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Review

Paving the way for adequate myelination: The contribution of galectin-3, transferrin and iron

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To Eduardo Soto, because he was always our scientific support and a model of friendship and generosity for all of us.

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ABSTRACT

Considering the worldwide incidence of well characterized demyelinating disorders such as Multiple Sclerosis (MS) and the increasing number of pathologies recently found to involve hypomyelinating factors such as micronutrient deficits, elucidating the molecular basis of central nervous system (CNS) demyelination, remyelination and hypomyelination becomes essential to the development of future neuroregenerative therapies. In this context, this review discusses novel findings on the contribution of galectin-3 (Gal-3), transferrin (Tf) and iron to the processes of myelination and remyelination and their potentially positive regulation of oligodendroglial precursor cell (OPC) differentiation. Studies were conducted in cuprizone (CPZ)-induced demyelination and iron deficiency (ID)-induced hypomyelination, and the participation of glial and neural stem cells (NSC) in the remyelination process was evaluated by means of both in vivo and in vitro assays on primary cell cultures.

1. Introduction

Oligodendrocytes (OLG) are glial cells in charge of myelin production in the central nervous system (CNS) and thus play a key role in demyelinating disorders, among which Multiple Sclerosis (MS) appears to exhibit the highest incidence [1–3]. Therefore, among the various trophic factors which have been identified to support OLG maturation and proliferation, e.g. fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1) and thyroid hormones [4–6], this review will focus on the roles of galectin-3 (Gal-3), transferrin (Tf) and iron in OLG differentiation.

OLG are known to produce most CNS Tf [7,8] and their maturation is directly related with the fact that the brain is the only organ in which Tf mRNA expression increases after birth, compelling evidence of Tf importance [9]. In this context, numerous studies published by our group since 1994 have attempted to determine whether Tf has an iron-independent trophic effect on myelin production. A critical question in assessing Tf trophic actions is whether apotransferrin (aTf, iron-free Tf) acquires iron once it is injected in vivo or from the cell culture media. Iron ubiquity and its high affinity for aTf suggest that it would rapidly bind to injected aTf even in small concentrations [10], although evidence seems to establish that it is aTf, and not iron binding to Tf, that has pro-differentiating effects [11].

On the basis of the key role of iron in OLG maturation and myelin production, and considering that hypomyelination as a consequence of iron deficits and the associated neurological sequelae persist long after these deficits have been corrected [12–14], studies in our lab targeted the possible ameliorating effects of an intracranial injection (ICI) of aTf in iron deficiency (ID) conditions, with results rendering a partial correction of myelin deficits. Subsequent assays in cultures of OLG isolated from control and ID animals revealed a smaller number of differentiated cells in ID conditions, followed by a partial recovery upon aTf treatment [15].

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Finally, it was in recent years that our group has started working on molecules apparently working as external signals in OLG differentiation, i.e. galectins (Gals), which are well known within the immune system [16], but not as widely characterized in connection with the CNS. We have identified an essential role for Gal–glycan interactions in regulating OLG differentiation leading to the control of myelin integrity and function and, in particular, we have assessed Gal-3 potential role in modulating neuroimmune processes [17].

2. Cuprizone and demyelination

The cuprizone (CPZ) model has been described as a useful tool to study demyelination and remyelination phenomena [18], with advantages such as easy reproduction and low mortality rates [19]. In mouse models, a CPZ diet has been shown to produce demyelination and OLG damage in the CNS – particularly in the corpus callosum (CC), [20] – without compromising other cell types [21–23], while its termination brings about spontaneous and almost complete remyelination in a matter of weeks [21,24,25].

Although Cammer [26] showed CPZ-induced cell damage in OLG-enriched glial cell cultures and mixed glial cell cultures from neonatal rat brains, the demyelinating effects of CPZ in vivo have proven to be very effective in mice but not in rats [20]. Rats and guinea pigs exposed to CPZ have been reported to show spongiform encephalopathy [27] but not demyelination. In turn, weaning Wistar rats fed a diet containing 0.5–2% CPZ have exhibited intramyelinic edema and OLG mitochondrial enlargement, among other abnormalities, in different areas of the cerebellum [28]. With these two exceptions, our group has pioneered the description of CPZ effects on myelin in rats [29].

Similarly to what has been described in mice [20], CPZ demyelination in rats stops upon termination of CPZ administration and is followed by spontaneous remyelination. Two weeks after toxin withdrawal, myelin yields increase substantially and myelin protein, phospholipid and galactolipid contents recover, although still remaining well below control values. A suitable model to evaluate remyelination strategies in rodents without involving the adaptive immune system, CPZ-induced demyelination by OLG degeneration in white and gray matter is accompanied by reactive gliosis [30–33], an increase in the number of resident microglia (MG) and, to a lesser extent, a rise in the number of peripheral macrophages [34]. In order to characterize the mechanism of CPZ-induced demyelination, we used rat primary oligodendroglial cell cultures and evaluated CPZ effects on cell viability, which was only significantly affected when either IFNγ or TNFα were present. In addition, in vivo experiments showed that the inhibition of microglial activation with minocycline prevented CPZ-induced demyelination. Taken together, our results demonstrate an active role for microglial cells in CPZ-induced oligodendroglial cell death and demyelination, through the production and secretion of pro-inflammatory cytokines [35].

3. Demyelinating diseases and oligodendrocyte damage. Endogenous sources of remyelination

Demyelination is defined as the process governed by the loss of myelin sheaths around neuronal axons and it is a consequence of oligodendroglial dysfunction or death, which, if sustained in time, inexorably leads to neuronal damage and neurodegeneration [36]. Among human demyelinating pathologies of the CNS, MS has a mean age of onset in young adulthood and clinical neurodegenerative manifestations in motor, sensory and cognitive disability. MS is considered a chronic autoimmune disease and is characterized by the emergence of demyelination foci in different brain areas, accompanied by a marked inflammatory response with microglial activation and astrogliosis [37]. Although the adaptive immune system plays a leading role in the acute pathogenesis of MS in most cases, primary oligodendropathy prevails in some patients [38,39]. An endogenous tissue response to CNS demyelination, remyelination tends to restore oligodendroglial population and myelin sheaths and is detected at early stages of MS. However, the process fails in the long run [40,41] and the pathological environment associated with the disease prevents successful long-term myelin recovery [42].

Much effort has been made lately in order to understand the pathophysiological complexities that unfold during MS and attention has been drawn toward developing effective strategies to stimulate myelin repair in the injured brain [43]. In this context, although animal models do not completely recapitulate human MS features, they continue to stand as useful tools for studying remyelination processes in vivo. In CPZ-induced demyelination models in rodents, several hormones such us thyroid hormones [44–47], sex hormones [48–50] or different growth factors [51–53] have been shown to stimulate myelin recovery. Despite their effectiveness in promoting remyelination, the exact mechanisms through which these factors trigger oligodendroglial generation are still unresolved.

Remyelination could proceed by two alternative mechanisms [54]: (a) a rapid response of local oligodendroglial precursor cells (OPC), which undergo differentiation/oligodendroglial maturation and (b) a process involving neural stem cell (NSC) activation and neural progenitor cell (NPC) proliferation from a subventricular zone (SVZ) niche, migration of progenitor cells toward damaged brain areas and terminal oligodendroglial differentiation [55,56].

In vitro studies are useful to dissect these particular mechanisms and allow puzzling out cell interactions and evaluating the effects of individual factors on specific cell types. OLG-enriched primary cultures have been extensively used as an in vitro model of oligodendroglial maturation. More recently, NSC and NPC biology research has become an exciting field of study within neurosciences where multipotent neural precursors can be manipulated in vitro to obtain OPC-enriched primary cultures.

4. Molecules modulating myelinogenesis, demyelination and remyelination

4.1. Galectin-3

Galectins (Gals) are a family of β-galactoside-binding lectins lacking specific individual receptors. They bind to cell surface glycoconjugates containing suitable oligosaccharides to form multivalent complexes and induce intracellular signals regulating cell survival and differentiation [57,58]. Gals also form complexes that crosslink glycosylated ligands to form dynamic lattices (Gal–glycan lattices, [59]). Gal-1 and -3 often have antagonistic roles in the immunological system: while Gal-3 plays pro-inflammatory roles, Gal-1 exerts anti-inflammatory effects [16]. Gal-3, a chimeric protein structurally composed of unusual tandem repeats of proline and glycine-rich short segments fused onto a carbohydrate-recognition domain (CRD), possesses multifaceted roles in physiological processes including the regulation of innate and adaptive immune responses [60].

Specifically in the CNS, our group was a precursor in establishing the relevance of Gal–glycan lattices in OLG physiology and identifying an essential role for Gal–glycan interactions in regulating OLG differentiation leading to the control of myelin integrity and function (Fig. 1). Our first findings showed a high expression of both Gal-1 and -3 in astrocytes (AST) and MG, and an upregulation of Gal-3 in differentiating OLG. This upregulation was accompanied by an increment in the activity of metalloproteinases

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