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Journal
Cell Host & Microbe, 13(4)

ISSN
1931-3128

Authors
Desvignes, Ludovic P
Ernst, Joel D

Publication Date
2013-04-01

DOI
10.1016/j.chom.2013.04.001

Peer reviewed

Published in final edited form as:
Cell Host Microbe. 2013 April 17; 13(4): 377–378. doi:10.1016/j.chom.2013.04.001.

Taking Sides: Interferons in Leprosy

Ludovic P. Desvignes[1] and **Joel D. Ernst**[1,*]
[1]New York University School of Medicine, 522 First Avenue, Smilow 901, New York, NY 10016, USA

Abstract

In a recent *Science* paper, Teles *et al.* (2013) show that type I and II interferons (IFNs) are reciprocally expressed in the polar immune forms of leprosy, with type I IFNs inducing IL-10 that interferes with the antimycobacterial effects of type II IFNs (IFNγ) at the site of infection.

Leprosy, caused by the bacterium, *Mycobacterium leprae*, has a long tradition as a stigmatized disease, but also serves as the paradigmatic human infection that evokes polarized cellular immune responses. The two polar forms of leprosy, termed tuberculoid and lepromatous, have clinical, microbiological, and immunological distinctions. Tuberculoid leprosy is characterized by few skin lesions, low numbers of bacteria in lesions, and histologically well-formed granulomas containing abundant CD4 T cells, while lepromatous leprosy is characterized by numerous infiltrative skin lesions, large numbers of bacteria in lesions, and poorly-formed granulomas with fewer lymphocytes. Since the seminal discovery that identified a predominance of Th1 CD4 T cells in lesions of tuberculoid leprosy, and Th2 cells in lepromatous lesions (1), which respectively activate the cellular and humoral immune responses, further investigation has yielded evidence that the proinflammatory cytokine IL-12 (2) and multiple other cytokines are differentially expressed at the site of disease in the polar forms of leprosy.

In a recent paper in *Science*, Teles *et al.* (3) present evidence that the anti-inflammatory cytokine IL-10 induced by type I interferons (IFNs) is a factor promoting lepromatous leprosy (Figure 1). The authors first characterized the transcriptional signatures of skin lesions from both forms of leprosy. To separate the broadly overlapping type I and type II IFN-induced signatures that they detected, they took advantage of publicly available gene datasets specific for responses to each type of IFN. They revealed an over-representation of type I IFN (IFNα/β)-induced genes, in particular IL-10, in lepromatous lesions while tuberculoid lesions are significantly enriched in transcripts induced by type II IFN (IFNγ), including those of the antimycobacterial vitamin D pathway. Teles *et al.* also showed that the transcriptional profile of reversal reaction (RR) lesions, which characterize a transition from the lepromatous toward the tuberculoid end of the spectrum, clusters with that of the latter. Interestingly, type I and type II IFN-driven signatures seemed to be mutually exclusive in each polar form of the disease. Beyond leprosy, the authors compared their results to recently published studies of blood transcriptional signatures in patients with active tuberculosis (3,4) and proposed a common type I IFN-inducible gene program which correlates with severity of mycobacterial infections. The authors then strengthened their case

*Correspondence: joel.ernst@med.nyu.edu.

by measuring the increased levels of *Ifnb* – one of the 14 type I IFNs, and *Ifnar1*, the specific receptor for type I IFNs, transcripts and proteins in lepromatous versus tuberculoid or RR lesions. They found a positive correlation between type I IFNs and IL-10 mRNA levels and co-localization of the corresponding proteins in lepromatous lesions. To decipher the functional correlation between these cytokines, they showed *in vitro* that human blood monocytes produce type I IFNs and IL-10 in response to live or sonicated *M. leprae* and that the production of IL-10 is at least partially dependent on type I IFNs signaling through their specific receptor. Finally, following a series of microarray analyses of skin lesions and *in vitro* experiments, the authors concluded that type I IFN-induced production of IL-10 in lepromatous lesions inhibits type II IFN-induced genes and networks, such as antimicrobial peptides or the vitamin D pathway, with a direct consequence on the ability of monocytes/macrophages to control the intracellular growth of *M. leprae*.

The reciprocal changes in cytokine expression in tuberculoid and lepromatous leprosy have revealed evidence for complex cytokine regulatory networks at the site of infection in a human disease, yet they leave open an important question: what is the initial determinant of the polar immune responses to *M. leprae*? Bacterial diversity is unlikely, given the extremely high relatedness of leprosy bacilli genomes worldwide (6), leaving differential host responses as the likely mechanism. Recent studies of human genetic susceptibility have revealed evidence for leprosy susceptibility determined by loci that include genes encoding NOD2 and RIP2K involved in intracellular bacterial recognition and signaling as well as the receptor for the inflammatory cytokine IL-23 (IL23R), along with other loci shared with susceptibility to Crohn's disease, another disease characterized by granulomatous inflammation and a link to microbial exposure (7). However, those studies compared subjects with leprosy to controls without leprosy, so it is unclear whether those loci also influence the polarity of T cell responses and the clinical and immunological form of the disease. Therefore, additional concerted efforts are needed to identify the initial determinants and responses that determine the ultimate immunological, microbiological, and clinical outcomes of *M. leprae* infection. These efforts will surely yield important information of great scientific interest, and these may have significance for vaccine and adjuvant design.

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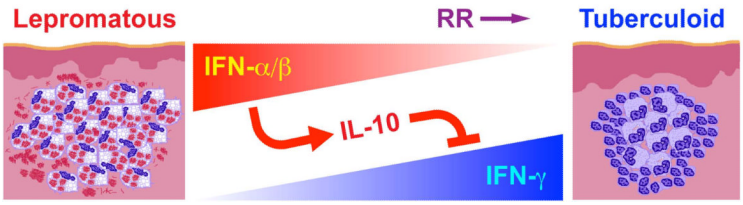

Figure 1. The role of interferons in the spectrum of leprosy

High bacterial loads, numerous lipid-rich, myeloid-derived foam cells and rare lymphocytes characterize lepromatous leprosy. Those lesions are associated with a type I interferon-, or IFN-α/β-, driven transcriptional signature, including the production of interleukin 10. IL-10 inhibits downstream anti-mycobacterial effectors induced by type II interferon, or IFN-γ, which are the hallmark of the better-controlled form, tuberculoid leprosy, and of reversal reaction (RR) lesions, a transitional form of the disease. In tuberculoid leprosy lesions, only few bacteria can be found in macrophages, surrounded by numerous $CD4^+$ T cells, organized in well-formed granulomas.