The role of cytokines in immunity to intracellular infections

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Abstract Intracellular infections are checked mainly by the cellular arm of the innate and specific immune response, and are controlled to a great extent by soluble mediators known as cytokines, which are essentially a means of communication of cells with one another. They play a role in amplification of the initial antigen stimulus and in selecting the most efficacious effector response directed toward eliminating or controlling the foreign antigen. Recruitment of the appropriate immune response is essential to prevent a fatal outcome. In this brief review, emphasis is placed on cytokines of importance in intracellular infections and interactions among these cytokines to give the final effector response in favour for or against the host.

Keywords: T-cells, macrophages, cytokines, intracellular infections, cell mediated immunity (CMI)

Visible manifestations of cell mediated immunity (CMI) such as delayed type hypersensitivity (DTH), granuloma formation and antimicrobial response, represent the final outcome of complex interactions among the cellular components of CMI and their different subsets. In such interactions, cytokines mediate signalling among the cells in the immediate vicinity as well as influencing the cells secreting them (paracrine and autocrine regulation). They are produced by all the cellular components of CMI and will target cells in the immediate vicinity expressing the specific cytokine receptors. They also could be produced in excess and spill over systemically and hence have effect on targets remote from the site of production. Examples of the latter could be demonstrated by fever, anorexia and weight loss induced by tumor necrosis factor (TNF) in chronic intracellular infections such as tuberculosis.

Cells of CMI and their cytokines. Broadly speaking there are two major mechanisms by which the specific immune system deals with infected target cells. Firstly, direct cytolysis of lymphocytes to infected cells results from direct cell-cell contacts. The signalling and mechanisms of inducing cytotoxicity is beyond the scope of this review. The other major mechanism is activation of the phagocytic system to destroy the intracellular microbes within the phagocyte itself. This increase in microbicidal activity is achieved via secretion of activating cytokines which upgrade the killing capacity of macrophages.

All subsets of lymphocytes, mononuclear macrophages, eosinophils as well as mast cells, contribute to the secretion of a network of cytokines in CMI. The complex cross interaction among these cytokines will determine the end effector response, whether it is in favour of eliminating the intracellular infection or damaging the host tissue. CD 4+ T-helper cells are classified into two subsets: Th-1 and Th-2 according to the profile of cytokines they secrete. Th-1 secrete interleukin-2 (IL-2) and interferon-γ but no IL-4,5,6,10.

Th-2 on the other hand secrete IL-4,5,6 and 10 but not IL-2 or interferon. Monocytic macrophages secrete an array of cytokines which are important in immunity to intracellular infections, but most important are the tumour necrosis factor (TNF), dihydroxycholecalciferol, granulocyte monocyte-colony stimulating factor (GM-CSF) and IL-12.

CD8 T-cells are also activated and participate in protection against intracellular microbial
infections. They appear to lyse infected target cells i.e. have direct cytotoxicity, and produce interferon-γ which activates microbicidal mechanism of macrophages.14

While other cells of chronic inflammatory response, such as mast cells and eosinophils, contribute actively for cytokine secretion, they are more important in defense against extracellular helminthic parasites than intracellular microbial infections.

**Th subset and their cytokines in immunity to intracellular infections:** Since Mossman defined Th-1 and Th-2 subsets using in vitro murine model in 1986,7,8 there has been an intensive search for an in vivo role of these subsets. The area of intracellular infection is an obvious one to investigate, since the cell mediated component of the immune response is a major factor in determining the outlook of infection, and T-cells have major roles to play. The presence of such subsets or their equivalents in humans has been widely accepted.9,16

The current evidence points to a protective role for Th-1 subsets, whose cytokines upgrade the cellular immune response, and hence macrophages and cytotoxic lymphocytes to eliminate the intracellular microbes.18,19 Th-2 cytokines, on the other hand, activates the humoral arm of the specific immune response and down-regulates the cell mediated immunity. As a result, little protection against intracellular infections is offered by Th-2 subsets, and they may even be responsible for immunopathology in certain intracellular infections such as listeria monocytogenes30 and visceral leishmaniasis.21

Although the above statement can hold true in many circumstances of intracellular infections in human and murine models, exceptions have been demonstrated. In human tuberculosis, macrophages activated by interferon-γ from Th-1 cells, synthesize 1-hydroxylase which is the responsible enzyme for 1-hydroxylation of 25 (OH) vitamin D3 to give 1,25-dihydroxy vitamin D3. The latter promotes maturation and activation of human macrophages.5,10,11 It also acts in synergy with interferon-γ to stimulate macrophages to synthesize and secrete tumor necrosis factor TNF.13 The present evidence points to TNF as being responsible for most of the immunopathology seen in human tuberculosis, such as weight loss and tissue damage and since there is no efficient activation of human macrophages to kill M. tuberculosis, it seems that the role of interferon-γ (a cytokine secreted by Th-1 subset) is immunopathological rather than protective.6,12,23 In murine models, however, interferon-γ mediated macrophage activation represents a major step in acquired resistance against tuberculosis and evasion from this mechanism contributes to mycobacterial virulence in mice.34,25 Such activation of mouse macrophage is inhibited by lipoarabinomann LAM in the cell wall of mycobacteria.26 This inhibition by LAM can also be demonstrated in human macrophages from lepromatous granuloma and thus may contribute to the pathogenesis of mycobacterial disease in humans.34,25,27

Interleukin-2 is the other major cytokine secreted by Th-1 subsets. Lack of, or depressed IL-2 production is responsible for tuberculin insensitivity seen in peripheral blood lymphocytes of patients with tuberculosis. These lymphocytes show poor proliferative response to tuberculin stimulation which could be reversed by the addition of exogenous IL-2.28,43 This may explain the dissociation between tuberculin sensitivity and antibacterial immunity in terms of sequestration or tapping of tuberculin-reactive lymphocytes at the site of tuberculous lesion, eg. tuberculous pleural effusion, which leads to depletion of this subpopulation from the periphery, eg in blood and skin. Demonstration of the importance of IL-2 in maintaining tuberculin reactivity of lymphocytes, has instigated clinical trials using IL-2 as an immunotherapeutic agent in the treatment of advanced drug resistant tuberculosis and non-tuberculous mycobacterial infections.29,30

Interleukin-6 is a cytokine secreted predominantly by Th-2 subsets which may have a role to play in immunity to intracellular infections. In vitro activation of murine macrophages infected with M. bovis has been achieved using rIL-6.31 The same results were reproduced when murine macrophages were activated to kill listeria monocytogenes using rIL-6.30 Further evaluation of the role of IL-6 in promoting immunity against intracellular infections is clearly needed.

**Cytokines of macrophages:** Tumor necrosis factor TNF is a major cytokine secreted by macrophages and to a lesser extent Th-1 subsets. In mycobacterial infections, its release from macrophages seems to be triggered by LAM in
the cell wall of mycobacteria. Release of TNF, however, does not occur at the massive shock-inducing level seen in gram-negative sepsis, but at a much lower level. TNF, as discussed above, seems to offer little protection against mycobacterial infections and it is responsible for a great deal of tissue damage seen in such infections. In tuberculosis, TNF-mediated tissue damage has much in common with the endotoxin-induced Schwartzman’s reaction seen in experimental animals.

The distortion of the normally protective role of TNF with consequent immunopathology seen in tuberculosis is a mystery but a few explanations have been offered. LAM content in the cell wall of mycobacteria may sensitize the host cells to the toxic effect of TNF, and hence LAM may further contribute to the virulence of mycobacteria. Also the raised level of agalactosyl-IgG seen in tuberculosis appears to correlate well with immunopathological response involving both T-cell activity and cytokine-mediated tissue damage. This raises the issue of the relevance of this abnormal IgG and its role in immunopathology. It is also highly likely that cross-reactivity between mycobacteria and host heat shock proteins are responsible for damaging the host cells by the same immune response raised against the mycobacteria, i.e., it is an autoimmune damage due to cross-reactivity with mycobacterial antigens.

Granulocyte-monocyte colony stimulating factor (GM-CSF) is a cytokine secreted predominantly by activated macrophages. It may contribute to activation of macrophages by upgrading their microbicidal potential. In an in vitro murine model, it has been shown to restrict the growth of M. tuberculosis inside macrophages, in a manner independent of reactive free oxygen radicals. The relevance of such observation to human models needs to be evaluated, as it is not clear yet if it is possible to upgrade the microbicidal potential of human macrophages against M. tuberculosis.

Interleukin-12 is produced mainly by monocytic macrophages and to a lesser extent B-lymphocytes, in response to both gram-positive and negative bacteria, bacterial products and intracellular infections. Its major biological activity is on T-lymphocytes and natural killer cells, on which it induces production of lymphokines, mainly interferon-γ and enhances cytotoxic activity of these cells. IL-12 has an important role in the host resistance to infection, in particular to intracellular pathogens, by activating macrophages through induction of interferon-γ from natural killer and T-cells and by enhancing cell-mediated immune responses, dependent on Th-1 cell development. Monocytes from HIV-positive individuals are impaired in their ability to produce IL-12 in response to bacterial stimulation, and exogenous IL-12 restores in vitro some of the depressed immunological functions, suggesting a defect in IL-12 production may have a pathogenic role in the immunodeficiency of HIV-infected individuals. The natural cytokine appears to provide a regulatory link between innate resistance and development of the antigen-specific adaptive immune response, by enhancing cell mediated immunity dependent on Th-1 cell development.

The above discussion shows the role of monocytic macrophages in different steps of the immune response against intracellular infections. They function not just as end effector phagocytic and killer cells, but actively secrete cytokines of importance in augmenting and directing development of the immune response against the invading organisms as well as having a major role in down-regulation of the cell mediated immunity after the foreign microbe has been eradicated. This last function may be achieved by secretion of prostaglandin E which exerts a negative feedback control on T-cell proliferative response.

**Conclusion**

Cells of the immune response against intracellular infections secrete an array of cytokines of prime importance in guiding the specific immune response to develop along the line of cell mediated immunity which can eradicate the infection. These cytokines are also important in upgrading the microbicidal capacity of macrophages and cytotoxicity of natural killer cells, although they do not exert much influence on cytotoxicity of specific lymphocytes against infected cells. The cytokines interact with each other in a complex network which is autoregulated for the purpose of upgrading the immune response as long as the foreign microbe is still present. Once the pathogen has been eradicated the positive signals fade down and negative signalling takes over to down regulate the immune response.
References

دور الحركيات الخلوية في المنااعة من العدوى داخل الخلايا

الخلاصة:

يتم غالباً فحص العدوى داخل الخلايا بواسطة الذراع الخلوي والاستجابة المناعية المحددة، ويتم السيطرة عليها إلى حد بعيد عن طريق الوسائط القابلة للذوبان، والتي تعرف باسم الحركيات الخلوية، والتي تعتبر من الناحية الجوهرية وسيلة لاتصال الخلايا بعضها ببعض. وهي تؤدي دوراً في مضايقة المحفز المبديئي لولدات المضادات وفي اختيار الاستجابة الأكثر فاعلية الموجهة نحو إزالة أو السيطرة على مولد الأجسام الغريبة. كما أن توفير الاستجابة المناعية المناسبة ضرورية لمنع حدوث نتيجة قاتلة. وفي هذه المراجعة الموضوعة ركزنا على الحركيات الخلوية ذات الأهمية في العدوى داخل الخلايا، والتفاعلات الداخلية بين هذه الحركيات الخلوية; لتوفير الاستجابة النهائية الفعالة لصالح أو ضد الجسم المستقبل.