5. Respiratory Tract Infection

Atsushi Saito, Kazuyoshi Kawakami and Futoshi Higa

The First Department of Internal Medicine, Faculty of Medicine, University of the Ryukyus, Okinawa

Key words: respiratory infection, host defence, Th1-Th2 cytokine

Introduction

For a better understanding of the pathogenic mechanism of infectious diseases it is important to know the molecular basis of how the host responds to microbial pathogens and eliminates them. Recent advances in immunology and molecular biology have led to the discovery of a large number of cytokines and cell surface molecules, which allows us to understand such pathogenic mechanisms at a molecular level. In this review we show an outline of the role of cytokines in the pathogenesis of respiratory infectious diseases.

Host defense mechanism

The neutrophil-based host defense mechanism predominantly operates to eliminate extracellular bacteria including Streptococcus pneumoniae and Staphylococcus aureus and fungi such as deeply infected Candida spp., Aspergillus spp. and Trichosporon spp. Oxygen radical intermediates and granular killing materials play major roles in this process. On the other hand, cellular immunity, mediated by helper T (Th) cells, cytotoxic T lymphocytes (CTL) and activated macrophages, is essential for the host resistance to intracellular infectious pathogens including Mycobacterium tuberculosis, Legionella spp., Listeria monocytogenes, Salmonella spp., Chlamidia spp. and Rickettsia spp., fungi such as Cryptococcus neoformans, mucocutaneously infected Candida spp. and Pneumocystis carinii, prototzoa including Toxoplasma gondii, Plasmodium spp., Leishmania spp. and Trypanosoma cruzii, and type-2 viruses, including herpes and measles virus, which directly transmit to the cells adjacent to infected cells. The neutrophil-based mechanism is almost ineffective against these microbes. Macrophages activated by interferon (IFN)γ strongly kill M. tuberculosis, Legionella and Salmonella which multiply within phagosomes. CTL play important roles in the elimination of L. monocytogenes and T. cruzii, which escape from phagosome to cytosol, and Chlamidia spp. and Rickettsia spp., which grow within epithelial and endothelial cells, respectively, and viruses whose antigens are presented in the context of MHC class I. In host resistance to extracellular bacteria, Mycoplasma pneumoniae and type-I viruses, including coxsackie and adeno virus, which are released to the extracellular site from infected cells in the process of viral transmission, humoral immunity is important. Antibodies work by aggregating microbes, activating complement and neutralizing bacterial toxins. Furthermore, they also potentiate neutrophil- and cellular immunity-based host defense mechanisms by increasing the phagocytosis of microbes through its opsonic activity. Finally, eosinophils play a central role in the elimination of helmhinh.

Infection and Th1-Th2 cytokine balance

In 1986, Mosmann et al (1) demonstrated that Th cells were divided into two different subsets on the basis of cytokines which they secreted. Th1 cells secrete IL-2, IFN-γ and lymphotoxin, while Th2 cells produce IL-4, IL-5, IL-6, IL-10 and IL-13. The former cells play a central role in cell-mediated immunity and the latter ones in the development of allergic reaction. Differentiation of these cells is critically regulated by cytokines secreted in the microenvironment: IL-12, secreted by macrophages and dendritic cells, is essential for Th1 cell development, while IL-4, synthesized by NKT cells, mast cells, basophils and eosinophils, promotes the differentiation of Th2 cells. Importantly, these cells mutually regulate each function through production of IFN-γ and IL-4 (2). Recently, the concept of Thl-Th2 balance has gained much attention of investigators studying the pathogenic mechanism of various diseases including infection.

We have investigated the significance of Thl-Th2 balance in infectious diseases using a murine model of pulmonary cryptococcosis. Mice with a targeted disruption of genes for IFN-γ, IL-12 and IL-18 were more susceptible to intratracheal infection with a clinically isolated strain of C. neoformans than control mice. The contribution of IL-12 seemed to be more profound than that of IL-18, because host resistance in the former mice was more severely impaired than in the latter ones. Furthermore, mice lacking both IL-12 and IL-18 were more susceptible to the infection than mice with either gene deleted (3, 4), which confirmed that these two cytokines act in a cooperative manner, as previously reported (5, 6). On the other hand, neutralizing antibody against IL-4 significantly reduces the number of live microbes in the lungs (7). Considered collectively, these data demonstrated that host resistance to cryptococcal infection is critically regulated by Thl-Th2 balance: predominant synthesis of Th1 cytokines over Th2 renders mice resistant to the infection, while a shift in the balance toward...
the Th2-dominant condition exacerbates it.

**Treatment with Th1-type cytokines in infectious diseases**

In the next series of investigations, we attempted to examine the therapeutic effect of IFN-γ, IL-12 and IL-18. For this purpose, mice were infected intratracheally with a highly virulent strain of *C. neoformans*. In this model, all mice suffered from severe meningoencephalitis and died within 6 weeks of infection (8). Treatment with either IL-12 or IL-18 significantly reduced the fungal load in the lungs and brain and extended their survival time (8–10). Such effect was much more profound in IL-12 than in IL-18. IFN-γ also showed a similar effect, although it was much weaker than other cytokines (11).

In another study from our laboratory, we obtained similar results in a murine model of fatal infection with *M. tuberculosis*. These data suggested that immunotherapy with Th1-type cytokines may be clinically effective in intractable infection with microbial pathogens, protection from which are mediated by cellular immunity.

Holland and coworkers (12) reported that IFN-γ is effective in the treatment of patients with disseminated atypical mycobacteriosis. Squires et al showed similar results in the same disease complicated in AIDS patients (13). We also tried a combined therapy with antituberculous agents and IFN-γ in intractable pulmonary tuberculosis caused by a multidrug-resistant pathogen in a patient with insulin-dependent diabetes mellitus. Although no report showing the clinical use of IL-12 in infectious diseases has been seen, clinical trials have already commenced for the therapy of malignant neoplastic diseases. It may be in the near future that this cytokine is clinically used for the treatment of infectious diseases. IL-18 has not yet been included in clinical trials.

**References**