The role of cell-mediated immunity (CMI) in intracellular infections

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Abstract Cell mediated immunity is a major defense against pathogens residing in intracellular environment. The cellular mechanisms involve complex interaction among numerous cells but the major components are the professional phagocytes and the antigen-specific T-lymphocytes.

After phagocytosis of the pathogen by a professional phagocyte, the pathogen may succeed to evade the intracellular killing mechanism of the phagocyte. However, such killing mechanisms can be upgraded by specific T-lymphocytes, which confer direct lytic activity (cytotoxicity) of the macrophage and microbe or upgrade the killing of bacteria by phagocytes without lysis. Such upgrading can be achieved via secretion of cytokines.


Keywords: T-lymphocytes, monocytic macrophages, intracellular pathogens, Th-subsets, cytokines, cytotoxicity, intracellular defense mechanisms

Intracellular parasites induce an immune response in which the cellular arm of immunity plays a far greater role than the humoral arm. The intracellular location of these organisms makes them inaccessible to the direct immune effect of serum at least not after they have been established intracellularly. The specific humoral immunity may have a prophylactic role to play in prevention of secondary infections eg. in the case of viral infections and some bacterial infections such as pertussis, preventing attachment of the parasite to the host cells and hence providing first line defense in secondary infections. Antibodies also assist in opsonisation whereby they help phagocytes to engulf bacteria and other parasites, and finally antibodies participate in triggering cytotoxicity by natural killer lymphocytes against virally infected cells in the process of antibody-dependent cell mediated cytotoxicity (ADCC). Otherwise, once the parasite has been established intracellularly, the cell-mediated immunity (CMI) takes over control of the infection, whether it is in favor of the host by elimination of the intracellular parasite (protective immunity) or immunopathology in the form of delayed type hypersensitivity (DTH) with host tissue damage. The final outcome of natural infection with intracellular parasites is determined by the relative contribution of each of these two components of CMI: the protective and the immunopathological components.1,2

There are examples of intracellular parasitic infections in which CMI is not in full control and a switch over to humoral response occurs with excess of antibody and immune-complex formation. In such examples the immuno-pathology is primarily induced by the specific humoral immunity, which is also ineffective in eliminating the parasite. Examples of such infections are lepromatous leprosy and the progressive form of leishmaniasis.

Intracellular pathogens, whether inside a professional phagocyte or a non-phagocytic host cell, have the means of surviving against the hostile factors of the intracellular environment. The interior of a professional phagocyte is naturally hostile and for such pathogens to survive this environment, they must have efficient evasion mechanisms to survive the battle. Such mechanisms include inhibition of phagosome-lysosome fusion, resistance to oxygen free radicals, nitrous oxide metabolites and lysosomal enzymes. However, the

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host cell is also capable of upgrading their hostility by receiving signals from the specifically activated T-lymphocytes. In this review, the role of the specifically activated T-lymphocytes and monocytic macrophages in achieving immunity against intracellular pathogens is discussed.

Cells of immunity against intracellular microbes The CD4-positive T-cells are of major importance in resistance against intracellular pathogens, where they activate macrophages to kill or inhibit the growth of intracellular organisms. They also have a direct lytic effect on monocyte-macrophages harboring the intracellular parasites (the direct cytotoxic effect) and cells having this property are referred to as cytotoxic lymphocytes (CTL).

The CD4+ T-helper cells are further subdivided into Th-1 and Th-2 subsets, according to the profile of cytokines they secrete. Although it was first defined in murine models, there is enough evidence at present to support the existence of such subsets in humans. Th-1 subsets secrete interferon-γ and interleukin-2, both of which contribute to upgrading of cellular immunity and downgrading of atopic type-1 hypersensitivity and hence the elimination of the intracellular infection. The Th-2 subsets secrete IL-4, 5, 6 and 10 and their effect on the immune response is opposite to that of Th-1. The current evidence at present points to a protective role for Th-1 against intracellular pathogens and widespread dissemination of intracellular infection whenever Th-2 subsets are activated. The CD8-positive T-cells are also involved in direct lysis of macrophages infected with intracellular organisms. They have been shown to confer resistance against M. tuberculosis and a variety of other intracellular pathogens. They also contribute in secreting cytokines which in turn upgrade the killing capacity of professional phagocytes. They are a rich source of interferon-γ 15 which increases the microbicidal capacity of the macrophage. The CD8+ T-cells recognize antigens in association with class-I MHC molecules and that makes them suitable for lytic activity of cells infected with viruses. In addition to antigen specific T-lymphocytes, there are natural killers (NK) and/or activated killer cells, the origin of either is uncertain, which may play a part in immunity against intracellular infections. These cells act in an MHC-unrestricted antigen-independent manner and they require

the presence of antibody on the target cell. Interleukin-12 and interferon-γ are potent activators of natural killers.

Monocytic macrophages are essential for immunity to intracellular pathogens and their depletion leads to failure to mount an effective immune response. Their function is not restricted to phagocytosis and killing of intracellular microbes. They function as crucial accessory cells in response to primary antigen and mitogen for the proliferation of T-lymphocytes and induction of T-helper cells, via production of cytokines such as interleukin-1 (IL-1). They also act as antigen presenting cells (APC) processing and presenting antigens to T-lymphocytes possessing receptors specific to that antigen. The antigen presenting capacity of the macrophage is independent of its function as an accessory cell secreting IL-1 and is also independent of MHC-class 2 expression on its surface. Other functions of macrophages of relevance to the immune response to intracellular microbes include their influence on haemopoiesis via production of cytokines such as granulocyte-monocyte colony stimulating factor (GM-CSF),12,13 and IL-12,37 as well as having a major role to play in down-regulation of cell mediated immunity.

Overall response to intracellular microbial infections The natural history of these infections usually runs a chronic course. The pathogens are phagocytosed by polymorphonuclear leukocytes and mononuclear phagocytes. Phagocytosis may be enhanced by antibodies and complements. Intracellular microbes can survive within polymorphs and, at least initially, within mononuclear phagocytes as well.

The histological landmark of tissue response to these infections is the formation of granuloma. This is a focal chronic inflammation with organization of the chronic inflammatory cells around the center. These cells include lymphocytes, monocytes, epithelioid giant cells, as well as eosinophil and mast cells. Cytokines produced by these cells play a major role in the formation of granuloma. Protective immunity against intracellular bacteria may be acquired after immunization with live bacteria responsible for the intracellular infection. The same criteria are needed for induction of DTH. However, incorporation of antigens into complete Freund's adjuvant or injection of antigens into lesions or
immunomodulation by BCG infection can afford protection.  

**Antimycobacterial Immunity** The immune response has been studied extensively in the case of mycobacterial infection. It appears that different T-cell subsets including CD4-positive αβ T-cells, CD8-positive αβ and γδ T-cells are all involved in antimycobacterial immunity. CD4-positive T-cells play an important central role in the immune response to M. tuberculosis. They express and regulate the acquired immune response which controls the primary infection and provides protection against exogenous reinfection. Failure of CD4-positive T-cell response contributes to progressive primary infection and reactivation of endogenous mycobacteria, like that which occurs in patients infected with the Human Immunodeficiency Virus.

The protective immune response which follows exposure to M. tuberculosis can be regulated by CD4-positive T-cells by activating macrophages through the cytokines they secrete, such as interferon-gamma (IFN-gamma), at least in the murine model, and GM-CSF which activate macrophages to contain and kill intracellular mycobacteria more effectively. Such killing by macrophages is possible by stimulating them to generate reactive nitrogen intermediates which seem to be more effective in killing intracellular mycobacteria than the pathway involving generation of free oxygen radicals.

It is not certain that human macrophages can be activated to kill virulent M. tuberculosis, although there is some evidence that human neutrophils can kill both virulent and avirulent strains of M. tuberculosis. This raises doubt about the role of macrophages as first line defense against human tuberculosis.

Experimental studies have demonstrated that the bulk of T-cell populations from M. tuberculosis and M. leprae infected individuals are cytotoxic to monocyte-macrophages pulsed with mycobacterial antigens. Cytoxicity appears to be a property of the CD4-positive T-cells present in these bulk populations. In humans, the CD4-positive T-cells may be the primary T-cells to express antigen specific cytotoxicity to macrophages infected with M. tuberculosis. In contrast to the murine model, the contribution of CD8-positive T-cell mediated cytotoxicity for mycobacterial antigens in humans appear to be quite minimal. Cytotoxic activity of CD4+ and CD8+ T-cells has been demonstrated in other intracellular infections such as hepatic phase of malaria and visceral leishmaniasis. The cytotoxicity of CD4-positive T-cells is MHC class 2 restricted and inhibited by antibodies to the adhesion molecule ICAM-1 (Intracellular Adhesion Molecule-1, or CD-54) and LFA-1 (Leukocyte Function Associated Antigen-1, or CD11a-CD18) which highlights the importance of this antigen-independent T-lymphocyte-macrophage interaction for cytotoxicity.

Cytotoxicity to monocytes pulsed with mycobacterial antigens, or with live mycobacteria, can be induced by CD4-positive T-cells and appears to be independent of the repertoire of lymphokines produced. Such cytotoxicity was not limited to CD4-positive T-cells recognizing mycobacterial heat shock proteins (HSP). It was rather mediated by T-cells specific for mycobacterial antigens other than HSP.

Heat shock proteins are molecules which are synthesized by host macrophages and bacteria in order to facilitate their survival. They are highly conserved phylogenetically showing a high degree of homology among different species. They possess potent immunogenicity and may play an important role in resistance against, and immunopathogenesis of, mycobacterial infections as a result of cross-reactivity. The exact contribution of these molecules to the immune response to mycobacteria is an area of high controversy.

Attention has been given recently to the role of γδ T-cells in antimycobacterial immunity. These cells in the mouse are found mainly in the skin, intestinal epithelium and lungs. They form a minority in the circulation (1-3%). In humans they are more uniformly distributed and comprise about 1-5% of the peripheral lymphocyte pool. Little is known about the antigens recognized by γδ T-cells. However, their antigen recognition seems to be, in the main, MHC unrestricted. Activated γδ T-cells are enriched in granulomatous lesions of tuberculosis, leprosy and leishmaniasis, as well as in synovial tissues from patients with rheumatoid arthritis which raises the question of the role of these cells in autoimmune pathology. Although γδ T-cells hybridomas recognize HSP, this molecule is only recognized by a small proportion of human γδ T-cells, which possibly recognize a carbohydrate antigen of M. tuberculosis such as the lipoarabinomannan of the cell wall. Monocytes
infected with live bacteria are more efficient than those infected with dead bacteria at inducing human γδ T-cell expansion. In contrast, killed bacteria preferentially induce CD4-positive γδ T-cell expansion. γδ T-cell expansion is supported by IL-2. They can secrete lymphokines such as IL-2 interferon-γ, lymphotoxin and can lyse macrophages in an antigen-specific as well as non-specific manner. Natural killer-like activity by γδ T-cells has been demonstrated in tuberculous pleural exudates. These cells may represent an earlier more primitive form of immune response to intracellular bacterial pathogens.

Conclusion Intracellular infections are encountered mainly by the cellular arm of the immune response, while the humoral arm plays a limited role in elimination of intracellular microbes.

The intracellular environment may be within a professional macrophage or a non-phagocytic cell such as the red blood cell. The pathogens have evolved means of evading the hostile intracellular defense mechanisms inside the macrophage. Successful elimination of the pathogen may depend upon efficient upgrading of the intracellular defense mechanisms via secretion of cytokines from specifically activated T-lymphocytes. Another major pathway for elimination of the parasite is cytotoxicity to infected cells with consequent lysis. T-lymphocytes recognize the presence of intracellular microbes by recognition of microbial molecules expression the surface of infected cells. The exact nature of these molecules for each microbe, is not fully defined yet.

Final outcome of the infection depends on how successful the immune response is in eliminating the pathogen, and the degree of immunopathology which may result as a consequence of the immune response.

References


دور المناعة المحفزة بالخلايا
في العدوى داخل الخلايا

الخلاصة:

تعد المناعة المحفزة بالخلايا من الوسائل الدفاعية الرئيسيه ضد المرضات الكامنة داخل الخلايا. وتشتمل الآليات الخلوية على تفاعل معقد بين عديد من الخلايا إلا أن العناصر الرئيسية هي الخلايا البلعمية المحتفزة، والخلايا اللمفاوية النائمة المولدية للمضادات.

بعد احتواء الخلايا البلعمية للعامل الممرض بواسطة خلية بلعمية محترفة يمكن أن يجعل العامل الممرض في تفادي آليات القتل داخل الخلايا البلعمية. إلا أنه يمكن رفع مستوى آليات القتل المذكورة بواسطة الخلايا اللمفاوية النائمة المحدودة والتي تعطي نشاطاً انحلالياً (تسمم خلوي) للخلايا البلعمية الكبيرة والمايكروب أو ترفع مستوى قتل البكتيريا لدى الخلايا البلعمية دون انحلال. ويمكن تحقيق رفع المستوى المذكور من خلال إفرار الحركيات الخلوية.

الكلمات الرئيسية: الخلايا اللمفاوية النائمة، الخلايا البلعمية، المرضات داخل الخلايا، الحركيات الخلوية، التسمم الخلوي، آليات الدفاع داخل الخلايا، المجموعات الفرعية.