postphagocytic events such as phagosome–lysosome fusion and inflammatory cytokine production. After a phagosome forms, the survival of *M. tuberculosis* within it seems to depend in part on reduced acidification due to lack of assembly of a complete vesicular proton-adenosine triphosphatase. A complex series of events is generated by the bacterial cell-wall lipoglycan lipoarabinomannan (ManLAM). ManLAM inhibits the intracellular increase of Ca^{2+}. Thus, the Ca^{2+}/calmodulin pathway (leading to phagosome–lysosome fusion) is impaired, and the bacilli survive within the phagosomes. The *M. tuberculosis* phagosome has been found to inhibit the production of phosphatidylinositol 3-phosphate (PI3P). Normally, PI3P earmarks phagosomes for membrane sorting and maturation, including phagolysosome formation, which would destroy the bacteria. Bacterial factors have also been found to block the host defense of autophagy, in which the cell sequesters the phagosome in a double-membrane vesicle (*autophagosome*) that is destined to fuse with lysosomes. If the bacilli are successful in arresting phagosome maturation, then replication begins and the macrophage eventually ruptures and releases its bacillary contents. Other uninfected phagocytic cells are then recruited to continue the infection cycle by ingesting dying macrophages and their bacillary content, thus in turn becoming infected themselves and expanding the infection.

VIRULENCE OF TUBERCLE BACILLI

M. tuberculosis must be viewed as a complex formed by a multitude of strains that differ in virulence and are capable of producing a variety of manifestations of disease. Since the elucidation of the *M. tuberculosis* genome in 1998, large mutant collections have been generated, and many bacterial genes that contribute to *M. tuberculosis* virulence have been found. Different patterns of virulence defects have been defined in various animal models—predominantly mice but also guinea pigs, rabbits, and nonhuman primates. The *katG* gene encodes for a catalase/peroxidase enzyme that protects against oxidative stress and is required for isoniazid activation and subsequent bactericidal activity. Region of difference 1 (RD1) is a 9.5-kb locus that encodes two key small protein antigens—early secretory antigen-6 (ESAT-6) and culture filtrate protein-10 (CFP-10)—as well as a putative secretion apparatus that may facilitate their egress; the absence of this locus in the vaccine strain *M. bovis* bacille Calmette-Guérin (BCG) has been shown to be a key attenuating mutation. The validity of a recent observation in *M. marinum* needs to be confirmed in *M. tuberculosis*; in *M. marinum*, a mutation in the RD1 virulence locus encoding the ESX1 secretion system impairs the capacity of apoptotic macrophages to recruit uninfected cells for further rounds of infection. The results are less replication and fewer new granulomas. Mutants lacking key enzymes of bacterial biosynthesis become auxotrophic for the missing substrate and often are totally unable to proliferate in animals; these include the *leuCD* and *panCD* mutants, which require leucine and pantothenic acid, respectively. The isocitrate lyase gene *icl1* encodes a key step in the glyoxylate shunt that facilitates bacterial growth on fatty acid substrates; this gene is required for long-term persistence of *M. tuberculosis* infection in mice with chronic TB. *M. tuberculosis* mutants in regulatory genes such as sigma factor C and sigma factor H (*sigC* and *sigH*) are associated with normal bacterial growth in mice, but they fail to elicit full tissue pathology. Finally, the mycobacterial protein CarD (expressed by the *carD* gene) seems essential for the control of rRNA transcription that is required for replication and persistence in the host cell. Its loss exposes mycobacteria to oxidative stress, starvation, DNA damage, and ultimately sensitivity to killing by a variety of host mutagens and defensive mechanisms.

INNATE RESISTANCE TO INFECTION

Several observations suggest that genetic factors play a key role in innate nonimmune resistance to infection with *M. tuberculosis* and the development of disease. The existence of this resistance, which is polygenic in nature, is suggested by the differing degrees of susceptibility to TB in different populations. In mice, a gene called *Nramp1* (natural resistance–associated macrophage protein 1) plays a regulatory role in resistance/susceptibility to mycobacteria. The human homologue NRAMP1, which maps to chromosome 2q, may play a role in determining susceptibility to TB, as is suggested by a study among West Africans. Studies of mouse genetics identified a novel host resistance gene, *ipr1*, which is encoded within the *sst1* locus; *ipr1* encodes an interferon (IFN)–inducible nuclear protein that interacts with other nuclear proteins in macrophages primed with IFNs or infected by *M. tuberculosis*. In addition, polymorphisms in multiple genes, such as those encoding for various major histocompatibility complex (MHC) alleles, IFN-γ, T cell growth factor β, interleukin (IL) 10, mannose-binding protein, IFN-γ receptor, Toll-like receptor 2, vitamin D receptor, and IL-1, have been associated with susceptibility to TB.

THE HOST RESPONSE, GRANULOMA FORMATION, AND "LATENCY"

In the initial stage of host–bacterium interaction, prior to the onset of an acquired CMI response, *M. tuberculosis* disseminates widely through the lymph vessels, spreading to other sites in the lungs and other organs, and undergoes a period of extensive growth within naïve unactivated macrophages; additional naïve macrophages are recruited to the early granuloma. Studies suggest that *M. tuberculosis* uses specific virulence mechanisms to subvert host cellular signaling and to elicit an early regulated proinflammatory response that promotes granuloma expansion and bacterial growth during this key early phase. A study of *M. marinum* infection in zebrafish has delineated one molecular mechanism by which mycobacteria induce granuloma formation. The mycobacterial protein ESAT-6 induces secretion of matrix metalloproteinase 9 (MMP9) by nearby epithelial cells that are in contact with infected macrophages. MMP9 in turn stimulates recruitment of naïve macrophages, thus inducing granuloma maturation and bacterial growth. Disruption of MMP9 function results in reduced bacterial growth. Another study has shown that *M. tuberculosis*–derived cyclic AMP is secreted from the phagosome into host macrophages, subverting the cell's signal transduction pathways and stimulating an elevation in the secretion of tumor necrosis factor α (TNF-α) as well as further proinflammatory cell recruitment. Ultimately, the chemoattractants and bacterial products released during the repeated rounds of cell lysis and infection of newly arriving macrophages enable dendritic cells to access bacilli; these cells migrate to the draining lymph nodes and present mycobacterial antigens to T lymphocytes. At this point, the development of CMI and humoral immunity begins. These initial stages of infection are usually asymptomatic.

About 2–4 weeks after infection, two host responses to *M. tuberculosis* develop: a macrophage-activating CMI response and a tissue-damaging response. The *macrophage-activating response* is a T cell–mediated phenomenon resulting in the activation of macrophages that are capable of killing and digesting tubercle bacilli. The *tissue-damaging response* is the result of a delayed-type hypersensitivity (DTH) reaction to various bacillary antigens; it destroys unactivated macrophages that contain multiplying bacilli but also causes caseous necrosis of the involved tissues (see below). Although both of these responses can inhibit mycobacterial growth, it is the balance between the two that determines the forms of TB that will develop subsequently. With the development of specific immunity and the accumulation of large numbers of activated macrophages at the site of the primary lesion, granulomatous lesions (tubercles) are formed. These lesions consist of accumulations of lymphocytes and activated macrophages that evolve toward epithelioid and giant cell morphologies. Initially, the tissue-damaging response can limit mycobacterial growth within macrophages. As stated above, this response, mediated by various bacterial products, not only destroys macrophages but also produces early solid necrosis in the center of the tubercle. Although *M. tuberculosis* can survive, its growth is inhibited within this necrotic environment by low oxygen tension and low pH. At this point, some lesions may heal by fibrosis, with subsequent calcification, whereas inflammation and necrosis occur in other lesions. Some observations have challenged the traditional view that any encounter between mycobacteria and macrophages results in chronic infection. It is possible that an immune response capable of eradicating early infection may sometimes develop as a consequence, for instance, of disabling mutations in mycobacterial genomes rendering their replication ineffective. Individual granulomas that are formed during this phase of infection can vary in size and cell composition; some can contain the spread of mycobacteria, while others cannot. LTBI ensues as a result of this dynamic balance between the