I. Basic Immunology

B. Immunoregulatory Mechanisms

1. Tolerance

LANDMARK ARTICLE:
Aluvihare VR, Kallikourdis M, Betz AG
Regulatory T cells mediate maternal tolerance to the fetus
Nat Immunol. 2004 Mar;5(3):266-71.

Pregnancy constitutes a major challenge to the maternal immune system, as it has to tolerate the persistence of paternal alloantigen. Although localized mechanisms contribute to fetal evasion from immune attack, maternal alloreactive lymphocytes persist. We demonstrate here an alloantigenin dependent, systemic expansion of the maternal CD25+ T cell pool during pregnancy and show that this population contains dominant regulatory T cell activity. In addition to their function in suppressing autoimmune responses, maternal regulatory T cells suppressed an aggressive allogeneic response directed against the fetus. Their absence led to a failure of gestation due to immunological rejection of the fetus.

2. Apoptosis

LANDMARK ARTICLE:
Li Yu, Ajjai Alva, Helen Su, Parmesh Dutt et al.Regulation of an ATG7-beclin 1 Program of Autophagic Cell Death by Caspase-8
Science June 2004;304: 1500 – 1502

Caspases play a central role in apoptosis, a well-studied pathway of programmed cell death. Other programs of death potentially involving necrosis and autophagy may exist, but their relation to apoptosis and mechanisms of regulation remains unclear. We define a new molecular pathway in which activation of the receptor-interacting protein (a serine-threonine kinase) and Jun aminoterminal kinase induced cell death with the morphology of autophagy. Autophagic death required the genes *ATG7* and *beclin 1* and was induced by caspase-8 inhibition. Clinical therapies involving caspase inhibitors may arrest apoptosis but also have the unanticipated effect of promoting autophagic cell death.

3. Anergy

LANDMARK ARTICLE
Boussiotis VA, Freeman GJ , Berezovskaya A, et al.
Maintenance of Human T Cell Anergy: Blocking of IL-2 Gene Transcription by Activated Rap1
Science 1997;278:124-8}

In the absence of costimulation, T cells activated through their antigen receptor become unresponsive (anergic) and do not transcribe the gene encoding interleukin-2 (IL-2) when restimulated with antigen. Anergic alloantigen-specific human T cells contained phosphorylated Cbl that coimmunoprecipitated with Fyn. The adapter protein CrkL was associated with both phosphorylated Cbl and the guanidine nucleotide-releasing factor C3G, which catalyzes guanosine triphosphate (GTP) exchange on Rap1. Active Rap1 (GTP-bound form) was present in anergic cells. Forced expression of low amounts ofRap1-GTP in Jurkat T cells recapitulated the anergic defect and blocked T cell antigen receptor (TCR)-and CD28-mediated IL-2 gene transcription. Therefore, Rap1 functions as a negative regulator of TCRmediated IL-2 gene transcription and may be responsible for the specific defect in IL-2 production in T cell anergy.