In this chapter, we review the principal TB vaccine strategies, status of current efforts, and discuss in detail some of the leading candidate vaccines currently in or entering clinical trials.

IMMUNITY TO TB

Biology and Immunology of MTB

MTB is a highly robust microbe capable of surviving in one of the most hostile of mammalian cells (11,12), the mononuclear phagocyte (MP), which is capable of killing a vast array of bacterial pathogens. Phagocytosis of microbes by MP results in the formation of phagosomes, which further mature from an early to a late stage and then fuse with lysosomes. Release of reactive oxygen and nitrogen intermediates together with discharge of lysosomal enzymes into the late phagosome destroys many bacterial pathogens. To counteract this, MTB arrests phagosome maturation at an early stage and prevents phagosome acidification (13). The neutral pH of the early phagosome provides a resource-rich milieu for MTB, giving access to nutrients as well as essential ions, notably iron. As a result, MTB replicates in resting macrophages. Even highly activated macrophages fail to achieve sterile eradication of the MTB predators, although they can block their multiplication and induce a state of dormancy (14). Once the activation status of MP is lowered, however, mycobacteria may resuscitate, leading to disease reactivation (11,15).

This scenario is not solely a matter between MP and MTB, as it occurs in the lung where macrophages form productive granulomas under the guidance of T lymphocytes (12,16). The productive granuloma comprises MP of different maturation stages, from freshly immigrating monocytes to giant cells arising from fusion of several infected macrophages (12,16). Resuscitation and reactivation of MTB occur once the delicate balance between MP activated by T cells and MTB is tipped in favor of the pathogen (14,15), culminating in the development of caseous cavitaries in which MTB multiplies unrestrained in the cellular detritus.

Although T lymphocytes are the major mediators of protection against TB, high titers of antibodies with specificity for numerous proteinaceous and nonproteinaceous mycobacterial antigens can be measured in sera of patients (17–19). Such antibodies have several potential antimycobacterial functions. Antibodies may attack free-living MTB, although this is a rare situation because MTB mostly resides within MP. However, with dissemination of free MTB from the primary site of implantation to other tissue sites, the pathogen may be vulnerable to attack by antibodies (20). Antibodies could also synergize with phagocytes since antibody binding to the Fc-receptor can induce potent effector mechanisms, including generation of reactive oxygen and nitrogen intermediates (21,22). Finally, preexisting antibodies in the lung could clear the few bacteria that enter the host before they can hide within macrophages. A potential new vaccine approach would be to attempt to stimulate high titers of IgA and IgG antibodies capable of eliminating MTB promptly after its inhalation and prior to its engulfment by alveolar macrophages (23).

Current vaccine design focuses on stimulation of a highly potent T-cell response in an attempt to contain or even eradicate MTB after it has established itself in the phagosome of macrophages (24) (Fig. 1). CD4 T cells are generally termed T helper (Th) cells because they help other cells to perform their functions in the best possible way (25) (Fig. 2). The Th cells further segregate in different subsets, all characterized by a distinct phenotype and a unique pattern of secreted cytokines, although some overlap in cytokine secretion occurs (Fig. 2).

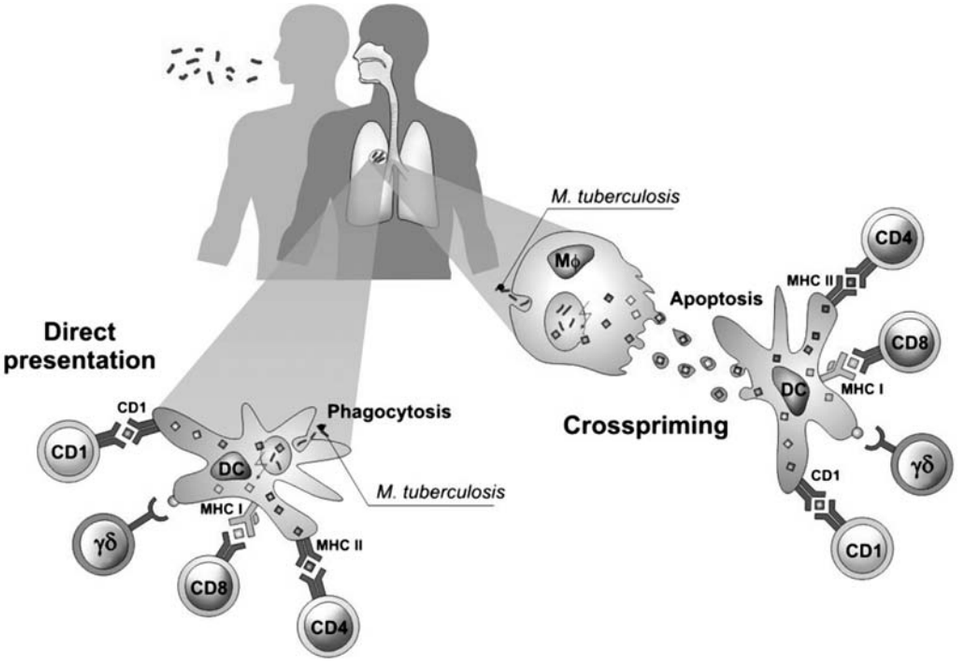

Figure 1 The different ways of antigen presentation in tuberculosis.