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MINI-REVIEW

Oligodendrocytes in neurodegenerative diseases

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Abstract **Oligodendrocyte is a highly specialized glial cell type in the vertebrate central nervous system, which guarantees the long-distance transmission of action potential by producing myelin sheath wrapping adjacent axons. Disrupted myelin and oligodendrocytes are hallmarks of some devastating neurological diseases, such as multiple sclerosis, although their contribution to neurodegeneration in a given disease is still controversial. However, accumulating evidence from clinical studies and genetic animal models implicates oligodendrocyte dysfunction as one of major events in the processes of initiation and progression of neurodegeneration. In this article, we will review recent progress in understanding non-traditional function of oligodendrocytes in neuronal support and protection independent of myelin sheath and its possible contribution to neurodegeneration. Oligodendrocytes play a pivotal role in neurodegenerative diseases among which special emphasis is given to multiple system atrophy and Alzheimer's disease in this review.**

Keywords Glia, oligodendrocyte, neurodegenerative disease, myelin sheath, multiple sclerosis, multiple system atrophy, Alzheimer's disease, Parkinson's disease

Introduction

Neurodegenerative diseases are characterized by chronic and progressive degeneration of selective neuronal populations. Besides the symptoms directly associated with neuronal degeneration, for example, motor dysfunction in Parkinson's disease (PD), there are many non-cardinal disturbances which, together with the cardinal symptoms, significantly affect normal life of their sufferings. Extensive research so far has identified many molecular and cellular factors that contribute to the initiation and progression of neurodegenerative diseases. Among them, glial activation, mainly astrocytes and microglia, takes an important place in the pathology of neurodegenerative disorders. This may be due to their widespread involvement in the maintenance and regulation of brain homeostasis (Mena and García de Yébenes, 2008; Heneka et al., 2010; Singh et al., 2011). However, as an important component of neuroglia, oligodendrocyte has received less attention in the field of neurodegenerative disease research. Understanding to functions of oligodendrocytes has been hindered by the classical views in which oligodendrocytes have been conceptualized as myelin-forming cells. Consequently, the knowledge about their functions in neurodegenerative processes is relatively limited and fragmentary.

The traditional view of oligodendrocytes is that they are destined to produce axon-wrapping myelin sheath by which saltatory conduction of action potential is guaranteed (Fig. 1). However, emerging evidence has suggested that oligodendrocytes exert supportive functions for neurons and their axons in a myelin sheath-independent manner (Nave and Trapp, 2008; Nave, 2010a, 2010b). Dysfunction of oligodendrocytes has been reported in several neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD). These diseases are considered to be not associated with myelin-forming cells (Roher et al., 2002; Mitew et al., 2010; Lee et al., 2012). The interesting observations prompt us to rethink our traditional views on oligodendrocytes and their possible roles in the pathogenesis of neurodegenerative disorders. In this article, we will review the recent progress on the myelin sheath-independent role of oligodendrocytes in neuronal survival and protection and their potential involvement in neurodegeneration.

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Oligodendrocytes are necessary for axon integrity

Traditionally, oligodendrocytes have been viewed as myelin-forming cells in vertebrate central nervous system, which support myelinated axons and promote action potential conduction by insulating effects of the multilayered myelin sheath. In the three main types of glial cell in the CNS, oligodendrocytes have the most special and intimate interactions with axons (Fig. 1). Loss of intact myelin sheath and oligodendrocytes is predominant pathological feature of several neurological diseases such as multiple sclerosis (MS) and leukodystrophies (Feigenbaum et al., 2000; Schiffmann and van der Knaap, 2004; Trapp and Nave, 2008). Interestingly, many of the myelin diseases are accompanied by axon damages, indicating the critical role of oligodendrocytes in the maintenance of axon integrity, although the exact molecular processes underlying these damages are still in debate. Recent findings obtained by genetic ablation of oligodendrocytes in adult mice strongly suggest that oligodendrocytes are necessary for axon integrity under physiological conditions (Ghosh et al., 2011; Pohl et al., 2011; Oluich et al., 2012). These studies were carried out by three independent research groups using distinct cell ablation strategies. Preferential diphtheria toxin receptor expression in mice was designed to be driven independently by three gene promotors, proteolipid protein (PLP), myelin oligodendrocyte glycoprotein (MOG) or myelin basic protein (MBP). Following diphtheria toxin administration in the adult animals, acute mature oligodendrocyte loss occurred and was followed by severe secondary axonal damage in all three genetically modified mouse lines. The resulted axonal damage was not attributable to excessive CNS inflammatory responses, given that there was only mild astrocyte and microglia activation and no peripheral immune cell infiltration was observed (Buch et al., 2005; Locatelli et al., 2012). These observations are in line with the hypothesis that oligodendrocytes can support their associated axons and maintain long-term functional integrity through mechanisms other than myelination (Nave, 2010a, 2010b; Nave and Trapp, 2008). These findings not only unravel the necessary role of oligodendrocytes in axonal integrity, but also provide good models for the study of the mechanisms of oligodendrocyte-to-neuron interaction and axon degeneration.

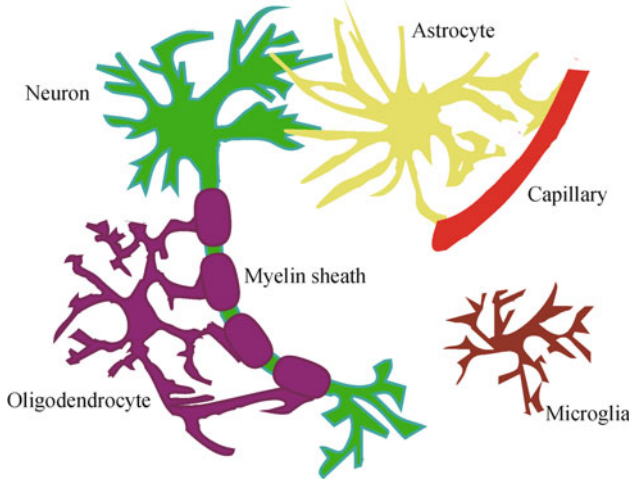

Figure 1 The intimate structural interaction between oligodendrocytes and neurons. Oligodendrocytes can wrap neighboring axons through multilayered myelin sheath.

Neurodegeneration induced by dysfunction of oligodendrocytes

There is mounting evidence that neurodegenerative diseases are complex disorders of selective neural systems involving of multiple cell types including astrocytes and microglia. As an important player in normal brain functions, however, the significance of oligodendrocyte under pathological conditions especially in neurodegenerative diseases has not been fully recognized. Emerging evidence demonstrates the potential roles of oligodendrocytes in this context. Dysfunction of oligodendrocytes induces pronounced neurodegeneration. *PLP* is a myelin related gene with selective expression in oligodendrocytes and Schwann cells. Either depletion or overexpression of this gene caused severe late-onset neurodegeneration in multiple CNS regions (Anderson et al., 1998; Griffiths et al., 1998). In these genetically modified mouse lines, axon degeneration became prominent in old age. In contrast, the myelin sheath of these mice appeared to develop normally. The *rumpshaker* mice harboring a spontaneously Ile to Thr mutation in 186 amino acid site of PLP is associated with hypomyelination of the central nervous system. This moue line showed a late-onset Wallerian-type degeneration accompanied by myelin changes (Edgar et al., 2004). Another clear experimental evidence, showing the supportive function of oligodendrocytes in axon health independent of myelin sheath, came from the study using 2',3′-cyclic nucleotide 3′ phosphodiesterase (CNP1) mutant mice in which the *CNP1* gene was disrupted by Cre insertion (Lappe-Siefke et al., 2003). The overall pattern of myelin proteins, amount and ultrastructure of the central myelin were almost the same as littermate controls in the absence of CNP1. However, by four months of age, progressive motor deficits in motor performance, axon pathology and reactive gliosis became more visible. In this mutant mouse line, the supportive role of oligodendrocytes in axon integrity was completely uncoupled from its role of myelin sheath maintenance, suggesting that dysfunction of oligodendrocytes is sufficient to cause secondary axonal neurodegeneration.

Further evidence supports this hypothesis. For example, absence of functional peroxisomes in oligodendrocytes resulted from inactivation of perioxisomal biogenesis factor-5 (PEX5), a factor known to be essential for peroxisomal protein import, caused wide-spread axonal degeneration,

progressive demyelination and pronounced neuroinflammation (Kassmann et al., 2007). These data highlight the importance of oligodendrocytes on neuroprotection. Similarly, neuroprotective function of oligodendrocytes was also observed in phosphatase and tensin homolog (PTEN) and dicer conditional knockout mice in which the respective genes were deleted specifically in oligodendrocytes (Shin et al., 2009; Harrington et al., 2010). More recently, two very interesting studies revealed that metabolite coupling between oligodendrocytes and neurons is important for neuronal survival and its deregulation contributes to neurodegeneration. In these studies, cytochrome c oxidase assembly protein 10 (Cox10) gene, a haem A farnesyl transferase essential for assembly of mitochondria complex IV, and monocarboxylate transporter 1 (MCT1) were depleted specifically in oligodendrocytes (Fünfschilling et al., 2012; Lee et al., 2012). More importantly, Lee *et al.* found that monocarboxylate transporter 1 (MCT1) was highly enriched in oligodendrocytes and its levels were reduced in ALS mouse models and neural samples of ALS patients, suggesting the involvement of oligodendrocytes in ALS pathogenesis (Lee et al., 2012).

Roles of oligodendrocytes in other protein aggregation-reletated neurodegenerative diseases, such as tauopathies and synucleinopathy, have also been documented. oligodendrocytes and myelin disturbance and their possible roles in the initiation and progression of AD and Huntington's disease (HD) have attracted more attentions from the scientific community in recent years (Desai et al., 2010; Mitew et al., 2010; Valenza et al., 2010; Valenza and Cattaneo, 2011). Animals with targeted expression of mutant tau in oligodendrocytes developed insoluble and filamentous tau aggregates in oligodendrocytes and axonal degeneration (Higuchi et al., 2005), demonstrating that mutant tau-induced oligodendrocyte dysfunction contributes at least partially, if not all, to the neurodegenetration of tauopathies such as AD.

The role of oligodendrocyte in the pathogenesis of Parkinson's disease (PD) remains elusive. However, like PD, multiple system atrophy (MSA) is another neurological disorder with synucleinopathy-related degeneration in the nigrostriatal dopaminergic system. The contribution of oligodendrocytes in the progression of this disease is highly significant, leading to a hypothesis that MSA is a primary oligodendrogliopathy based on the cellular hallmark, the glial cytoplasmic inclusions (GCIs) (Wenning et al., 2008). Tansgenic mice targeting overexpression of the human alpha-synuclein under differrent oligodendrocyte specific promoters developed dopaminergic neuron degeneration and even hippocampal and cerebrocortical neurodegeneration (Kahle et al., 2002; Shults et al., 2005; Yazawa et al., 2005).

Oligodendrocytes in AD and normal aging

AD is a devastating neurodegenerative cognitive disease of which increasing age is the most important risk factor (Breteler et al., 1992). The pathogenesis of AD involves of many factors and cell types including oligodendrocytes, although it is still elusive how these myelin-producing cells contribute to AD pathogenesis. Oligodendrocytes express different isoforms of beta-amyloid precursor protein in cultures (Garcia-Ladona et al., 1997). Toxic beta-amyloids can induce pronounced white matter damage *in vivo* and death of oligodendrocyte *in vitro* (Jantaratnotai et al., 2003; Lee et al., 2004; Desai et al., 2011). In the white matter of AD patients, increased beta-amyloid peptides and significant decrease of the MBP, PLP, and CNP were observed, indicating that the white matter degeneration occurs in AD (Roher et al., 2002). In the gray matter, a similar focal demyelination was also observed in both AD patients and mouse AD models (Mitew et al., 2010). A triple-transgenic AD mouse model which harbors the human amyloid precursor Swedish mutation, presenilin-1 (M146V) knock-in mutation, and tau (P301L) mutation exhibited region-specific abnormalities in brain myelination patterns prior to appearance of amyloid and tau pathology (Desai et al., 2009). What is more interesting is that oligodendrocyte dysfunction is also the case in brain aging (Sloane et al., 2003; Tanaka et al., 2005; Lasiene et al., 2009; Kohama et al., 2011). Dysfunction of white matter may be involved in cognition decline in brain aging. The degeneration of specific neurons affected in AD could be recapitulated in oligodendrocyte-specific tau transgenic mice (Higuchi et al., 2005; Rowe et al., 2007; Kohama et al., 2011). Thus, a novel hypothetical model was proposed by Bartzokis in 2004, in which AD pathology is thought to be related to the protracted development of oligodendrocytes in brain regions, where are the most vulnerable in AD, such as the frontal lobe and medial temporal lobe. Late myelination in these brain regions were extensively correlated to early changes in AD (Bartzokis, 2004).

Oligodendrocytes in MSA

MSA is a late-onset, progressive, neurodegenerative disease belonging to a group of neurological diseases termed alpha-synucleinopathies which also include PD and Dementia with Lewy bodies (Kahle, 2008; Fellner et al., 2011; Ubhi et al., 2011). Most of the MSA patients are sporadic and incidence of this disease increases dramatically with aging, indicating the involvement of environmental factors in disease progression (Dickson et al., 1999; Soma et al., 2006; Stefanova et al., 2009). The clinical symptoms of MSA involve multiple brain regions and systems including motor impairment, behavioral alterations and autonomic dysfunction (Benrud-Larson et al., 2005; Pfeiffer, 2007). Cytoplasmic inclusions predominantly found in oligodendrocytes are the hallmarks of MSA pathology. The major component of the inclusions is alpha-synuclein. In addition to oligodendrocytes, aggregation in neurons and neurites was also reported (Kato and Nakamura,

1990; Kato et al., 1991; Papp and Lantos, 1992; Arima et al., 1998; Papp et al., 1989; Spillantini et al., 1998; Tu et al., 1998; Wakabayashi et al., 1998).

Investigations from animal models and postmortem human patients suggest that oligodendrocyte dysfunction may contribute to both disease initiation and progression (Kahle et al., 2002; Ozawa et al., 2004; Shults et al., 2005; Yazawa et al., 2005; Stemberger et al., 2010). Postmortem study performed by Ozawa et al. found a significant correlation between the frequency of GCIs and the severity of neuronal cell loss, and between these pathological changes and disease duration, which highlights the important role of oligodendrocyte dysfunction in MSA progression (Ozawa et al., 2004). Investigations on transgenic animals with specific alpha-synuclein overexpression in oligodendrocytes greatly extended our understanding of how oligodendrocytes participate in MSA pathology. In these transgenic models, microglia and astorcyte are activated in many brain regions and reactive oxygen species and proinflammatory cytokines derived from these glial cells may greatly promote disease progression, in addition to their contribution to disease initiation. Stefanova and her colleagues found that in PLP-alpha-synuclein transgenic mice, microglia accumulated early and progressively in specific affected brain regions and

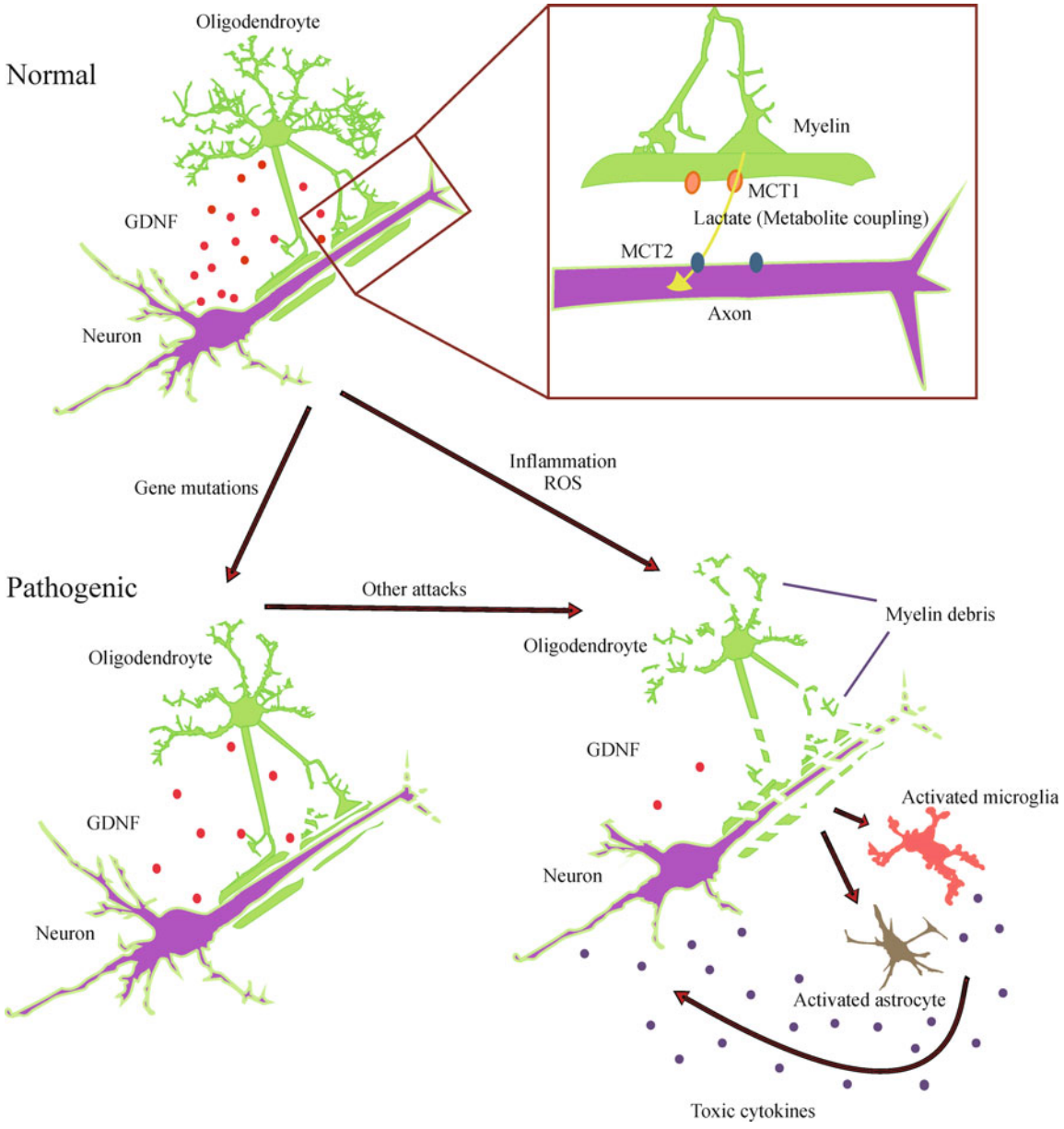

Figure 2 Mechanisms of neurodegeneration induced by oligodendrocyte dysfunction. Series of insults can cause dysfunctions or even death of oligodendrocytes which in turn results in axon or neurodegeneration through myelin breakdown, neuroinflammation, lactate uncoupling, decreased neurotrophic factors secretion and other unknown mechanisms.

related to early nigral neuronal loss and striatal dopaminergic terminal loss which could be significantly relieved by early long-term suppression of microglia activation through minocycline treatment (Stefanova et al., 2007). These observations demonstrate that activated microglia-mediated neurotoxicity is one of critical steps in the progression of neurodegeneration induced by overexpression of alpha-synuclein in oligodendrocytes in MSA transgenic models.

Besides of neuroinflammation mediated by microglia, overexpression of alpha-synuclein in oligodendrocytes can significantly decrease their glial cell-derived neurotrophic factor (GDNF) levels *in vivo* and *in vitro* (Ubhi et al., 2010). Similarly, the reduction in GDNF levels was also observed in brain samples of MSA patients. Conversely, GDNF infusion in MBP-alpha-synuclein transgenic mice ameliorated neurodegenerative alterations and benefited to behavior performance (Ubhi et al., 2010). Together, these findings indicate overexpression or aggregation of alpha-synuclein in oligodendrocytes can cause wide-spread pathological changes, including alteration of neurotrophic factors, neuroinflammation and oxidative stress which convergently contribute to MSA pathogenesis. It is amazing that tansgenic mice targeted human alpha-syunuclein under PLP promoter developed MSA-like lesions in multiple brain regions releted to the non-motor autonomic symptoms, suggesting that oligodendrocytes play central roles in differrent disease stages and pathological progression of MSA (Stemberger et al., 2010). More detailed investegations in these transgenic models will greatly enhance our understanding to the pathogenesis of diseases and step up our efforts to identify novel therapeutic targets for disease intervention.

Concluding remarks

In summary, oligodendrocytes are multi-functional glial cells in the central nervous system and they actively play important roles under both physiologic and pathological conditions (Fig. 2). Their dysfunction contributes to several common neurodegenerative diseases including ALS, MSA and AD, although the precise molecular and cellular mechanisms still need to be unraveled. More detailed investigations in these diseases mentioned herein and even others that appear not to be associated with oligodendrocytes yet will significantly broaden our understanding of disease pathogenesis and oligodendrocyte pathophysiology and help to identify new therapeutic targets.

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Compliance with ethics guidelines

Yingjun Liu and Jiawei Zhou declare that they have no conflict of interest. This article does not contain any studies with human or animal subjects performed by any of the authors.

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