INTERFERON-β CONTROLS NON-TUBERCULOUS MYCOBACTERIAL INFECTION IN MICE

Mohd-Nor Norazmi
School of Health Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

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Mycobacteria other than Mycobacterium tuberculosis complex and M. leprosy are collectively known as Non-tuberculous Mycobacteria (NTM). NTM are a diverse family of environmental acid-fast bacteria that are found in water, soil, plants and animals. NTM are also known as environmental mycobacteria, atypical mycobacteria, mycobacteria other than tuberculosis (TB), or rapidly growing mycobacteria. There has been no reports of animal-to-human or human-to-human transmission of NTM. It is fairly well-established that immune suppression contributes to the susceptibility of opportunistic NTM infection. NTM cause a variety of human diseases, particularly chronic lung infections, especially in immunocompromised patients, including HIV-infected patients. The clinical manifestations of NTM infection may be indistinguishable from those of the more pathogenic and contagious TB (which is caused by M. tuberculosis) thus complicating the diagnosis and treatment of either mycobacterial infection, especially in areas of low-resource setting where confirmatory diagnosis is difficult.

Great efforts have been taken to reduce the incidence of TB globally. Modest but encouraging results from these efforts are now apparent although much more needs to be done to alleviate, or at least, to effectively control this intractable disease. One of the major issues of the TB pandemic is its close relationship with HIV/AIDS. However, while TB cases show a decreasing, albeit modest trend, the cases of clinical NTM infections in many countries are reportedly on the rise. Given the importance of NTM, in particular, of M. avium complex (MAC) infections in HIV/AIDS, more efforts should be put into understanding the pathogenesis of NTM infection in and managing this opportunistic infection.

The protective immune response against both NTM and M. tuberculosis is primarily based on cell-mediated immunity, particularly in the induction of the T-helper 1 (Th-1) cytokine pathway – represented by the production of interleukin-12 (IL-12) and the type II interferon (IFN), interferon-gamma (IFN-γ). Thus, like TB, mutations in the IFN-γ receptor or IFN-γ signaling cascade, and mutations in the cytokine receptors which promote Th-1 response such as IL-12R, predispose individuals to NTM infections. Recently, an association between increased eosinophil counts and IgE levels – considered as surrogate markers for the Th-2 type immune response – and pulmonary MAC infection has been reported. Autoantibodies against IFN-γ have also been reported to predispose to NTM infection. However, the protective role of Th-1, especially of IFN-γ in TB may not be so clear cut. A few studies have demonstrated the detrimental effect of IFN-γ in TB, including hyper-inflammation. The protective effect of IFN-γ may be dependent on a multitude of interacting factors which is still not well understood, including perhaps, the involvement of type I IFN. Although this observations have been reported for M. tuberculosis, it may also be applicable for NTM.

Both the innate and adaptive immune response seem to be important in controlling NTM infections. Type I IFNs, such as IFN-α and IFN-β, are important messengers in the host response against various microorganisms, including bacterial infections, and may influence the immunity against mycobacterial infection. Type I IFN activates a multitude of interferon-stimulated genes through the activation of various transcription factors which leads to either beneficial or detrimental consequences in bacterial infections (for reviews see refs. and). The beneficial effect of type I IFN may be through the upregulation of antimicrobial effectors, such as iNOS and proinflammatory cytokines. In contrast, detrimental effects of these cytokines may be through the
induction of IL-10 and IL-1 receptor antagonist, suppression of proinflammatory cytokine production or attenuation of IFN-γ-induced macrophage activation, as has been reported in Listeria monocytogenes and M. tuberculosis infections. Although the route of infection may influence the effect of type I IFN, such as in L. monocytogenes infection, there is some consensus that type I IFN may actually promote rather than control M. tuberculosis infection. However, the involvement of type I IFNs in controlling NTM infection has not been clearly demonstrated.

Here, in this issue of Virulence, Ruangkiattikul et al. showed that type I IFN, namely, IFN-β plays a crucial role in the clearance of NTM infection in mice. This may be one of the first reports to clearly demonstrate the importance of type I IFN in controlling NTM infection, which is in contrast to the role of this cytokine in TB. The study focused on the effects of the obligate pathogen, Mycobacterium avium ssp paratuberculosis (MAP) and the opportunistic M. smegmatis (MSM) infection in mouse macrophages and in C57BL/6 mice, with the former mycobacterium representing the more virulent form of the 2. They demonstrated that MSM, the less virulent strain of NTM, induced significantly higher levels of IFN-β which resulted in its clearance whereas MAP did not readily induce this cytokine. They demonstrated that MSM was more efficient in activating the cGAS-STING-TBK1-IRF3/7 pathway probably through the release of extracellular bacterial DNA (eDNA) into the cytosol which activates Ifnb. They suggested that the more efficient the release of eDNA, the stronger the stimulation of the cGAS-STING-TBK1-IRF3/7 pathway and the higher the induction of IFN-β. Thus, they observed that MAP-infected macrophages contained significantly less eDNA and was less efficient in inducing the production of IFN-β. Hence the extent of IFN-β induction may determine the duration and severity of NTM infection in the host. Whether the efficiency of Ifnb induction correlates with the pathogenicity or virulence of various other NTM remains to be elucidated.

However, it can be speculated that the less efficient induction of the host type I IFN response by MAP may contribute to specific immune evasion mechanism of this mycobacterium which facilitates its persistence and pathogenesis. Indeed type I IFN seems to be important in the clearance of MAP infection, since exogenous IFN-β promoted the clearance of the bacteria from the host.

Current literature suggests that type I IFNs have either beneficial or detrimental effects on the regulation of the immune response during viral and bacterial infection (for reviews see refs. and 15). While type I IFN secretion by macrophages promoted M. tuberculosis growth as has been described previously, it may have an opposite effect on NTM growth and pathogenesis. Ruangkiattikul et al. provided evidence that type I IFN is essential in clearing NTM infections, although several questions on the detailed mechanism of how this occurs remain to be answered. NTM comprise a diverse group of mycobacteria and each may respond to type I IFN differently. However, at least for 2 of them, which are almost at opposite ends of the pathogenic spectrum, type I IFN seem to have a beneficial role for the host. Further understanding of the role and mechanism of type I IFN in NTM infection may pave the way for future therapy against this increasingly important environmental mycobacteria in specific clinical settings as has been suggested for TB.

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ORCID
Mohd-Nor Norazmi http://orcid.org/0000-0002-2817-6441

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