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Mighty Bugs: Leprosy Bacteria Turn Schwann Cells into Stem Cells

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For intracellular parasites that strongly prefer infecting a particular cell type, systemic spread is challenging. Masaki et al. show that the leprosy bacterium cleverly expands its repertoire by driving dedifferentiation of Schwann cells, their preferred host, to cells with stem cell properties that can subsequently redifferentiate into mesodermal lineages.

Leprosy is an age-old scourge for human civilization that despite recent successes in therapy and prevention still represents a significant global health problem (Scollard et al., 2006). Its causative agent is *Mycobacterium leprae,* an obligate intracellular bacterial pathogen. Although *M. leprae* became the first bacterium identified as a cause of human disease, it has kept its secrets well. *M. leprae* exhibits a strong tropism for Schwann cells (Stoner, 1979), the glial population that ensheath axons of the peripheral nervous system (Jessen and Mirsky, 2005) (Figure 1). The pathogen's predilection for these cells is the primary cause for sensory loss and sensorimotor dysfunction in leprosy patients (Stoner, 1979). In recent years, clues have been obtained that indicate how *M. leprae* recognizes and enters Schwann cells and how it modifies the properties of its host cells to its own advantage. An unresolved issue is how *M. leprae* spreads from Schwann cells to other cell types, including skeletal and smooth muscle cells during late stages of this chronic disease. In this issue of *Cell*, Masaki et al. (2013) identify an unexpected mechanism by which the pathogen triggers its dissemination. Intriguingly, this involves dedifferentiation and reprogramming of its host Schwann cell to a stem-cell-like state.

Previous studies have shown that interactions between several bacterial adhesins and α2 laminin in the Schwann cell basal lamina mediate bacterial attachment and that α-dystroglycan and ErbB2 serve as receptors on the Schwann cell surface (for review see Pinheiro et al., 2011; Rambukkana, 2010). These primary contacts not only mediate entry of *M. leprae* into its host cell but also induce dedifferentiation by activating Erk1/2 signaling. The resulting immature Schwann cells provide a much better environment for the bacterium than differentiated cells, especially those that are myelinating. Their ability to proliferate furthermore increases the pool of cells in which the bacteria can replicate (Figure 1).

Masaki et al. (2013) now show that if confronted with high bacterial load for extended periods, infected Schwann cells dedifferentiate even further, losing their lineage characteristics and adopting an expression profile indicative of a mesenchymal stem cell. As an early event in this reprogramming process, the transcription factor Sox10 is exported from the nucleus to the cytoplasm, followed by downregulation of its expression and methylation of its gene. Considering that Sox10 is not only a critical factor of myelination but also an essential determinant of Schwann cell identity (Finzsch et al., 2010), it is very likely that Sox10 inactivation and elimination is a key event in extinction of lineage properties and a central step in the bacterial reprogramming strategy.

When further kept in mesenchymal stem cell medium the bacteria-laden stem-cell-like cells develop a series of remarkable properties (Figure 1). They are not only strongly proliferative but also highly migratory, which may be an important factor in pathogen dissemination. These cells are also capable of redifferentiating into various mesodermal cell types and of integrating into skeletal and smooth muscles, thereby spreading *M. leprae* directly to these tissues. Finally, Masaki et al. find that these infected cells with stem cell properties secrete a cocktail of immunomodulatory molecules that attract macrophages to which *M. leprae* is transferred. This results in granuloma formation, and the infected macrophages serve as another vehicle for systemic pathogen dissemination.

Two aspects make this study particularly exciting: first, it shows that a pathogen is capable of exploiting the genomic plasticity of a highly specialized differentiated cell by erasing its identity and reprogramming it. Second, it provides plausible mechanisms for pathogen dissemination during the course of leprosy.

As with every study, there are limitations and caveats. Most results are obtained in cell culture and in vivo validation is confined to a nude mouse model in which Schwann-cell-derived cells with stem-cell-like properties were transplanted into skeletal muscle after cardiotoxin-induced injury. This limitation is inevitable as no animal model exists that recapitulates the essential features of the human disease (Pinheiro et al., 2011; Rambukkana, 2010). As a consequence, it is currently very difficult, if not impossible to show Schwann cell reprogramming in vivo, let alone in the patient. Additionally, it is unclear whether a reprogrammed cell in vivo completely resembles and behaves as its counterpart in vitro. To a large extent,

this depends on the signals it receives from its environment, and these may vary from in vitro culture. As a result, reprogrammed cells in vivo may well implement alternative or additional developmental choices depending on the properties of their niche. The blood-nerve barrier adds another layer of complexity in vivo because its presence influences migration of infected Schwann-cell-derived stem-cell-like cells and macrophages.

Beyond its immediate relevance for the pathophysiology of leprosy, the current study establishes an experimental system that may yield valuable insights into both Schwann cell and stem cell biology. To exploit this potential, researchers need to better define the underlying molecular mechanisms. Considering the known role of Sox10 in Schwann cell identity and the relevance of identity loss for reprogramming, it will be important to figure out how *M. leprae* interferes with Sox10. Does the bacterium directly target this host cell transcription factor? Does it actively cause Sox10 export from the nucleus, degradation and gene silencing? And if so, by what mechanisms? It will also be interesting to learn whether loss of Sox10 is the single most important factor for reprogramming or whether this event sets the stage for the action of other factors after Schwann cell identity loss. The ability of Sox10 to interact physically and functionally with transcription factors, chromatin remodelers, and histone modifiers is certainly compatible with a prominent role (Jacob et al., 2011; Weider et al., 2012; Wißmüller et al., 2006). The future will tell.

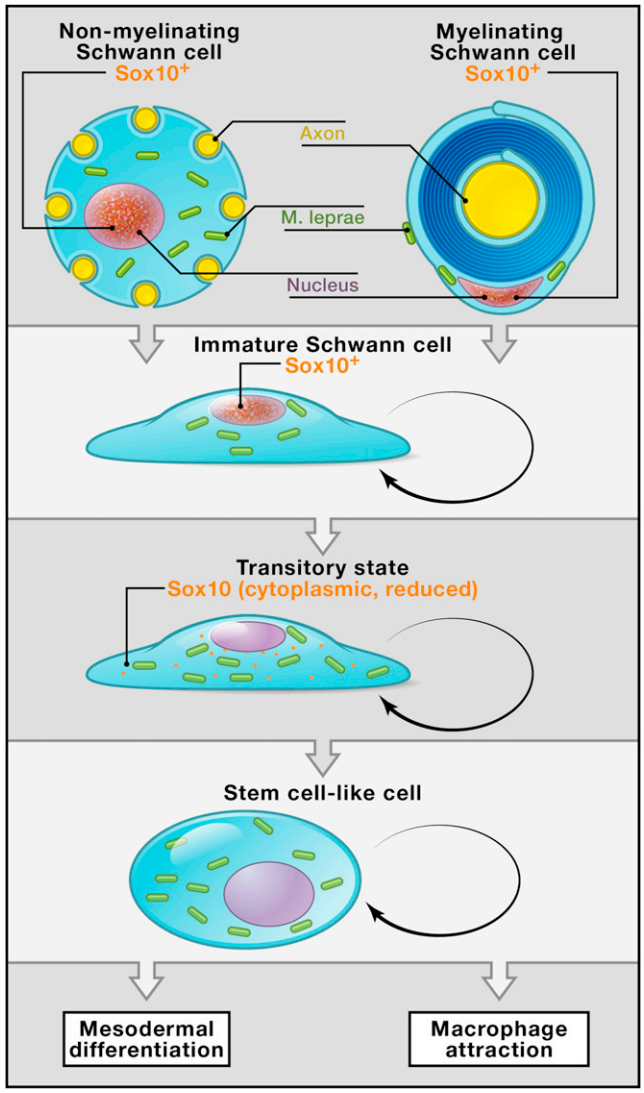

Figure 1. Infected Schwann Cells Acquire Stem-Cell-like Properties
M. leprae infects mature nonmyelinating and myelinating Schwann cells in contact with axons and causes their dedifferentiation to immature Schwann cells. According to Masaki et al. (2013) the transcription factor Sox10 is expelled from the nucleus and degraded as the bacterial load increases. Following identity loss, former Schwann cells are reprogrammed to stem-cell-like cells with the ability to redifferentiate into infected mesodermal cells and attract macrophages, resulting in extensive bacterial dissemination. The curved blue arrows indicate the capacity for cell proliferation.

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