New insights and tools to combat leprosy nerve damage

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Accepted for publication 24 November 2011

Leprosy nerve damage: immune and non-immune mechanisms

Nerve damage no doubt is the most feared complication in leprosy since it causes most of leprosy’s characteristic and stigmatizing disabilities. Paradoxically and sadly, however, its etiology and pathogenesis remain poorly understood, its clinical management difficult and its prevention far out of sight. Leprosy nerve damage particularly occurs during leprosy reversal reactions, which represent idiopathic episodes of increased host inflammatory responses and cell-mediated immune reactivity, often accompanied by acute inflammation and destruction of peripheral nerves and other forms of immunopathology. Well documented characteristics of leprosy reactions include: increased T cell reactivity to antigens of *M. leprae*, lesional infiltration by activated T cells, enhanced local expression of inflammatory cytokines such as TNF-α and cellular adhesion molecules, increased local macrophage activation and increases in levels of pro-inflammatory circulating cytokines in the blood.

In the early phase of infection, *M. leprae* can attach to myelinated Schwann cells (SC) and induce rapid nerve demyelination. This process of early nerve damage is mediated directly, at least in part, by the *M. leprae* specific cell wall constituent phenolic glycolipid, in the absence of any immune cells, and is dependent on intracellular signaling through the ErbB2 receptor tyrosine kinase. Despite the importance of early nerve damage, innate-immunity associated with this early process does not explain fully a series of clinical observations in leprosy. First, it is well known that episodes of acute nerve damage mostly occur during type-1 leprosy reactions, and often can cause severe and even irreversible nerve damage. Although immunosuppressive drugs can be helpful in mitigating those events, not all patients respond adequately to such regimens, unfortunately. In addition, the process of demyelination and nerve damage seen in patients with multibacillary leprosy which have high bacterial loads in their lesions is mostly chronic and relatively slow. These patients are immunologically distinct as they present with low or non existing T cell mediated immunity to antigens of *M. leprae* while displaying high *M. leprae* specific antibody titers. Thus, in the absence of strong
cellular immunity and inflammation, the process of neurodegeneration is slowly, even in the presence of high bacillary loads. These observations therefore suggest that leprosy nerve damage is a multi-step process: during the early phase of infection \textit{M. leprae} specifically targets peripheral nerves and induces contact-dependent myelin breakdown, which may continue to progress slowly and asymptptomatically, or as silent neuropathy.\textsuperscript{4} Secondly, during enhanced cellular immunity and inflammatory responses, acute episodes of inflammatory nerve damage can take place, in which immune cells play a significant role.\textsuperscript{3,5} Inflammatory immune reactions thus play an important role in the full manifestation of leprosy nerve damage. This has implications for effective treatment and management of nerve damage.

**Mechanisms of immune mediated nerve damage in leprosy**

Despite decades of research, the precise pathogenesis of leprosy nerve damage remains enigmatic. This is certainly not \textit{a testimonium paupertatis} of the leprosy research community, since the same roadblocks in understanding exist in most, if not all, other human inflammatory and auto-immune diseases, including arthritis, inflammatory bowel disease, auto-immune diabetes, multiple sclerosis and peripheral demyelinating neuropathies.

As outlined, the strong association of leprosy nerve damage with enhanced immune reactivity and inflammation, and the efficacy of immune suppressive treatment indicate an important role for the host immune system in its pathogenesis. But which pathways could be involved in immune mediated nerve damage? Several have been proposed but few have been demonstrated.

**DIRECT, COGNATE IMMUNE PATHWAYS OF SC DAMAGE**

Infected SC can present phagocytosed \textit{M. leprae} antigens to CD4\textsuperscript{+} or CD8\textsuperscript{+} T cells with cytotoxic activity, which can attack and damage SC in a \textit{M. leprae} specific fashion. Canonical pathways of cellular killing include: (i) exocytic granule mediated killing (these cytolytic granules contain preformed perforin, granzymes and likely also the microbicidal molecule granulysin), and (ii) activation of apoptosis/programmed cell death pathways, e.g. through Fas- or TNF-R like receptors. Experimental evidence has been obtained supporting the first pathway.\textsuperscript{6} SC express CD1 molecules such that unconventional, CD1 restricted \textit{M. leprae} specific T cells may also participate in SC and nerve damage. Furthermore, “nonspecifically activated” NK cells may participate in these SC damaging liaisons.

An alternative but not mutually exclusive possibility is that \textit{M. leprae} infection induces SC to express self-antigens to which peripheral T cells are insufficiently tolerized. Self-reactive T cells can amplify SC damage and neural pathology. In this respect it is of note to mention that during chronic inflammation, auto-reactive immune T cells and auto-antibodies are often induced or activated, and this might also occur in leprosy, although this has never been analysed. T cell induced SC killing or apoptosis may induce self reactivity through uptake of apoptotic cells by dendritic cells, which can efficiently prime naive T cells through a process termed “cross-priming”.

A more recently discovered pathway of inflammatory tissue damage is that mediated by Th17 cells. Although Th17 cells and IL-17 are suspects in leprosy, no evidence to identify these has been reported yet. Th17 cells play a prominent role in many inflammatory disorders, including chronic arthritis, psoriasis and asthma. Mycobacterium activated human
Macrophages produce high levels of IL-23, which could support Th17 expansion in leprosy lesions.\textsuperscript{7} Th17 responses thus may well contribute to SC damage in leprosy, through cognate interactions or through soluble mediators (IL-17, TNF-\(\alpha\)). This should be explored in the nearby future, also given the local over-expression of TNF-\(\alpha\).

**INDIRECT, BYSTANDER PATHWAYS OF IMMUNE DEPENDENT SC DAMAGE**

It is also possible that SC are not recognized directly by immune cells, but are primarily susceptible to toxic or cytopathic molecules produced by inflammatory cells, including IL-17 and TNF-\(\alpha\). \textit{M. leprae} can exert direct cytopathic effects on SC through the induction of lipid droplets which are associated with \textit{M. leprae} survival and induction of pro-inflammatory cytokines.\textsuperscript{8} Besides T- and NK-cells, neutrophils and macrophages can release toxic oxygen and nitrogen intermediates as well as (metallo-)proteases,\textsuperscript{9} involved in remodeling the extracellular matrix. Alternatively, SC surface receptors may be triggered directly by \textit{M. leprae}, which activating SC apoptosis, such as TLR2.\textsuperscript{10}

**Expanding our outlook**

There are several candidate pathways potentially involved in leprosy nerve damage, but experimental proof to validate or refute these is limited. It is important to identify the relevant pathogenic pathways of leprosy nerve damage, in order to find new angles and targets for treatment and prevention of this ancient stigmatizing disease of the poor. Naturally, given the limited resources available for leprosy, leprosy researchers would do well working closely together and keep a keen eye on developments in other chronic inflammatory diseases – where investments are possible at a completely different scale – and adopt major discoveries and tools in leprosy. In addition, such proactive interdisciplinarity will help bringing leprosy out of its isolationism in the global research arena. Future initiatives would benefit from stimulating fresh outlooks, and linking leprosy to other research activities and clinical studies. Examples of this might be (clinical and basic) research on powerful anti-inflammatorials developed in auto immunity, which may very well be applicable in the management of leprosy neuritis.

Finally, basic research will be needed to identify surrogate markers or correlates of leprosy inflammation and nerve damage. Such biomarkers, or rather biomarker-signatures could have tremendous value in the prediction, early detection and monitoring of leprosy nerve damage, including treatment response and the occurrence of relapses. Given the key role of immune cells in leprosy nerve damage, it is likely that such markers will come, at least in part, from detailed dissection of the human immune response to \textit{M. leprae}. At this stage, it is unknown what precisely precipitates acute reactional episodes in leprosy, but the observation that they occur more frequently during the first months following anti-leprosy chemotherapy suggests that \textit{M. leprae} breakdown products may be involved. It is also unknown if immune mediated nerve damage is dependent on and follows early \textit{M. leprae} contact dependent damage. This is an important issue, as it would urge developing highly sensitive tools to measure early nerve impairment.
References