between individual myelin sheaths that are interspersed along the axon in both the CNS and PNS (Chang et al., 2016). In the CNS, oligodendrocytes are involved in the clustering of voltage gated sodium channels at high densities at nodes of Ranvier (Kaplan et al., 1997; Rasband, 2004; Chang et al., 2016; Rasband and Peles, 2016). Clustering of voltage gated ion channels at nodes across the axon allows for the regeneration of the action potential as it propagates towards its target.

The function of myelin may not be limited to the maintenance of the action potential. Indeed, myelin and the oligodendrocyte provide metabolic support to its associated axon and are instrumental to its survival (Hinman, 2014). Lentivirus shRNA mediated disruption of monocarboxylate transporter 1 (MCT1), a lactate transporter enriched

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in oligodendrocytes, results in axon degeneration in the optic nerve (Lee et al., 2012). Furthermore, live imaging of ex vivo optic nerves, which express an axonal ATP sensor (ThyAT), following MCT1/2 inhibition results in reduction in axonal ATP levels (Trevisiol et al., 2017). These data suggest that oligodendrocytes provide metabolic support to underlying axons via lactate transport in addition to altering the conduction process for the action potential.

Adding to the growing list of myelin functions is its role in plasticity and non-synaptic forms of memory. Though this field is still in its infancy, accumulating evidence in both mouse and human studies suggests that the central nervous system uses myelin as a means to modulate action potential dynamics via the direct manipulation of myelin production and ensheathment of naked axons or the remodeling of existing sheaths of myelin. By altering the level of myelin on the axon, the CNS is capable of actively modulating the conduction speed of the action potential and in effect, altering a neuron's signaling onto its postsynaptic partner (Bergles and Richardson, 2016). Indeed, there is now evidence that certain forms of motor learning necessitate rapid changes in myelin structure and that memory consolidation may also occur at the level of the myelin sheath (Bergles and Richardson, 2016). This is an emerging concept known as “myelin plasticity”—that the effects of myelin on axonal conduction and axonal support can be modulated by brain activity and used to enhance or alter neuronal signaling (Almeida and Lyons, 2017; Kaller et al., 2017). At this point, the question still remains as to the signaling cascades that are involved in this process. However, the evidence suggests that one mechanism of action is the neuron's capacity to signal onto oligodendrocyte precursor cells (OPC), a resident stem cell in the brain that functions in part to differentiate into myelinating oligodendrocytes in the developing and adult brain and drive them to mature. A neuron that is more active in a behavior or in a learning paradigm signals to adjacent OPCs, and this may result in new myelin formation (Purger et al., 2016; Almeida and Lyons, 2017; Kaller et al., 2017). The second potential mechanism of action in myelin plasticity lies in activated axons signaling directly onto associated myelin sheaths and induce remodeling. That is, the neuron orchestrates changes in myelin architecture either by extension or retraction of the myelin sheath – termed internode – or in the change in thickness of the myelin wraps (Almeida and Lyons, 2017; Kaller et al., 2017).

To date, our conception of myelin suggests that it coexists with the underlying axon and nodes of Ranvier as a dynamic, functional unit that ensures the fidelity of electrical impulses by 1) altering the electrophysiological characteristics of the axolemma 2) providing for the high metabolic costs of long distance neuronal signaling, and 3) actively tuning neuronal signaling.

2. Aged related myelin deficits

Age related myelin deficits in the central nervous system have been demonstrated in multiple species. A recent in vivo analysis of myelin formation by cortical oligodendrocytes in mice demonstrate that while myelin formation occurs throughout the life of the animal -providing further evidence that myelin plasticity is a lifelong process- aberrations become apparent in advanced age (Hill et al., 2018). Analysis of P910 mice demonstrate a decrease in oligodendrocyte and myelin density and the formation of myelin abnormalities such as myelin spheroids and single internode loss along cortical axons (Hill et al., 2018). Age related myelin deficits are also documented in primates. Analysis of myelin deficits in the deep layers of the visual cortex in young (5–10 year) and aged (25–33 year) rhesus monkeys demonstrate overt structural disruption such as the formation of cytoplasm enclosing splits along the main myelin sheath as well as 1-μm in diameter fluid filled cavities that cause the myelin sheath to bulge out from the axon (Peters et al., 2000; Peters, 2002). Similar defects were also shown in myelin sheaths in the corpus callosum ventral to the prefrontal cortex in aged Rhesus monkeys (Peters and Sethares, 2002).

Disruption in myelin structure suggests a worsening of the conduction properties of neural impulses along a myelinated axon. Indeed, there are several examples of aged related changes in conduction velocity in neurons of the central nervous system (Peters, 2002). Extracellular recording of pyramidal tract (PT) neurons in the motor cortex of a small cohort of aged cats (16–17 year) demonstrates a significant decrease in their median conduction velocity following antidromic stimulation of the medullary pyramidal tract (Xi et al., 1999). Similarly, in alpha motor neurons of the cat spinal cord, aged cats (14–15 year) demonstrate a decrease in conduction velocity relative to young adult cats (1-3 year) (Morales et al., 1987).

3. Loss of white matter as a consequence of stroke

With the importance of myelin to CNS function, it stands that its disruption or loss in instances of disease or injury can be devastating. Indeed, the disruption of myelin architecture is the pathological hallmark of white matter stroke (WMS), a recurrent neurovascular disease which results in ischemia of small blood vessels in white matter tracts.

Human imaging studies in patients suggest that WMS begin as acute infarcts, some of which are transient. Those that remain either persist as white matter hyperintensities or form 3-5 mm cerebral spinal fluid filled cavities known as lacunes (Wardlaw et al., 2015). A closer look at the pathology of WMS lesions in post mortem brains demonstrates hallmark signs of damage including white matter disruption, microglial activation, astrogliosis, myeloid cell infiltration, and axonal degeneration (Wardlaw, 2008; Bailey et al., 2012; Wardlaw et al., 2015). Curiously, an examination of myelin and axonal architecture disruption in post mortem human WMS samples demonstrates that axons within the *peri* infarct border, the peripheral region surrounding the stroke core, are relatively intact. However, there appears to be a specific disruption in both myelin architecture and nodes of Ranvier and their associated paranodes in areas up to 150% of the infarct diameter. At areas further away from the infract, myelin remains intact but the nodes and paranodes are noticeably disrupted (Hinman et al., 2015). White matter stroke is increasingly common with age and these white matter lesions expand locally (Loos et al., 2018). In fact, the expansion of ischemic white matter disease is most prominent in the corpus callosum and immediately adjacent callosum-frontal lobe white matter tracts (Gouw et al., 2008). These data suggest a temporally coupled sequence of pathological events by which nodal and paranodal domains are disrupted first, resulting in later demyelination followed potentially by axonal degeneration. These studies also indicate that the “peri-infarct region” or white matter that is adjacent to the core of the stroke, is a particularly important research target because it is the site of de-stabilized axoglial interactions and progressive myelin and axonal injury. This axonal degeneration could be due to the loss of metabolic support from the degenerated myelin sheath.

Once considered a form of “silent stoke”, early lesions produced by WMS often result in subtle neurological deficits such as visual field impairment, motor disturbances, and frailty (Vermeer et al., 2007). However, much of these deficits go unnoticed, so patients that present with early WMS are often unaware of them. As noted, WMS is progressive and early lesions both grow in size and accumulate as the patient ages (Sozmen et al., 2012; Wardlaw et al., 2015). The consequences of advanced progression of WMS in human patients is vast. From a systems level, WMS is associated with hemiparesis, gait abnormalities, verbal processing deficits, and disruption of executive function (Sozmen et al., 2012). Indeed, vascular dementia caused by progressive WMS stands as a leading cause of human dementia second only to Alzheimer's disease and is also associated with an increase prevalence of late onset depression (Iadecola, 2013; Wardlaw et al., 2015).

WMS is relatively common and accounts for 25% of all stroke subtypes (Bamford et al., 1991; Schneider et al., 2004; Rosenzweig and Carmichael, 2013). Though the etiology of WMS is currently unknown, there are several predictors. MRI analyses of human patients found a

correlation between metabolic syndrome (a medical condition defined by obesity, hypercholesterolemia, hypertension, and diabetes) subcortical white matter lesions, silent lacunar infarcts, and periventricular hyperintensities (Bokura et al., 2008; Park et al., 2008) Finally, WMS is highly correlated with age. Indeed, in a striking statistic, most people will have WMS infarcts by 80 years of age (Leeuw et al., 2001).

4. White matter stroke: differential pathology in the young and aged brain

The most profound observation that has emerged from the examination of mouse models of WMS is the brain's failure to remyelinate following injury. Several models of WMS have been developed and characterized in the past decade, all of which have allowed for the examination of mechanisms that underlie neural and glial degeneration following WMS. From these studies, it is becoming clear that the brain's failure to remyelinate following WMS and the molecular mechanisms that underpin this phenomenon, set ischemic injury apart from the other central nervous system demyelinating disorders such as multiple sclerosis.

Focal microinjection of vasoconstrictors such as N(5)-(1-lminoethyl)-L-ornithine HCL (LNIO) or endothelin-1 into subcortical white matter tracts such as the corpus callous have provided a great deal of information regarding both the pathological and behavioral consequences of WMS. However, evidence demonstrating the off-target effects of endothelin-1 on the modulation of differentiation of various cell progenitors, including OPCs, has pushed this model out of favor in place of LNIO (Gadea et al., 2009; Soh et al., 2016). Initial characterization of the LNIO WMS model and an age effect was conducted by Rosenzweig and Carmichael, 2013. In this study, WMS was induced in three different aged cohorts of mice: 3 (young), 15 (middle aged), and 24 months (aged). It was determined that while all three cohorts showed canonical injury pathologies, each age group showed varying degrees of injury in tissue measure outcomes, behavioral deficits, and rates of recovery. Variations in CNS inflammatory response were seen in neutrophil and microglia/macrophage infiltrates across young and aged mice. Infiltrates were localized to the infarct in young animals and were distributed more widely across the motor cortex in older mice. Increases in myelin and axon degeneration as well as apoptosis of oligodendrocytes was found across all age groups, but degeneration was considerably worse in older mice. Finally, functional motor deficits were observed in all three groups, however, recovery was only seen in younger and middle-aged mice. These data suggest that while primary tissue damage from WMS is indiscriminate across age groups, recovery is specific to the young brain. Indeed, evidence in both human and mouse suggests that myelin repair and recovery in multiple sclerosis (MS) is also age dependent (Huang and Franklin, 2012). An analysis of the remyelination phase in MS models following focal demyelination in aged and young rats demonstrated a delay in recruitment of OPCs to the lesion as well as decreased rates of differentiation in older rats (Sim et al., 2002). Epigenetic analysis of aged versus young mice in a cuprizone model of MS suggests changes is histone acetylation in the aged brain hinders the OPCs ability to differentiate into mature oligodendrocytes. These data point to various biological mechanisms that hinder remyelination in models to MS and provide reason for further exploration of the differential biological profiles of OPCs and oligodendrocytes in the aging brain following WMS. These data also evoke prior analyses of the temporal evolution of white matter hyperintensities in human imaging studies, which demonstrates the capacity for a subset of white matter hyperintensities to regress in size rather than cavitate (Wardlaw et al., 2015) This progression in human WMS stresses a translational goal of understanding why partially damaged white matter tracts progress towards greater damage.

5. White matter stroke: a failure to remyelinate

One potential cause for the brain's failure to remyelinate after WMS is the specific disruption of the proliferating OPCs ability to mature into oligodendrocytes. As mentioned previously, OPCs are a resident stem/progenitor cell, which is found evenly tiled across the entire brain and comprise roughly 5% of the total cellular population (Zawadzka et al., 2010). The most well characterized role of OPCs is their capacity to differentiate into mature myelinating oligodendrocytes both in early postnatal development and into adulthood (Rivers et al., 2008; Zawadzka et al., 2010). A precursor step to the genesis of oligodendrocytes is the exit of mitotic OPCs from their cell cycle. Upon exit, OPCs down-regulate their lineage markers (NG2 and PDGFRα) and transition into a mature state.

In the rodent brain, the majority of myelin is synthesized by adult-generated oligodendrocytes derived from a subset of mitotic OPCs during the first 4–6 weeks of life (Young et al., 2013; McKenzie et al., 2014). However, post mitotic OPCs continue to differentiate into mature oligodendrocytes well into adulthood, albeit at a slower rate (Young et al., 2013) Indeed, measurements of cell cycle time of OPCs in the corpus callosum demonstrate that it significantly increases from 2 days at postnatal day 6, 9 days at postnatal day 60, and 70 days at postnatal day 240–540. Furthermore, aged brains generate less oligodendrocytes, which parallels the decline in cell cycle time for OPCs (Psachoulia et al., 2009). Of note is that despite the increase in cell cycle time, the process of generation of adult, mature oligodendrocytes do not stop with age as even at 8 months of age, OPCs continue to divide and differentiate into mature oligodendrocytes both in the cortex and corpus callosum (Psachoulia et al., 2009).

An analysis by Sozmen et al. (2016) of OPC proliferation and maturation dynamics in the mouse brain after WMS provides a mechanistic understanding of the brain's failure to remyelinate after ischemic injury. Following WMS, there is a significant increase in local OPC proliferation in the periinfarct region of white matter stroke. The periinfarct regions is that part of the subcortical white matter that is adjacent to the lesion itself but shows preservation of axons and partial damage to myelin. Of these post mitotic OPCs that respond to the stroke and divide, 4–13% differentiate into astrocytes while the remaining cells remain in a immature or progenitor state, as indicated by surface marker expression. Shunting of OPCs into an astrocytic fate was not detected in the unstroked corpus callosum and the function of these astrocytes after the stoke is currently unknown. However, OPC transition into astrocytes has been reported in in vitro cultures of OPCs derived from the optic nerve as well as OPCs in the grey matter of the ventral posterior forebrain of an NG2 reporter line (Kondo and Raff, 2000; Zhu et al., 2008). Furthermore, analysis of the lesion site following stab wound in rats demonstrates that proliferating OPCs in the lesion border express markers for immature astrocytes (Alonso, 2005). Interestingly, in this same study the authors found that dexamethasone induced inhibition of OPC proliferation disrupted the structure of the glial scar suggesting that astrocytes derived from proliferating OPCs specifically take part in the formation of the scar.

OPCs respond to the initial ischemia in WMS both by proliferation and migration towards the lesion, however they fail to differentiate. An understanding of the molecular mechanisms behind this differentiation block might lead to the development of strategies to percipitate white matter repair. A candidate signaling molecule in the inhibition of OPCs is Nogo receptor (NgR1) and its co-receptor Lingo-1. NgR1 is a glycosyl phosphatidylinositol (GPI) anchored protein which forms a ternary complex with p75 and LINGO-1, which is enriched in postnatal neurons (Mi et al., 2004). The NgR1/p75/Lingo-1 receptor complex binds to myelin associated growth inhibitory molecules such as a NogoA, myelin associated protein (MAG) and oligodendrocyte myelin glycoprotein (OMgp), all of which have been implicated in axon growth inhibition (Mi et al., 2004). Nogo signaling between oligodendrocytes and OPCs has also been implicated as a modulator of myelin formation. Knock out

of NogoA significantly increases internodes per oligodendrocyte in the cerebral cortex suggesting that NogoA functions as a cell to cell inhibitory cue for myelin formation (Chong et al., 2012). Furthermore, ultrastructural analysis of descending myelinated axons in the spinal cord of an NgR1 knockout model demonstrates the disruption of paranodal loops and myelin decompaction providing further evidence of the critical role Nogo signaling plays in myelin dynamics (Lee et al., 2017). Therapies that block Lingo-1 promote remyelination in models of MS and have been taken to human clinical trials (Mi et al., 2007). NgR1 binds more than just Nogo, but in fact, interacts with extracellular matrix proteins that contain glycosoaminoglycans such as chondroitin sulfate proteoglycans (CSPGS) and heparin sulfate and dermatan sulfate proteoglycans, glypicans and syndecan (Mironova and Giger, 2013; Shen, 2014). The NgR1 receptor complex transduces negative growth and myelination signals from a large range of interacting molecules.

To test a possible role for NgR1 signaling in the OPC differentiation block in WMS, an analysis of the transcriptional changes in the genes that code for NgR1 binding or interacting proteins was performed on the white matter at distinct times after stroke: an early OPC proliferative period (5 days after WMS) and a period of very limited differentiation (15 days after WMS). WMS significantly induced CSPG molecules including aggrecan, versican, and brevican, and the heparan sulfate proteoglycan core proteins glypican 2 and syndecans 1 and 3. There is an age effect observed in that aggrecan, versican, syndecan 1, and glypican 2 are induced to a greater extent in aged stroke. Interestingly, leucine-rich glioma inactivated 1 (Lgi1), cartilage acidic protein-1B (LOTUS), and disintegrin and metalloproteinase domain-containing protein 22 (ADAM22), three negative regulators of NgR1 signaling, are reduced after stroke (Thomas et al., 2010; Sato et al., 2011). The reduction in Lgi1, Lotus, and Adam22 levels following WMS is of greater magnitude in the aged brain.

This data provides evidence that the inhibitory capacity of myelin associated proteins and proteins involved in Ngr1 signaling are involved in the remyelination deficits associated with WMS. In addition to cell-cell signaling systems, there is evidence that failure to clear myelin debris may also limit repair after WMS. Microglia and macrophages are involved in phagocytosis of myelin debris following injury (Smith, 1999; Rotshenker, 2003; Schafer et al., 2014). Indeed, prior analysis of white matter infarcts has demonstrated differential distribution patterns of activated microglia/macrophage infiltrates in young and aged brains following white matter stroke (Rosenzweig and Carmichael, 2013). Microglia and macrophages are known to clear myelin debris in both the aging brain as well as in demyelinated disorders such as multiple sclerosis and neural injury (Neumann et al., 2009; Hill et al., 2018). Analysis of myelin debris clearance in the aged mouse brain demonstrates the accumulation of myelin debris inside microglia in the cerebral cortex, corpus callosum, and hippocampus (Hill et al., 2018). Curiously, in this same study, in vivo time-lapse imaging of microglia in the aged mouse cortex demonstrate limited interaction between microglial processes and myelin spheroids suggesting that engulfment and phagocytosis is a passive process (Hill et al., 2018). Furthermore, a study of the role of young blood derived macrophages play in remyelination following toxin induced focal demyelination in the mouse spinal cord demonstrates that following engulfment of myelin debris by macrophages, remyelination is induced (Ruckh et al., 2012). This suggests that removal of myelin debris, and presumably embedded myelin inhibitory factors, promotes remyelination. Unfortunately, because modeling WMS in mice is a relatively new field, very little work has been conducted on the role microglia and blood derived macrophages play in myelin clearance and their possible role in white matter repair.

Though, this is not to suggest that microglia are the sole source of myelin clearance in the injured brain. Indeed, the corpus callosum is heavily populated with GFAP positive astrocytes (Yoon et al., 2017). CNS astrocytes phagocytose structural debris including myelin in a model of middle cerebral artery occlusion (Morizawa et al., 2017) and have a role in phagocytosis of synapses in development. (Liddelow and Barres, 2017). The differential role of astrocyte versus microglial phagocytosis of myelin debris, created after WMS, is not yet resolved. Myelin debris inhibits axonal regeneration and repair recovery in peripheral nerve regeneration and in MS models of white matter injury (Neumann et al., 2009). It is likely that the dynamic balance of myelin debris creation and clearance play a role in tissue repair in WMS. This data underscores the importance of rigorous mechanisms for the proper myelin debris clearance and points to alterations in signaling cascades brought on by the post stroke white matter environment as a driver of remyelination deficits.

It should be noted, however, that remyelination failure due to OPC differentiation obstruction may be a wide spread phenomenon in neurological disease. The distinguishing factor across varying disease states being the mechanism of action underpinning the process. A recent investigation of fibrinogen, a blood coagulation protein found deposited in brain tissue after break down of the blood brain barrier such as in hemorrhagic stroke or Alzheimer's Disease, specifically disrupts OPC differentiation kinetics in in vitro OPC cultures as well as in demyelinating lesions in the CNS – a process thought to governed by BMP receptor signaling (Petersen et al., 2017). Similarly, a large molecular weight form of hyaluronan, a glycosaminoglycan secreted by astrocytes in demyelinated lesions in human and mouse models of MS, also prevents remyelination via the obstruction of OPC differentiation (Back et al., 2005). This finding may relate to NgR1 signaling, as noted above. In models of MS, the formation of myelin debris within the area of the lesion is inevitable. Indeed, Nogo and NgR1 signaling pathways are associated with MS and contribute to the failure of axon regrowth within the borders of the lesion (Lee and Petratos, 2013). These studies indicate that there are multiple signaling systems that block OPC differentiation, and that they may be distinct across disease types. A disease associated with chronic BBB leakages leads to fibrinogen deposition in white matter, such as in Alzheimer's disease (Petersen et al., 2017). Astrocyte production of hyaluronan plays a role in cerebral ischemia in early development (Back et al., 2005). Reactivation of NgR1 binding partners in the ECM, and diminished NgR1 inhibitors plays a role in WMS, especially in the aged brain (Sozmen et al., 2016). This suggests the existence of multiple, converging mechanisms in demyelinating lesions all of which function to modulate OPC function.

6. Stimulating remyelination

A major obstacle to WMS recovery is inducing robust remyelination in a safe and effective way. There is now sufficient evidence which demonstrates a link between neural activity and myelination in the healthy adult human and mouse brain. The prevailing hypothesis is that inhibitory and excitatory neurons can drive the formation of new myelin via the activation of maturation programs in OPCs and remodeling existing myelin wraps via the direct signaling onto internodes. Indeed, it is now hypothesized that this mechanism underpins the consolidation of some forms of memory in myelin. Emerging evidence of this phenomenon has paved the way for the development of new hypotheses regarding the role myelin plays in neural plasticity and has provided new evidence for the existence of non-synaptic forms of learning and memory. This section will discuss the proposed mechanisms involved in myelin plasticity, evidence for this phenomenon in humans, and the utility these concepts may play in the development of therapeutic paradigms for WMS recovery (Purger et al., 2016; Almeida and Lyons, 2017; Kaller et al., 2017).

6.1. Motor learning drives myelination

To begin, there have been a variety of studies across several motor-based behavioral paradigms, which demonstrate that motor learning drives myelin dynamics in a healthy adult brain. In

immunohistochemical stains for myelin and MRI fractional anisotropy (FA), the measurement of the directional dependence of water diffusion across cellular structures, analysis of rats subjected to a learned, repetitive skilled reach task demonstrate increased myelination in subcortical white matter. Increased FA and MBP signal intensity correspond both with the learning rate of the animal as well as the overall state of the subcortical white matter in the hemisphere contralateral to the trained paw (Sampaio-Baptista et al., 2013). In line with these conclusions, analysis of mice subjected to the complex wheel - a running wheel with irregular spaced rungs of which the mouse has to develop motor strategies to master – show similar effects (McKenzie et al., 2014). Indeed, in this study, mice trained on the complex wheel saw an initial upregulation of OPC proliferation followed later by an increase in oligodendrogenesis. This phenotype was blocked through inhibition of oligodendrogenesis via knockout of myelin regulatory factor (myrf) prior to training. Myrf is a transcription factor involved in OPC differentiation (Bujalka et al., 2013). Curiously, myrf knockout after training and thus after acquisition of the motor program did not hinder the animal's performance on the wheel, suggesting that recall of the motor memory imprinted onto the wheel did not necessitate new myelin formation, or OPC differentiation. These data suggest that acquisition of a novel, complex motor program underlies mechanisms of myelin genesis in the adult brain. This also brings to mind the potential for similar motor tasks in models of stroke. Indeed, combination immunotherapy against growth inhibiting Nogo-A along with high intensity skilled reach training in rats following a large cortical thrombotic stroke resulted in significant regeneration of the cortical spinal tract and motor recovery (Wahl et al., 2014). Though remyelination is not specifically addressed in this study, it stands that a significant portion of axon fibers in this tract are myelinated (Sengul and Watson, 2012).

Human studies suggest a correlation between newly acquired motor learning programs and changes in myelin signal. In a longitudinal study, diffusion tensor imaging (DTI) in healthy adults during the process of juggling training, a profoundly complex visuo-motor skill, demonstrate a significant alteration in myelin architecture in the intraparietal sulcus, a convergence point between the visual and somatosensory cortices (Scholz et al., 2009). In a related cross sectional DTI study, varying degrees of piano playing and practice correlate with increased myelin signal in varying regions of the brain – each region correlating with the amount of time practiced. For example, people who began piano practice during childhood present with an increase in myelin in the internal capsule while those that began during adolescence present with increases in the splenium and body of the corpus callosum (Bengtsson et al., 2005). These data indicate that complex, learned motor programs may drive increases in myelin and this may be instrumental to the acquisition of the motor program. However, due to the innate limitations of human imaging technology, there are several caveats. To begin, it is unclear if increases in myelin structure are due to increases in actual myelin amount or if this is due in part to increases in axonal diameter. Analysis of axonal morphology in mouse hippocampal brain slices determined that action potential induction resulted in an increase in axonal shaft diameter (Chéreau et al., 2017). If changes in myelin structure are due to increases in myelin amount, it is unclear if this is due to the formation of de novo sheaths via OPC maturation or remodeling of previously established internodes into thicker or longer sheaths. Recent studies of cortical myelination over time in the adult mouse, indicate that experience-dependent plasticity does not alter internode length, but does increase the number of myelin sheaths (Hughes et al., 2018). However, what is clear is that learned motor programs in mice and humans result in a form of plasticity independent of the traditionally held locus of learning, synaptic boutons. It could very well speak to our need to consider myelin plasticity as a phenomenon that occurs in conjunction with axonal growth and that these structures should be regarded as a functional unit. Though it is still uncertain as to how motor activity is driving changes in myelin structure, one hypothesis is that activation of neuronal circuits that underlie motor tasks are driving much of this phenomenon.

6.2. Neural activity drives de novo myelin formation

Signaling from neurons to OPCs plays a modulatory role in OPC proliferation and differentiation. In vitro analysis of OPCs demonstrates that indeed, glutamate signaling drives OPC proliferation, maturation, and migration (Gallo et al., 1996; Gudz et al., 2006). In one such study, with OPC and dorsal root ganglion co-cultures, vesicular glutamate release from axonal varicosities onto local OPCs increased calcium transients, as well as activation of signaling cascades resulting in MBP synthesis (Wake et al., 2011). Interestingly, OPC processes tended to localize with vesicular glutamate transporter 2-enriched axonal varicosities where local calcium transients were recorded. Furthermore, extended co-culture of neurons with OPCs resulted in the preferential formation of myelin sheaths – presumably from newly differentiated mature oligodendrocytes – onto electrically active axons (Wake et al., 2015). However, disrupting NMDAR expression in OPCs and oligodendrocytes in in vivo preparations via genetic deletion of the NMDAR subunit NR1 yields little change to the mouse brain. Analysis of an NR1 conditional knockout mouse driven by the Olig1 promoter demonstrated normal oligodendrocyte density, OPC proliferation, myelin signal in western blot preparations of cortex and white matter, and normal myelin compaction as assessed by electron microscopy (Biase et al., 2011).

However, alternative neuronal signaling molecules do exist, which may prove to be involved in OPC differentiation, implying an ability of the brain to compensate for loss of one neuron-OPC signaling system. Molecular profiling in OPCs in the mouse brain has revealed the enrichment of several subtypes of purinergic receptors. Evoked action potentials in dorsal root ganglion neurons in in vitro preparations resulted in the rise of intracellular calcium inside OPCs, which was blocked following purinergic receptor antagonism (Stevens et al., 2002). Assessment of culture medium of dorsal root ganglion cells following action potential stimulation found a significant rise in ATP concentration (Stevens and Fields, 2000). Further analysis of activity dependent release of ATP demonstrates its non-vesicular release from volume-activated anion channels specifically from dorsal root ganglion axons isolated in multicompartment culture chambers following stimulation (Fields and Ni, 2010). Finally, purinergic signaling in these same preparations inhibited OPC proliferation and promoted their differentiation into myelinating oligodendrocytes (Stevens et al., 2002).

Though the precise signaling molecules associated with neural activity induced OPC maturation are still in debate, there is evidence that directly modulating the activity of neurons of the central nervous system effects myelination of axons. The first study to demonstrate this in vivo came from an analysis of OPC proliferation and maturation following high frequency electrical stimulation of the medullary pyramid in adult rats (Li et al., 2010). Histological analysis of the stimulated dorsal cortical spinal tract following stimulation demonstrated an increase in BrdU, a thymidine analog that is incorporated into newly synthesized DNA during cellular mitosis, co localization with markers for OPCs and mature oligodendrocytes relative to the unstimulated tract (Li et al., 2010). Furthermore, optogenetic stimulation of neurons in the motor cortex of juvenile and adult mice resulted in increased OPC proliferation and maturation into oligodendrocytes in both the motor cortex and the underlying corpus callosum. Animals subjected to the paradigm also demonstrated altered motor function and increased levels of myelin. Transmission electron microscopic analysis of axonal fibers in the corpus callosum indicated thicker myelin sheaths while MBP staining of the same area showed increased signal after stimulation (Gibson et al., 2014). That optogenetic stimulation resulted in thicker myelin sheaths is curious because it is unclear if increased myelin signal is due to newly differentiated oligodendrocytes forming myelin wraps around previously naked axons or if previously

established myelin wraps are changing as a result of axonal signaling. It is a question of de novo myelin synthesis versus myelin remodeling.

6.3. The case for myelin remodeling

The evidence for myelin remodeling – the change in the architecture of preexisting myelin internodes- is limited due in part to the challenge of actively monitoring myelin sheath dynamics, including parsing out changes in myelin sheath thickness relative to axon caliber, in real time. However, there is some evidence for changes in myelin length in established sheaths in various regions of the mouse and zebrafish central nervous system. Some of which is brought about by neural activity induced modulation. Analysis of the optic nerve, a heavily myelinated axon tract in the central nervous system, after monocular deprivation and genetic deletion of vesicular glutamate transporter 2, resulted in a shortening of internodal length with no apparent change in myelin thickness or in the total number of myelinated axons (Etxeberria et al., 2016). This suggests that neural activity initiated by visual stimulation modulates myelin architecture via the retraction or elongation of individual myelin sheaths. However, a 2-photon longitudinal study of individual myelin sheaths in the superficial layers of the sensory cortex provides conflicting evidence that newly formed myelin sheaths do indeed increase in length upon initial establishment. These sheaths eventually stabilize and remain so even after sensory enrichment (Hughes et al., 2018). In the developing zebrafish undergoing active myelination, live calcium imaging indicates that neural activity drives both elongation and retraction in individual myelin sheaths. Indeed, evoked action potentials in axons of the larval zebrafish spinal cord evoked calcium transients in individual myelin sheaths resulting in changes in internodal retraction and extension (Krasnow et al., 2018). Curiously, recent experiments using light induced degeneration of individual myelin sheaths in the zebrafish provides further evidence of myelin remodeling. Targeted ablation of a single internode, flanked by uninjured myelin sheaths resulted in both surviving sheaths extending their length into the newly exposed axons or the formation of an entirely new sheaths (Auer et al., 2018).

7. WMS recovery in human patients

Physical exercise and repetitive motor tasks function as a widely used therapeutic paradigm in human stroke recovery and these may impact remyelination in WMS. Indeed, increased levels of self-reported physical activity in a population of 70-year-old adults is correlated with less white matter lesions as assessed by diffusion imaging, suggesting that exercise may be white matter protective (Gow et al., 2012). The available evidence in mouse models suggest that motor activity modulates myelin dynamics in both the cortex and underlying white matter tracts (Sampaio-Baptista et al., 2013; McKenzie et al., 2014). However, the level and type of physical exertion necessary to drive these processes in the mouse models is profound. Mice trained on the complex wheel were given ad libitum access for 11 days and ran on average 5–7 km per night (McKenzie et al., 2014). Mice subjected to skilled reach underwent 30-min pretraining sessions for 3 days followed by 15-min training sessions for 11 days (Sampaio-Baptista et al., 2013). This level of activity may be unsuitable for an aged human population that present with symptomatic white matter lesions: it is not just juggling or playing the piano. It is also unclear if activation of motor circuits via physical activity modulates myelin dynamics in non-motor regions of the brain. So far animal studies using motor activity to drive myelination have focused their analyses of OPC differentiation and changes in myelin in motor areas. WMS in human populations are found globally across white matter tracts in the brain, some of which are not directly involved in motor processing. Analyses of cognitive deficits in WMS patients revealed that formation of lesions along white matter tracts that connect circuits necessary for memory encoding and retrieval (uncinate fasciculus, inferior longitudinal fasciculus) predict deficits in episodic memory (Lockhart et al., 2012). It may be that motor circuit activity-based therapeutic strategies may be insufficient to repair myelin associated with cognitive deficits. Rather, direct modulation of OPC and oligodendrocyte kinetics using anatomically defined therapies may be necessary to drive white matter repair in human WMS patients. Direct optogenetic modulation of cortical motor neurons drives OPC proliferation and maturation in the corpus callosum ventral to the motor cortex. Perhaps targeted stimulation of brain regions and associated white matter tracts presenting with white matter lesions using transcranial magnetic stimulation may prove fruitful. Indeed, there is growing interest in using TMS, a method which has been shown to safely activate neuronal ensembles in human beings, as a means for recovery in cases of psychiatric disease, which may prove useful in neurological disorders such as stroke. Furthermore, prospective transcriptomic analyses of OPCs following activity induced remyelination will likely reveal targetable gene networks involved directly in the recovery process.

8. Conclusion

The emergence of a mouse model of WMS has provided a new and critical glimpse into the pathophysiology of this devastating disorder. Though the field is recent, incredible strides have been made towards an understanding of the mechanisms that govern both the cellular and molecular consequences of white matter stroke. Of particular note is the revelation of the role that extracellular growth inhibitory molecules play in remyelination failure. In parallel, the recent advent of the myelin plasticity field has provided important insights into myelin biology in the healthy adult brain, of which may prove instrumental towards the development of novel therapies for WMS. Most importantly, there is now compelling evidence for neural activity induced myelination in in vitro oligodendrocyte and neuron co-cultures as well as in the adult human and mouse brain. This provides an incentive to translate these approaches into potential forms of therapy. Though these approaches have not been tested in either human or mouse cases of WMS, there is reason to believe that both specific forms of motor learning and direct neural stimulation may prove useful in the development of white matter therapy following stroke. By either subjecting mice to motor learning paradigms such a skilled reach or the complex wheel or stimulating motor neurons in the motor cortex using optogenetics, we may be able to induce remyelination and repair following WMS. Furthermore, we can use these models as a platform to delve deeper into the molecular systems that govern oligodendrocyte development and myelin repair in the adult and aged brain following white matter stroke. These approaches will not only further our understanding of the pathophysiology of WMS and repair but also provide new molecular targets for future therapeutics.

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