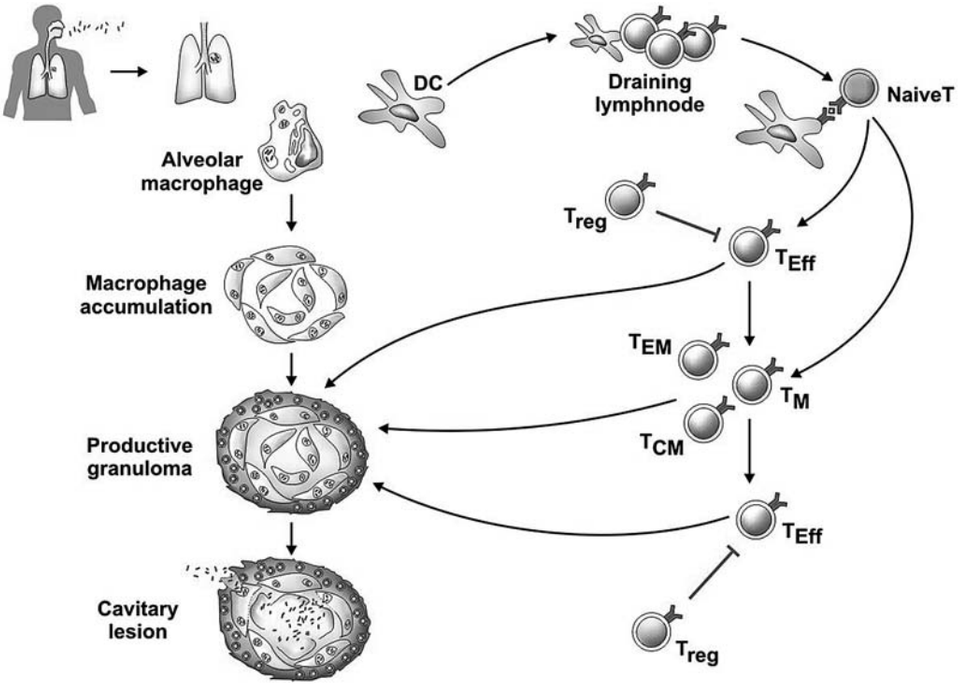

Figure 3 Development of immunologic memory during tuberculosis.

understood (Fig. 3). Development and maintenance of memory is promoted by the cytokines IL-2, IL-7, and IL-15, which are all members of the same family, and central memory T cells are stimulated by these cytokines to differentiate into terminally differentiated effector T cells (51). Because MTB persists in the host, it could be argued that continuous stimulation provided by mycobacterial antigens will sustain rapid activation of rapidly dividing effector T cells (52). Yet, in the peripheral blood of latently infected individuals, both memory T cells and terminally differentiated effector T cells have been identified (53). Some evidence suggests that early effector T cells preferentially produce IFN-γ only whereas terminally differentiated effector T cells are capable of producing multiple cytokines, notably IFN-γ, TNF, and GM-CSF and therefore, may possess greater protective efficacy (52). Future studies will be required to define more precisely these T-cell sets and the cytokines they produce, and to correlate them with protection and pathogenesis in TB.

In the context of TB, directing T cells into the lung and then attracting them to the productive granuloma is of particular importance. In other systems, both effector memory T cells and central memory T cells have been identified in the airways, thus softening the segregation between these two phenotypes (54). In contrast to other tissue sites, we know only little about the chemokines and adhesion molecules that direct the trafficking of T cells to the lung (55). Yet, it appears that the chemokine CCL5 (RANTES) and the homologous receptor CCR5 on T cells are interesting candidates for lung-specific T cells (54). Similarly, CXCR3 and its ligands CXCL9 (MIG), CXCL10 (IP-10), and CXCL11 (I-TAC) are also candidates for lung accumulation of T cells (54). A very recent study has provided evidence in experimental TB of mice that Th17 cells are among the first T cells to enter the lung in TB and then trigger the chemokines CXCL9, CXCL10, and CXCL11. These chemokines attract CD4 T cells of Th1 type, which then restrict growth of MTB (41). Despite limited knowledge about the chemokines and the adhesion factors involved in T-cell migration to the lung, it will be important for any vaccine to induce T cells that can enter the lung to contact and combat MTB, either at the stage of invasion or latent infection.

TYPES OF TB VACCINES

More than one type of TB vaccine is likely to be needed to reduce the global burden of TB. Four main types of vaccines have been explored in preclinical studies in animal models (Tables 1 and 2) and in clinical studies. First, a more potent ''prime'' vaccine to replace BCG in newborns and nonimmunized tuberculin-negative adults is a high priority (Table 3). Such a vaccine must not only be more potent than BCG but at least as safe. Second, a booster vaccine is needed for individuals who have already been immunized with BCG (Table 4). Such a vaccine will need to be a heterologous booster vaccine because homologous boosting with BCG appears ineffective in both preclinical and clinical studies (56–62). Heterologous prime-boost strategies incorporating a replacement vaccine for BCG as the prime, such as a more potent recombinant BCG (rBCG) vaccine, are also being explored. Third, a postexposure vaccine that can boost the immunity of individuals already exposed to MTB is needed. Whether the booster vaccine for BCG (or for a BCG replacement vaccine) noted above can also serve this role or whether a different type of vaccine would be more efficacious in the postexposure setting remains to be determined. Finally, a