Initiation of autoimmunity by disruption of central T cell tolerance

Drug-induced lupus is a side effect of long-term therapy with some 39 medications currently in use. This syndrome resembles the well-described autoimmune disease systemic lupus erythematosus and offers an opportunity to examine how a small foreign molecule can profoundly alter immune homeostasis to produce a systemic autoimmune disease. We have developed a mouse model for drug-induced lupus using procainamide-hydroxylamine (PAHA), the reactive metabolite of procainamide, the most common lupus-inducing drug.

Injection of PAHA into the thymus of normal, adult mice resulted in the appearance of chromatin-reactive T cells in the thymus and subsequently in the spleen and accumulation of IgG anti-chromatin autoantibodies in the circulation, characteristic of patients with procainamide-induced lupus.

The cellular basis for induction of autoreactive T cells by the presence of PAHA in the thymus was explored using mice transgenic for a model T cell receptor, specific to a peptide from pigeon cytochrome c (PCC). Normally when T cells develop in the thymus they must recognize through their antigen receptor peptides derived from self-proteins bound to the major histocompatibility complex, and this process of positive T cell selection is normally followed by an inability to respond to the selecting self-peptide. In the presence of PAHA instead of the development of mature T helper cells that are tolerant to PCC, T cells arose that responded to various forms of PCC that usually behave as low-affinity antigens. Therefore, PAHA prevents developing T cells from acquiring immune tolerance to the low affinity-selecting self-antigens. When similar antigens are encountered in the periphery, expansion of autoreactive T cells occurs.

We propose that chromatin-derived peptides may be abundant antigens participating in positive T cell selection, possibly explaining the predominance of chromatin-reactive T cells when PAHA interferes in this process. These studies are the first to show that disruption of immune self-tolerance associated with positive selection can result in autoimmunity and add weight to the view that development of non-responsiveness during positive selection is critical for maintaining immune tolerance to self.

Cannabinoid therapy against brain tumors

Cannabinoids, the active components of Cannabis sativa (marijuana) and their derivatives, are known to produce a wide spectrum of central and peripheral effects with potential therapeutic value, e.g., analgesia, anticonvulsion, antiemesis, and alleviation of intraocular pressure. One of the most intriguing and unexplored actions of cannabinoids is their ability to inhibit the growth of transformed cells in culture. In this work we sought to determine whether cannabinoids inhibit the growth of transformed cells in vivo and the mechanism by which they exert their antiproliferative effect. Intratumoral administration of delta-9-tetrahydrocannabinol (the main active component of marijuana) and WIN-55,212-2 (a potent synthetic cannabinoid) to rats induced the eradication (1/3 of the animals) or the regression (1/3 of the animals) of malignant brain tumors (glioblastomas). Because the antiproliferative effect of cannabinoids was also evident in immune-deficient mice, this action seems to be direct and not mediated by an enhanced immune-related response. Cannabinoid treatment did not produce any substantial side effect in the conditions used. Further experiments determined that cannabinoids signal glioblastoma cell death by a pathway involving specific cannabinoid receptors, the generation of the lipid ceramide and the activation of a protein kinase cascade. Glioblastomas are among the most malignant forms of cancer, and to date their therapeutic treatment is only palliative. Our data may provide therefore the basis for a new therapeutic approach for the treatment of these tumors.

Drosophila genome sequence, a model for the human

The genome sequence of the fruit fly Drosophila melanogaster was reported in a recent issue of Science (March 24, 2000). This achievement is a milestone in the history of biology. Drosophila has been one of the most important model organisms in basic research for over 80 years, and has been used to elucidate many fundamental principles. In recent years, it has become clear that the