Cytokines in infectious diseases

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Interest in cytokines in infection is increasing exponentially both because of the central role these peptide molecules have in immune responses in a wide spectrum of human responses in health and disease and because they are likely to be pivotal in the development of new therapies and vaccine strategies. Immunity to infections and attempts by pathogens to avoid the host defence system provide some of the most elegant insights into the multitude of cytokine functions.

This review is an update of some of the more recent developments in cytokine biology. It will not cover all aspects of cytokines in infection, but rather illustrate general principles, using examples found in infectious diseases of major pathogenic significance, and indicate how knowledge is being transferred to the clinic. The areas considered are:

- The proinflammatory response
- Cellular recruitment to areas of infection
- The T helper (TH) 1/2 dichotomy
- Genetic influences on cytokine secretion
- Molecular mimicry by pathogens.

Figure 1. The proinflammatory cascade is initiated by lipopolysaccharide (LPS) interacting with LPS-binding protein (LBP) and binding to the CD14 receptor of human macrophages/monocytes. This stimulates diverse intracellular signalling pathways, including activation of the key transcription factor NF-κB. Transcription of cytokine genes occurs rapidly (within 15 min for tumour necrosis factor (TNF)), followed by translation to, and secretion of, protein. In addition, downregulatory pathways are activated with secretion of cytokines such as transforming growth factor-β (TGF-β) and interleukin (IL)-10. Positive and negative feedback loops operate within the system. Abnormal regulation of cytokine secretion leads to an exaggerated, harmful proinflammatory response.

Sepsis, spirochetes and the proinflammatory response

Bacteraemia leading to a systemic inflammatory response and then admission to the intensive care unit with multiorgan failure, including the acute respiratory distress syndrome, is a familiar clinical scenario. It is clear that much of the morbidity and mortality in affected patients is due to an uncontrolled proinflammatory response rather than directly to the pathogen. In Gram-negative infection, this response is driven by bacterial lipopolysaccharide (LPS) interacting first with LPS-binding protein and then with the CD14 receptor on monocytes and macrophages (Fig 1).

Tumour necrosis factor (TNF) and interleukin (IL)-1 are produced early in the antibacterial immune response and initiate a cascade of secretion of proinflammatory mediators. Early therapeutic intervention in a number of...
Phase III clinical trials attempted to reduce the secretion or activity of TNF and IL-1 but results have proved disappointing in acute infection although this approach has been successful in chronic inflammatory disorders. One reason for the lack of success is that patients present after inflammatory responses have been initiated. Indeed, recent data have indicated only weak correlations between plasma cytokine concentration and survival. Two other approaches are of current interest:

- The therapeutic inhibition of the systemic inflammatory response by giving downregulatory mediators, of which IL-10 is the prototype.
- The investigation of local tissue cytokine production, as opposed to systemic secretion, with the long-term aim of modulating this.

Treatment of infections due to spirochetes, particularly therapy for *Borrelia recurrentis* (louse-borne relapsing fever), frequently precipitates a Jarisch-Herxheimer reaction (JHR). This is characterised by sudden onset of a systemic inflammatory response, with pyrexia, tachycardia and hypertension associated with killing of the pathogen and release of cell wall constituents. Initial studies indicated that this potentially fatal clinical deterioration was coincident with a transient, pulsatile release of proinflammatory cytokines. Unlike sepsis, it is therefore possible to predict the onset of cytokine release. Therapy directed against early inflammatory mediators such as TNF might be expected to have an impact, and in clinical studies anti-TNF inhibited the JHR without affecting the patients’ response to treatment.

**Mycobacterial infection, granuloma formation and T cell-derived cytokines**

**Tuberculosis**

Tuberculosis kills over three million people each year, and at any one time up to 20 million are suffering from active infection. Although these numbers are huge, the fact that about one-third of the world’s population are actually infected with the causative organism, *Mycobacterium tuberculosis*, indicates that the immune system contains the infection in most cases. There is an urgent need for better therapies for tuberculosis, both because of the emergence of significant drug resistance and because current six-month therapeutic regimens are associated with major compliance problems. One possible solution would be to combine immunological and pharmacological approaches to treatment — hence the increasing interest in the role of cytokines in this infection.

Granuloma formation is the principal tissue immune response to *M. tuberculosis* and appears to be dependent on TNF secretion. Interferon (IFN)-γ, another important proinflammatory cytokine, also has a key role in immune responses to mycobacteria despite *M. tuberculosis* itself apparently being able to downregulate many of the actions of this cytokine. However, there are well characterised patients who are susceptible to recurrent mycobacterial infection and have deletions in the IFN-γ receptor chain.

Granuloma formation is consequent upon recruitment of monocytes and T lymphocytes to areas of infection. Such cell influx is dependent on the chemotactic cytokines or chemokines (Table 1). Chemokines are divided into groups on the basis of structural motifs relating to cysteine residues. They are secreted by epithelial cells and alveolar macrophages which are the first line of defence against *M. tuberculosis*. In animal models, antibodies directed against chemokines such as IL-8 prevent cellular influx and granuloma formation. Clinical possibilities include the use of chemokines to improve therapeutic responses or to augment appropriate cellular recruitment to sites of vaccination.

**Leprosy**

A good illustration of the TH1/TH2 paradigm of cytokine production is provided by leprosy (Fig 2). It presents with a wide clinical spectrum, one end of which is tuberculoid disease with granuloma formation, few organisms and immune-mediated pathology. The other end of the spectrum is leproma-
tous leprosy, characterised by poor granuloma formation and high tissue levels of mycobacteria. In tuberculoid leprosy, the immune response is characterised by the presence of TH1 cells which favour granuloma development and killing of the pathogen, whereas in multibacillary lepromatous disease the downregulatory TH2 cells predominate. Exactly why one form should develop in any one patient is not known, and indeed patients can progress through the spectrum of disease. In addition, it should be remembered that the strict division of T cells into TH1 and TH2, which was derived from murine research, may not be directly applicable to disease in man.\(^6\)

One particular problem in leprosy is that reversal reactions are often associated with therapy. Essentially, these reactions consist of an upgrading of the inflammatory response and they appear to be driven by TNF release. Thalidomide is an anti-TNF agent and has been used with success in treating such patients presenting with erythema nodosum leprosum\(^6\). Thalidomide is not an ideal agent because of its well-known teratogenic properties, but the principle of anticytokine therapy is here to stay.

Viral infections and cytokine receptors

The role of cytokines in HIV and other viral infections is complex. One area which has recently come into focus concerns the involvement of cytokine receptors in the pathogenesis of infection. HIV is now known to use not only the CD4 receptor but also the G-protein-coupled chemokine receptor family to gain access to various cell types\(^7\). Indeed, the cellular tropism of the virus appears to depend on local expression of chemokine receptors. These receptors are divided into subfamilies which interact mainly with either CC chemokines or CXC chemokines. It transpires that macrophage-tropic strains of HIV gain access to cells expressing the CCR5 receptor and T cell tropic strains use the CXCR4 receptor. Novel therapeutic approaches are the use of chemokines or analogous compounds to inhibit viral entry into cells.

Disease is known to progress extremely slowly in certain HIV seropositive patients. In general, macrophage tropic viruses predominate early in infection, and therefore it is initially important for virus to be able to enter such cells using the CCR5 receptor. However, some patients are homozygous for a 32 bp deletion in the CCR5 receptor, and this mutation confers significant protection against HIV-1\(^8\).

### Table 1. Chemokine families (defined on the basis of structural motifs involving cysteine residues).

| Motif: | CXC | CC | C | CXXXC |
|--------|-----|----|---|------|
| Examples: | IL-8 | MCP-1 | *Lymphotactin | *Fractalkine |
| Gro α,β,γ | Eotaxin | RANTES | | |
| IP-10 | | | | |

| Chemotactic for: | Neutrophils | Monocytes | Resting T cells | NK cells |
|------------------|-------------|------------|-----------------|---------|
| T cells          | T cells     | Eosinophils| Basophils       | Dendritic cells |

Note: the list of chemokines and their functions is not intended to be exhaustive.

* only member of group

IL = interleukin
IP = interferon-inducible protein
MCP = monocyte chemoattractant protein
RANTES = regulated upon activation normal T cell expressed and secreted

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**Figure 2. A simplified version of the T helper (TH)1/TH2 paradigm.** The nature and dose of antigen presented by the antigen-presenting cell (APC) may also influence whether the TH1 or the TH2 phenotype is manifest (positive influences: solid lines; negative feedback: dashed lines; IFN = interferon; IL = interleukin).
Malaria and genetic influences on cytokine secretion

Malaria causes over two million deaths each year worldwide, principally among children. Proinflammatory cytokines such as TNF appear to have a pathogenic role, acting in part via upregulation of adhesion molecules. The influences of genetic predisposition are clearly seen in this disease. In a case-controlled study of Gambian children, those homozygous for the TNF2 allele, a variant of the TNF promoter region, were more likely to die or develop severe disease. Thus, a cytokine gene polymorphism appears to have a direct effect on survival in infection. However, since this gene is maintained in the Gambian population at a high frequency, it is likely to confer some other selective advantage. Unfortunately, malaria is another infection for which the direct approach of interfering with TNF secretion has failed to show therapeutic benefits, although treatment was associated with defervescence.

Cytokines and molecular mimicry

One of the most fascinating aspects of cytokine biology is the way in which the system has been hijacked by microorganisms trying either to evade or to utilise the human immune response. Epstein-Barr virus encodes a gene for viral IL-10 which is likely to down-regulate host antiviral immunity, although exactly how this is done remains uncertain. Many viral genomes encode chemokine receptors. In the case of the US28 sequence of cytomegalovirus, this may act as a decoy to the natural host immune response by interfering with chemokine action. In contrast, the recently described chemokine receptor homologue found in Kaposi's sarcoma-associated herpesvirus 8 stimulates cellular proliferation. Other infectious agents utilise the chemokine system to gain access to host cells; for example, Plasmodium vivax uses the ubiquitous chemokine receptor, the Duffy antigen, to enter human erythrocytes. There are many examples of pathogens modulating cytokine action in infectious diseases, which is highly suggestive that increasing our understanding of cytokine biology is almost certain to lead to novel anti-infective therapies.

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