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Signaling mechanisms for the survival of *M. leprae* in the peripheral nervous system

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Among the bacterial pathogens *Mycobacterium leprae* uniquely invade differentiated Schwann cells, the glial cells of the adult peripheral nervous system (PNS), and eventually cause neurological injury, the hallmark of clinical leprosy. Our studies on the cell biology of Schwann cell infection with *M. leprae* have contributed to an understanding of the early stage of infection and the life cycle of *M. leprae* within the PNS. Myelinated and non-myelinated Schwann cells, the two major glial cell types in the PNS, show distinct functional responses to *M. leprae* infection. Although *M. leprae* binds to both these cell types, it is the non-myelinated or myelin-free Schwann cells that are highly susceptible to *M. leprae* invasion and preferentially harbor *M. leprae*. On the other hand, myelinated Schwann cells, the abundant phenotype in the adult PNS, are largely resistant to *M. leprae* invasion. Interestingly, leprosy bacteria have evolved to generate a myelin-free Schwann cell pool during early infection by inducing demyelination and cell proliferation. We provide evidence that *M. leprae* achieve this by using a major Schwann cell signaling system that comprises of axonal ligand neuregulin-1 and its receptors, ErbB2 and ErbB3 that play critical roles during Schwann cell development and myelination. We have shown that extracellular *M. leprae* directly bind to ErbB2 receptor tyrosine kinase on myelinated Schwann cells in an atypical manner that does not involve usual dimerization with its partner ErbB3; activated ErbB2 transduces the downstream Ras-Raf-Mek-Erk signaling and subsequently causes demyelination. In non-myelinating Schwann cells, which are quiescent in adult peripheral nerves, *M. leprae* use somewhat different tactics since they can efficiently invade this phenotype; intracellular *M. leprae* cause these quiescent Schwann cells to re-enter the cell cycle by inducing the Erk1/2 signaling not by canonical Ras-Raf-Mek pathway, but via a novel signaling involving PKC-epsilon and LCK pathway. In this manner, *M. leprae* eventually generate a myelin-free cell population susceptible to infection. We also address how intracellular *M. leprae* maintain infected Schwann cells in myelin-free stage, since de-differentiated cells usually undergo re-differentiation and remyelination following nerve injury. We found that intracellular *M. leprae* inhibit the myelination program of Schwann cells by turning off the myelin gene transcription. One of the mechanisms by which *M. leprae* downregulate myelin gene expression is by inhibiting a novel nuclear signaling by the cytoplasmic domain of ErbB3, which we found to function as a putative transcriptional activator for the major myelin gene Mpz. Together, these findings suggest that *M. leprae* use Schwann cell signaling mechanisms for bacterial survival within the PNS. Understanding these cellular mechanisms in details will aid in developing novel therapeutics and/or diagnostics to prevent the nerve damage at the early stage of *M. leprae* infection. Importantly, these studies are also likely to provide new insights into our understanding of the biology of Schwann cells.