

Neuroprotection and neuroregeneration: roles for the white matter

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Abstract

Efficient strategies for neuroprotection and repair are still an unmet medical need for neurodegenerative diseases and lesions of the central nervous system. Over the last few decades, a great deal of attention has been focused on white matter as a potential therapeutic target, mainly due to the discovery of the oligodendrocyte precursor cells in the adult central nervous system, a cell type able to fully repair myelin damage, and to the development of advanced imaging techniques to visualize and measure white matter lesions. The combination of these two events has greatly increased the body of research into white matter alterations in central nervous system lesions and neurodegenerative diseases and has identified the oligodendrocyte precursor cell as a putative target for white matter lesion repair, thus indirectly contributing to neuroprotection. This review aims to discuss the potential of white matter as a therapeutic target for neuroprotection in lesions and diseases of the central nervous system. Pivot conditions are discussed, specifically multiple sclerosis as a white matter disease; spinal cord injury, the acute lesion of a central nervous system component where white matter prevails over the gray matter, and Alzheimer's disease, where the white matter was considered an ancillary component until recently. We first describe oligodendrocyte precursor cell biology and developmental myelination, and its regulation by thyroid hormones, then briefly describe white matter imaging techniques, which are providing information on white matter involvement in central nervous system lesions and degenerative diseases. Finally, we discuss pathological mechanisms which interfere with myelin repair in adulthood.

Key Words: Alzheimer's disease; multiple sclerosis; oligodendrocyte precursor cells; spinal cord injury; thyroid hormone; traumatic brain injury; white matter; white matter imaging

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Introduction

Neurodegenerative diseases and central nervous system (CNS) lesions due to trauma or vascular accidents are significant health concerns. The Global Burden of Diseases study estimated that in 2017, the total number of disability-adjusted life years attributable to neurological disorders was 21 million in the EU, and 41.1 million in the WHO European region. The total number of deaths was 1.1 million in the EU and 1.97 million in the WHO European region, with neurological disorders as the third leading cause after cardiovascular disease and cancer (Deuschl et al., 2020).

Great effort has been made to develop incisive therapeutic tools to cure or to slow the clinical course of neurological diseases and lesions, and to understand the mechanisms leading to the related functional impairment. Most of this effort has been focused on neurons as the main cell of the gray matter (GM) and on related neuroprotective strategies. However, many failures in related clinical trials have severely hindered research (Dhir et al., 2020).

Over the last few decades, two events have contributed to turning researchers' attention to the white matter (WM), both as a component of CNS disease pathology and as a potential therapeutic target.

The first event was the discovery of a new cell type, the oligodendrocyte precursor cell (OPC), in the mature CNS in the late 1980s (Dawson et al., 2003). OPCs are the precursors of oligodendrocytes, responsible for myelin development during embryogenesis, turnover, and repair in the mature CNS, being the number of oligodendrocytes depending on the OPCs number. These precursors are generated during development to allow myelination, but a pool of undifferentiated precursors remains all over the mature CNS. These quiescent unipotent stem cells can be activated again by different stimuli, which are present in the inflammatory microenvironment to trigger the proliferation, migration, and differentiation (Nishiyama et al., 2021). These cells can repair myelin and re-myelinate axons, thus indirectly contributing to neuroprotection. Remyelination is currently the only known self-repair ability of the CNS, potentially providing full anatomical and functional neuroregeneration.

The second event was the introduction of imaging techniques to visualize and measure WM in clinical settings (Wozniak and Lim, 2006). WM accounts for a large percentage of CNS volume, ranging from 20% in the cerebral cortex (Mota et al., 2019) to 80% in the spinal cord (Henmar et al., 2020). It is formed by the axons and their myelin sheaths and consists of a multilamellar membrane structure. This structure is created by the spiral wrapping and subsequent compaction of the oligodendrocyte plasma membrane and facilitates the efficient transmission of electrical signals in neural pathways (Simons and Nave, 2016). Diffusion tensor imaging (DTI) can detect WM alterations invisible to conventional imaging techniques (Lubetzki et al., 2020), and has permitted the visualization of WM alterations in WM diseases such as multiple sclerosis (MS), in CNS lesions such as spinal cord injury (SCI), and neurodegenerative pathologies such as Alzheimer's disease (AD) (Tae et al., 2018).

Starting from the assumption that remyelination is crucial for the prevention of neurodegeneration, and that spontaneous myelin repair is commonly observed in the mature CNS, this review aims to discuss the potential of the WM and OPCs as targets for neuroprotective therapies in lesions and chronic neurodegenerative diseases of the CNS. We consider three different diseases: MS, as an example of WM primary pathology; SCI as an example of CNS lesion; and AD as an example of chronic progressive neurodegenerative disease.

Search Strategy and Selection Criteria

All years were chosen in the search, but giving more importance to the publications of the last 5 years. These searches were performed between June and September 2021. Studies cited in this review were searched on the NCBI PubMed database using the following keywords: thyroid hormone AND oligodendrocyte precursor cells; white matter imaging; myelin repair; remyelination; oligodendrocyte precursor cells AND remyelination block; thyroid hormone metabolism; multiple sclerosis AND white matter; spinal cord injury AND white matter; traumatic brain injury AND white matter; Alzheimer's diseases AND white matter. Articles related to central nervous system pathologies but without a specific focus on white matter were excluded.

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Oligodendrocyte Precursor Cells, Developmental Myelination and the Role of Thyroid Hormone: a Brief Summary

Myelination is a process whereby oligodendrocytes wrap their plasma membrane around the axons, insulating it and ensuring proper propagation of the axon potential from the neuron cell body to the presynaptic nerve ending. During embryonic development, oligodendrocytes derive from OPCs, which are generated from neural stem cells, multipotent cells of the neural tube, which are also the common precursor of neurons and astrocytes. The OPC population is generated in three temporally different waves, spatially organized in a ventral-dorsal direction. In rodents, the first wave arises in the ventral ventricular zone from the medial ganglionic eminence and the anterior entopeduncular area (at embryonic day (E) 12.5) soon after neural tube closure. At E15.5, a second wave originates from the lateral and caudal ganglionic eminences, followed by a third wave from the dorsal subventricular zone at birth (E21/P0). OPCs originating from the first ventral wave appear to have a backup function, replaced postnatally almost in their entirety unless the following two waves are perturbed (van Tilborg et al., 2018; Kuhn et al., 2019). In the spinal cord, a ventral wave of OPC production in the promotor neuron domain (E12.5) is followed by a production of cells in the dorsal precursor domains (E15.5). Contrary to that which occurs in the encephalon, the second wave of OPC generation produces only 20% of the population (van Tilborg et al., 2018). OPCs proliferate and migrate, populating the entire developing CNS and triggering the differentiation/maturation into mature oligodendrocytes, finally wrapping the axon to form the myelin sheets.

This cell population is regulated by hormones. Like most of the cells in adult mammalian organisms, OPCs depend on thyroid hormones (THs) to maintain metabolic pathways and regulate the expression of target genes. The thyroid status of a cell is not only dependent on proper thyroid gland function, but also on a complex biochemical process occurring at the TH target cells. The thyroid gland synthesizes thyroxine (T4) through the uptake of both iodine, which acts as a pro-hormone, and triiodothyronine (T3), the active form, at a ratio of 80 (T4) to 20 (T3) %. THs are distributed throughout the blood and cerebrospinal fluid by four types of TH distributor albumin, transthyretin, thyroxine-binding globulin, and a number of lipoproteins (Pagnin et al., 2021). The main TH distributor responsible for the delivery of THs to tissues is transthyretin, a homo-tetrameric protein produced mainly by liver and choroid plexus epithelial cells, which moves T4 from the blood into the cerebrospinal fluid and the brain parenchyma (Alshehri et al., 2020).

The THs then cross the plasma membrane via specific transporter proteins such as MCT8, a ubiquitous transporter. In the CNS, MCT8 is expressed in adult tissues and during development by glial cells, neurons, and along the blood-brain barrier, the latter being the main route of TH entry into the CNS. Both T3 and T4, as well as the inactive metabolite rT3, bind to MCT8 with high affinity.

The T4/T3 plasma ratio is reversed at a cellular level, where deiodinase (Dio) enzymes remove iodine atoms from a specific position, converting T4 to T3 (Dio2), and T3 to T2 (Dio1, Dio3) or T4 to rT3 (Dio3) (Calzà et al., 2015, 2018; Luongo et al., 2019). T3 exerts its genomic action through TH receptors (TRs; TR α and TR β), a class of nuclear receptors, which regulate the expression of target genes, including myelin protein-encoding genes, in combination with other nuclear receptors such as RXR γ (Baldassarro et al., 2019, 2021a). T3, T4, T2, and rT3 also have non-genomic, rapid-onset actions, at mitochondria, cytoskeleton, and metabolism levels (Davis et al., 2016). Some of these non-genomic pathways are mediated by specific integrins located in the plasma membrane (mainly α v β 3), involving ERK1/2, MAPK or PI3K-AKT, enabling the trafficking of TRs into the nucleus and mediating gene expression regulation and post-translational protein synthesis (Pagnin et al., 2021).

CNS development and particularly myelination is strictly dependent on THs, which derive from maternal blood prior to the functional maturation of the fetal thyroid gland between 3 and 13 gestational weeks. Maternal/fetal TH production then overlaps during the second half of gestation, with postnatal myelination being fully regulated by newborn TH production (Pagnin et al., 2021). Inadequate TH levels during prenatal development lead to irreversible physical and mental retardation, resulting in a severe condition known as "cretinism", where myelinating abnormalities and WM lesions are preeminent (Stenzel and Huttner, 2013). Maternal subclinical hypothyroidism, due to factors such as prenatal exposure to thyroid-disrupting chemicals, a large class of environmental pollutants, which alter thyroid gland physiology, TH plasma transportation, intracellular balance, and TR availability (Mughal et al., 2018), is also associated with poor neurological and intellectual development (Liu et al., 2018; Zhang et al., 2021). Finally, the key role of intracellular TH concentration in brain development is illustrated by the Allan-Herndon-Dudley syndrome, in which mutations on the *SLC16A2* gene lead to the production of pathological and dysfunctional variants of the MCT8 protein (Pagnin et al., 2021).

THs are the essential driver of OPCs differentiation. T3 acts via genomic and non-genomic mechanisms to drive the OPC out of the cell cycle and to activate the differentiation (Lee and Petratos, 2016), being the intracellular level of T3 the key determinant of proliferation/differentiation switch (Pagnin et al., 2021). While the association between low TH, elevated TSH and rT3 levels and poor neurodevelopmental outcomes in prematurity, intrauterine growth restriction, and neonatal hypoxia (Pereira and Procianny, 2001)

have been thoroughly established in both clinical practice and preclinical research, the diagnostic and therapeutic aspects of these outcomes are still controversial (Eerdeken et al., 2019). TH treatments have been proposed and tested for these perinatal injuries to favor WM maturation, with contrasting results.

Following the action of T3 at the cell cycle level, many other soluble and contact factors deriving from axons, astrocytes, microglia, vasculature, and extracellular matrix tightly regulate OPC biology till proper myelin sheath formation (Baydyuk et al., 2020) (Figure 1). These signals act via transcriptional and translational regulation, epigenetic controls including miRNA, histone modifications, and DNA methylation (Tiane et al., 2019), and the arrangement of the actin cytoskeleton (Bercury and Macklin, 2015). Astrocytes act on OPCs through the secretion of different growth factors, including platelet-derived growth factor (PDGF), fibroblast growth factor, and leukemia inhibitory factor, and the interleukin (IL)-6, promoting the proliferation and survival of OPCs. They also secrete endothelin-1 and extracellular matrix (ECM) components, regulating migration and differentiation. Fibronectin stimulates migration/proliferation and the potentiation of PDGF-A action by integrin signals (α v β 1 and α v β 3), and both fibronectin and laminin promote the extension of the oligodendrocyte processes. Growth factors are also secreted by endothelial cells and pericytes, used by OPCs as a scaffold for migration. Finally, while microglial cells do not appear to be essential for adult OPC survival and differentiation, in response to noxious stimuli induce maturation or cell death, depending on their state of activation (Baydyuk et al., 2020).

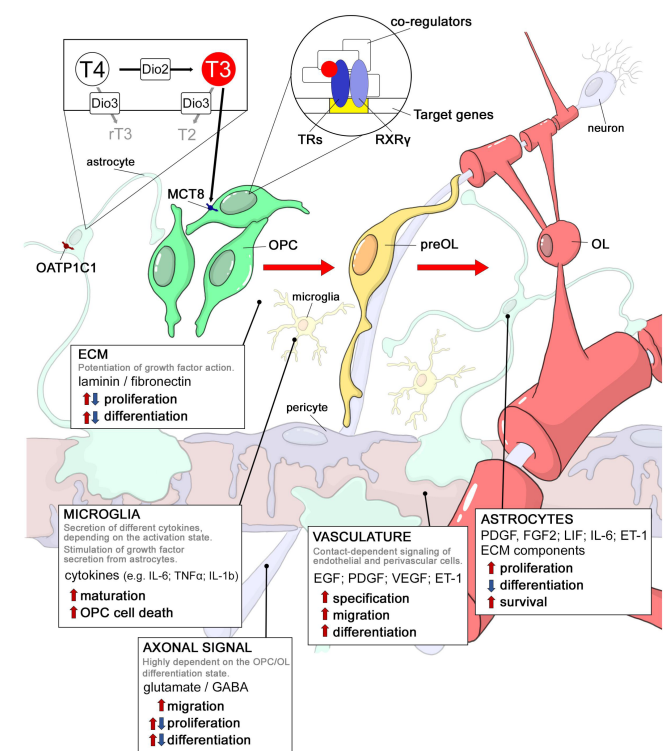


Figure 1 | Influence of different factors on OPC differentiation.

Schematic representation of thyroid hormone tissue metabolism and the main extrinsic factors regulating OPC proliferation, migration, differentiation, and oligodendrocyte maturation. Dio2: Deiodinase 2; Dio3: deiodinase 3; ECM: extracellular matrix; EGF: epidermal growth factor; ET-1: endothelin-1; FGF2: fibroblast growth factor 2; IL-1 β : interleukin-1 beta; IL-6: interleukin-6; LIF: leukemia inhibitory factor; MCT8: monocarboxylate transporter 8; OATP1C1: organic anion transporter family member 1C1; OL: oligodendrocyte; OPC: oligodendrocyte precursor cell; PDGF: platelet-derive growth factor; rT3: reverse triiodothyronine; RXR γ : retinoid X receptor gamma; T2: 3,5-diiodothyronine; T3: triiodothyronine; T4: thyroxine; TNF α : tumor necrosis factor alpha; TRs: thyroid hormone receptors; VEGF: vascular endothelial growth factor.

OPCs and mature oligodendrocytes also express neurotransmitter receptors. Neuronal activity can therefore regulate OPC migration, proliferation, differentiation, and myelination, and the main neurotransmitters involved in this process appear to be glutamate and GABA. Glutamate acts as a chemoattractant, accelerating integrin-mediated motility through AMPA receptors. Depending on the differentiation state of the OPC, glutamate may act also as a maturation inducer. The GABA $_A$ receptor reduces OPC proliferation, while GABA $_B$ enhances it [reviewed by Baydyuk et al. (2020)]. Actually, OPCs are electrically sensitive, form synapses with neurons, support blood-brain barrier integrity, and mediate neuroinflammation (Akay et al., 2021).

Seeing Is Believing: White Matter Imaging

The development of new imaging techniques has finally allowed researchers

to assess the impact of WM alterations in adult human CNS lesions and chronic neurodegenerative diseases. Conventional MRI permits the evaluation of cerebral macrostructure in many pathological situations and is widely used to monitor longitudinal white matter changes, disease progression, and the effects of treatment. But more innovative techniques, such as diffusion MRI, show the geometry and integrity of the underlying microstructure and quantify the severity of tissue damage, specifically decreased myelin content and axonal integrity (Bailey et al., 2014). DTI is an MRI-based technique, which uses anisotropic diffusion to visualize and estimate the organization of the WM in neuronal tissue (Fiani et al., 2020). It can be used in association with fiber tractography, a 3D reconstruction technique to assess neural tracts using DTI data, and permits clinicians to detect disease features such as inflammation, edema, demyelination, and hemorrhage (Zaninovich et al., 2019). Other new imaging techniques in addition to DTI appear to offer better sensitivity in detecting demyelination/remyelination. These include the relaxation along a fictitious field MRI technique, which displays a distinct pattern of changes in the remyelination phases when used in combination with DTI and magnetization transfer (MT), reflecting not only the myelin content but also the architecture of myelin sheets, as well the presence of gliosis (Holikova et al., 2021). The relaxation along a fictitious field 4 technique has demonstrated its efficacy, and sometimes its superiority over DTI in a rat model of demyelination (Lehto et al., 2017), especially in MS models where it appears to be a sensitive method for the detection of subtle abnormalities, not only in normal-appearing WM but also in the deep gray matter in multiple sclerosis (Filip et al., 2020). These advanced quantitative MRI techniques have not yet been integrated into clinical practice, where more conventional MRI scans remain the modalities of choice for monitoring clinical disease progression (Filip et al., 2020). Finally, the application of 9T MRI to WM analysis has allowed *in vivo* analysis of distinct WM fiber tracts in experimental animals (Schaeffer et al., 2017).

Overall, MRI-based myelin imaging methods show a good reproducibility and correlation with histology, as also confirmed by imaging in animal models, thus offering a powerful instrument for monitoring remyelination-enhancing therapies (van der Weijden et al., 2021). Their application in animal models also allows robust end-point identification in a translational perspective. For example, it is possible to monitor the progression of WM injury in SCI in rats by DTI, by assessing myelination status and evaluating when WM-directed therapies may be appropriate and how these should be used (Wu et al., 2020). DTI technology in SCI in monkeys has permitted the longitudinal monitoring of lesion evolution, separating axon degeneration and demyelination into different sensory and motor tracts to compare spinal cord anatomy with behavioral assessments, and the evaluation of secondary degeneration, not only at the lesion site but also in remote segments above and below the injury (Mishra et al., 2020). Prior to DTI, the tissue adjacent to the injury site was presumed to be healthy if conventional MRI suggested normal anatomy, while preclinical studies using DTI have indicated that this perilesional area may harbor evolving pathology (Herrera et al., 2008).

Myelin Repair in Adulthood: Oligodendrocyte Precursor Cell Differentiation Impairment, Inflammation, and Thyroid Hormone Tissue Metabolism

When myelination is complete after birth, some OPCs remain quiescent, forming the adult pool of precursors present in the GM and WM of the mature CNS. OPCs are the most abundant proliferative population in the adult CNS, representing 5–8% of all cells, and can be recognized by the expression of membrane markers such as NG2 and PDGF. OPCs are not a homogeneous population – those in the WM are more responsive to PDGF-A and are morphologically and genetically more mature than the precursors in the GM (Kuhn et al., 2019).

The OPCs in GM are also less mature, less responsive to astrocyte signals, and less sensitive to interferon γ and tumor necrosis factor α detrimental effects. Thus, probably due to these intrinsic differences, it has been described that remyelination in GM is more fast and efficient than in WM (Lentferink et al., 2018).

OPC density throughout the entire CNS is kept under tightly regulated homeostatic control, with OPCs which have undergone apoptosis or differentiation being rapidly replaced. Newly generated OPCs derive from the resident pool by asymmetric division, a mechanism, which permits maintenance of the quiescent pool and production of the differentiating cells. New OPCs can be also generated by the neural stem/progenitor population in the mature CNS, such as those of the subventricular zone. Physiological OPC turnover decreases with age due to the gradual lengthening of the cell cycle, accumulation of intracellular cell cycle inhibitors, or the decrease of growth factor availability (Akay et al., 2021).

OPCs and the WM are highly vulnerable to various types of damage, both during development and adulthood. In fact, OPCs and oligodendrocytes are vulnerable to all agents which are toxic for neurons, such as oxygen/glucose deprivation, inflammatory cytokines, and glutamate (Baldassarro et al., 2017, 2020). Severe WM damage is a common occurrence in neonates exposed to perinatal hypoxia/ischemia, which contributes to the consequent severe neurocognitive deficit (Shao et al., 2021a). DTI studies have demonstrated associations between WM integrity and cognition measures during

adolescence in children suffering neonatal hypoxia-ischemia, showing for example that reduced information processing speed is mediated in part by the reduced integrity of major WM tracts (Gosar et al., 2020).

In the meantime, OPCs can be activated in the case of WM injury, can fully differentiate in mature oligodendrocytes, thus providing an anatomical and functional myelin repair. As the initial step of this process, the OPCs are activated to migrate to the lesion site and proliferate. Inflammation is a fundamental trigger to induce remyelination, and the balance between proliferation and differentiation induction is maintained by a series of factors. The soluble factors mainly secreted by the immune system and astrocytes, for example, such as growth factors (fibroblast growth factor 2, EGF, and PDGF), cytokines, and chemokines, are fundamental for initiating the process by inducing OPC proliferation (Armada-Moreira et al., 2015) (Figure 1).

Under certain conditions, however, and for reasons still poorly understood, the OPCs fail to differentiate fully into myelinating oligodendrocytes, and myelin damage exposes the nude axons to the inflammatory microenvironment and degeneration. This OPC differentiation block is a key event in pathologies with WM damage as a primary or secondary event. Inflammation plays a key role in the demyelination/remyelination balance, sometimes acting as a two-faced Janus which stimulates OPC proliferation but blocks differentiation, depending partly on the intensity of the inflammation itself (Spaas et al., 2021). A variety of molecules are involved in this complex process, but tissue inflammation is a common denominator in conditions such as MS and SCI, due to the action of inflammatory cytokines as transforming growth factor- β 1, tumor necrosis factor α , IL-1 β , IL-6, IL-17, and interferon γ (Baldassarro et al., 2020; Spaas et al., 2021).

The pathological mechanisms leading to myelin damage may act directly on the oligodendrocyte cell, or solely on myelin sheaths preserving the cell body (Bradl and Lassmann, 2010), with the OPC being induced to differentiate and form new myelin in both cases. It has been observed that partially injured oligodendrocytes are capable of participating in myelin repair in some animals, including humans (Duncan et al., 2018).

As already discussed, the tissue and intracellular concentration of THs are key components of the proper OPC differentiation machinery. The strict relationship between TH and the WM in adulthood as well as during development is confirmed by the abnormalities in various fiber tracts (Singh et al., 2014), and a significant reduction in the WM volume in cortical and cerebellar areas has been observed in adult hypothyroid patients and measured using diffusion tensor tractography (Singh et al., 2013). Hyperthyroidism also has an impact on adult WM structure, where microstructural alterations in the WM have been observed, in keeping with the results of preclinical studies (Aslan et al., 2020). A large body of literature indicates that inflammation modifies TH intracellular uptake; the intracellular conversion of the inactive T4 to the active T3; TR availability and binding, and T3 inactivation (D'Intino et al., 2011). An impairment of Dio2 and an increase in Dio3 activities are the main alterations, inducing a reduced tissue availability of T3 (Fernández et al., 2016). This leads to a severe impairment of the molecular machinery of TH cellular targets, including OPC differentiation, in a condition known as “non-thyroidal illness syndrome” or “euthyroid sick syndrome”, in which circulating TH concentration does not reflect the TH tissue and intracellular concentration (Fliers and Boelen, 2020).

Given the importance of restoring a proper OPC differentiation capacity during the remyelination, a number of drugs have been proposed to enhance remyelination, some of which act by stimulating OPC differentiation. Examples include IRX4204 (ClinicalTrials.gov identifier: NCT02438215) and bexarotene (EudraCT number: 2014-003145-99), both RXR γ agonists; the antipsychotic drug quetiapine fumarate (ClinicalTrials.gov identifier: NCT02087631); the LINGO-1 antagonist opicinumab (ClinicalTrials.gov identifier: NCT01864148; NCT03222973); the cytochromeP450 inhibitor clemastine (ClinicalTrials.gov identifier: NCT02040298), and thyroid hormone (ClinicalTrials.gov identifier: NCT02760056) (Balestri et al., 2021).

Various pathologies cause an alteration in this complex molecular machinery, leading to an OPC/oligodendrocyte deficiency and consequent WM damage. In the following paragraphs, OPC/oligodendrocyte alterations in example diseases are illustrated and discussed for the impact on neurodegeneration, and the proof-of-concept related to TH replacement therapies are discussed as an example of WM-directed neuroprotective therapies.

Multiple sclerosis

As the most widespread and most thoroughly researched inflammatory demyelinating disease in humans, MS has been the “pivot” condition for investigating WM imaging and OPC biology. While conventional MRI techniques are routinely used to visualize lesion load, advanced MRI allows the exploration of changes in tissue composition (Cercignani and Bouyagoub, 2018). DTI has been widely used to examine the WM, GM, optic nerve, and spinal cord of MS patients at different stages of the disease, contributing to a better understanding of the different pathophysiological substrates of the disease, and the complexity of its clinical evolution (Filippi et al., 2016), as well as for treatment monitoring. Magnetic resonance spectroscopy can show axonal damage even in normal-appearing white matter, thus supporting the view that WM lesions ultimately lead to neuron degeneration. Cortical gray matter atrophy has in fact been demonstrated in MS, where cortical lesions responsible for cognitive disability are more common in secondary progressive MS, where OPCs are not activated than in the relapsing-remitting form, where OPCs can repair myelin damage (Pflugshaupt et al., 2016).

In the most common clinical variant (relapsing-remitting), the clinical onset of the disease and the acute symptomatic phase are characterized by what is known as “active lesions” in the WM, massively infiltrated by peripheral immune cells and macrophages. Subsequently, the plaque microenvironment evolves to include a myriad of inflammatory cytokines, which lead to astrocyte and microglia activation, demyelination, and axonal damage (Psenicka et al., 2021). During this phase, and in this variant of the disease, OPCs proliferate and differentiate into mature oligodendrocytes, fully repairing the WM damage and restoring anatomical and functional integrity. However, this process progressively fails due to repeated relapses and OPC pool exhaustion or aging, while in the chronic progressive form it fails to begin at all. *In vivo* and *in vitro* models have permitted researchers to identify the role of OPCs in remyelination failure, showing that the exit of the OPC from the cell cycle is blocked by inflammatory cytokines, thus preventing terminal differentiation (Psenicka et al., 2021). The OPC differentiation block has also been identified in human MS tissue samples (Kuhlmann et al., 2008).

The re-establishment of an appropriate intracellular environment, namely the TH level, is recognized as a pre-requisite for orchestrating the machinery which drives the OPCs out of the cell cycle toward terminal differentiation (Lee and Petratos, 2016). A number of preclinical studies have explored the administration of TH, TH analogs, or TR ligands to overcome inflammation-induced remyelination impairment in many inflammatory demyelinating experimental diseases. The pilot condition in these studies was experimental allergic encephalomyelitis, the most widely used animal model for MS, in which we demonstrated that exogenous TH administration improves remyelination and neuroprotection by partially correcting tissue hypothyroidism (Fernandez et al., 2004; Dell’Acqua et al., 2012). Several independent labs have confirmed these results in many different animal models of demyelinating diseases (reviewed in (Calzà et al., 2018), and a clinical trial (NCT02760056) was finally established (Wooliscroft et al., 2020).

MS offers a seminal example of the major role of WM, not only for proper axonal function but also for axonal protection from damage due to the inflammatory microenvironment. If myelin is not properly repaired, retrograde degeneration leads to neuron death, a mechanism, which makes MS the reference disease for the development of neuroprotective strategies based on OPC/oligodendrocyte and WM integrity (Psenicka et al., 2021).

Spinal cord and traumatic brain injury

Quantitative MRI for WM study was subsequently extended to other conditions, including SCI and traumatic brain injury. Both of these conditions are characterized by a primary lesion, triggered by the injury, followed by a phase known as “secondary degeneration” and by stabilization after several months. SCI is a seminal condition for myelinated neural tract analysis, including both axons and respective myelin sheaths. MRI has permitted researchers to map not only the extent of the primary damage but also its extension rostrocaudally, as well as the rearrangements in brain connectivity following lesion (Seif et al., 2019). Brain DTI analysis has shown myelin decrease and progressive structural changes along the neuroaxis following trauma in acute and chronic SCI patients (Ziegler et al., 2018), showing unexpected correlations between brain volume and neurological deficits (Ziegler et al., 2018), as well as volume changes in the brain related to the atrophy of myelinated axons and their cell bodies within the gray matter of sensory and motor cortices (Seif et al., 2019).

Extensive oligodendrocyte and OPC cell death occurs during the first two weeks following injury in the epicenter as well as regions distal to the lesion (Hassannejad et al., 2019). Extensive OPC proliferation subsequently occurs over time and within the first two weeks post-injury, producing oligodendrocytes responsible for the de novo ensheathment of a maximum of 30% of myelinated spinal axons at the injury epicenter 3 months after SCI (Assinck et al., 2017).

TH treatment has been also proposed to overcome the inflammation-induced OPC differentiation block in SCI. Several different biomaterial-assisted local delivery systems have been proposed, thus avoiding the risk of hyperthyroidism connected with systemic delivery. Hydrogel-based drug (Shultz et al., 2017) and polymeric scaffold local delivery systems also containing anti-inflammatory drugs at doses comparable to safe human doses promoted new mature oligodendrocyte formation and myelination in rat SCI, also improving locomotor functional outcomes (Bighinati et al., 2020).

Alzheimer’s disease

AD is characterized by a long biological history, one which precedes clinical onset by decades, progressively evolving until the classical pathological landmarks (intraneuronal fibrillary tangles and extracellular amyloid plaques) appear, and every stage of the AD process is characterized by WM alterations (Shao et al., 2021b). Volumetric MRI measures are a current standard as outcome measures in clinical trials assessing disease-modifying therapies in AD (Anderson et al., 2012): DTI has indicated a decreased fractional anisotropy value in mild cognitive impairment patients when applied to WM study, and WM diffusivity changes were associated with the progression of AD (Lo Buono et al., 2020). A dysconnectivity between the entorhinal cortex and hippocampus in patients with mild cognitive impairment and AD has also been observed by diffusion kurtosis imaging, alterations suggesting that AD pathology may propagate stepwise along WM pathways in a condition known as “disconnection syndrome”, and that the clinical expression of AD may be supported by the selective vulnerability of pyramidal neuron subtypes and the consequent loss of cortico-cortical connections (Kamagata et al., 2020).

Concomitant with the increase in β -amyloid plaques, the cerebral matter of AD patients shows a significant decrease in the myelin proteins (myelin basic protein, proteolipid protein, 2',3'-cyclic-nucleotide 3'-phosphodiesterase), indicative of WM degeneration. *In vitro* studies have also demonstrated the apoptosis of undifferentiated OPCs and differentiated mouse oligodendrocytes following exposure to amyloid peptide β_{1-42} (Tognatta and Miller, 2016). An age-related decrease in myelin basic protein immunostaining and OPC density, together with a decline in the number of OPC replications, has also been described in 3Xtg AD mice (Vanzulli et al., 2020).

AD pathology also includes neuroinflammation, and it has been suggested that AD-associated inflammation enhances OPC susceptibility to the oxidative stress associated with the hostile AD microenvironment (Bandyopadhyay, 2021). Interestingly, an association between thyroid function and AD has also emerged, and it has been suggested that low CNS TH levels may predispose to AD via increasing APP expression, and consequently to A β peptide and β -amyloid levels (Figuerola et al., 2021).

Notably, OPC dysfunctions have also been described in other neurodegenerative and psychiatric diseases, like Parkinson’s and Huntington’s diseases, schizophrenia, and major depressive disorders (Clayton and Tesar, 2021). In amyotrophic lateral sclerosis, although motoneuron degeneration is responsible for the clinical phenotype, the accumulation of pathological proteins (superoxide dismutase 1, TAR DNA binding protein 43) in oligodendrocytes, myelin alterations, and defective OPC maturation have been reported (Raffaiele et al., 2021). Finally, molecular deficits linked to energy metabolism and solute transport in oligodendrocytes as well as in neurons contribute to the pathogenesis of cortical lesions in Creutzfeldt-Jakob disease (Andres Benito et al., 2018).

Concluding Remarks

While neuroprotection is a recognized target in many forms of neurological damage and chronic neurodegenerative diseases, most of the clinical trials on neuroprotection in MS, the reference WM disease, either failed, were interrupted, or provided inconclusive results (Huntemann et al., 2021). We believe that three points must be considered for successful clinical translation of preclinical data supporting therapies for myelin repair in adulthood.

The first point relates to the *in vitro* step of the drug discovery pipelines, which should consider regional OPC heterogeneity and specific pathophysiology. Most chemical entities in *in vitro* screening programs are based on primary cortical fetal OPCs: these cells are not exposed to *in vitro* conditions, which mimic the inflammatory microenvironment, making them unsuited to determining whether potential drugs can effectively overcome the OPC differentiation block related to inflammation (Manousi et al., 2021). These cells are also unfit for studies related to adult OPC pathologies, which differ from those affecting fetal OPCs (Windrem et al., 2004). The use of primary cortical OPCs also ignores the lineage induction phase, however, this critical step can be investigated by deriving OPCs from neural stem cells (Baldassarro et al., 2021b), and taking into consideration regional heterogeneity (Hayashi and Suzuki, 2019).

The second point relates to clinical study design, which should include WM monitoring in primary neurodegenerative diseases also.

The third point regards the longitudinal evolution of the pathologies since both CNS lesions and chronic degenerative diseases are evolving conditions. The study of the potential role of pharmacological approaches to improve myelin restoration requires stringent clinical trial design, adopting the appropriate time windows for treatments, as suggested by preclinical studies.

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