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Mini Review

What happens when Schwann cells are exposed to *Mycobacterium leprae* – A systematic review

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ABSTRACT

Mycobacterium leprae, the pathogen that causes human leprosy, has a unique affinity for infecting and persisting inside Schwann cells, the principal glia of the peripheral nervous system. Several studies have focused on this intricate host-pathogen interaction as an attempt to advance the current knowledge of the mechanisms governing nerve destruction and disease progression. However, during the chronic course of leprosy neuropathy, Schwann cells can respond to and internalize both live and dead *M. leprae* and bacilli-derived antigens, and this may result in divergent cellular pathobiological responses. This may also distinctly contribute to tissue degeneration, failure to repair, inflammatory reactions, and nerve fibrosis, hallmarks of the disease. Therefore, the present study systematically searched for published studies on *M. leprae*-Schwann cell interaction *in vitro* to summarize the findings and provide a focused discussion of Schwann cell dynamics following challenge with leprosy bacilli.

Introduction

Mycobacterium leprae (*M. leprae*) is an obligate intracellular pathogen of humans that selectively targets peripheral nerves causing a chronic and insidious neurological disorder termed leprosy neuropathy (Scollard et al., 2015; Serrano-Coll et al., 2018). *M. leprae* has a unique predilection to infect non-myelinating and myelinating Schwann cells, the enwrapping glia of the peripheral nervous system (Hagge et al., 2002; Hess and Rambukkana, 2019; Mietto et al., 2020). Once intracellular, this pathogen provokes multiple alterations in Schwann cells, affecting both early and late cellular events, including modifications in the glucose and lipid metabolism and trafficking (Medeiros et al., 2016; Rosa et al., 2021; Girardi et al., 2023), myelin dismantling and lipid droplet accumulation (Tapinos et al., 2006; Mattos et al., 2011a; Elamin et al., 2012; Jin et al., 2017; Mietto et al., 2020), neurotrophin secretion (Nogueira et al., 2020), and changes in gene expression (Casalenovo et al., 2019; de Souza et al., 2022), leading to Schwann cell reprogramming to an immature, highly proliferative phenotype (Hess and Rambukkana, 2019). Interestingly, the progression of leprosy neuropathy occurs even after the end of the treatment and achievement of clinical cure (Penna et al., 2023). This is probably related to the ability of dead *M. leprae* and associated antigens, such as phenolic glycolipid I (PGL-1) and lipoarabinomannan (LAM), to provoke perturbations in Schwann cells and nerve damage by multiple mechanisms. For example, PGL-1 and LAM have been reported to induce myelin breakdown *in vitro* and *in vivo* (Rambukkana et al., 2002; Bahia El Idrissi et al., 2015), a phenomenon also elicited by live *M. leprae* that reportedly benefits bacilli survival intracellularly (Mietto et al., 2020).

Leprosy neuropathy is a long-lasting, multi-complex disease caused by different triggers, affecting Schwann cells and other non-neuronal cells that populate the nerve. However, it remains to be clarified whether these Schwann cell alterations in response to *M. leprae* are at the basis of the pathogenesis of leprosy neuropathy. Moreover, because there is no gold-standard rodent model that resembles human leprosy neuropathy, the investigation of Schwann cells in leprosy relies mostly on *in vitro* and *in vivo* (human biopsies) analysis. Over the past decade, novel findings have been made regarding what happens to Schwann cells after exposure to leprosy bacilli (live or dead) or its antigens. As such, a review of these Schwann cell-centered mechanisms and their possible impact on the progression of nerve pathology is needed to provide a perspective on how this intricate glia-pathogen interaction may provoke or underlie the disease. Thus, in this respect, this systematic review aims to provide an overview of the major findings in the field to help unravel the complexity involving nerve pathology and the

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Schwann cell modifications at the molecular, phenotypic, and metabolic levels following exposure to leprosy bacilli.

Methods

Search strategy

To ascertain the mechanisms involved in the Schwann cell-*M. leprae* interactions, a systematic literature review was conducted considering articles available from January 1964 to February 2023. The published literature was reviewed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (www.prisma-statement.org) (Page et al., 2021). Our patient/population, intervention, comparison, and outcomes (PICO) question was "What are the observed changes in Schwann cells exposed to *Mycobacterium leprae*?". The electronic database PubMed was systematically searched using the following MeSH search terms: "Schwann cell" AND "*Mycobacterium leprae*" OR "leprosy" in all fields of publication, with results restricted to publications in English. The search was performed independently by two authors (LB and MS).

Study selection and eligibility criteria

The two inclusion criteria were experimental *in vitro* studies that analyzed modifications in Schwann cells after being exposed to *M. leprae* and written in English. These studies employed distinct types of Schwann cells, including those obtained from rodent models (mice and rats) and from human sources (primary cells and cell lineages). These Schwann cell sources are indicated throughout the text. The exclusion criteria were as follows: i) studies in which the experiments were restricted to co-culture of Schwann cell with another cellular type; ii) studies with missing and/or ambiguous time points; iii) duplicate publications; iv) non-experimental studies (reviews, viewpoints, perspectives, letters to the editor); and v) clinical studies. Two blinded researchers (LB and MS) independently analyzed all the retrieved articles according to the pre-specified selection criteria. When information was absent or incompatible from the first author but reported by the second author, or when the data given by the two authors was contradictory, these discrepancies were solved by a third author (BM). Titles and abstracts were initially screened, and potentially eligible studies underwent a full-text assessment.

Results

We initially found a total of 344 articles in PubMed using our search strategy. After screening, a total of 38 studies were included in the present review and underwent data extraction. These articles were categorized into four groups according to the type of functional change described in the *M. leprae*-exposed Schwann cell: i) protein expression and secretion, ii) phagocytosis, iii) cell cycle and death, and iv) metabolism. For each published study, our attention focused on the methods implemented (Schwann cell source, control group, exposure to live or dead *M. leprae*, and time points) to understand why data may be convergent or divergent.

Protein expression and secretion

Pro-inflammatory versus anti-inflammatory dynamics

With the apparent controversy in the field regarding pro-inflammatory *versus* anti-inflammatory dynamics in *M. leprae*-exposed Schwann cells, it is evident that additional studies investigating how live bacilli, dead bacilli, and *M. leprae*-derived antigens, combined or not, may impact the Schwann cell inflammatory phenotype are needed. Here, we observed that the main divergent factor may be related to the use of viable *versus* dead *M. leprae* as the stimulus. Overall, although not conclusive, a pro-inflammatory profile tends to be associated with exposure to dead *M. leprae*, whereas an anti-inflammatory profile seems to occur after infection with live bacilli. For instance, a transient increase in the mRNA levels for transforming growth factor beta (TGF-β) was seen only at 1 h after exposure of human ST8814 Schwann cells to dead *M. leprae* (Oliveira et al., 2005; Petito et al., 2013). In these two studies, the authors observed that both mRNA and protein levels returned to basal (non-infected) levels at 3 h and 6 h of exposure to dead bacilli. Another study using primary rodent Schwann cells observed that irradiated *M. leprae* resulted in reduced TGF-β mRNA levels after 12 days of stimuli exposure (Hagge et al., 2002). Accordingly, TGF-β protein release was evaluated by de Souza et al. (2022), who observed no statistically significant difference between the levels from non-infected and dead *M. leprae*-exposed Schwann cells, but noted a significant increase in TGF-β levels in the supernatant of live *M. leprae*-infected human ST8814 Schwann cells when compared to the other two groups at 24 h.

An increase in the mRNA and protein levels of the pro-inflammatory mediator, tumor necrosis factor (TNF)-α, has been observed in human ST8814 Schwann cells challenged with dead bacilli (Andrade et al., 2016; de Souza et al., 2022). However, exposure of ST8814 Schwann cells to irradiated *M. leprae* inhibited the TNF-α-induced NF-κB-dependent transcription, suggesting that the dead pathogen decreases the overall basal level of NF-κB transcription activity, which may play an important role in the mycobacterium tolerance by the host (Pereira et al., 2005). Moreover, Bergsteinsdottir et al. (1991) also noted a significant interleukin (IL)− 1 activity 48 h after exposing purified rat Schwann cells to dead *M. leprae*. A recent study by de Souza et al. (2022) profiled the transcriptome of human Schwann cells after 24 h of challenge with viable and dead *M. leprae*. The authors observed that dead *M. leprae* induced a significant increase in mRNA transcripts for TNF-α, CXCL10, and IL-6 in these Schwann cells when compared to the levels of those exposed to viable bacilli. On the other hand, exposure to viable *M. leprae* led to an increase in mRNA transcripts for IL-23 and MCP-1/CCL2 when compared to the levels of non-stimulated cultures. In addition, analysis of cytokine levels in Schwann cell culture supernatants displayed augmented TNF-α, IL-8, CCL2, and CXCL10 levels following 24 h of interaction with dead *M. leprae* in comparison to the levels of the non-stimulated cultures. Reciprocally, viable *M. leprae* induced higher levels of TGF-β, IL-6, IL-8, IL-10, CCL2, and CXCL10, when compared to the levels of non-stimulated cultures. In summary, this set of experiments suggests that dead bacteria promote a pro-inflammatory response, while the viable pathogen tends to elicit an anti-inflammatory profile. Interestingly, another study from de Léséleuc et al. (2013) found that live *M. leprae* infection did not induce IL-6 and CCL2 protein release in primary human Schwann cells at 48 h.

As part of this inflammatory reprogramming, *M. leprae* exposure appears to activate other genes related to the innate immune response, like Toll-like receptor (TLR) 2, TLR4, CCL2, IL-1 receptor associated kinase 4 (IRAK4), and IL-18 in primary purified mouse Schwann cells (Masaki et al., 2014). CCL2 expression was further verified by de Souza et al. (2022), who found that both dead and viable *M. leprae* increase CCL2 expression. Together, these results are consistent with the notion that dead bacilli are likely involved in the induction of the pro-inflammatory response following interaction with Schwann cells.

Nerve degeneration and regeneration

The robust repair potential of peripheral nerves is associated with the capability of Schwann cells to acquire a repair phenotype that supports axonal regrowth after injury and/or during disease (Mietto et al., 2015; Jessen and Mirsky, 2019). However, nerve regeneration in leprosy patients is frequently incomplete and our understanding of the mechanisms of repair remain limited. Therefore, we next aimed to gather information on how *M. leprae* would affect the repair biology of Schwann cells. Rodrigues et al. (2010) found that dead *M. leprae* induces insulin-like growth factor I (IGF-I) expression in human primary Schwann cells from nerve biopsy when compared to the level of non-stimulated control cultures. Furthermore, in the presence of IGF-1

blocking antibodies, *M. leprae* was unable to rescue the Schwann cells from apoptosis caused by fetal cattle serum withdrawal from the culture medium. This suggests that dead *M. leprae* and its antigens could mediate a potential anti-apoptotic effect over Schwann cells. Moreover, the activation of these pro-survival pathways in infected or exposed Schwann cells are related to host cell dedifferentiation, demyelination, and infection spread, rather than nerve protection. This can be attributed to the fact that IGF-1 and protein kinase B (PKB/AKT) are central players in anabolic signaling as inducers of long chain fatty acid accumulation, which directly impacts axonal physiology. In addition to that, work from Singh et al. (1997a), using primary Schwann cells from two mouse strains (SW and C57BL/6) observed that live *M. leprae* infection did not affect the protein levels of the neurotrophic factor, nerve growth factor (NGF), when compared to those of non-infected control cultures. Moreover, in a recent study using human primary Schwann cells, Nogueira et al. (2020) observed that exposure to sonicated *M. leprae* significantly reduced neurotrophin (NT)-4 and brain-derived neurotrophic factor protein levels at 48 h, when compared to the levels of non-infected cells, while not affecting the expression profile of NGF and NT-3.

Ninjurin 1 (NINJ1) is an adhesion molecule upregulated in axotomy, nerve damage, and regeneration (Araki and Milbrandt, 1996; Kubo et al., 2002). Thus, Cardoso et al. (2007) evaluated its potential role in the *in vitro* glial infection model of leprosy. After 3 h in the presence of dead *M. leprae*, Schwann cell cultures (human ST8814 lineage and human primary cells from nerve biopsy) exhibited upregulated *NINJ1* gene expression. Matrix metalloproteinases (MMPs) are extracellular proteinases known to mediate demyelination and breakdown of the blood-nerve barrier in peripheral neuropathies. Considering the *M. leprae*-Schwann cell binomial, Oliveira et al. (2010) demonstrated that dead bacilli augmented *MMP2* and *MMP9* gene expression in ST8814 Schwann cells very early upon interaction (*i.e.*, at 6 h). Moreover, the inhibition of TNF-α blocked *MMP9* gene upregulation in dead *M. leprae*-stimulated Schwann cell cultures, suggesting that *Mycobacterium*-induced TNF-α expression is likely to be associated with MMP expression and signaling. Moreover, Singh et al. (1997b) observed that viable *M. leprae* induced cell surface laminin expression along with collagen (types I, III and IV) secretion in SW murine Schwann cells. Interestingly, stimulation with heat-killed *M. leprae* had no effect on these extracellular matrix protein levels.

While investigating 9-O-acetyl GD3, a ganglioside involved in anti-apoptotic signaling and nerve regeneration, Ribeiro-Resende et al. (2010) demonstrated that protein levels of this molecule were significantly elevated in ST8814 Schwann cells following 24 h of exposure to inactivated *M. leprae*. Moreover, this study showed that blocking 9-O-acetyl GD3 significantly reduced the activation of the MAPK (ERK1/2) pathway and Schwann cell proliferation, two effects of *M. leprae* on the host cell that are known to result in demyelination. Since cytosolic nucleic acids trigger the type 1 interferon (IFN) response, this pathway may play an important role in host cell reprogramming by an intracellular pathogen, such as *M. leprae*. Following this rationale, de Toledo-Pinto et al. (2016) analyzed the early expression of IFN-stimulated genes in primary human Schwann cells infected with live *M. leprae* for up to 48 h using DNA microarrays. Among the screened genes, the gene encoding $2'-5'$ oligoadenylate synthetase-like (OASL) underwent the greatest upregulation in infected cultures, at about 24-fold higher than the non-infected control, and its expression was further validated by qRT-PCR analysis.

Furthermore, de Souza et al. (2022) observed that Schwann cells stimulated with dead *M. leprae* had greater expression of genes related to neuropathy, *i.e.*, *WNK*, *IFNB*, *IKBKA*, and *HLA-DQA1*, genes for Schwann cell reprogramming, *i.e.*, *GJA1* and *RAF1*, and genes for neural regeneration, *i.e.*, *KCNJ10*, *OLIG1*, *SHH*, and *SOSTDC1*. Conversely, viable *M. leprae* seemed to upregulate genes related to Schwann cell plasticity and dedifferentiation, such as *BDNF*, *JUN*, *SOX10*, *ERBB2*, and *MAPK11*. Essentially, this study proposed that dead *M. leprae* stimulates the upregulation of genes related to peripheral neuropathy and nerve regeneration, while live bacilli increase expression of Schwann cell plasticity and dedifferentiation genes. Erb-B2 receptor tyrosine kinase 2 (ERBB2), in particular, is known to participate in the demyelination and dedifferentiation processes induced by *M. leprae* (Tapinos et al., 2006), and thus, its upregulation within the *M. leprae*-exposed Schwann cell culture model is highly interesting. Accordingly, Masaki et al. (2013) demonstrated the capacity of live *M. leprae* to reprogram mature Schwann cells to an immature phenotype, and this phenomenon was associated with bacilli dissemination and persistence in the nerve. As for the transcription factors cJUN, KROX-20, and SOX10, Casalenovo et al. (2019) analyzed their expression as protein, along with the levels of the receptor p75NTR, in infected murine Schwann cell cultures. Although no statistical change was noted in cJUN expression, there was, indeed, a marked downregulation of KROX-20 and SOX10, which was accompanied by a significant elevation in p75NTR expression, when compared to the levels of non-stimulated control cells.

Exploring novel targets in neuropathy and leprosy-induced bone absorption, Silva et al. (2010) observed that dead *M. leprae* downregulated phosphate-regulating gene with homology to endopeptidase on the X chromosome (PHEX) at both the mRNA and protein levels, in human ST8814 Schwann cells, and this may be a potential mechanism governing bone resorption mediated by *M. leprae*-exposed Schwann cells. Mistry et al. (1992) demonstrated that live and dead bacteria increased the synthesis of the stress-inducible 70 kDa heat shock protein (HSP) in primary monkey Schwann cell cultures, from 24 h up to 1 week *in vitro*, suggesting a possible link between HSP70 signaling in Schwann cells and nerve immunopathology. In addition, Birdi et al. (1997) observed that SW mouse-derived Schwann cells, stimulated with live and sonicated *M. leprae*, expressed bacilli antigens on the glial surface for up to 5 days *in vitro*, which likely has implications for the immunological role of Schwann cells in antigen presentation and nerve damage.

Major histocompatibility complex

Genome-wide association studies have suggested that mutations in key genes are directly related to leprosy predisposition. The major histocompatibility complex (MHC) was found to be highly associated with leprosy susceptibility (Fava et al., 2019). However, the role of Schwann cell antigen presentation during *M. leprae* infection has been poorly explored and, therefore, needs further clarification.

Samuel et al. (1987a) found that neither viable nor dead *M. leprae* could induce the expression of MHC class II in Schwann cells. These cells were obtained from 2 to 3-year-old Wistar Furth rats and the interaction was carried out with 1×10^7 organisms/ml, for up to 28 days. Other experiments done by the same group (Samuel et al., 1987b) showed that the expression of MHC class II by primary human Schwann cells exposed to irradiated or fresh *M. leprae*, at 1×10^7 and 5×10^6 organisms/ml, respectively, remained negative for up to 68 days of interaction. Samuel et al. (1987b) used Schwann cells obtained from peripheral nerves of the upper or lower limbs of human fetuses. The treatment of the infected cultures with 100 U/ml of interferon gamma (IFN-γ) for 72 h promoted the expression of MHC class II. However, this result was also observed in Schwann cells cultures not stimulated with this pathogen. In summary, this pair of studies did not find key changes induced by the infection *per se* in terms of the Schwann cell MHC expression.

Phagocytosis

The first retrieved evidence for phagosome-lysosome fusion in *M. leprae*-infected primary murine Schwann cells was the detection of numerous phagosomes containing *M. leprae* after 72 h of infection (Steinhoff et al., 1989). Moreover, by using acid phosphatase staining, the authors observed that these phagosomes were surrounded by electron-dense material, suggesting lysosome-phagosome cellular fusion and, therefore, the potential of Schwann cells to degrade the phagosome-residing bacteria. However, later events, such as the

potential of the bacilli to escape into the cytoplasm, remain unexplored. More recently, differences between how live and irradiated bacilli are capable of modulating the endocytic pathways of the host cell were addressed by Alves et al. (2004). By applying specific kinase inhibitors, the authors prevented phagocytosis of both live and irradiated *M. leprae*. In contrast, the inhibition of protein kinase A (PKA), either by RpcAMP or KT5720, did not result in the same outcome. Furthermore, dead *M. leprae*, but not live bacteria, co-localized with acidified compartments within Schwann cells at 4, 24, and 48 h, indicating that impairment in phagosome maturation may be an active change driven by the pathogen towards benefiting its persistence intracellularly.

Cell cycle and death

Early studies on Schwann cell-*M. leprae* interaction found a reduction of thymidine incorporation in rodent Schwann cells sheltering *M. leprae* (Samuel et al., 1987a, 1987b). Although these findings suggested the inhibition of DNA synthesis, an alternative explanation is that Schwann cells in the S phase may not phagocytize *M. leprae*. In contrast, another study by Tapinos and Rambukkana (2005) showed that intracellular *M. leprae* promote G1/S-phase transition through MEK-independent and Lck-dependent ERK1/2 signaling in a primary human Schwann cell model. Later, an experiment using a serum-starved model of human Schwann cell-*M. leprae* interaction corroborated a bacilli protective role, as it showed cell proliferation and death resistance in infected cultures when compared to the control (Rodrigues et al., 2010). Additionally, this same study found that *M. leprae* challenge of serum-starved Schwann cells delays caspase-3 activation at early time points (4 h and 8 h) when compared to non-infected cultures. This difference, however, was not maintained after 24 h of incubation. Paradoxically, two studies showed higher apoptosis rates in ST8814 Schwann cells stimulated with irradiated *M. leprae* (Oliveira et al., 2005; Silva et al., 2008). The latter study found no statistical difference in BAX and BAK protein levels in infected Schwann cells compared to the levels of the non-stimulated control. This data, assessed by flow cytometry and densitometry analysis, points to the hypothesis that the mechanisms leading to apoptosis in ST8814 Schwann cells may not involve the BCL2 family.

Metabolism

It is increasingly apparent that *M. leprae* viability may depend on the pathogen-driven modifications of the host cell metabolism. This modulation seems to occur through changes in multiple pathways, such as lipid droplet biogenesis, mitochondrial respiration, and free radical defense. Many studies with different methods have shown that *M. leprae* induces lipid droplet biogenesis in unmyelinated rodent and human (Mattos et al., 2011a, 2011b; Guerreiro et al., 2013; Jin et al., 2017; Díaz Acosta et al., 2018; Rosa et al., 2021) and myelinated murine Schwann cells (Mietto et al., 2020). The internalized pathogen then recruits the cytoplasmic lipid droplets *via* cytoskeletal rearrangement and PI3K signaling (Mattos et al., 2011a). Interestingly, by using myelin-loaded primary mouse Schwann cells, Mietto et al. (2020) demonstrated the ability of live *M. leprae* to enhance myelin breakdown into lipid droplets by augmenting the autophagic myelin destruction pathway. This myelinophagic event was proposed to benefit *M. leprae* viability inside Schwann cells.

Taking into consideration that leprosy bacilli induce lipid droplet production, many research groups have investigated the role of PPARγ, a nuclear receptor/transcriptional factor that regulates lipid metabolism, during infection. In this regard, crosstalk between PPARγ and CD206 was found to mediate lipid droplet formation given that pretreatment with a PPARγ antagonist (GW9662) reduced lipid droplet formation induced by live *M. leprae* 48 h post-infection (Díaz Acosta et al., 2018). Additionally, the literature has demonstrated that lipid droplet biogenesis favors *M. leprae* intracellular survival in multiple Schwann cell sources (Mattos et al., 2011a, 2011b; Díaz Acosta et al., 2018; Mietto et al., 2020; Rosa et al., 2021), indicating that the modulation of lipid metabolism in the Schwann cell is a conserved mycobacterium survival strategy.

Medeiros et al. (2016) observed that infected human ST8814 Schwann cells secrete less lactate than uninfected cells. Girardi et al. (2023) confirmed this by determining the fate of lactate within the metabolism reprogramming. In this study, lactate supplementation was associated with an increase in intracellular lipid body deposition. Moreover, exposure of Schwann cells to ^{14}C-labeled lactate resulted in enhanced ^{14}C-phospholipids and fatty acid levels in live *M. leprae*-challenged cultures. Together, this set of experiments suggests deviation of lactate carbons to lipid synthesis. *M. leprae* is able to bind and activate ERBB2, known to induce demyelination *via* induction of the PI3K-AKT signaling cascade (Tapinos et al., 2006; Tapinos and Rambukkana, 2005). Activated phosphoinositide 3-kinase (PI3K), in turn, activates PKB/AKT, an enzyme that controls lipid homeostasis by activation of ATP-citrate lyase, which converts citrate to acetyl-CoA, the first step of lipid synthesis. Girardi et al. (2023), through investigation of the downstream elements of this cascade, showed higher phosphorylated AKT (p-AKT) in live *M. leprae*-infected human Schwann cell protein extracts in comparison to the that of the non-stimulated control group. Furthermore, the use of the AKT-phosphorylation inhibitor triciribine reverted the lactate deviation to fatty acids through PI3K/AKT signaling, corroborating the role of this pathway in metabolism remodeling.

The ability of *M. leprae* to prevent the reduction of mitochondrial transmembrane potential and delay caspase-3 activation was also evidenced in a serum-starved Schwann cell model (Rodrigues et al., 2010). However, a study by Medeiros et al. (2016) reported a reduction in mitochondrial membrane potential and a drop in oxygen consumption in infected human Schwann cells (not serum-starved), suggesting that the pathogen may inhibit the host's mitochondrial respiration. This data was complemented by an observed increase in glucose uptake, as measured by uptake of a glucose analog (2-NBDG). The augmented glucose uptake was associated with an increase in the activation of the pentose phosphate pathway, followed by a decrease in mitochondrial activity in ST8814 Schwann cells (Medeiros et al., 2016; Borah et al., 2019). Taken together these data demonstrated that the extra glucose was diverted to the pentose cycle in infected cells, supporting *M. leprae* amino acid synthesis and reductive power to drive *de novo* lipid synthesis in the host cell. These results were supported by experiments showing upregulation in glucose-6-phosphate dehydrogenase (G6PDH) and malic enzyme expression in infected Schwann cells (Medeiros et al., 2016). Moreover, *M. leprae* viability in Schwann cells was found to be dependent on the pentose pathway. In fact, blockage of this signaling pathway using 6-ANAM rescued the host cell from the metabolism rewiring, reverting the lactate production and mitochondrial membrane potential of Schwann cells to basal levels. Through microarray analysis, Guerreiro et al. (2013) screened for early changes (*i.e.*, 24 h) in the genetic signature of human primary Schwann cells infected with live *M. leprae*. Among the significantly modulated genes, the authors observed 11 genes involved in the oxidative phosphorylation pathway, including 7 targets related to mitochondria. More recently, another study demonstrated the relationship between the lactate carbon deviation to long chain fatty acid synthesis, and its negative impact on neurons (Girardi et al., 2023).

Perspectives

Disruption of the basic activities of Schwann cells are, undoubtedly, associated with the pathogenesis of leprosy neuropathy (Fig. 1). However, the exact mechanisms arising from this process that contribute to nerve degeneration and failure to repair, hallmarks of the disease, are fragmented in the literature. Therefore, the cumulative data systematically collected from the literature and discussed in this review shed light on the intimate relationship between the pathogen-driven changes in the

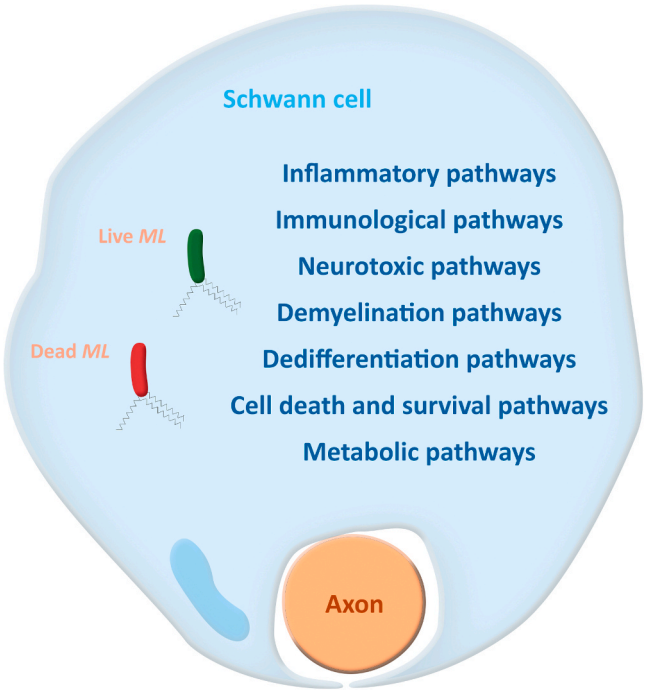

Fig. 1. Schwann cell pathways modulated by leprosy pathogen. Primary Schwann cells and cell lineages have been consistently used as *in vitro* models to elucidate leprosy neuropathogenesis. In this figure, we summarize major Schwann cell-centered signaling pathways influenced by live and dead *M. leprae*, which are reportedly associated with nerve pathology and disease progression. Although pivotal discoveries have been made, future *in vivo* and *ex-vivo* studies involving live and dead bacteria along with *M. leprae*'s antigens are important to characterize the complexities of leprosy neuropathy. Such models may favor the interaction of leprosy pathogenic elements with the cellular and structural components that build the nerve, thus providing a microenvironment which closely resembles the human disease.

host Schwann cell and the *M. leprae* intracellular survival. Together, this review summarized the results into four major areas affected during this host-pathogen communication as a unifying phenomenon that may explain the multiple pathogeny routes in leprosy. The full understanding of what happens to the Schwann cell after being infected and/or challenged with leprosy bacilli is a growing field for advancing our current view of leprosy pathogenesis and its underlying mechanisms. Moreover, knowing that human leprosy neuropathy involves the contribution of live and dead bacilli, as well as *M. leprae*-derived antigens, additional studies mixing these pathogenic triggers are urgently needed to help decipher their mutual effects on Schwann cell biology and disease progression. In the last decades, *in vitro* evidence has, undoubtedly, demonstrated that *M. leprae* has the unique capacity to modify multiple Schwann cell responses. However, their actual contribution for the long-term *in vivo* leprosy pathogenesis in complex tissue remains to be fully explored and characterized. Considering the limitations in employing human *in vivo* studies and access to nerve biopsies, an armadillo leprosy neuropathy model has arisen as a promising experimental platform. This model resembles the major hallmarks seen in the human disease when challenged with leprosy pathogen, and will hopefully provide the basis for better questions to generate novel hypotheses in the field of nervous system pathology, infection, and disease. Remarkably, the available literature about the interaction between *M. leprae* and Schwann cells is permeated with apparent contradictions, a scenario that demanded the present review. For reasons of methodological rigor, our inclusion/exclusion criteria limited the manuscripts included in this review strictly to studies using *in vitro* Schwann cell cultures, which may be considered a limitation of this study. Therefore, future systematic reviews gathering data from patients and whole nerve analysis are needed to further consolidate published knowledge about the pathogeny of leprosy from a clinical point of view.

Ethics statement

Ethical approval for human and animal research was not required for this systematic review.

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Author contribution

LB, MS, and BM collected and analyzed the data. **LB, MS, FL, and BM** wrote, reviewed & edited the manuscript. **BM** conceptualized and supervised the study. All authors read and approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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