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·Review·

Oligodendroglia and neurotrophic factors in neurodegeneration

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Myelination by oligodendroglial cells (OLs) enables the propagation of action potentials along neuronal axons, which is essential for rapid information flow in the central nervous system. Besides saltatory conduction, the myelin sheath also protects axons against inflammatory and oxidative insults. Loss of myelin results in axonal damage and ultimately neuronal loss in demyelinating disorders. However, accumulating evidence indicates that OLs also provide support to neurons via mechanisms beyond the insulating function of myelin. More importantly, an increasing volume of reports indicates defects of OLs in numerous neurodegenerative diseases, sometimes even preceding neuronal loss in pre-symptomatic episodes, suggesting that OL pathology may be an important mechanism contributing to the initiation and/or progression of neurodegeneration. This review focuses on the emerging picture of neuronal support by OLs in the pathogenesis of neurodegenerative disorders through diverse molecular and cellular mechanisms, including direct neuron-myelin interaction, metabolic support by OLs, and neurotrophic factors produced by and/or acting on OLs.

Keywords: oligodendroglia; neurodegenerative diseases; neuron-glial communication; neurotrophic factors; myelination

Introduction

Myelination in the central nervous system (CNS) is a process by which axons are ensheathed with multiple layers of specialized insulating membranes of oligodendroglial cells (OLs). This vertebrate-specific property enables the saltatory propagation of action potentials, which is essential for rapid information flow in the CNS. Myelin deficiency is the cause of numerous human neurological disorders, either due to the loss of well-formed myelin as a result of immune and/or toxic insult (demyelination) or failures in *de novo* myelin development (dysmyelination, also referred to as leukodystrophies). Multiple sclerosis (MS) is the most prevalent demyelinating disease and is caused by immune attacks on myelin in the brain and spinal cord[1]. In addition, OLs are known to be highly sensitive to glutamate excitotoxicity[2], and thus are vulnerable to many insults in the CNS, including hypoxia, ischemia, and possibly epilepsy[2,3]. In contrast, diseases of dysmyelination are often caused by genetic alterations in genes that play crucial roles in myelination and thus manifest as a failure of *de novo* myelination. The X-linked Pelizaeus–Merzbacher disease is a classic example of CNS dysmyelination disorder, which is caused by genetic alterations in the *PLP1* locus that encodes the proteolipid protein[4], the most abundant structural myelin protein in the CNS. In addition, a rapidly increasing volume of molecular and neuroimaging evidence has also uncovered genetic abnormalities that affect OL genes critical for CNS myelination and white-matter impairment in psychiatric disorders, represented by schizophrenia[5,6]; these abnormalities are thought to underlie long-range disconnectivity in the brain[6].

Traditionally, OLs are primarily recognized as the myelin-producing factories in the CNS. However, more recent discoveries clearly demonstrate the crucial functions of OLs in neuroprotection through multiple mechanisms[7].

Besides protecting axons by the insulating myelin sheath, OLs produce many neurotrophic factors (NTFs) that are well known to promote the survival of neurons[8-14] as well as advancing OL differentiation and myelination, especially during CNS myelin lesion and repair[15-17]. In fact, an even more sophisticated neuron–astroglia–OL interaction loop involving astroglia-produced trophic factors has also been suggested for OLs to achieve CNS myelination and protection[18, 19]. In addition, emerging evidence indicates that OLs play major roles in supporting axonal metabolism[20]. Importantly, an increasing number of recent reports indicate that OL impairment contributes to the onset and/or progression of neurodegeneration.

In this article, we review recent discoveries regarding the potential impact of OLs and CNS myelin impairment on several neurodegenerative diseases. Besides the protection of axons by the insulating myelin membrane, we also discuss NTFs and growth factors produced by OLs and/or acting on OLs during CNS lesion formation and repair, which have key impacts on neuronal survival, axonal longevity, and myelination.

Function of OL-Dependent Myelination in Neuroprotection

The best-recognized demyelinating disorder in the CNS is MS. This debilitating disease stems from repetitive inflammatory autoimmune attacks on CNS myelin. The accumulation of damage from recurring inflammatory insults often leads to progressively worsening neurological symptoms[1]. Although MS is clearly a myelin disorder, an increasing body of evidence suggests that the accompanying loss of axonal integrity and eventual neurodegeneration are the underlying causes of permanent neurological dysfunction. In fact, axonal transection is seen in active demyelinating lesions even early in the disease and appears in nearly all lesions[21]. It is important to note that long-term disability is not proportional to the degree of demyelination but rather to the secondary axonal loss[22]. In addition, immunomodulatory therapies that effectively suppress inflammation fail to prevent axonal loss, which continues into the progressive phase of chronic MS[23]. Thus, besides inflammatory insults, the loss of support by OLs must also play key roles in the axonal loss and irreversible neuropathology in MS.

The protective role of the myelin sheath for axons has long been recognized[24]. In animal models with non-immune-based demyelination, slow progressive axonal degeneration is also well-documented, which demonstrates not only the essential role of myelin in maintaining long-term axonal integrity[24,25], but also that loss of myelin can lead to axonal degeneration independent of immune insult. Oxidative damage is one detrimental factor for axons upon myelin loss. In MS lesions, oxidative damage is evident with oxidized lipids detected in axonal spheroids[26]. The increases in reactive oxygen and nitrogen likely contribute to the mitochondrial damage seen in MS lesions and mouse models of demyelination[27-29]. Impaired mitochondrial function may create an energy-deficiency that stimulates an increase in mitochondria in demyelinated axons in MS lesions as compared to age-matched controls[30]. It has been suggested that this mitochondrial damage results in diminished ATP levels, which impairs the function of the Na^+/K^+ ATPase. As these demyelinated axons are still transmitting action potentials, Na^+ accumulates in the axon and eventually causes a reversal of the Na^+/Ca^{2+} exchanger, leading to Ca^{2+} accumulation in the axon[31,32]. The influx of Ca^{2+} can activate many Ca^{2+}-dependent proteases, such as calpains, that cause alterations in signaling pathways and degradation of cytoskeleton proteins, leading to the disruption of axonal transport[32,33]. Interestingly, remyelination in mouse models restores ion channel clustering and alleviates mitochondrial accumulation in demyelinated axons to nearly normal levels[34,35].

Cytoskeletal abnormality within axons is another commonly-observed consequence of myelin defects, although the precise mechanism remains undefined. Aberrant neurofilament phosphorylation detected by SMI32 staining, a surrogate marker of axonal damage, occurs in the demyelinated corpus callosum of cuprizone-treated mice[36], a well-characterized model of demyelination without T-cell activation[37]. Genetic mouse models that harbor mutations in myelin structural genes have also helped in elucidating the roles of OLs in governing axonal cytoskeletal architecture[7,38,39]. For example, mice null for the periaxonal myelin protein, myelin associated glycoprotein (MAG), display normal-appearing myelin, but reduced axon caliber, neurofilament phosphorylation, neurofilament spacing, and microtubule stability, which together are thought to underlie

axon degeneration[39]. MAG interacts with the complex gangliosides GD1a and GT1b on the axon surface[40]. Mice null for *Galgt1*, a gene responsible for the synthesis of complex gangliosides including GD1a and GT1b, display reductions in axon caliber and neurofilament spacing similar to the MAG-null mice[41]. Moreover, axons in mice double-null for MAG and *Galgt1* are phenotypically comparable to those in MAG-null and *Galgt1*-null mice, suggesting that MAG/ganglioside binding governs neurofilament integrity and long-term axon stability[41]. One clue for myelin regulation of the axonal cytoskeleton comes from the discovery that the axonal surface contactin/Caspr complexes interact with myelin membrane proteins NF155 (neurofascin) and Tag1 (transient axonal glycoprotein 1) at the paranode to form an axon–myelin junction[42]. The intracellular domain of Caspr interacts with Protein 4.1B that connects this complex to the axon cytoskeleton[42]. Interestingly, the localization of Caspr at these junctions appears to be myelin ligand-dependent[42], suggesting possible roles of myelin proteins in regulating the axonal cytoskeleton.

Another example suggesting that axon–myelin interaction, rather than merely shielding the axon from extracellular insults, is key to maintaining axonal health, comes from studies of proteolipid protein (PLP), the most abundant CNS myelin protein. Mice with PLP deficiency display axon swelling and degeneration despite the formation of nearly normal amounts of myelin[38]. This finding uncouples the role of PLP as the major myelin structural component from its neuroprotective effect. Recent reports also uncovered the essential function of PLP in controlling the abundance of the NAD-dependent deacetylase SIRT2 in the myelin compartment[43,44]. Considering the function of SIRT2 in regulating the acetylation of numerous proteins, including α-tubulin that supports the arborization of OL processes and myelin sheath formation[45], PLP-dependent axonal protection may involve a broad downstream pathway to be defined in the future.

Neuroprotection Involves Growth Factors and Neurotrophic Factors Produced by and/or Acting on OLs to Enhance Myelination

Despite the clear roles of myelin membrane in protecting axons, targeted ablation of OLs in a mouse model induces axonal pathology without widespread demyelination[46], suggesting that OLs support axonal health beyond simply providing myelin to shield axons from extracellular insults. One promising mechanism is mediated by the action of NTFs. Although dysregulated NTF levels are not the original cause of demyelination or neurodegenerative diseases, deficiency of NTFs such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), has been reported in classic neurodegenerative diseases[47-51]. Trophic factors are also reduced in progressive MS[52,53], and this may contribute to the irreversible progression and neurodegeneration. On the other hand, neuroprotective and pro-myelinating effects are clearly demonstrated by exogenous NTFs. In the classic neurodegenerative disorders, BDNF and NGF are well-recognized as having anti-amyloidogenic properties[54,55]. Intranasal administration of NGF in an Alzheimer's disease (AD) mouse model prevents the progression of neurodegeneration[55]. In addition, the glial-derived neurotrophic factor (GDNF), produced by astroglia and OLs, has received increasing attention for its neuroprotective activity. GDNF significantly reduces dopaminergic neuronal loss when produced from transplanted cells in a mouse model of 6-hydroxydopamine-induced Parkinson's disease (PD)[56]. Viral delivery and *ex-vivo* administration of GDNF also prevents neuronal loss in Huntington's disease (HD) models[57,58]. Furthermore, NTFs have beneficial effects on CNS lesions, including spinal cord regeneration and myelin repair in both animal models and ongoing clinical trials[16,59-62].

Neuronal protection by NTFs that involves OLs could be achieved through two possible mechanisms: (1) survival of neurons and OLs, and (2) stimulation of OL-dependent remyelination after injury[12,63-65]. In the experimental autoimmune encephalomyelitis (EAE) model of MS, NTFs clearly have neuronal protective and pro-myelination effects. These NTFs include classic neurotrophins such as NGF and BDNF, insulin-like growth factor 1 (IGF-1), GDNF, epidermal growth factor (EGF) and the more recently-identified neurocytokine family members ciliary neurotrophic factor (CNTF) and leukemia inhibitory factor (LIF)[9-11,13-15,66-68]. Recombinant NGF suppresses the clinical phenotype and neuropathological changes in EAE[16]. In addition to enhancing neuronal survival and myelination, NGF also suppresses inflammation by modulating immune cells[16].

Direct evidence indicating the requirement of endogenous neurotrophic factors for myelin repair comes from the delayed remyelination in Bdnf$^{+/-}$ mice that are BDNF-deficient[17]. Moreover, induced deletion of the Bdnf gene at early stages of EAE significantly increases the axonal damage and loss[64, 69]. Although immune cells express many NTFs[70], bone marrow chimeras revealed that CNS-derived BDNF mediates axonal protection in EAE[69]. In addition, in the non-immune cuprizone demyelination-remyelination model, marked up-regulation of mRNAs encoding NTFs in glial cells was reported by Gudi and colleagues[71]. Interestingly, BDNF, CNTF, and EGF are primarily elevated in the remyelinating corpus callosum, consistent with their demonstrated function in enhancing myelin repair[71]. In contrast, GDNF and LIF are mainly elevated in the demyelinating phase, and increased expression of IGF-1, FGF2, and TGF-b occurs during both demyelination and remyelination. Thus, distinct NTFs may act at different stages after injury despite their overlapping function in neuronal protection and promoting OL differentiation for myelin repair.

Dynamic changes of NTFs and growth factors in MS patients with active and progressive disease are also correlated with the predicted neuroprotective and pro-myelinating effects of trophic factors. Similar to myelin insult-induced elevation of NTFs in animals[71-73], NGF, LIF and GDNF levels in the cerebrospinal fluid (CSF) collected from MS patients with active disease are significantly elevated compared to those from clinically stable patients or healthy controls[16,74]. Interestingly, NGF is increased in the CSF from relapse-remitting MS patients, specifically during the relapse phase when active demyelination and remyelination occur[16]. In contrast, NGF is not increased in secondary progressive MS. Moreover, although EGF is increased in the remyelinating corpus callosum after cuprizone-induced demyelination[71], it is significantly reduced in the CSF from primary and secondary progressive MS patients[53]. Considering the roles of EGF in promoting OL differentiation[65,68,75], reduction of EGF is thought to be a contributing factor that may impede remyelination in the chronic progression of MS[53].

OLs harbor receptors for all the aforementioned NTFs, and thus can respond to these pro-myelination signals regardless of which cell type produces them. In fact, overexpressing the EGF receptor (EGFR) specifically in OLs enhances OL differentiation and myelination, as well as remyelination following focally-induced demyelination in the mouse corpus callosum[76]. On the other hand, OLs express most of these NTFs[9-11,13,14]. Therefore, besides protecting axons by the myelin sheath, OLs may also provide neurotrophic support through the production and secretion of NTFs. Among the above NTFs, BDNF expression in the brain is subject to sophisticated regulation, which has been extensively characterized in neurons[77-80]. However, how BDNF expression is regulated in OLs is much less understood. The expression of BDNF in mammals is controlled by at least eight promoters (Fig. 1). Exons derived from these promoters are spliced into the common coding sequence[77,81], resulting in distinct 5'UTRs that play important roles in BDNF localization and expression, especially for activity-dependent translation in neuronal somatic and dendritic compartments[82]. Interestingly, the relative abundance of each BDNF mRNA isoform produced by the OPC cell line CG4 is rather different from that in the hippocampus, which is enriched in neurons but harbors minimal numbers of OLs (Fig. 1). Which BDNF isoform(s) is up-regulated in OLs during remyelination remains elusive. Moreover, whether the posttranscriptional mechanisms that control BDNF protein production in neurons are also used by OLs are challenges for future studies.

Unlike BDNF that is expressed universally in neurons and glia, LIF appears to be primarily expressed in astroglia[19,83]. The current model predicts that LIF is released by astroglia in response to ATP liberated by axons that are firing action potentials, and acts on OLs to promote myelination and myelin repair by advancing OL progenitor differentiation, myelination, and the organization of nodes of Ranvier[19,84,85]. Loss of LIF severely impairs OL differentiation, leading to delayed OL maturation in the optic nerve of Lif$^{-/-}$ mice[18]. CNTF is another neurocytokine that promotes myelination[86]. The most abundant CNTF expression is found in Schwann cells and sciatic nerve[87]. In the CNS, CNTF is known to be expressed and released by astroglia[88]. Although immunostaining indicates co-localization of CNTF with multiple surface markers of OL-lineage cells in the brain[89], it is currently unclear whether OLs also produce and release CNTF. Nonetheless, transplantation of CNTF-expressing adult OL precursor cells has been shown

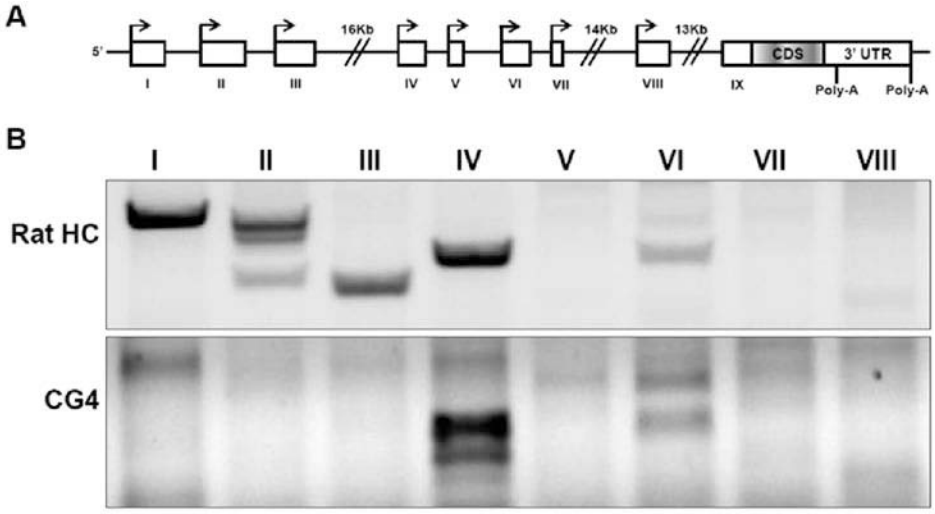

Fig. 1. Brain-derived neurotrophic factor (BDNF) isoforms containing distinct 5'UTRs are differentially expressed in cultured oligodendroglial cells (OLs) as compared to neuron-enriched hippocampus. A: Alternative BDNF promoters (I–VIII) give rise to BDNF mRNA isoforms containing distinct 5'UTRs encoded by the corresponding exons (marked by Roman numerals underneath). The common coding sequence (CDS) is indicated by a shaded box, followed by the 3'UTR which contains two alternative polyadenylation sites (Poly-A). B: RT-PCR of BDNF isoforms I–VIII with isoform-specific primers using total RNA isolated from rat hippocampus (HC) and the OL-cell line CG4.

to promote remyelination and functional recovery in spinal cord injury[90].

LIF and CNTF share the gp130 receptor, which co-operates with LIF-specific and CNTF-specific receptor subunits on OLs. Notably, both LIF and CNTF lack a signal peptide and cannot be secreted by conventional mechanisms. Thus, these poorly-secreted neurocytokines may only effectively act on adjacent cells and axons. This is consistent with the fact that direct administration of CNTF to motor neurons in the spinal cord, at their cell bodies, fails to have beneficial effects in a nerve regeneration model[91], whereas transplantation of CNTF-producing OLs effectively advances myelination in a focal manner[90]. Moreover, CNTF expression in the CNS is thought to be lesion-dependent. Astroglia increase the production of CNTF *in vivo* upon induced stroke[92]. In contrast, astroglial CNTF production is reduced when they are co-cultured with neurons[92]. An intriguing possibility is that CNTF levels are up-regulated when neuronal contact is disrupted by injury. Whether such a mechanism is also used by OLs and Schwann cells to produce and release CNTF is an interesting question to be addressed by future studies. A working model is postulated in Fig. 2 to illustrate the co-operation of axons, astroglia, and OLs to produce classical NTFs (represented by BDNF) and LIF/CNTF neurocytokines, which act on OLs to achieve neuroprotection through myelination as well as trophic factor production by OLs.

Impaired OL Function in Classic Neurodegenerative Disorders

The majority of research on classic neurodegenerative disorders is centered around the view that neuronal death is the initial impetus to pathogenesis. However, accumulating studies have reported white matter alterations including loss of OLs and reduction of OL-specific proteins, even in the early phase of many such disorders[93-96]. A well-recognized commonality among these diseases is axonal degeneration before the loss of the soma[97-99]. In addition, NTFs produced by OLs and/or acting on OLs to elicit neuroprotection and promote myelination, including BDNF, CNTF and LIF, are implicated in these diseases[100,101]. Considering the role of OLs in trophic support and axonal health, whether and how OLs are involved in the onset and/or progression of neurodegenerative disorders are important questions attracting increasing attention.

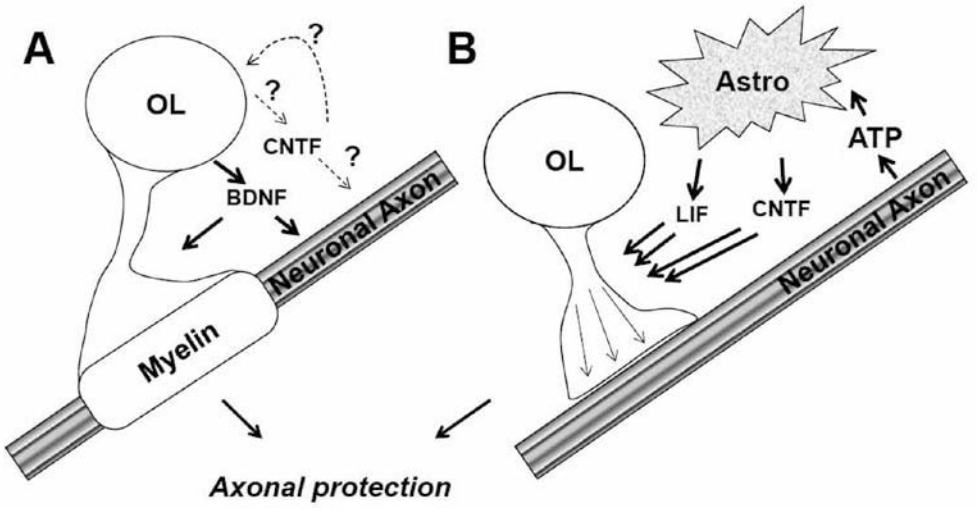

Fig. 2. A: Oligodendroglial cell (OL)-derived brain-derived neurotrophic factor (BDNF) can be secreted and act on neurons to enhance survival and on OLs to promote myelination, both leading to axonal protection. In model B, activity-dependent release of ATP from axons stimulates the astroglial expression of leukemia inhibitory factor (LIF), which acts on OLs to promote myelination and axonal protection. Ciliary neurotrophic factor (CNTF) is known to be expressed in astroglia, and can act on OLs to promote myelin repair. Whether CNTF can also be produced by OLs needs further investigation.

Alzheimer's Disease

AD is the most common form of dementia, characterized by a progressive loss of cognition and the inability to perform simple tasks, with extensive neuronal death and atrophy in the cerebral cortex. Two major hypotheses have been postulated regarding the mechanisms underlying the neuronal loss in AD: (1) formation of amyloid-beta (Aβ) plaques; and (2) hyperphosphorylation of tau and formation of neurofibrillary tangles[97]. Interestingly, the neurons most affected in AD are those most recently myelinated[102]. In fact, extensive white-matter loss has been reported in postmortem brains from AD patients[93]. Further evidence supporting the involvement of OLs in AD pathology comes from the report that Aβ treatment induces OL death in culture[103]. Injection of Aβ into rat white matter also causes loss of OLs and myelin[104]. In addition, mice carrying a mutation in presenilin-1, a gene frequently mutated in familial AD cases, display a heightened sensitivity to toxic insult of OLs and demyelination[105]. Moreover, triple-transgenic mice with mutations in APP, presenilin-1, and tau have defects in OLs and myelin even before the signs of amyloid or tau malfunction[106]. However, injection of vectors expressing intracellular antibodies against $A\beta_{1-42}$ restores OL marker expression and myelin integrity[107], raising the intriguing question whether OL impairment is a causative factor in the early phase of AD pathology.

Huntington's Disease

HD is a genetic neurodegenerative disorder leading to loss of coordination and cognitive function due to autosomal dominant inheritance of an extended CAG trinucleotide repeat that produces an expanded poly-glutamine tract within the huntingtin protein (Htt)[98]. The mutant form of Htt (mHtt) aggregates and forms inclusions, which are thought to disrupt neuronal function and eventually lead to neuronal death. However, Htt expression is not restricted to neurons, but is universal in glial lineages as well[108, 109]. In fact, the expression of mHtt specifically in astroglia of transgenic mice leads to neuronal degeneration[110], suggesting the involvement of glia in HD pathology. Specifically, recent neuroimaging studies point to OL pathology in HD. For instance, MRI imaging revealed a reduction of white-matter volume in HD patients as compared to normal controls[111]. Moreover, reduced white-matter volume has even been observed in presymptomatic HD brains and often correlates with measures of cognitive impairment, suggesting that OL dysfunction may precede neuronal loss[94,95,111,112]. Interestingly, myelin breakdown and neurodegeneration have been observed along axons myelinated during early development[113].

Increased OL density has also been observed in the damaged regions of postmortem HD brains[114,115], possibly as a result of a failed attempt to repair lost myelin.

Parkinson's Disease

PD is the second most common age-related neurodegenerative disorder and affects the dopaminergic neurons of the substantia nigra, resulting in early motor symptoms and later cognitive impairment[99]. Classified as a synucleinopathy, PD neurodegeneration is due to the accumulation of α-synuclein in Lewy bodies followed by cell death[99]. Current evidence suggests a lack of OL involvement in the initiation of PD but does point to a role in PD progression[116]. While α-synuclein filaments have been reported in non-myelinating OLs, they do not appear until clinical symptoms are already evident[117,118]. However, neurons affected by α-synuclein often show decreased myelination and increased association with non-myelinating OLs[119,120]. Moreover, complement-activated OLs, which are often seen in degenerating brains, have been detected in PD brains[121]. These data suggest that although OLs may not be involved in PD initiation, they likely contribute to the exacerbation of PD pathogenesis by removing a source of trophic factors for the survival of remaining neurons.

Neurodegenerative Diseases as a Result of OL Impairment

OL and myelin abnormalities in the above neurodegenerative disorders could be causative in the etiology of the diseases or a consequence of neuronal damage, and these are currently difficult to clearly distinguish. However, recent findings provide strong evidence that dysfunction of OLs causes neurodegeneration in the CNS, represented by the case of multiple system atrophy (MSA).

MSA is a devastating neurodegenerative disease characterized by a unique synucleinopathy in which glial cytoplasmic inclusions (GCIs) with α-synuclein as the major component, rather than neuronal synucleinopathy, dominate the affected brain regions[122]. In particular, GCIs in oligodendroglia is the pathological hallmark of MSA. The lifespan of MSA patients is ~8 years after the onset of symptoms[123], and the pathogenesis is considered to be primary OL dysfunction in the affected brain regions responsible for the clinical phenotypes, including autonomic dysfunction, muscle rigidity, and ataxia[124]. The formation of GCIs is predicted to increase OL susceptibility to the inflammatory cytokine TNF-α and to oxidative stress[125-127]. *In vitro* studies suggest that α-synuclein aggregation is enhanced by phosphorylation at serine-129 and can be induced by the oligodendroglia-specific protein tubulin polymerization-promoting protein (TPPP)[128]. Overexpression of α-synuclein and TPPP in cultured OLs causes OL apoptosis in a serine-129-dependent manner[129], although which of the kinases known to phosphorylate serine-129 is responsible for the pathogenic accumulation of α-synuclein in OLs of the MSA brain remains elusive.

Perhaps the most definitive evidence for the causative role of OL-specific synucleinopathy in MSA comes from transgenic mice that express human α-synuclein specifically in OLs under the PLP, CNP, or MBP promoters that drive transcription in OLs[130-132]. These mice display extensive myelin impairment and persistent neuronal degeneration in many brain areas, recapitulating those affected in MSA patients. Interestingly, overexpression of human α-synuclein under the control of neuronal or OL promoters leads to reduced expression of NTFs derived from OLs[133]. Furthermore, specific reduction of GDNF is seen in transgenic mice that over-express human α-synuclein specifically in OLs, and infusion of GDNF partially rescues the behavioral deficits and neuronal loss seen in these mice[133]. Finally, reduced GDNF levels have also been detected in the frontal cortex white matter and cerebellum of human MSA samples[133]. Thus, reduced NTF production in OLs as a result of synucleinopathy may be an underlying mechanism for the neurodegeneration in MSA.

OL abnormality as a cause of axonal degeneration is reinforced by a recent discovery by Lee and colleagues, who reported that deficiency of monocarboxylate transporter 1 (MCT1, also known as SLC16A1) in OLs results in axonal damage and neuronal loss independent of demyelination[134]. MCT1 is primarily expressed in OLs, with a defined function to export lactate from OLs and provide energy metabolites to neurons. The authors demonstrated that axonal toxicity can be achieved by reduced lactate release from OLs upon MCT1 disruption, suggesting that OL-dependent axonal energy metabolism is a fundamental mechanism by which OLs support axons and neurons. It is important to mention that the same MCT1 trans-

porter is reduced in patients and mouse models of amyotrophic lateral sclerosis (ALS)[134], another devastating neurodegenerative disorder that involves TDP-43 inclusion besides frontotemporal lobar degeneration, raising the possibility that insufficient axonal energy support through OLs may be an underlying mechanism for ALS as well as axonal degeneration in other diseases yet to be elucidated.

Concluding Remarks and Perspectives

The functional importance of myelinating glia in axonal protection and neuronal survival has become increasingly appreciated in recent years and is still under vigorous investigation. Besides the classical view of axonal protection by insulating myelin membranes, emerging evidence suggests that neuronal support independent of the shielding effects of myelination may have an even more profound functional impact on axonal health and neuronal survival. Prevailing issues with clinical relevance are the multi-component functional loops involving NTFs and OLs. Classical NTFs, originally thought to be produced by neurons, are now known to be expressed in OLs as well, and exogenous NTFs can elicit neuroprotection. In addition, the production of NTFs is markedly increased within acute CNS lesions that involve vigorous OL repopulation. In contrast, NTFs and growth factors are reduced in repetitive injuries as well as in chronic neurodegeneration, and this reinforces the functional importance of trophic-factor production and secretion, including those provided by OLs. Moreover, neuron protection can be achieved by sophisticated tripartite interactions between axons, astroglia, and OLs that involve axonal activity-dependent release of astroglia-produced neurocytokines that act on OLs (Fig. 2). However, despite the functional importance, the molecular mechanisms that regulate NTF expression and secretion in OLs remain largely elusive; these mechanisms could differ from those used by neurons as represented by BDNF isoform expression (Fig. 1). Considering the fact that the “lesion NTFs” of the LIF and CNTF family are poorly secreted, perhaps their potent function in neuroprotection and myelination depends on OLs and astroglia located close to the axons. Understanding how NTFs, growth factors, and neurocytokines are regulated in OLs and signal to OLs, especially in response to CNS damage, is the next challenge, which will have great impact on not only demyelinating diseases, but also on inherited leukodystrophies, aging-dependent and familial cases of neurodegenerative disorders, as well as in CNS lesions represented by spinal cord injury.

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