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Bacterial-induced cell reprogramming to stem cell-like cells: new premise in host–pathogen interactions

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Bacterial pathogens employ a myriad of strategies to alter host tissue cell functions for bacterial advantage during infection. Recent advances revealed a fusion of infection biology with stem cell biology by demonstrating developmental reprogramming of lineage committed host glial cells to progenitor/stem cell-like cells by an intracellular bacterial pathogen *Mycobacterium leprae*. Acquisition of migratory and immunomodulatory properties of such reprogrammed cells provides an added advantage for promoting bacterial spread. This presents a previously unseen sophistication of cell manipulation by hijacking the genomic plasticity of host cells by a human bacterial pathogen. The rationale for such extreme fate conversion of host cells may be directly linked to the exceedingly passive obligate life style of *M. leprae* with a degraded genome and host cell dependence for both bacterial survival and dissemination, particularly the use of host-derived stem cell-like cells as a vehicle for spreading infection without being detected by immune cells. Thus, this unexpected link between cell reprogramming and infection opens up a new premise in host–pathogen interactions. Furthermore, such bacterial ingenuity could also be harnessed for developing natural ways of reprogramming host cells for repairing damaged tissues from infection, injury and diseases.

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Background

The body's lineage-committed differentiated tissue cells are the residence of many bacterial pathogens that cause numerous human diseases. These pathogens often establish infection in their preferred niches by manipulating or subverting differentiated cell functions [1,2]. However, to accomplish these daunting tasks bacterial pathogens must fulfill several criteria [1,3]. For intracellular bacteria, many additional challenges and careful orchestrations are necessary to evade host immune attack, sustain bacterial survival and promote dissemination. Therefore, intracellular bacteria usually take precautions and reside within their favorable host niches for colonization and to gain full advantage of properties their preferred host cells offer. Although tissue niches with limited immune cell traffic are safe haven for propagation of intracellular bacteria, their dissemination, the next crucial step of bacterial life cycle after colonization, particularly via systemic routes is challenging due to bacterial confinement to their specialized tissue niches. Better understanding of how intracellular bacteria overcome such challenges and pass infection to other tissues provide new tools for targeting the progression of bacterial infections.

New research continues to identify specific host cell functions and pathways that are required for many different bacterial pathogens during their infectious processes [4–8]. Developing strategies that target the crucial host cell functions required for infection would have broad-spectrum efficacy and much less likelihood to permit pathogens to acquire resistant mutation and become drug resistant. Thus, usage of host-encoded functions essential for infection could be particularly timely, since the emergence of drug-resistant bacterial strains is a major concern for public health [9,10]. However, tackling such host-encoded functions as strategies for combating infection is challenging, since diverse pathogens use different tactics for their survival and propagation. Although tailor-made strategies for targeting individual pathogens with specific host requirements are possible, it is more beneficial and cost effective if we are able to identify common molecular host targets or pathways that can be applied to many bacterial pathogens simultaneously. Because pathogens are co-evolved alongside hosts with many common or evolutionary conserved strategies for cell manipulation, discovery of novel host cell modifying mechanisms from model organisms provide new insights into host-encoded functions that could be shared with many bacterial pathogens. It is likely that potentially effective common host-encoded functions can be identified from those bacterial pathogens, which are known to depend substantially or totally on host cell functions for every phase of their bacterial life cycle. *Mycobacterium leprae*, the causative organism for human leprosy, is one such intracellular

pathogen that totally depends on host cells for maintaining bacterial survival and propagation [11], and thus could be a model organism for identifying both novel and common host-encoded functions.

One common property of host cells is the genomic plasticity, the extent to which host cells can alter their transcriptome in such a manner that allows these cells to adapt to changes in microenvironment [12]. Plasticity exists in adult tissue cells to varying degrees and this property is responsible for natural repair processes following tissue damage, often due to endogenous repair cell or stem/progenitor cell populations [13,14]. It is now known that indeed adult tissue cell plasticity can be manipulated experimentally by changing expression of genes to reprogram somatic cells back to embryonic stage or change lineage commitment both *in vitro* and *in vivo* [15–17]. Plasticity of host cells can also be subjected to manipulation by intracellular bacterial pathogens. In this review, we describe how bacterial pathogens hijack plasticity of tissue cells to manipulate host cells during infection using ML and its preferred host niche, Schwann cells, as a model system. We also briefly discuss the implications of these findings for bacterial infectious diseases in general, and how such bacterial ingenuity can be employed as a potential strategy for converting somatic cells to stem cell-like cells for tissue regeneration.

Experimental manipulation of host cell plasticity

During mammalian development embryonic cells undergo a highly complex developmental program by acquisition, deletion or maintaining multiple transcriptional, epigenetic, and signaling programs to acquire various lineage-committed cell types of distinct functions. Although such terminally differentiated cells are stable in terms of operating their lineage committed programs in order to maintain the identity and specific cell functions in different tissues, recent advances have revealed that these committed programs of adult tissue cells are remarkably plastic and can easily be manipulated experimentally [12,16,18]. New areas of investigation for cell fate manipulation have rapidly evolved by the success of ectopic expression or deletion of crucial genes required for either maintaining embryonic state or specific tissue lineage development, which are sufficient for reprogramming developmentally committed tissue cells all the way back to embryonic stem cells or converting into other cell phenotypes [19,20]. These revelations have attracted a wide range of interest as a strategy for cell manipulations which can eventually be harnessed for use in regenerative medicine, and also as research tools to gain new insights into basic developmental processes [21].

Hijacking notable plasticity of adult Schwann cells by *M. leprae*

Among differentiated tissue cells, Schwann cells, the glial cells of the adult peripheral nervous system (PNS), which derive from neural crest precursors and comprise myelin-forming and non-myelin-forming phenotypes [22,23], can be considered as an example of sophistication in cell differentiation. Yet they show remarkable plasticity illustrated by the ability of adult Schwann cells to switch between differentiated and de-differentiated states following nerve injury [24,25]. In response to injury-induced signaling, myelinated Schwann cells switch off the myelination program following loss of axonal contact and acquire a phenotype resembling immature Schwann cells, re-enter cell cycle and de-differentiate (Figure 1). These de-differentiated Schwann cells in turn promote regeneration of axons and the myelin sheath, and in this manner adult Schwann cell plasticity contributes to the regeneration capacity of adult PNS even after severe injury [26].

Intriguingly, leprosy bacteria use adult Schwann cells with this notable plasticity as the natural primary target for the establishment of infection within the PNS. ML is a strictly obligate intracellular pathogen with a severely degraded bacterial genome, unable to generate its own energy and metabolic needs fully and thus depends totally on host cell functions for bacterial survival [11]. By selecting Schwann cells, ML have acquired several survival advantages [11,27]. Recent studies have suggested that ML use the regeneration properties of the PNS for the expansion of the bacterial niche within Schwann cells [27–29].

Setting the stage: from terminal differentiation to de-differentiation

In adult peripheral nerves, Schwann cells are developmentally matured and have acquired the stage of terminal differentiation necessary for fully functional Schwann cell-axon units. ML 'simplifies' this sophisticated terminal differentiation by initiating myelin damage pathways and inducing cells to re-enter the cell cycle by activation of canonical and non-canonical Erk1/2 signaling pathways [29,30]. In fact, this was the first example to show that demyelination can be caused by activating Schwann cell Erk1/2 signaling without nerve lesions or inflammatory responses [28,29]. Subsequent studies using transgenic mouse models in which Erk1/2 signaling is sustained in adult PNS have further confirmed that, indeed, like in infection with ML, transgenic activation of Erk1/2 signaling in adult nerves could also elicit demyelination without lesions [31].

As in experimentally induced or natural nerve injury responses, ML-induced demyelination also generates de-differentiated cells [28; Figure 1]. These Schwann cells maintain their lineage commitment in an immature state lacking the myelin sheath, and are usually equipped with properties for promoting remyelination of damaged nerves [32]. Interestingly, such de-differentiated Schwann cells are highly susceptible for ML invasion and are also likely to be a more favorable phenotype for intracellular bacterial growth [27]. Additionally, these Schwann cells also serve as