

Demyelination in Peripheral Nerves: Much to Learn from Leprosy Neuropathy

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Leprosy is a chronic infectious disorder of the peripheral nervous system (PNS) caused by the infection of non-neuronal nerve cells, preferentially Schwann cells and resident macrophages, by *Mycobacterium leprae* (ML) [1]. There is growing evidence suggesting that damage to the myelin sheath is due to a disturbed Schwann cell response in conjunction with immune cell participation [2-4]. Although demyelination is not easily found in neuropathic leprosy nerve biopsies (Figure 1), nerve conduction studies routinely used in leprosy referral centers indicate that demyelination occurs during most leprosy reactional episodes [5]. Moreover, nerve conduction analyses show that part of these patients recover from previous lesions after 6-month corticosteroid treatment (Jardim MR - personal communication). Other drugs that favor re-myelination are worth being investigated (Figure 1).

Since ML infection may also lead to up regulation of a large set of immune genes during the early stages of infection and recognizing that pro-inflammatory cytokines/chemokines are able to induce the breakdown of myelin in peripheral nerves, it is more likely than not that the demyelination process in leprosy neuropathy could also be immune-mediated [9,10]. Taking into account that peripheral nerve demyelination encompasses a multitude of signaling pathways as well as the orchestration of complex glial-axon-immune cell interactions, the complete understanding of the factors underlying the breakdown of myelin after ML infection requires further elucidation.

In this area of research, our group has consistently been shedding light on the role played by ML in modulating the inflammatory network of cytokines produced by Schwann cells and macrophages *in vitro* and in human peripheral nerves. Over the last decade, we have observed higher levels of mRNA for tumor necrosis factor (TNF) and their downstream-regulated metalloproteinases (MMP)-2 and -9 in leprosy nerves [11,12]. Moreover, TNF has also been detected in the dermis, epidermis, and serum of leprosy reactional skin lesions [13-15]. In the

highly activated inflammatory infiltrates, higher levels of TNF mRNA have been detected than in the insidious processes of peripheral nerves, strongly indicating that this mediator plays an important role in the pathogenesis of neural injury in leprosy [11].

In addition, TNF is a central regulator of tissue inflammation in a variety of infections besides autoimmune and neurodegenerative disorders [16,17]. With regard to the PNS, Schwann cells, which constitutively express the TNF protein in non-injured nerves, robustly increase production after injury while also releasing a broad spectrum of pro-inflammatory mediators, including IL-1 β , MCP-1, MIP-1, TGF- β , and galectin-3 [10,18]. The early release of inflammatory mediators by Schwann cells and resident macrophages attracts additional immune cells to the damaged peripheral nerves, thus inducing an inflammatory burst in the infected nerves, chronically followed by axonal and myelin degeneration. In fact, while lack of IL-1 β and TNF signaling impaired immune cell influx towards injured peripheral nerves in mice, higher levels of TNF were linked to neuropathic pain [19]. As such, leprosy patients frequently report neural pain sensations in consonance with the higher TNF expression observed in leprosy nerves [12,20].

In the paper entitled "Inflammatory Cytokines Are Involved in Focal Demyelination in Leprosy Neuritis", we explored the role of TNF signaling as a major candidate for involvement in segmental demyelination during leprosy disease [21]. The above study observed that TNF, together with its receptor (TNFR) and the TNF-Converting Enzyme (TACE) were most often expressed by Schwann cells in the peripheral nerves of leprosy patients. However, our *in vitro* study showed that although ML upregulated the expression of membrane-bound TNF, it did not induce cytokine secretion in these cells. The bacteria were also able to induce gene expression of TNF receptor 1 (TNFR1), whose activation has been associated with many neurodegenerative diseases like multiple sclerosis [22]. Furthermore, ML was seen to induce IL-23 secretion, a cytokine linked to the onset of immune-mediated demyelination [23]. Likewise, TNF by itself was able to increase the secretion of IL-6 and IL-8 in Schwann cell cultures, indicating its potential contribution to the escalating inflammatory response during nerve injury.

The current review highlights the importance of both ML and TNF in eliciting demyelination related to Schwann cell infection. Even though ML did not induce TNF secretion, its ability to upregulate membrane-bound TNF and TNFR1 expression was demonstrated. Thus, ML renders Schwann cells more sensitive to the exogenous TNF levels in the nerve originated from resident macrophages in

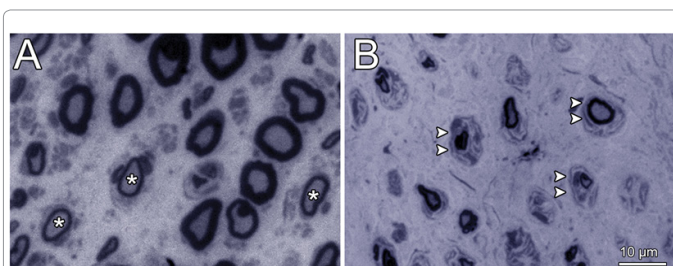


Figure 1: Semithin sections (0.5- μ m-thick) of human nerve biopsy specimens of leprosy patients. Evidence of remyelinated fibers in leprosy patients with reactional neuritic episodes. A) Transverse semithin section showing remyelinating axons (asterisk) with relatively thin, myelin-sheath wrapping axons. B) Concentric onion-bulb Schwann cell proliferation encompassing axons. This is an attempt to remyelinate nerve fibers (arrowheads). Note the reduced quantity of myelinated fibers during this stage of leprosy disease due to secondary axonal degeneration.

The mechanisms involved in nerve fiber damage in leprosy neuropathy have become controversial since Rambukkana and collaborators reported acute myelin stripping after direct ML binding to myelinated Schwann cells *in vitro* [6,7]. Conversely, Hagge and co-authors (2002) followed up of ML infection in myelinated Schwann cell-neuron-co-cultures for 30 days and observed no morphological alterations in the myelin structure of infected fibers *in vitro* [8].

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the early stages of injury and, later on, from recruited inflammatory cells. In view of the fact that this cytokine has been reported to be involved in demyelination, the induction of IL-23 by the bacteria once again reinforces the significant role played by Schwann cells in driving the initial immune response in the early stages of infection and, consequentially, their pivotal contribution to nerve injury [23-25].

The magnitude and underlying mechanisms entailed in nerve demyelination in leprosy neuropathy are subjects of debate. A more complete understanding of the host-pathogen interaction with the axon-myelin unit is crucial to the development of potential therapies for leprosy patients. In addition, our experience indicates that nerve conduction studies are a more reliable and reproducible method to detect myelin loss than routine nerve biopsies. However, these continue to be performed because they are the only means at our disposal to reliably confirm leprosy disease in patients that have no dermatological lesions or positive acid-fast bacilli skin smears.

In this regard, two recent publications provide very novel information regarding future directions to be explored in detailing how myelin is broken down after nerve injury. Both articles have elegantly demonstrated that insulted Schwann cells digest their own myelin by activating intrinsic autophagic-signaling pathways [26,27]. Although there are few reports linking leprosy progression and autophagic genes a possible correlation between demyelination and the regulation of autophagic-related genes in infected Schwann cells deserves further investigation [28,29]. This is a prospective hot topic in the ML-Schwann cell crosstalk field that could elicit alternative views on the possible reasons behind myelin damage in leprosy disease.

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