BALANCING TOLERANCE AND AUTOIMMUNITY: CONTROLLING HARMFUL IMMUNE RESPONSES

Abul K. Abbas, MBBS
University of California San Francisco

The immune system exists in an equilibrium, such that activation of the system to defend against pathogens is balanced by the mechanisms of tolerance, which prevent aberrant and harmful responses to self antigens. The most important mechanisms of T cell tolerance to self antigens are deletion of self-reactive T cells during their maturation in the thymus, inactivation of the cells by the engagement of inhibitory receptors of the CD28 family, mainly CTLA-4 and PD-1, and suppression of the response by regulatory T cells (Treg), which are generated in the thymus and peripheral tissues. Tregs respond to tissue antigens by developing an enhanced capacity to suppress immune responses and by migrating to tissue sites of inflammation. A fraction of these Tregs survive as long-lived memory Tregs, and are able to limit subsequent inflammation in the tissue. Elucidating the stimuli that generate and maintain functional Tregs in the periphery will likely be valuable for manipulating immune responses in inflammatory diseases and for optimal vaccination and cancer immunotherapy. We have used transgenic and knockout mouse models to address the mechanisms of the generation and activation of Tregs in tissues. Our studies indicate that antigen and cytokines are the major stimuli that induce peripheral Tregs and control the balance of effector and regulatory cells. In particular, the growth factor IL-2 is essential for the generation and maintenance of functional Tregs. These studies are leading to renewed attempts to exploit Tregs and IL-2 treatment to control harmful immune responses.