Peripheral nerve injury causes a partial or total loss of motor and sensory functions as a result of axonal disruption and subsequent axonal disintegration as well as demyelination distal from the point of injury. Although peripheral nerves are, in contrast to the central nervous system, able to regenerate and reinnervate, functionality is not always restored completely due to insufficient reinnervation or remyelination, and injury may result in sequelae such as neuropathic pain. The degenerative processes following peripheral nerve injury are generally referred to as Wallerian degeneration (Gaudet et al., 2011).

In rodents, the initial response to injury occurs within 24 hours and is characterized by Schwann cells detaching from their associated axons accompanied by degeneration of the insulating myelin sheaths and a subsequent breakdown of axonal integrity; Schwann cells rapidly dedifferentiate and start proliferating. These dedifferentiated Schwann cells and resident macrophages are among the first cells to recognize the injury and secrete pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and chemokines, e.g., monocyte chemoattractant protein 1 (MCP-1), both of which propagate the recruitment of hematogenous monocytes and macrophages, respectively (Meyer zu Hörste et al., 2007; Gaudet et al., 2011). This well-orchestrated cellular response to injury allows for the timely clearance of cellular and myelin debris in order to enable axon regeneration from the newly unaffected proximal stump. One crucial factor that is known to determine the speed of axonal regrowth is cyclic adenosine monophosphate (cAMP) (Hannila and Filbin, 2008).

We have recently investigated whether modulation of lysophospholipid signaling using the immunomodulatory drug fingolimod (also named FTY720) may promote nerve regeneration in a mechanical injury model of the peripheral nervous system (Szepanowski et al., 2016). Fingolimod is a first-in-class sphingosine-1-phosphate (SIP) receptor agonist that is thought to exert a “functionally antagonistic” effect on the SIP, receptor subtype by facilitating its internalization. It thereby prevents the egress of SIP, expressing activated lymphocytes from lymph nodes (Brinkmann et al., 2010). Additionally, fingolimod has been reported to act as an inhibitor of the lysophospholipase autotaxin, thereby reducing lysophosphatidic acid (LPA) biosynthesis (van Meeteren et al., 2008). Both SIP and LPA are bioactive lysophospholipids that address specific G-protein coupled receptors. SIP and LPA receptors have been recognized to be widely expressed in the nervous system and have been associated with a variety of physiological and pathological processes. Not surprisingly, there have been numerous studies indicating direct effects of fingolimod on cells of the central nervous system, including neuroprotective and remyelinating properties (Groves et al., 2013). To evaluate the regenerative potential of fingolimod and to distinguish its immunosuppressive properties from potential direct effects on the peripheral nervous system in vitro, the increase in cAMP expression was investigated for cell culture experiments involving SIP, receptor expressing CHO cells that short-term incubation with fingolimod causes persistent SIP signaling from intracellular compartments, leading to sustained inhibition of SIP formation (Mullershausen et al., 2009). In this context, it has been suggested that the SIP,-G-ade nylate cyclase system might be internalized as a ternary complex, thereby suppressing enzymatic activity of adenylyl cyclase as long as the ligand fingolimod is bound (Ja link and Moleenaar, 2010). In contrast to inhibition of cAMP formation in vitro, the increase in axonal cAMP observed in our recent study may be the result of a long-term treatment regime with fingolimod for more than two weeks, where constantly high concentrations of fingolimod may potentially affect the dynamics of receptor internalization, leading to a spatial segregation of SIP, and adenylyl cyclase by “trapping” de novo synthesized SIP, in intracellular compartments and allowing for an increased activation of membrane-associated adenylyl cyclase during the course of axonal regeneration (Figure 1). As such, potentially beneficial effects of fingolimod may be...
Based on early stimulation of axonal sprouting via neurotrophic factors released by Schwann cells as well as an attenuation of LPA signaling. At later stages, fingolimod may support axon outgrowth via an abrogation of S1P signaling, allowing for an increased CAMP response in the regenerating nerve.

Certainly, there is a need for future studies to further elucidate the molecular mechanisms underlying the presumptive neuroregenerative effects of fingolimod. The current development of novel S1P receptor agonists with greater specificity to S1P receptor subtypes may dramatically expand our understanding of the role of lysophospholipid signaling in physiological and pathophysiological conditions of the nervous system. However, given the emerging body of evidence so far, modulation of lysophospholipid signaling appears not only to be a highly relevant therapeutic target for immunomodulation, but could possibly also represent a promising target for inducing clinically meaningful improvements after primary and secondary nerve damage.


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