Multiple the role of Galectin-3 in Promoting Sufficient Myelination

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Abstract

Understanding the molecular basis of Central Nervous System (CNS) demyelination, remyelination, and hypomyelination is crucial for the development of future neuroregenerative therapies given the prevalence of well-known demyelinating disorders like Multiple Sclerosis (MS) and the growing number of pathologies recently found to involve hypomyelinating factors like micronutrient deficits. This review highlights recent research on the role of iron, transferrin, and galectin-3 (Gal-3), as well as their ability to positively influence the development of Oligodendroglial Precursor Cells (OPCs), in the processes of myelination and remyelination. The involvement of glial and Neural Stem Cells (NSC) in the remyelination process was assessed using both in vivo and in vitro assays on primary cell cultures in studies on Cuprizone (CPZ)-induced demyelination and Iron Deficiency (ID)-induced hypomyelination.

Keywords: Multiple sclerosis • Microglia • Demyelination • Oligodendrocyte • Galectin-3 • Remyelination

Introduction

Oligodendrocytes (OLG) are glial cells responsible for myelin production in the central nervous system (CNS), and they consequently play a significant role in demyelinating illnesses, the most common of which is Multiple Sclerosis (MS) [1-3]. Therefore, this review will concentrate on the functions of galectin-3 (Gal-3), transferrin (Tf), and iron in OLG differentiation among the various trophic factors that have been identified to support OLG maturation and proliferation, such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1), and thyroid hormones [4-6]. The brain is the only organ in which Tf mRNA expression rises after birth, providing strong evidence of Tf significance [7]. OLG are known to produce the majority of CNS Tf [7,8]. In this context, our lab has published multiple research since 1994 in an effort to ascertain if Tf has a trophic impact that is independent of iron on the production of myelin. Whether apotransferrin (aTf, iron-free Tf) collects iron after being injected in vivo or from the cell culture media is a key question in evaluating Tf trophic activities. Even in low concentrations, iron would bind to injected aTf quickly due to its ubiquity and strong affinity for it [9,10], but the findings seems to show that aTf itself, not iron binding to Tf, is what causes pro-differentiating effects. Studies in our lab focused on the potential ameliorating effects of an intracranial injection (ICI) of aTf in Iron Deficiency (ID) conditions, with results rendering a partial correction of myelin deficits. This is because iron plays a critical role in OLG maturation and myelin production, and because hypomyelination as a result of iron deficits and the associated neurological sequelae persist long after these deficits have been corrected [11–14]. Finally, it was only in recent years that our group began working on molecules that appear to work as external signals in OLG differentiation, namely galectins (Gals), which are well known within the immune system, but not as widely characterised in connection with the CNS. These molecules were found in OLG cultures isolated from control and ID animals, and subsequent assays in these cultures revealed a smaller number of differentiated cells in ID conditions, followed by a partial recovery upon aTf treatment. We have determined that Gal-glycan interactions are crucial for controlling OLG differentiation, which in turn regulates myelin integrity and function. In particular, we have evaluated Gal-3's capacity to modulate neuroimmune processes [15-17].

Cuprizone and Demyelination

The Cuprizone (CPZ) model, which has benefits including simple reproduction and low mortality rates has been described as a helpful tool for studying demyelination and remyelination phenomena. A CPZ diet has been demonstrated in mouse models to cause demyelination and OLG damage in the CNS, especially in the Corpus Callosum (CC), without endangering other cell types, while its cessation results in spontaneous and nearly complete remyelination in a matter of weeks [18]. The demyelinating effects of CPZ in vivo been shown to be very successful in mice but not in rats, despite Cammer, showing CPZ-induced cell destruction in OLG-enriched glial cell cultures and mixed glial cell cultures from neonatal rat brains. It has been noted that rats and guinea pigs exposed to CPZ exhibit spongiform encephalopathy but not demyelination. Additionally, weaning Wistar rats fed a diet containing 0.5%-2% CPZ showed abnormalities in various regions of the cerebellum, including intra-myelinic edoema and OLG mitochondrial enlargement. With these two exceptions, our lab was the first to describe the effects of CPZ on rat myelin.

When CPZ injection is stopped, CPZ demyelination in rats ends and is followed by spontaneous remyelination, which is similar to what has been observed in mice. Myelin yields significantly increase two weeks after toxin withdrawal, and myelin protein, phospholipid, and galactolipid contents recover—although they still fall far short of control values. The CPZ-induced demyelination by OLG degeneration in white and grey matter is accompanied by reactive gliosis, an increase in the number of resident microglia (MG), and, to a lesser extent, an increase in the number of peripheral macrophages. This model is useful for evaluating remyelination strategies in rodents without involving the adaptive immune system. We examined the effects of CPZ on cell viability in rat primary oligodendroglial cell cultures in order to characterise the mechanism of CPZ-induced demyelination. Cell viability was only severely impacted when either IFNc or TNFa were present. Additionally, in vivo tests demonstrated that minocycline's inhibition of microglial activation prevented CPZ-induced demyelination [19-22].
Our findings show that microglial cells actively contribute to CPZ-induced oligodendroglial cell death and demyelination by producing and secreting pro-inflammatory cytokines.

Damage to oligodendrocytes and demyelinating conditions. Endogenous remyelination sources

Demyelination is the term used to describe the process of losing the myelin sheaths that surround neuronal axons. It is a result of oligodendroglial malfunction or death, which, if prolonged over time, inevitably causes neuronal damage and neurodegeneration.

The average age of beginning of human demyelinating disorders of the CNS is young adulthood, and clinical neurodegenerative aspects of MS include motor, sensory, and cognitive impairment. MS is regarded as a chronic autoimmune illness and is characterised by demyelination foci developing in various brain regions along with a significant inflammatory response that includes microglial activation and astrogliosis. Even

though the adaptive immune system predominately contributes to the acute pathogenesis of MS in the majority of patients, primary oligodendropathy still predominates in some cases. Remyelination, an endogenous tissue response to CNS demyelination, is shown in the early stages of MS and tends to repair the oligodendroglial population and myelin sheaths. Long-term myelin healing is not successful due to the failure of the process and the pathological milieu associated with the disease.

Recently, a lot of work has gone into understanding the pathophysiological complexity that arise with MS, and attention has been focused on creating efficient methods to encourage myelin repair in the wounded brain animal models are nevertheless valuable resources for investigating remyelination processes in vivo in this setting, despite the fact that they do not perfectly replicate human MS characteristics. Several hormones, including thyroid hormones, sex hormones or various growth factors, have been shown to promote myelin recovery in rodent models of CPZ-induced demyelination. Despite being effective at encouraging remyelination, it is still unclear how exactly these factors cause the generation of oligodendroglia.

Two alternative mechanisms for remyelination could take place:

- A rapid response of local Oligodendroglial Precursor Cells (OPC), which differentiate and mature into oligodendroglia.
- A procedure involving Neural Stem Cell (NSC) activation and Neural Progenitor Cell (NPC) proliferation from a Subventricular Zone (SVZ) niche, migration of progenitor cells towards damaged brain areas, and terminal oligode.

Molecules modulating myelinogenesis, demyelination and remyelination

A family of lectins that bind to b-galactosides but lack particular individual receptors is known as galectins (Gals). In order to induce intracellular signals governing cell survival and differentiation, they bind to cell surface glycoconjugates containing the appropriate oligosaccharides to create multivalent complexes. Gals can also form complexes called Gal-glycan lattices, which crosslink glycosylated ligands to create dynamic lattices. Gal-1 and Gal-3 frequently play opposing functions in the immune system: Gal-1 has anti-inflammatory actions, whereas Gal-3 has pro-inflammatory effects. Gal-3, a chimeric protein with a distinctive tandem repeat structure made up of proline- and glycine-rich short regions fused onto a Carbohydrate-Recognition Domain (CRD), plays a variety of roles in physiological processes, including the control of innate and adaptive immunological responses. Our team was a pioneer in demonstrating the importance of Gal-glycan lattices in OLG physiology and establishing a critical function for Gal-glycan interactions in controlling OLG development, which in turn controls myelin integrity and function, specifically in the CNS. In MG and Astrocytes (AST), both Gal-1 and -3 were highly expressed, while Gal-3 was upregulated in OLG that was differentiating.

The metalloproteinases MMP, which control Gal-3's biological activity during OLG development, were also upregulated in tandem with this increase. The N-glycosylation profile seen in immature versus differentiated OLG is consistent with the surprising finding that recombinant Gal-3 therapy promoted OLG differentiation in a dose- and carbohydrate-dependent manner. Surprisingly, compared to OPC incubated with Gal-3-deficient MG, OPC cultivated in medium conditioned by Gal-3-expressing MG produced a greater number of differentiated OLG (myelin basic protein^{+} (MBP^{+}) cells). Our in vivo results provided substantial support for these conclusions.

The number of myelinated axons and myelin twists (lamellae) was significantly reduced in *Lgals3/mice*, according to the morphometric analysis of ultrastructural studies. Additionally, the g-ratio (the ratio of the axon diameter to the axon diameter wrapped in myelin) was found to be higher in *Lgals3/mice*, suggesting that myelin sheaths are wrapped around axons more loosely. These findings were supported by behavioural research in *Lgals3/mice*, which revealed lower anxiety levels similar to those seen during the earliest stages of CPZ-induced demyelination. Finally, compared to neurospheres obtained from mice of the Wild Type (WT) strain, those isolated from *Lgals3/mice* displayed a weaker commitment to an oligodendrocyte fate.

Additional research by our team shows that oligodendroglial differentiation is promoted by glial-derived Gal-3 but not Gal-1. Overall, Gal-3 supports myelin function and integrity, which is crucial for the recovery from inflammatory demyelinating diseases. Bibliographic data demonstrate Gal-3's negative effects in prion-infected brain tissue and its increase by inflammatory stimuli. Gal-3 has also been suggested to play a part in the control of inflammation brought on by lipopolysaccharide. Gal-3, on the other hand, mediates the activation and growth of the focal cerebral ischemia caused by MG. Furthermore, after receiving an injection of Myelin Olg Glycoprotein (MOG), *Lgals3/mice* show a reduction in the severity of Experimental Autoimmune Encephalomyelitis (EAE). The process of demyelination and remyelination in the CPZ model can be studied without peripheral inflammation due to the CPZ-mediated reduction of T cell activity. This is critically important because immune-driven demyelination models like EAE make it challenging to distinguish between immune-driven and brain-intrinsic effects. The number of resident MG and, to a lesser extent, peripheral macrophages rises as a result of CPZ-induced demyelination, and these cells are able to phagocytose myelin debris mostly due to the activation of the phagocytic receptor TREM-2b.

Given that myelin can inhibit OPC differentiation, phagocytosis of myelin debris by MG and macrophages is crucial for the beginning of remyelination. As a result, myelin phagocytosis is lacking in *Lgals3/MG* because myelin phagocytosis is mediated by CR3/MAC-1 and SRAI/II, which are controlled by Gal-3-dependent activation of PI3K.

To assess Gal-3's contribution to demyelination, we used a 6-week CPZ administration paradigm in adult Lgal-s3/mouse. Although our results showed that Lgals3/ and WT mice were equally susceptible to CPZ up to week 5, OPC produced in CPZ-treated Lgals3/ mice showed diminished arborization, a potential indicator of poor differentiating capacity. Surprisingly, CPZ-treated *Lgals3/mice* showed an increase in the number of caspase-3-activated microglial cells, but CPZ-treated WT mice had heightened microglial activation as demonstrated by ED1 expression and the dramatic elevation of phagocytic receptor TREM-2b. Both WT and *Lgals3/mice* showed lower innate anxiety in behavioral assessments as early as the second CPZ week, however only *Lgals3/mice* showed a decrease in locomotor activity and spatial working memory. Overall, our findings suggest that MG Gal-3 expression modulates their phenotype in response to CPZ-induced demyelination. These findings also demonstrate that OPC produced in response to CPZ-induced demyelination in Lgals3/ mice have decreased differentiation capacity, which may be related to the inhibitory effects of impaired Lgals3/ MG phagocytosis of myelin debris. Additionally, our earlier research showed that conditioned media from Gal-3-expressing (but not Lgals3/) MG successfully promote OLG differentiation, which may also help to explain this. Remyelination failure may be caused by a break in OPC differentiation, as shown in earlier articles. Due to a failure in Gal-3-induced OPC differentiation, Lgal-s3/ mice may exhibit a delay in remyelination. Additionally, because *Lgals3/mice* show late remyelination in a setting that is improperly conditioned by MG, myelin created from scratch is abnormal and appears loosely wrapped around axons.

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