INTERFERONS IN IMMUNITY TO
CHLAMYDIA PNEUMONIAE

av

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Abstract

The cytokine IFN-γ is the architect behind an amazing immunological program of host resistance to intracellular bacterial and protozoan infections. IFN-γ activates macrophages, making them into inhospitable habitats for parasites attempting to grow inside them. The family of obligate intracellular Gram-negative bacteria Chlamydia is an example of such pathogens. The overall aim of this thesis was to unravel resistance to infection with the human respiratory pathogen C. pneumoniae. Specific focus was placed on innate immune responses to C. pneumoniae and the regulation and role of IFN-γ in the outcome of infection. An experimental mouse model of lung infection and a macrophage model of in vitro infection were used for this purpose.

A protective role for infection-induced IFN-γ in restricting C. pneumoniae growth in vivo was observed, though IFN-γ was not required for resolution of infection. IL-12 and/or IL-23 was a necessary but not an absolute requirement for expression of IFN-γ. IFN-γ-dependent protection was in part mediated by iNOS expression. TNF-α, known to be synergistic with IFN-γ, was not required for restricting Chlamydial growth. Innate immune cells in the lung constituted an important source of IFN-γ and were essential for restricting C. pneumoniae growth and for containment of bacteria in the lungs. However, NK cells were not implicated in such protective IFN-γ release. On the other hand, lung macrophages isolated from C. pneumoniae-infected mice expressed IFN-γ. Moreover, bone marrow-derived macrophages (BMMφ) conferred upon transfer to RAG1−/−/IFN-γ− mice, enhanced resistance to C. pneumoniae infection via their ability to release IFN-γ. Innate IFN-γ was however not required for protection conferred by CD4+ or CD8+ T cells. Innate and T cell-derived IFN-γ are also non-redundant (complementary) in protecting mice against C. pneumoniae.

C. pneumoniae-infected BMMφ also expressed IFN-γ in vitro. Such IFN-γ release was IL-12-independent but required instead IFN-α/β and restricted Chlamydial growth. IFN-α/β, and not IFN-γ, was required for iNOS-mediated protection in BMMφ. The molecular details of BMMφ-derived IFN-γ expression revealed a TLR4-MyD88-dependent pathway of IFN-α and IFN-γ induction. Also surprising was the presence of a TLR4- and MyD88-independent, infection-induced NF-κB activation and pro-inflammatory cytokine expression. Phosphorylation of STAT1 during infection was IFN-α/β-dependent, and necessary for increased IFN-γ expression and for restricting Chlamydial growth. Expression of IFN-γ and restriction of C. pneumoniae growth also required NF-κB activation, but such activation was independent of IFN-α/β, revealing a dual pathway of C. pneumoniae-induced IFN-γ expression in BMMφ: a TLR4-MyD88-IFN-α/β-STAT1-dependent pathway, and a TLR4-independent pathway leading to NF-κB activation.

IFN-α/β was also protective in vivo by cooperating with IFN-γ for activation of STAT1, which was required for restricting Chlamydial growth. Different from the in vitro situation, IFN-γ was sufficient on its own for this effect and did not require IFN-α/β for its expression.

In summary, IFN-γ is important for restricting C. pneumoniae growth. Innate IFN-γ is protective both in lungs and in BMMφ. IFN-α/β are pivotal in regulating protective responses in BMMφ, including IFN-γ release, but are dispensable for IFN-γ expression and protection in vivo. This discrepancy may be a qualitative feature in C. pneumoniae pattern recognition by different cell types; lung cells convey the generation of protective, IL-12-driven responses, while IFN-α/β-driven protection in BMMφ is essential.

Keywords: Chlamydia pneumoniae, TLR, IFN-α/β, IFN-γ, macrophages, T cells

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