Immunity Against Mycobacteria

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ABSTRACT

Mycobacterium tuberculosis is the most prevalent infectious pathogen in the world, largely due to its unique interactions with the human immune system. Even in a normal host, a frequent outcome of infection with *M. tuberculosis* is failure to completely eradicate the organisms, despite the development of cell-mediated immunity. Viable organisms persist in a state in which they do not progressively replicate, leading to latent infection, which carries a risk of breakdown into active (reactivation) tuberculosis at some point later in life. Key features of the immune response against mycobacteria are reviewed here, and potential mechanisms by which the organisms may subvert these host defenses are discussed. Despite the multicellular nature of the host response to infecting mycobacteria, the organisms cannot be eradicated and contribute to the ongoing worldwide epidemic with tuberculosis.

KEYWORDS: Mycobacteria, immunity, cytokines, granuloma

Objectives: Upon completion of this article, the reader should be able to summarize the various components of the normal host immune response to mycobacterial infections, and to describe several means by which mycobacteria can evade that host immune response.

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Infection with *Mycobacterium tuberculosis* remains at epidemic levels globally. One third of the world's population is infected with this organism, making tuberculosis the most prevalent infectious disease. Annually, 8 million people contract the disease, and there are 2 million deaths worldwide each year, with increasing prevalence predicted over the next several decades.[1,2] Effective curative therapy for this disease requires protracted (months in duration) medication administration and compliance, and is therefore problematic, especially in underdeveloped areas of the world. Vaccine development to date has been disappointing, with the currently available *Mycobacterium bovis* bacille Calmette-Guérin (BCG) vaccine failing to provide consistent protection against the disease in adults, especially so for pulmonary tuberculosis. *M. tuberculosis* is also a unique pathogen in that once infection occurs, even in the face of an intact host immune system it is not eradicated but establishes a chronically persistent, or latent, state. Viable organisms remain sequestered by the host's immune system, though they fail to progressively replicate. Subsequently, in approximately 15% of those latently infected, the infection may "reactivate" with the development of overt, progressive, pulmonary disease. Impairments in the immune system may be linked to reactivation, but much remains to be discovered about control, or lack thereof,

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of infection by *M. tuberculosis*. Immunity against mycobacteria is reviewed here.

OVERVIEW OF THE HOST RESPONSE

Tuberculous infection is initiated via the inhalation of airborne microorganisms into the terminal airspaces of the lung. There is a progression of inflammatory and immune events that occurs in the immunocompetent host, beginning when the organisms are ingested by the resident alveolar macrophages (AMs), which are capable of initiating an early inflammatory reaction in the lung. This requires the recruitment of monocytes from the bloodstream into the infected area of the lung. These early events following infection are mediated by the production of proinflammatory cytokines, including tumor necrosis factor (TNF), interleukin (IL)-1, and IL-12, from the macrophage once it has engulfed the mycobacteria. In addition to the recruitment of mononuclear cells, initial events occur to stimulate and expand a population of specific T lymphocytes that will produce a cell-mediated immune reaction. However, prior to the development of a specific immune response, the organisms are poorly contained and mycobacteremia occurs, with systemic distribution of the organisms. Several sites may be seeded, which could later represent foci of breakdown of latent infection into progressive infection, including the apices of the lung and the adrenal glands. Once antigen-presenting cells (AMs or, more likely, dendritic cells) have processed the engulfed mycobacterial proteins, they present antigens in the context of major histocompatibility complex (MHC) class II surface molecules to naive $CD4^+$ lymphocytes. This is one of the initial steps in the development of acquired specific immunity to the organism. The antigen-presenting cells produce IL-12 to bias the immune reaction to T helper 1 (Th1) and IL-1, which stimulate the $CD4^+$ lymphocytes to produce IL-2 as well as to upregulate lymphocyte IL-2 surface receptor. The net result is the rapid clonal expansion of specific $CD4^+$ Th1 lymphocytes, which produce interferon gamma (IFN-γ), a cytokine that activates the macrophages that have engulfed mycobacteria to become mycobactericidal. There are several mechanisms for bactericidal activity, which will be reviewed shortly. The intended effect is eradication of the bacteria. However, viable mycobacteria usually persist in the lung, and over the next 7 to 14 days, there is ongoing accumulation of macrophages and lymphocytes, eventually culminating in granuloma formation. This structure represents the manifestation of cell-mediated immunity to wall off the focus of infection and further limit the spread of the tuberculous infection. Despite this multicellular immune response, viable bacteria frequently persist in the cells within the granuloma but fail to progressively replicate, and latent infection is established. In the future, if the host's immune response is compromised (as with aging), or is otherwise compromised [e.g., loss of $CD4^+$ lymphocytes due to infection with human immunodeficiency virus (HIV)], progressive mycobacterial replication occurs, the amplification of the immune response leads to necrosis and tissue destruction with local spread of the bacteria, and "reactivation" of the infection into progressive tuberculosis occurs. This breakdown of the control of infection occurs in approximately 10 to 15% of those latently infected with *M. tuberculosis*.

CELLULAR COMPONENTS OF THE IMMUNE RESPONSE

As already mentioned, successful containment of the mycobacteria by the host requires a multicellular response for full manifestation of cell-mediated immunity. The major components of that cellular response include monocytes, macrophages, and lymphocytes.

Monocytes/Macrophages

Cells of the monocyte/macrophage lineage play key roles in both the establishment of immunity to mycobacteria as well as the maintenance of the immune reaction. The AM is the first responder to encounter mycobacteria entering the lung through the aerosol route. Dendritic cells, the classic antigen-presenting cells, likely also play a role in infection with mycobacteria, but the exact role of these cells in tuberculous infection in the lung is an area of active investigation. One possible outcome, if the AMs are in an activated state, is that ingested organisms are immediately killed and thus eliminated without development of a systemic immune response. How commonly this occurs is unknown. Another outcome of phagocytosis of mycobacteria by AMs (if the AMs are not in an activated state, and therefore, not immediately able to eliminate the organisms) is initial replication and dissemination of the bacteria. Depending on the host's ability to then mount an immune response, two possibilities exist. In an immunocompromised host, immunity may not be sufficient to contain the organisms, and progressive bacterial replication may occur, leading to clinically apparent progressive primary tuberculosis. The infection usually disseminates hematogenously, presenting as miliary tuberculosis.[3] Patients recently infected (especially children), alcoholics, peripartal females, those with diabetes mellitus, patients receiving corticosteroids or other immunosuppressants, and those infected with HIV are at heightened risk for disseminated disease.[3,4] Alternatively, in a host able to mount an immune response, the AM initiates that reponse to contain the bacteria. The outcome is the cell-mediated granulomatous response previously described, in which viable bacteria persist in a controlled environment as a latent infection.

Table 1 Risk Factors for Development of Active Tuberculosis in Latently Infected Individuals

Recent tuberculosis infection
Human immunodeficiency virus (HIV) infection
Injection drug use
Radiographic evidence of prior TB (untreated)
Underweight by $\geqslant$ 5%
Silicosis
Diabetes mellitus
Head and neck carcinoma
Chronic renal failure
Postgastrectomy
Jejunal–ileal bypass
Organ transplantation

Compiled from information from Cohn et al.[5]

Latently infected hosts remain at risk for developing disease throughout their lifetimes, with many recognized predisposing factors for reactivation (Table 1).[5]

The AM has several roles in the initial infection with *M. tuberculosis*. Phagocytosis of relatively small numbers of organisms initiates the host response in the alveolar space. Toll-like receptors (TLR), mannose receptors, CD14, and complement receptors are some of the cell surface receptors by which the mycobacteria are internalized.[6,7] There are redundancies in the process of phagocytosis of mycobacteria. Once organisms are internalized, the AM is stimulated to produce reactive oxygen and nitrogen intermediates and proinflammatory cytokines, processes likely dependent upon the virulence of the mycobacterial strain and the size of the inoculum. An area of active investigation is the process of phagosome–lysosome fusion after ingestion of the organisms. Mycobacteria have developed means of subverting the host response, which normally functions to kill ingested organisms. The phagocytic process results in mycobacteria in membrane-lined vacuoles, or phagosomes. Killing of the ingested organisms requires fusion of the phagosome with lysosomes, leading to acidification of the microbe-containing compartment (termed "maturation" of the phagosomes). However, virulent mycobacterial strains have mechanisms of inhibiting the fusion of the lysosome with the phagosome, preventing acidification and thus remaining viable intracellularly in the phagosome. Under this circumstance, the host macrophage then eventually dies by apoptosis or necrosis, releasing the viable organisms into the surrounding environment. The mechanisms by which the mycobacteria induce failure of phagosome maturation have not been fully identified, but possibilities include diminution of adenosinetriphosphatases (ATPases) in the vacuole (normally responsible for the decrease in pH),[8] inhibition of increased cytosolic calcium (normally a sequela to phagocytosis), abnormalities in the function of the protein coronin 1, and alteration in cholesterol content of the phagosome vacuole.[9,10]

There exists one (and possibly more) host mechanisms to counteract the organisms' ability to subvert host defenses. The natural resistance-associated macrophage protein (NRAMP) 1, a product of the bcg^r gene, is a cation transporter, and confers the ability of the host macrophage to acidify its vacuoles and thus restrict the growth of certain intracellular pathogens. Mice expressing bcg^r have lower organism burdens after inoculation with virulent mycobacterial strains as compared with those of the susceptible genotype (bcg^s).[11] Human *NRAMP1* gene polymorphisms correlate with an increased risk of developing tuberculosis.[12]

Macrophages are also able to overcome the failure of phagosome maturation when activated by IFN-γ. This cytokine allows the macrophage to acidify the phagosome to a pH of approximately 5, thereby facilitating bactericidal activity.[13] Critical to mycobacterial growth restriction in the IFN-γ–activated macrophage is the production of reactive nitrogen intermediates.[14,15] Although early sources of IFN-γ are present [i.e., natural killer (NK) cells], this cytokine is primarily produced by $CD4^+$ Th1 lymphocytes. Recent evidence suggests that lung macrophages themselves are capable of the production of IFN-γ when stimulated concomitantly with both mycobacteria and IL-12,[16] raising the possibility that autocrine stimulation may play a role in the early events of mycobacterial infection. A population of specific $CD4^+$ lymphocytes is expanded after infection, in a process beginning with the production of IL-12 by APCs. IL-12 creates the appropriate milieu for expansion of Th1 lymphocytes preferentially, as opposed to Th2 lymphocytes. This cytokine also plays a role in the maintenance of the specific Th1 effector lymphocyte population after infection is established.[17] IL-12 is produced early by the APC upon phagocytosis of the bacilli and is considered part of the innate response to mycobacterial infection.[18] This cytokine has been shown to be interdependent with other early cytokines produced after exposure to mycobacteria, in particular, IFN-γ and tumor necrosis factor alpha (TNF-α).[19] Although early studies indicated that IL-12 was critical to protection against infection with *M. tuberculosis*,[20,21] subsequent work suggests that it is the p40 subunit of IL-12 that is critical for protection,[22] which, in combination with a novel p19 subunit, constitutes a newly described cytokine, IL-23, which is expressed in the lungs of mice infected with *M. tuberculosis*.

IL-1 seems to have a role in the inflammatory reaction after mycobacterial infection, but further study is needed.[23] TNF has been more extensively evaluated and plays an important role in containing a mycobacterial challenge. As previously mentioned, this cytokine is produced early after infection by cells of the mononuclear lineage and serves to acutely amplify the inflammatory response to limit organism proliferation. It also functions to maintain the structure and integrity of

the granuloma in later phases of the infection.[24–26] Mice without functional TNF rapidly develop overwhelming, fatal mycobacterial infection, and patients with rheumatoid arthritis treated with the TNF antagonist infliximab have been reported to have high rates of tuberculosis early after therapy is initiated.[27] Other early cytokines also play roles in the coordination of the host inflammatory response to mycobacteria, including IL-18, which plays a role in the induction of IFN-γ. IL-18 is produced by monocytes and macrophages, and results in the upregulation of IFN-γ messenger ribonucleic acid (mRNA) and protein production.[28] IL-18 has been demonstrated to correlate with the extent of clinical disease (as well as with circulating IFN-γ levels) in humans with tuberculosis, and to have a role in the limitation of organism growth (in mice deficient for IL-18).[29,30] The IL-18 knockout mice had a phenotype (of mycobacterial growth) intermediate between wild type mice and IFN-γ knockout mice, consistent with a complementary role for IL-18 and IL-12 in the induction of IFN-γ in mycobacterial infection. Thus there are many redundancies in the host response to mycobacteria, which serve the goal of containment of the organisms.

The Th2 cytokines may play roles in mycobacterial inflammation as well, but our knowledge of those exact roles remains incomplete. IL-10, produced by monocytes, macrophages, and lymphocytes, is upregulated after mycobacterial infection and downregulates IFN-γ production.[31,32] In transgenic mice, upregulation of IL-10 leads to worsening of infection with *M. bovis* BCG despite continued Th1 cytokine production,[33] and IL-10 deficient mice infected with *M. bovis* BCG have accentuated Th1 cytokine responses and lower organism burdens than control mice.[34] The balance between IFN-γ and IL-10 production in any one infected patient may determine whether effective immunity is established or anergy supervenes and may thus influence the outcome of the mycobacterial infection.[35] Whether the host or mycobacterium, or both, are responsible for the cytokine balance is unclear.

IL-4 has also been shown to be produced by lymphocytes in the setting of mycobacterial infection but appears in a delayed fashion compared with the Th1 cytokines.[31] Mice deficient in IL-4 demonstrate impaired ability to control the infection, despite elicitation of higher IFN-γ production from the IL-4–deficient mouse splenocytes in vitro.[36] Possibly the IL-4–dependent humoral component of specific immunity is more important than previously thought, or IL-4 may be required to prevent overexuberant inflammation resulting in excessive proliferation of the bacteria. The exact function of Th2 cytokines in mycobacterial infection requires further study.

Mycobacteria may also downregulate cytokine production by macrophages, an effect that is variable depending on the microbial strain. Stimulation of macrophages with mycobacterial cell wall components [e.g., lipoarabinomannan (LAM)] in vitro demonstrates this effect, with LAM from virulent strains inducing significantly less TNF and IFN-γ than that from avirulent strains.[37] Other macrophage antimycobacterial functions, such as nitric oxide production and activation for microbicidal activity, are also downregulated more significantly by stimulation with LAM from more virulent, as compared with less virulent, mycobacterial strains. Thus variations in microbial antigens may provide another means by which the pathogen subverts normal host defense mechanisms at the macrophage level.

Macrophages are also a source of chemokines, which play roles in inflammatory cell recruitment to infected tissues. There is an ever expanding repertoire of chemokines being discovered, and several are known to play important roles in antimycobacterial activity. Numerous other chemokines are also upregulated at sites of infection with tuberculosis because of the complexity of the cellular response, but those required for the recruitment of activated Th1 lymphocytes seem most important. These fall into the CC (or β) and CXC chemokine families (named according to the position of cysteine [C] residues relative to other amino acids [X]) and comprise macrophage inflammatory protein (MIP)-1α, MIP-1β, and regulated upon activation, normal T cell expressed and secreted (RANTES) from the CC chemokine family, and monokine induced by IFN-γ (MIG), IFN-induced protein (IP)-10 and, IFN-inducible T cell-α chemoattractant (I-TAC) from the CXC (non-ELR, meaning lacking a GluLeuArg amino acid motif) family.[38,39] The bronchial epithelium produces MIG, IP-10, and I-TAC, and production of these chemokines is upregulated in patients with active pulmonary tuberculosis.[39] The CC chemokines MIP-1α, MIP-1β, and RANTES are also induced by infection of mononuclear cells and are present in bronchoalveolar lavage fluid of patients with active tuberculosis.[40,41] Murine studies confirm similar patterns of chemokine induction in the lung after infection with *M. tuberculosis* or exposure to mycobacterial purified protein derivative.[42,43] Macrophage chemotactic protein (MCP)-1 is another chemokine that is upregulated during mycobacterial infection and plays a role in recruiting monocytes to sites of infection.[42–44] Thus multiple chemokines are important in the recruitment of specific cells that mediate the granulomatous inflammatory reaction, which functions to contain the infecting microbes.

Lymphocytes

The second major cell type involved in control of mycobacterial infection is the T lymphocyte. The interface in the host response between the initial, innate response and the adaptive immune system serves to

clonally expand populations of several subsets of lymphocytes that are specific for various mycobacterial antigens. It is the APCs in the lung (dendritic cells, and possibly AMs) that initially scavenge the lung for mycobacterial antigens, process those antigens into small peptides, traffic to the regional lymph nodes, where they present the antigenic components to naive lymphocytes (primarily $CD4^+$ lymphocytes but also $CD8^+$ cells) in the context of cell surface MHC antigens. $CD4^+$ lymphocytes require antigen to be presented in the context of MHC Class II molecules, whereas $CD8^+$ lymphocytes are stimulated by antigen presented in the context of MHC Class I molecules. Once the appropriate lymphocytes have encountered the processed antigens in the presence of IL-12 produced by the APCs, they become activated. This results in increased production of IL-2 (which further stimulates lymphocyte proliferation) and facilitates clonal expansion of the Th1 (or a Tc1 $CD8^+$ cytotoxic T lymphocyte) antigen-specific population. It is unclear what the exact role of the AM is in antigen processing and presentation because the dendritic cell serves as the primary APC for most tissue sites. Various organs, especially those with extensive epithelial surfaces (including the lung), are populated by dendritic cells of a naive or immature phenotype (primarily characterized by surface marker expression and functional status) that are primed for antigen processing and which undergo a maturation process after encountering antigens from the invading pathogen. Maturation involves changing the surface marker molecule profile and functional profile (i.e., cytokine production), and is accompanied by migration to the regional lymphoid tissue. It is there that the mature dendritic cell presents its processed antigen (via surface MHC molecules) to the naive lymphocytes populating the lymphoid tissue, for priming and stimulation of the specific T lymphocyte population. The expanded population of antigen-specific lymphocytes, expressing the appropriate adhesion molecules on their surface, then "home" back to the lung, the site of original infection, where they contribute to the cell-mediated immune response. Due to the nature of the inciting pathogen, in this case intracellular *M. tuberculosis*, the dendritic cells elaborate IL-12 after contact with the mycobacteria. This creates the appropriate milieu for the naive T lymphocytes responding to the presented antigen to polarize to the Th1 phenotype. Thus they are able to produce IL-2 and IFN-γ, the prototypical cytokines of the Th1 subset.

The recruitment of the specific, expanded population of T lymphocytes to the lung provides a source of IFN-γ locally at the site of the infection. This cytokine activates AMs to become mycobactericidal, further amplifying the host response to the tuberculous organisms. Thus, for an infection with mycobacteria that the AM is not initially able to contain, expansion of a specific $CD4^+$ Th1 lymphocyte population, capable of amplifying the AM response, is critical. $CD4^+$ lymphocytes are essential to the control of mycobacterial infections, as shown in numerous reports of rapidly, progressive, fatal infection in animal models in which that population of lymphocytes has been depleted.[45–47] The central role of $CD4^+$ lymphocytes in controlling mycobacterial infection is also evidenced by the high rates of tuberculosis in the HIV-infected population.[4,48] It is through production of IFN-γ that $CD4^+$ lymphocytes mediate antimycobacterial activity. IFN-γ is a critical component of mycobacterial containment as evidenced by animal models of accelerated,[49,50] fatal infection in the absence of this cytokine, as well as by reports of disseminated disease in humans with genetic abnormalities in the IFN-γ receptor.[51,52] Recently described are polymorphisms in the IFN-γ gene, one variant of which is associated with low IFN-γ production in vitro and confers a heightened risk of developing tuberculosis.[53] Therapy with IFN (α or γ) has been added to the antimicrobial regimen in humans with mycobacterial infections, with modest positive results.[54,55] Further trials, perhaps targeted to those patients with demonstrated relative deficiencies of IFN-γ, are awaited.

Mycobacteria have been described to downregulate T lymphocyte function, which may provide another means of subverting normal host defense mechanisms. Patients infected with *Mycobacterium leprae* have diminution of the ζ chain of the T cell receptor (TCR), an integral part of the signal transduction pathway for lymphocytes. Furthermore, the loss of the ζ chain of the TCR is greater in lepromatous leprosy patients [characterized by higher organism burden and less robust delayed type hypersensitivity (DTH)] than in those with tuberculoid leprosy (characterized by lower organism burden and more robust DTH).[56] The TCR ζ chain signal transduction alterations were accompanied by decreased expression of tyrosine kinase ($p56^{lck}$) and the nuclear transcription factor kappa B (NF-κB) p65, leading to loss of the Th1 type deoxyribonucleic acid (DNA) binding pattern. The end result was lower production of IFN-γ by the lymphocytes from patients with the most severe ζ chain abnormalities, those with lepromatous leprosy. Preliminary work from our laboratory, as well as others, suggests that similar mechanisms (loss of TCR ζ chain and signal transduction pathway alterations) occur in lymphocytes of patients with active pulmonary tuberculosis, and that resolution of the TCR and signal transduction alterations occurs with successful response to antituberculous therapy.[35,57] Thus mycobacteria have the capability to cause dysregulation of the effector lymphocyte arm of the host immune response, evading clearance mechanisms, thereby furthering the persistence of infection.

$CD8^+$ lymphocytes also play a role in containing mycobacteria. They appear in the lungs of infected mice early after infection, albeit in fewer numbers than $CD4^+$

lymphocytes, and are capable of secreting IFN-γ.[58] The role of cytolytic mechanisms that characterize $CD8^+$ lymphocytes, such as release of granules containing perforin and granzyme (molecules capable of inducing cell lysis and destruction) upon contact with an infected target cell, is controversial in tuberculous infection.[59,60] Other investigators have reported that the primary role of $CD8^+$ T cells in murine pulmonary infection follows the acute phase and is important in maintaining the state of latency (during which viable bacteria are present but fail to progressively replicate).[61] Their role in latency maintenance seems to be mediated through IFN-γ production.

Preliminary evidence suggests other subsets of lymphocytes may also play roles in defenses against mycobacteria, but more investigation is needed to clarify the roles of these cells. In mice deficient in mature B lymphocytes [μ-chain knockout (μMT) mice], there are greater organism burdens after infection with *M. tuberculosis* or BCG, but certain host responses are preserved. However, the precise mechanism by which B cells contribute to antimycobacterial protection is unclear.[62] Also unclear is the role of γδ T cells, which are most prevalent in tissue sites near epithelia.[63] Although not implicated in the control of early bacterial proliferation, this subset of cells may play a role in maintaining the lymphocytic and mononuclear cells of the granuloma because mice in which γδ T cells are knocked out demonstrate aberrant tissue inflammation and excessive necrosis in the lungs of infected mice.[64] These changes are associated with earlier mortality in the knockout mice.

THE GRANULOMA

The ultimate result of activation of host immune cells after infection with mycobacteria is a localized collection of these cells in the infected tissue, the granuloma. This structure is the manifestation of delayed-type hypersensitivity and is usually present in situations in which there is persisting antigen. Mycobacterial infections are only one example of diseases characterized by granuloma formation, others being fungal infections, sarcoidosis, berylliosis, and hypersensitivity pneumonitis. As previously mentioned, even when the human host successfully controls mycobacterial infection, there remain low levels of viable organisms (usually within granulomas), which carry the risk (10–15% lifetime risk in the normal host, which is markedly accelerated to 10% annually in the HIV-infected host) of resuming progressive replication, leading to reactivation tuberculosis.

The granuloma is a very complex structure, many aspects of which are incompletely understood. In general terms, it represents the approximation of antigen (persisting organisms), activated macrophages, and activated lymphocytes in the host's ongoing attempt to contain and eradicate the infecting mycobacteria. The intimate association of these cell types is likely due to chemokine production for cellular recruitment to the tissue and is necessary for the paracrine activation by locally produced cytokines (i.e., activated lymphocyte IFN-γ stimulation of macrophages). The macrophages in the granuloma can differentiate into larger cells known as epithelioid cells, which may fuse to form a characteristic multinucleated giant cell. These reactions are most likely provoked by the persisting antigen. The macrophages and epithelioid cells form the center of the granuloma and are surrounded by lymphocytes at the periphery (Fig. 1). Detailed immunohistochemistry studies of murine lung granulomas revealed that the majority of the lymphocytes are $CD4^+$, with fewer, generally more peripheral, $CD8^+$ lymphocytes.[65] Interestingly, late after infection, B cells (surface marker B220+) were detected in the central portions of lymphocyte collections. The exact significance of this population to the ongoing infection remains to be elucidated, but a humoral component to mycobacterial immunity cannot be excluded.[66] The $CD4^+$ lymphocyte subset is essential to the containment of mycobacterial replication and to the formation of granulomas. In $CD4^+$ lymphocyte knockout mice, an aberrant lung cell collection, with macrophages and granulocytes, occurs in response to mycobacterial infection but fails to limit bacterial proliferation, leading to shortened survival in the knockout mice.[47]

Another characteristic of tuberculous granulomas is death of the cells in the center of the spheroid granuloma, probably due to the intense inflammation that is occurring there (the full manifestation of delayed-type hypersensitivity), with resultant caseation necrosis (so named due to its resemblance to cheese). This material appears eosinophilic on histologic hematoxylin and eosin staining and is characteristically teeming with mycobacteria (released from the necrotic macrophages). If the necrosis is extensive enough to result in tissue damage, these structures may eventuate in cavity formation. Spread of this highly infectious necrotic material may occur via the bronchus by expectoration, providing a highly infectious aerosol inoculum and thereby perpetuating the infection.

SUMMARY

Thus, despite numerous redundancies in the immune response to mycobacteria, and even in the face of the marshaling of multicellular adaptive immune response defense mechanisms, the immunocompetent host is frequently unable to eliminate infecting mycobacteria. The organism is particularly well adapted to evade the host's mycobactericidal mechanisms on many fronts and to persist, with viable organisms present, for many years. This ability of mycobacteria to evade clearance by normal hosts is undoubtedly responsible for the fact that tuberculosis remains the most prevalent infectious

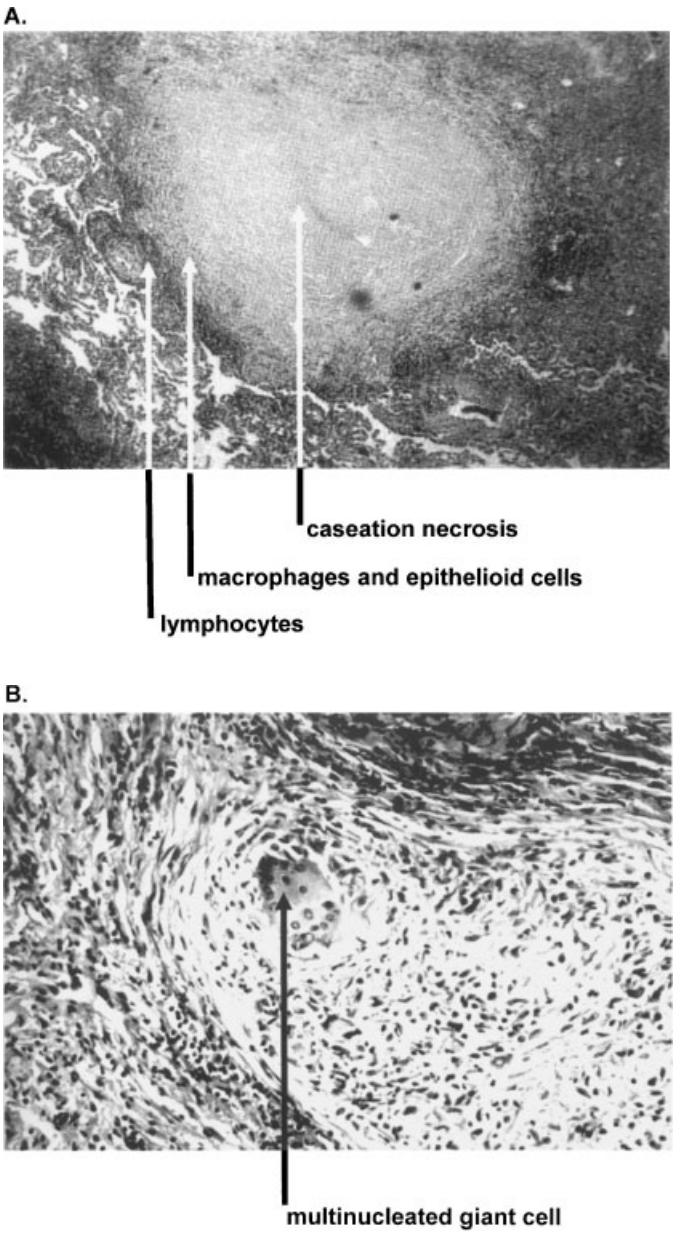

Figure 1 (A) Low-power view of a tuberculosis granuloma with extensive central caseation necrosis, surrounded by macrophages and epithelioid cells and peripheral lymphocytes. (B) Higher-power view of a tuberculous granuloma with a multinucleated giant cell in the midst of epithelioid cells.

pathogen in the world, despite all attempts to achieve eradication of the infection with available therapies. Further elucidation of the mycobacterial mechanisms responsible for evasion of host defenses may lead to new immunomodulators that can be added to the antimycobacterial therapeutic armamentarium.

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