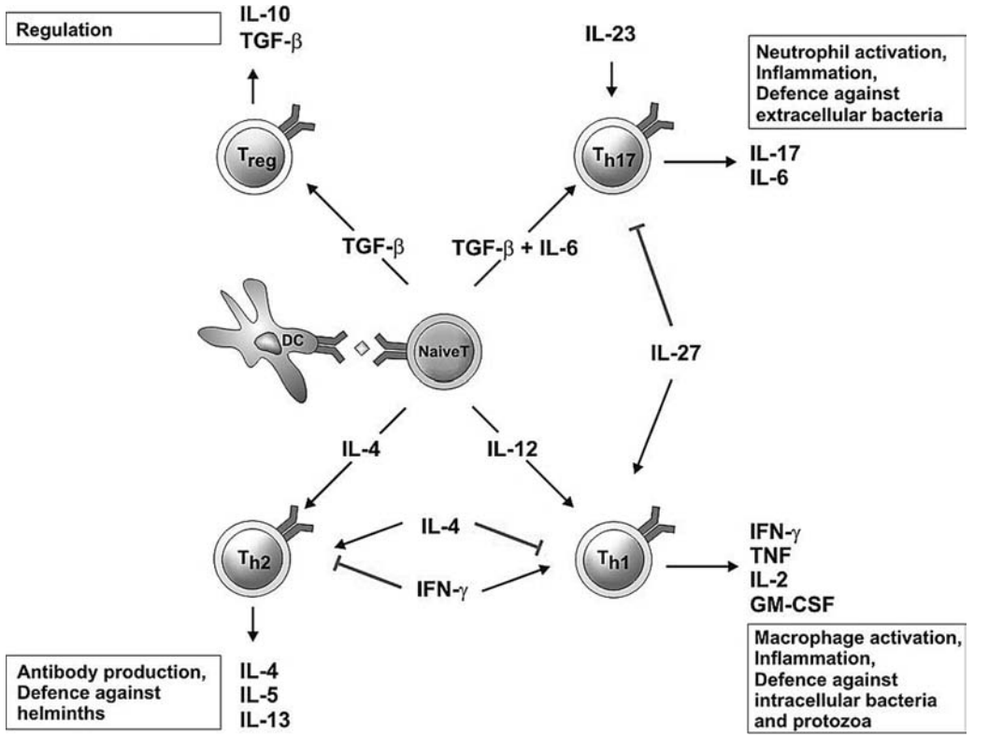

Figure 2 Stimulation of different CD4 T cells and their main biological functions. *Source*: From Ref. 52.

However, during their maturation, Th cells may change their cytokine secretion pattern. Until recently, only two Th cell populations were known, named Th1 and Th2 cells (26). Th2 cells help in antibody production and defense against helminths. Once activated, they produce the cytokines interleukin-4 (IL-4), IL-5, and IL-13, which primarily act on basophils, eosinophils, and B lymphocytes. Th2-cell stimulation is promoted by IL-4. IL-12, produced by infected MP and dendritic cells (DC), promotes development of Th1 cells, which produce interferon gamma (IFN-γ), tumor necrosis factor (TNF), IL-2, and granulocyte-monocyte colony-stimulating factor (GM-CSF). IFN-γ and TNF activate macrophages, IL-2 activates CD8 T cells, while GM-CSF's role in defense against TB remains unclear. IFN-γ also promotes Th1 cell development but blocks generation of Th2 cells. In contrast, IL-4 favors Th2 cell development but blocks that of Th1 cells. Tumor growth factor (TGF)-β has been known for a long time but only more recently has been demonstrated to play a role in Th cell polarization. TGF-β alone favors the development of suppressive T cells termed T regulatory (Treg) cells, which produce IL-10 and TGF-β, both inhibitory for many T cells (27,28). In the presence of IL-6, however, TGF-β favors generation of Th17 cells, which are then sustained by IL-23 (29–31). In contrast, IL-27 blocks differentiation of Th17 cells, and at the same time favors development of Th1 cells. Th17 cells produce IL-17 and IL-6 and have been associated with pathologic inflammation, but they also seem to play a role in defense against extracellular bacteria (29–31).

With respect to TB, Th1 cells are critical to protective immunity and also contribute to pathogenesis. The role of the Th1-associated cytokines IL-12, IFN-γ, and TNF has been well-established, with most convincing data using knockout (KO) mice deficient in IFN-γ or TNF signaling (32–35). Reactivation of TB in rheumatoid arthritis patients treated with antibodies interfering with TNF-α signaling demonstrated the important role of this cytokine in controlling latent MTB infection in humans (36). TGF-β also participates in the formation of the fibrotic wall around granulomatous lesions, and hence participates in immunity to TB (37,38). Th2 cells are probably of little value, and due to the production of IL-4, which impairs Th1 responses, may even be harmful (39). Indeed, increased proportions of Th2 cells have been described during active TB. The role of Th17 cells in TB remains to be established (40,41). Recent experiments in the mouse model have identified γ/δ T cells of main producers of IL-17 in TB (42). It is interesting in this context that earlier studies using IL-6 KO mice found a role for IL-6 in protection against a high load of MTB (43). Finally, in an adoptive transfer model, depletion of regulatory T cells greatly enhanced protection afforded by CD4 T cells (44). Treg cells have also been identified in TB patients (45–48).

CD8 T cells also produce cytokines, notably IFN-γ and TNF, and they attack infected macrophages. Concomitant with lysis of infected host cells, perforins and granulysins produced by these cytolytic T lymphocytes (CTLs) can also attack MTB directly (49,50). CD8 T cells protect through killing of MTB. Whether it is this mechanism or the secretion of IFN-γ and TNF or both, CD8 T cells are known to contribute to protective immunity, particularly at later stages of infection (15).

In TB, the roles of effector T cells, memory T cells, and terminally differentiated effector T cells, remain incompletely