IN BRIEF

IMMUNE TOLERANCE

Interactions between PD-1 and PD-L1 promote tolerance by blocking the TCR-induced stop signal

Fife, B. T. *et al. Nature Immunol.* 27 Sep 2009 (doi:10.1038/ni.1790)

By studying the behaviour of T cells in pancreatic lymph nodes and islets, Bluestone and colleagues show that the inhibitory molecule programmed cell death 1 (PD1) keeps T cells in a tolerant state by preventing them from forming prolonged contacts with antigen-bearing dendritic cells. Islet-antigen-specific T cells that were transferred into non-obese diabetic mice were made tolerant by injection with insulin-coupled, chemically fixed splenocytes. The tolerant state could be reversed by blockade of PD1 or its ligand but not by blockade of cytotoxic T lymphocyte antigen 4 (CTLA4), another negative regulator of T cell function. PD1 blockade reduced T cell mobility in pancreatic lymph nodes, increased the duration of T cell–dendritic cell contacts and caused autoimmune diabetes. The effect was antigen specific, suggesting that PD1 inhibits stop signals induced by T cell receptor ligation.

APOPTOSIS

Membrane-bound Fas ligand only is essential for Fas-induced apoptosis

O' Reilly, L. A. *et al. Nature* **461**, 659–663 (2009)

The induction of T cell apoptosis by FAS ligand (FASL; also known as TNFSF6) through its receptor FAS (also known as TNFRSF6) is required for the termination of chronic immune responses, and mice and humans with mutations in the genes encoding FAS or FASL develop lymphadenopathy and autoimmunity. FASL is expressed as both membrane-bound and secreted forms but the relative contribution of these two forms to apoptosis was not known. O'Reilly ***et al.*** show that membrane-bound but not secreted FASL triggers target cell killing and activation-induced cell death of T cells, which is necessary to prevent splenomegaly, lymphadenopathy, hypergammaglobulinaemia and autoantibody accumulation. By contrast, mice that expressed only secreted FASL succumbed to glomerulonephritis and histiocytic sarcoma. So, membrane-bound FASL is essential for cell killing and protects against autoimmunity, whereas high levels of secreted FASL promote autoimmunity and tumorigenesis through non-apoptotic functions.

TUMOUR IMMUNOLOGY

Functional interaction of plasmacytoid dendritic cells with multiple myeloma cells: a therapeutic target

Chauhan, C. *et al. Cancer Cell* **16**, 309–323 (2009)

Multiple myeloma is an incurable disease owing to the resistance of myeloma cells to drug-induced cytotoxicity, which involves the interaction of myeloma cells with the bone marrow microenvironment. In this study, bone marrow of patients with multiple myeloma was found to contain higher numbers of plasmacytoid dendritic cells (pDCs) than normal bone marrow. Although these pDCs had defective antigen-presenting functions, they triggered growth of, prolonged survival of and conferred drug resistance to multiple myeloma cells. Co-culture of pDCs and multiple myeloma cells induced the expression of growth and chemotactic factors for both cell types. ***In vitro*** incubation of pDCs from the bone marrow of patients with multiple myeloma with CpG-containing oligodeoxynucleotides restored their T cell stimulatory activity and reduced their ability to promote multiple myeloma cell growth. So, pDCs are a potential therapeutic target for the treatment of multiple myeloma.