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Review

Thyroid hormone and remyelination in adult central nervous system: a lesson from an inflammatory-demyelinating disease

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Abstract

Re-myelination in the adult CNS has been demonstrated in different experimental models of demyelinating diseases. However, there is no clear evidence that re-myelination is effective in multiple sclerosis (MS), the most diffuse demyelinating disease. Moreover, chronic disabilities in MS are believed to be due to remyelination failure and consequent neuron damage and degeneration. Due to the presence of numerous oligodendrocyte precursors inside demyelination plaques, reasons for remyelination failure are unknown. In this paper, we reviewed data from embryonic development and in vitro studies supporting the primary role of thyroid hormone in oligodendrocyte maturation. We also reviewed personal data on the possibility of promoting myelination in chronic experimental allergic encephalomyelitis (EAE), a widely used experimental model of MS, by recruiting progenitors and channeling them into oligodendroglial lineage through the administration of thyroid hormone.

Theme: Development and regeneration
Topic: Cell differentiation and migration

Keywords: Remyelination; Experimental allergic encephalomyelitis; Thyroid hormone; Oligodendrocyte precursor cell; Neural stem cells

Contents

1. Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS), which can progress over decades and ultimately lead to permanent

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disabilities in humans. Different pathogenic events, i.e. inflammation, immune attack, demyelination and oligodendrocyte death, scar formation, axonal pathology, neuron distress and death, can occur in the different phases of the disease, involving many cell types, i.e. ependymal and endothelial cells, peripheral inflammatory and immune cells, including mast cells, macrophages and lymphocytes, astrocytes, microglia and neurons [32,53,68]. Moreover, also immature cells, e.g. neural stem cells and oligodendrocyte precursor and/or progenitor cells (OPCs), seem to be actively involved in repair attempts [26].

The main pathological feature in MS is lesion of the myelin sheaths, leading to the appearance of multiple areas of demyelination in the CNS and to axonal pathology. Axonal pathology and subsequent degeneration, which has been recognized as a major early event for the chronology of disabilities, correlate with both permanent disabilities and brain atrophy in advanced MS [85]. In spite of the severity of the damage, demyelination could be repaired, since a large number of oligodendrocyte precursor cells (OPCs) are present in the CNS. When labeled using antisera against the proteoglycan NG2, it has been estimated that OPCs account for 5–8% of the total number of cells in the adult CNS [56]. However, although there is evidence of remyelination in different experimental conditions in the adult central nervous system (CNS), re-myelination attempts observed in early plaques in MS are not followed by repair of the lesion [63]. In particular, myelin is inappropriately thin for the corresponding axon and internodes are shorter, so that the resultant remyelination is morphologically and functionally inadequate [38,76]. The reason for this is still unknown, also considering that a significant number of OPCs and premyelinating oligodendrocytes are found in early lesions in MS tissue [30,73], although they are in a quiescent state in chronic lesions [81]. There are many possible speculative explanations of re-myelination failure in MS [38,76], including quantitatively inadequate recruitment and/or differentiation of OPCs [74]; axons not receptive to remyelination [30]; inappropriate support of growth factors by astrocytes and/or other inflammatory cells [67]; and unfavorable or hostile extracellular microenvironment with regard to matrix proteins, adhesion and soluble molecules [75].

The possibility that an inadequate number of OPCs is present in demyelination plaques in MS suggested attempting to introduce a larger number of cells able to differentiate into myelinating oligodendrocytes in order to promote remyelination [34,39,40,65,76]. Different attempts at cellular therapy, using engineered, olfactory ensheathing, Schwann, oligodendrocytes, OPCs, embryonic and adult neural stem cells, have been proposed with contradictory results. However, the rationale for this approach is not clear, since it is widely accepted that MS lesions contain a substantial number of premyelinating oligodendrocytes, indicating that the potential for repair is not limited by the loss of these cells. On the contrary, the number of OPCs is greater than before demyelination in early MS, meaning that new oligodendrocytes are generated during the disease [27]. Overall, the positive effects on clinical course described in some of these attempts have been attributed not to the newly generated myelin-forming cells, but to the growth factor release promoted by these cells.

Another possible explanation for remyelination failure in MS is that OPCs are unable to turn into remyelinating oligodendrocytes in MS. According to this view, attention should be devoted to the attempt to rescue endogenous OPCs and to turn reluctant OPCs into myelinating oligodendrocytes by acting on the OPCs themselves, or by potentiating extracellular signals from axons, astrocytes or other cells type favoring this.

2. Remyelination in adult CNS and during inflammatory-demyelinating diseases

Remyelination, the process by which myelin sheaths are restored to demyelinated axons, is one of the few spontaneous regenerative processes that occur within the adult mammalian CNS. It is generally accepted that the process of remyelination represents a recapitulation of myelination during development. For example, the Notch pathway, which is implicated in cell fate determination in premyelinating oligodendrocytes during development, is re-expressed in MS tissue [50]. A widely accepted model of remyelination proposes that new adult OPCs are generated by division, these newly generated cells being able to migrate into demyelinated areas thanks to the guidance provided by molecules released by different cells during inflammation, toxic or immune attack, and subsequently differentiating into myelinating cells [56,76]. OPCs are disseminated within the white and gray matter of the adult CNS, and can be also be generated from stem cells present in different areas of the CNS. Consequently, a potentially unlimited number of myelinating cells could be recruited in the adult CNS. In experimental inflammatory-demyelinating diseases, but also in MS, OPCs [29,66] and also neural stem cells [20,64,71] re-enter the cell cycle and proliferate, also due to the effects of proinflammatory cytokines which are secreted during acute EAE [31]. Moreover, newly generated PSA-NCAM-positive cells, which are believed to be precursors of OPCs [13], appear during acute EAE [20]. Although the molecular signals responsible for this activation have not yet been identified, it is likely that inflammation and remyelination are linked [26]. In fact, inflammation enhances the migration of OPCs [78], the depletion of macrophages impairs myelination [55] and different growth factors affecting cell cycle regulation are expressed in inflammatory cells in both EAE and MS [54].

Strategies to enhance reluctant myelination are under active investigation, as remyelination failure is one of the most frustrating questions in MS research [38]. Different strategies have been proposed to achieve this therapeutic