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CELLULAR MICROBIOLOGY

Mycobacterium leprae turns back the clock

Manipulation of infected cells is a widespread mechanism used by pathogens to ensure their survival and spread. Now, Rambukkana and colleagues reveal that *Mycobacterium leprae* goes one step further, reprogramming the infected cells into a stem cell-like state to ensure bacterial dissemination.

M. leprae establishes infection in adult Schwann cells (the glial cells of the peripheral nervous system), where it is sheltered from immune responses by the blood–brain barrier and is provided with factors that promote its survival. Previous work had also shown that *M. leprae* infection, as well as other neuronal injury, induces demyelination of Schwann cells, making them more susceptible to infection; these cells are known as dedifferentiated Schwann cells because they are less mature than those associated with adult nerves.

To investigate this further, the authors isolated Schwann cells from adult mice and examined *M. leprae* infection *in vitro*. Interestingly, they observed that the cells upregulated numerous genes in response to infection, including some associated with embryonic development and chromatin remodelling. Moreover, the transcription factor SOX10, the master regulator of Schwann cell differentiation and homeostasis, was exported from the nucleus in infected cells, indicating that infection perturbs transcription events specific to the Schwann cell lineage. Further analysis showed that infected cells switched off genes associated with Schwann cell differentiation and switched on early developmental genes. In particular, the authors observed an upregulation of genes associated with epithelial–mesenchymal transition (a cellular dedifferentiation process that is vital for morphogenesis during development), such as those encoding the transcription factors TWIST1, TWIST2, SNAIL2 and MSX2, accompanied by decreased methylation of their promoters. These changes depended on the presence of high numbers of intracellular bacteria.

These observations suggested that the infected Schwann cells had reverted back to a highly immature stage that differs from dedifferentiated Schwann cells generated by injury (which retain expression of SOX10). Consistent with this, infected Schwann cells that had been cultured in mesenchymal stem cell (MSC) medium lacked all Schwann cell-specific markers and instead had acquired new markers, including some expressed by MSCs (a diverse set of multipotent progenitor cells). Importantly, the authors confirmed that these cells were directly derived from infected Schwann cells and could themselves give rise to bone and fat precursors, as is typical of MSCs. Thus, the authors conclude that *M. leprae* triggers reprogramming of infected Schwann cells into what they term progenitor/stem cell-like cells (pSLCs).

So what is the purpose of this reprogramming event? pSLCs could also differentiate into skeletal or smooth muscle cells, which are known to harbour *M. leprae* during leprosy, so the authors hypothesized that this facilitates bacterial dissemination to muscle. To examine this *in vivo*, they used a skeletal muscle injury model in which damaged muscle fibres are spontaneously replenished by regenerative muscle. Infected pSLCs were found to either fuse to or fully integrate into myofibres 14–21 days after injection into the injured muscle, spreading the bacterium to the tissue. Similarly, infected pSLCs were detected within smooth muscle in the muscle–skin interphase.

In addition, the authors observed that, *in vitro*, pSLCs secreted immunomodulatory factors that attracted macrophages and promoted macrophage maturation and survival. *In vivo* analysis using the skeletal muscle injury model revealed that *M. leprae* was efficiently transferred from infected pSLCs to recruited macrophages, which themselves infected other tissue macrophages, thus spreading the infection. This was found to be mediated through the formation of granuloma-like structures (a hallmark of mycobacterial infection) comprising infected pSLCs and macrophages, the latter of which were observed to migrate out of the structures to promote further bacterial spread.

The authors propose that *M. leprae*-triggered reprogramming of Schwann cells into pSLCs serves to disseminate the bacterium to other tissues through two mechanisms. First, infected pSLCs migrate to and spontaneously differentiate into skeletal and smooth muscle cells, passively transmitting the infection to these tissues. Second, through the secretion of immunomodulatory molecules, pSLCs and recruited macrophages form a secondary niche for the bacterium, facilitating bacterial expansion and dissemination. Further work is now needed to determine the signals that drive this reprogramming event.

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ORIGINAL RESEARCH PAPER Masaki, T. *et al.* Reprogramming adult Schwann cells to stem cell-like cells by leprosy bacilli promotes dissemination of infection. *Cell* **152**, 51–67 (2013)