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The Immunogenic Peptide for Th1 Development and Its Adjuvant Activity

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Immune responses to infectious microbes and foreign antigens are regulated by a series of interactions among T cells, B cells, and antigen-presenting cells (APCs) such as macrophages (M□) and dendritic cells (DCs). The inverse relationship between antibody production and cell-mediated immune responses such as delayed type hypersensitivity (DTH) was experimentally manipulated by varying the dose, route of administration, and form of antigen used to immunize animals. Both antibody production and DTH responses to protein antigen are dependent on the helper function of $CD4^+$ T cells. Mosmann *et al.* (1986) clearly demonstrated that $CD4^+$ Th cells can be classified into two subsets, namely type 1 (Th1) and type 2 (Th2), based on their distinct patterns of cytokine production. Th1 cells produce IFN□ and are responsible for directing cell-mediated immune responses such as DTH responses leading to the eradication of intracellular pathogens such as bacteria, parasite, and virus. Th2 cells produce IL-4 and IL-5 and have been implicated in humoral immune responses and the eradication of helminthes, but they may also result in inflammatory damage during allergic manifestations and atopy. Defining the cellular and molecular mechanisms of Th1 and Th2 differentiation should lead to rational strategies for manipulating immune responses for prophylaxis and therapy. In the last 15 years since the first description of Th1 and Th2 subsets and their roles in various diseases became a major focus, it is now possible to propose models for the preferential induction of a Th1 subset by immunogenic peptide.

One of the major protein antigens secreted from *M. tuberculosis* is Ag85B that is conserved across mycobacterial species and belongs to the Ag85 family of proteins. Ag85B has been shown to be the most potent antigen species yet purified in humans and in mice. Furthermore,

strong Th1 responses have been elicited *in vitro* from PPD^+ asymptomatic individuals using purified or recombinant forms of Ag85. Thus Ag85B is a major target of human T cell response to *M. tuberculosis* and a leading vaccine candidate. In addition, Ag85B has been shown to induce partial protection in murine models of infection. Vaccination with plasmid DNA containing *M. tuberculosis* genes encoding hsp65, the 38-kDa PstS-1 homologue and the Ag85 complex is an effective means of inducing protective immunity in animal models.

Peptide-25 of Ag85B is able to preferentially prime and activate Th1 cells *in vivo*. Peptide-25 is not a mycobacterial superantigen and may contribute to disease pathogenesis by inducing local release of a spectrum of cytokines from Peptide-25-reactive Th1 cells together with APCs. Understanding the structural details of the recognition of Peptide-25 by TCR, the intracellular signaling and the intercellular communication network by which they trigger Th1 development is a major challenge for future research. Such research will generate information required for the rational design of a new generation of immunogenic peptide with Th1 adjuvant activity tailored to elicit specific effector functions.