Immunoregulation of cytokines in infectious diseases (leprosy), future strategies.

RAM PYARE SINGH *

[Received 25 May 1998/ Accepted 19 June 1998]

Key words: Cytokines, Cell mediated immunity, Mycobacterium leprae, Immunoregulation, Infectious diseases.

Summary. Leprosy is a dynamic disease model in which distinct Mycobacterium leprae- responsive T cell subsets play an important role in host defense and control clinical and immunological spectrum. Th1 cells are associated with tuberculoid leprosy patients that have strong M. leprae -specific CMI-DTH responses. Th2 cells are expressed in lepromatous leprosy patients that are characterized by strong humoral immune responses and lack of T cell responses. Recently cytokines are thought to play immunoregulatory role in both the protection and immunopathogenesis of the host. Recombinant cytokines for immunotherapy have been used for controlling mycobacterial infections including leprosy. The diversity of T-cell subsets contributing to Th1 and Th2 cell derived cytokines, other major cytokines of the immune system, their sources, modes of action and possible therapeutic potentials are discussed.

Introduction

Cell mediated immunity plays an important role in host defense against infections. The role of cytokines have been demonstrated in mycobacterial infections, both in human and in experimental animals. Important roles of cytokines in vivo have been learned from the models of infectious diseases. Recently, the use of knock out mice with genetic disruptions in cytokines or cytokine receptor genes and use of anti cytokines antibodies have been explored to study the mechanisms of cytokine-pathogen interactions. Type 1 subset (Th1) produces interleukin-2 (IL-2), interferon-\(\gamma\) (IFN-\(\gamma\)) and lymphotoxin, facilitating cell-mediated immunity appropriate for intracellular and viral pathogens. Type 2 subset (Th2) produces IL-4, IL-5, IL-6, IL-10 and IL-13 favoring humoral immune responses. In addition another subset known as THO type which produce all cytokines that are associated with Th1 and Th2 subsets.

Immunoregulatory role of cytokines

Cytokines are important to acquire resistance against intracellular bacteria, with IFN-\(\gamma\) being of paramount importance (Fig.1). IL-2, IFN-\(\gamma\), TNF-\(\alpha\), granulocyte macrophage colony stimulating factor (GM-CSF), IL-4, IL-10, IL-12 and recently cloned IL-18 (interferon gamma inducing factor) play role in host defense.
against infections\(^2\)\(^,\)\(^3\)\(^,\)\(^4\) . TNF-\(\alpha\) is produced by macrophages infected with intracellular bacteria and synergizes with IFN-\(\gamma\) in mobilization of antibacterial effector functions\(^4\) . IL-10 which is also produced by macrophages antagonizes IFN-\(\gamma\). TNF-\(\alpha\) is crucial for the formation of granulomatous lesions because TNF neutralization with monoclonal antibodies prevents granuloma formation in \(M.\ bovis\) BCG-infected mice\(^7\) . A strong correlation between the expression of TNF-\(\alpha\) and leprosy disease activity have been reported, suggesting that TNF-\(\alpha\) is a prognostic indicator/ marker for inflammation in leprosy\(^8\),\(^15\) .

Both \textit{in vivo} and \textit{in vitro}, IL-12 is a potent inducer of T helper Type1 (Th1) responses, whereas it inhibits Th2-type 2 (IL-4) responses\(^16\),\(^17\) . Many studies have demonstrated that IL-12 plays an early and control role in the resistance to bacterial and parasitic infections\(^18\),\(^19\) . The potential protective effects of IL-12 have been documented both \textit{in vivo} and \textit{in vitro} in many parasitic diseases, fungal infection including mycobacteria\(^11,\)\(^18,\)\(^19\) .

The interferon-\(\gamma\) inducing factor/IL-18 has been cloned and sequenced recently by a Japanese group\(^20\) . Recombinant human interferon gamma inducing factor enhanced the production of IFN-\(\gamma\) and granulocyte /macrophage colony-stimulating factor (GM-CSF) , and partially inhibited IL-10 production in mitogen stimulated PBMC cultures, and also induced natural killer (NK) cell cytotoxicity\(^20\),\(^21\) . Together with IL-12, strong induction of IL-18 gene expression, its therapeutic efficacy and potential benefits \textit{in vivo} and \textit{in vitro} including \textit{Mycobacterium leprae} infection have been documented\(^12\),\(^13\) . Recently, mRNA of IL-12 P-40 and IL-18 expression has been reported in genetically resistant C57BL/6 mice infected with \textit{M. leprae}\(^19\) .

Cross regulation of cytokines has also been demonstrated. In leprosy, there exists a strong correlation between the patterns of cytokine production and disease manifestations. In tuberculo-leprosy (TT, and BT), IFN-\(\gamma\) and IL-2 have been associated (Th1-type response) whereas in lepromatous leprosy IL-4 and IL-10 (Th2-type response) have been associated\(^5\),\(^22\) . The time course of infection in mouse models and humans is thought to be balanced by these two distinct T-cell cytokine patterns\(^22\),\(^23\) . Th1 cytokines, IL-2 and IFN-\(\gamma\) are generally associated with resistance to infection, whereas Th2 cytokines, IL-4 and IL-10 are associated with progressive disease. Table-1 depicts a list of the main cytokines of relevance to infectious disease.

### Therapeutic Application of Cytokines

For therapeutic application recombinant human IL-2 was administered in the skin of leprosy patients to study the DTH reactions, as a result a selective destruction of parasitized macrophages and a 10-100 fold reduction in the number of acid-fast bacilli at the site of injection was observed\(^24\) . Prolonged administration of recombinant IL-2 in the leprosy patients enhanced CMI, and reduced bacillary index\(^6\) .

The therapeutic effect of IFN-\(\gamma\) injections have been tried in leprosy infection. Results of the many experimental and clinical trial indicate that IFN-\(\gamma\) is an effective therapeutic agent\(^6\),\(^25\),\(^27\) . Enhanced level of \(H_2O_2\) and \(O_2\) release as well as an increased ability of lesional macrophages to be stimulated in vitro to release reactive oxygen intermediates (ROIs) have also been reported. Recently, Modlin’s group in USA showed the ability of IFN-\(\gamma\) to modulate the balance between IL-12 and IL-10 production in leprosy\(^28\) .

### Future perspectives/strategies:

In addition to above mentioned cytokines role in infectious diseases (Leprosy), the use of knockout mice with genetic disruption in
Table 1. Compilation of the major cytokines of the immune system which directly contribute anti-microbial/anti-bacterial resistance

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Major Source</th>
<th>Acts on</th>
<th>Mode(s) of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>Macrophage</td>
<td>T,B cells,</td>
<td>Proliferation/Attraction of phagocytes, inflammatory</td>
</tr>
<tr>
<td></td>
<td>Monocytes</td>
<td>Many cells</td>
<td></td>
</tr>
<tr>
<td>IL-2</td>
<td>T cells</td>
<td>T,B cells</td>
<td>Proliferation</td>
</tr>
<tr>
<td>IL-3</td>
<td>T cells</td>
<td>Bone marrow</td>
<td>Haemopoiesis</td>
</tr>
<tr>
<td>IL-4</td>
<td>T, B cells, Mac</td>
<td>B cells, Mac</td>
<td>Macrophage activation, differentiation of Th2 cells</td>
</tr>
<tr>
<td>IL-5</td>
<td>T cells</td>
<td>B cells, Eosinophil</td>
<td>Proliferation, differentiation</td>
</tr>
<tr>
<td>IL-6</td>
<td>T cells, Macrophage</td>
<td>B cells, Liver</td>
<td>Macrophage activation, Differentiation.</td>
</tr>
<tr>
<td>IL-7</td>
<td>T cells</td>
<td>B cells</td>
<td>Proliferation/Differentiation.</td>
</tr>
<tr>
<td>IL-8</td>
<td>Monocyte</td>
<td>PMN</td>
<td>Movement activation</td>
</tr>
<tr>
<td>IL-9</td>
<td>T cells</td>
<td>Mast cells</td>
<td>Growth</td>
</tr>
<tr>
<td>IL-10</td>
<td>T, B, Macrophage</td>
<td>T cells</td>
<td>Inhibition of Macrophage function, suppresses inflammatory cytokines enhances B-cell proliferation</td>
</tr>
<tr>
<td>IL-11</td>
<td>Bone Marrow</td>
<td>Bone marrow</td>
<td>Erythropoiesis</td>
</tr>
<tr>
<td>IL-12</td>
<td>B cells, Macrophage NK cells</td>
<td>IPN-γ Production, stimulates differentiation of Th1 cells</td>
<td></td>
</tr>
<tr>
<td>IL-13</td>
<td>T cells</td>
<td>T cells</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>IL-15</td>
<td>many cells, Macrophage, T cells and fibroblasts.</td>
<td>Proliferation, cytotoxicity, isotype switching.</td>
<td></td>
</tr>
<tr>
<td>IL-17</td>
<td>T cells</td>
<td>Stromal cells</td>
<td>Inflammatory</td>
</tr>
<tr>
<td>IL-18</td>
<td>Kupffer cells, activated macrophage</td>
<td>Spleen cells, T cells</td>
<td>Proliferation</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>NK cells, T cells, Mac, NK cells</td>
<td>Macrophage activation</td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td>Macrophage, T cells Liver</td>
<td>Macrophage activation, inflammatory</td>
<td></td>
</tr>
<tr>
<td>GM-CSF</td>
<td>T cells</td>
<td>Bone marrow</td>
<td>Granulocyte, Mac production</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Macrophage, T cells Many cells</td>
<td>Inhibition of macrophage functions</td>
<td></td>
</tr>
</tbody>
</table>

Chemokines | Macrophage, endothelial cells, T cells | Attraction of phagocytes |

IL= Interleukin; TNF= Tumor necrosis factor ;TGF= Transforming growth factor; NK= Natural killer cell; Mac =Macrophage; PMN =Polymorphonuclear leukocyte .

Modified from the interplay between cytokines and T cells in immunity to intracellular bacteria. In : Mustafa AS, Attiyah RJ, Nath I, Chugh TD.(eds).T-cell subsets and cytokines interplay in infectious diseases., S Karger, Basel (Switzerland),169-180,1996.
cytokines/cytokines receptor genes, nude mice, and use of anti cytokines antibodies will further revolutionize studies in immunotherapy. It is plausible and worth experimenting on recently discovered transcriptional factors viz. LSIRF/IRF4 which are required for mature B and T lymphocyte subsets functions. Factors like NF-kB, ZAP70, RANTES, STAT 1-6, Nrampl, various chemokines and their receptors like CCR5, CCR3, CXCR may play an important role in immunoregulation.

Concluding Remarks

Cytokines play an important role in the host defense against leprosy infection. Intracellular cross talk between T-cell subsets, cytokines, macrophages, NK cell and other phagocytic cells including dendritic cell in a coordinated manner is essential to develop a protective host immune response. Experimental trials as well as many studies suggests that cytokines are having therapeutic potential. However, at present we do not know fully the diversity of T-cell and various molecular mechanisms involved in signal transduction including various cell surface molecules, receptors and molecular immunoregulation.

Acknowledgments

This work was supported by Science and Technology Agency, Japan. I express my sincere gratitude and benevolence to Drs. H Saito, Kazuo Kobayashi, and Yoshiko Kashiwabara for my STA fellowship. I also thanks Drs. Yumi Maeda, Ken Hashimoto for assistance in careful review and reference search.

References

10) Bermudez LE, Champsi J. Infection with Mycobacterium avium induces production of interleukin-10 (IL-10) and administration of anti IL-10 antibody is associated with enhanced resistance to infection in mice. Infect Immun 61: 3093-3097 (1993).


12) Zhang Tiantuo, Kawakami Kazuyoshi, Qureshi Mahboob Hossain, Okamura Haruki, Kurimoto Masashi, Saito Atsuhi. Interleukin-12 (IL-12) and IL-18 synergistically induce the fungicidal activity of murine peritoneal exudate cells against Cryptococcus neoformans through production of gamma interferon by natural killer cell. Infect Immun 65:3594-3599 (1997).


23) Heinzel FP, Sadick MD, Holaday BJ, Coffman RL, Locksley RM. Reciprocal expression of interferon-γ or interleukin-4 during the resolution or progression of murine leishmaniasis: evidence for expansion of distinct helper T


