T-LYMPHOCYTE ACTIVITY IN AUTOIMMUNE DISEASES

CS Lau, KK Tong, CC Mok, D Chan and RWS Wong.
Division of Rheumatology, University Department of Medicine, Queen Mary Hospital, Hong Kong.

Immunological tolerance is the acquisition of unresponsiveness to self antigens and it is essential for the preservation of the integrity of the host. A variety of mechanisms maintain self tolerance, including clonal deletion, clonal anergy, and active suppression. The breakdown of these mechanisms leads to autoimmunity. Although it is not known what initiates abnormal autoimmune responses, or whether systemic and organic-specific autoimmune diseases have similar aetiologic mechanisms, almost all of these disorders are linked with specific major histocompatibility complex (MHC) genotypes. One of the functions of the MHC is to present antigenic peptides to T-helper (Th) cells. There is now strong evidence from appropriate animal models by neonatal thymectomy, utilisation of mice homozygous for the *nu* mutation, treatment with anti-CD4 antibody, and cell transfer experiments that Th cells play a central role in the pathogenesis of almost all autoimmune diseases. They do so by acting as cytotoxic cells or as helper cells for autoantibody production.

Th cells can produce a wide range of different cytokines and it has now become apparent that once Th cells (Th0) are activated, they polarise towards the production of either 'Th1' cytokines which include interleukin-2 (IL2), interferon-γ (IFNγ) and tumour necrosis factor-β (TNFβ), or 'Th2' cytokines such as IL4, IL5, IL6 and IL10. Th1 cytokines mainly drive macrophage and cytotoxic T cell activation, while Th2 cytokines induce antibody production. There is normally a delicate balance between Th1 and Th2 cell activity and evidence is accumulating that the development of certain autoimmune disorders is associated with disturbances in this balance. For example, over-expression of Th1 cytokines is seen in models of rheumatoid arthritis (RA), multiple sclerosis (MS) and autoimmune diabetes mellitus (DM), while that of Th2 cytokines is seen in Sjogren's syndrome and systemic lupus erythematosus. Our Division plans to examine the control mechanism(s) of Th cell activity as well as the cellular and humoral immune responses in 2 of these conditions, namely RA and SLE. However, it is envisaged that such work may be extended to other autoimmune disorders with similar Th cell pathology.

The role of cytokines is of particular interest. For example, IL10 is produced by Th2 cells as well as peripheral blood lymphocytes and monocytes and has been suggested to have a contributory role in the pathogenesis of SLE, and reciprocal effects on RA. IL12 and IL15 are 2 newly defined cytokines that are produced primarily by macrophages. These cytokines have similar biological functions and both potentiate the polarisation of Th0 to Th1 cells and inhibit Th2 responses. IL12 and IL15 may therefore be expected to enhance the development of RA and have suppressive effects on SLE. Another potential cause of autoimmunity may be related to defects in active suppression. Although the role and mechanism of action of active suppression in regulating immune responses are not fully understood they may be related to changes in activity of T suppressor cells (Ts). The potential regulatory role of IL10, IL12, IL15 and Ts on cellular and humoral immune response as well as Th1/Th2 activity in RA and SLE will be discussed.