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Factors that determine mycobacterial infection

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Keywords

Disseminated tuberculosis, G-CSF, *Mycobacterium tuberculosis*, NF-IL-6, superoxide

Context

Tuberculosis is a common disease, especially in immunocompromised persons. It is important that we understand the molecular mechanisms by which this organism evades the body's defenses so that new drugs can be developed. Alveolar macrophages are targets of mycobacterial infection. Activated macrophages and secreted lymphokines such as interferon, tumor necrosis factor, and interleukins play a vital role in protection against this infection. The factors that control the production of these lymphokines, and the role of neutrophils in early mycobacterial infection, are not clear. In this study, the authors evaluated the role of nuclear factor interleukin 6 (NF-IL-6) in early mycobacterial infection.

Significant findings

NF-IL-6 knockout mice developed disseminated tuberculosis when infected with *Mycobacterium* by an airborne route. In comparison with wild-type mice, these animals lack granuloma formation, and show impaired superoxide anion generation and mycobacterial killing by neutrophils. The knockout mice showed normal levels of expression (in the lung tissue and splenocytes) of interferon-?, tumor necrosis factor (TNF), and IL-12, and normal amounts of macrophage nitric oxide production, but expressed less granulocyte-colony stimulating factor (G-CSF) than did wild-type mice. Neutrophil ability to kill the mycobacteria, and both endocytosis and morphology of endosomes, was restored by G-CSF in the knockout mice. Thus, NF-IL-6 may be critical in mycobacterial infection.

Comments

Patients with tuberculosis have elevated concentrations of various cytokines, including TNF, and various interleukins, which can cause cachexia. The authors showed that (contrary to general belief) neutrophils are necessary for the early phase of defense against mycobacteria and that failure of neutrophils to generate adequate amounts of superoxide anion is responsible for the ability of the mycobacteria to survive and proliferate. They also showed that neutrophil superoxide anion generation is dependent on G-CSF production. NF-IL-6 is a transcription factor that is evidently critical for G-CSF production and subsequent neutrophil activation. This study raises several interesting possibilities. Is it possible that G-CSF can be used to upregulate neutrophil and, possibly, macrophage superoxide production in humans? If so, can G-CSF aid in the elimination of mycobacteria? It is now necessary to show that NF-IL-6 is defective in people with tuberculosis. As human recombinant G-CSF is currently available, its possible benefit as a therapeutic agent could now be investigated in patients with tuberculosis.

Methods

NF-IL-6 knockout mice, nitric oxide assay, ELISA, RT-PCR, superoxide anion assay

Additional information

References

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