IN BRIEF

NK CELLS

The activating receptor NKp46 is essential for the development of type 1 diabetes

Gur, C. *et al. Nature Immunol.* 20 Dec 2009 (doi:10.1038/ni.1834)

Although type 1 diabetes is thought to be a T cell-mediated disease, natural killer (NK) cells also infiltrate the pancreatic islets of diabetic humans and non-obese diabetic (NOD) mice. In both healthy and diabetic subjects, pancreatic β-cells were shown to express ligands for the NK cell activating receptor NKp46 and promoted degranulation of NK cells both *in vitro* and *in vivo*. NK cells were not present in healthy pancreatic islets but were detected in pre-diabetic and diabetic NOD mice. NKp46-deficient mice developed less severe disease in a streptozotocin-induced model of diabetes, and early or late antibody-mediated blockade of NKp46 function markedly reduced diabetes incidence and severity in NOD mice. NKp46-specific antibodies did not deplete NK cells but promoted the downregulation of NKp46 and this inhibited NK cell degranulation.

TUMOUR IMMUNOLOGY

Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma

Davis, R. E. *et al. Nature* 7 Jan 2010 (doi:10.1038/nature08638)

Constitutive nuclear factor-κB (NF-κB) signalling occurs in the activated B cell-like subtype of diffuse large B cell lymphoma (ABC DLBCL); NF-κB signalling blocks apoptosis and is central to the pathogenesis of this lymphoma. The signalling adaptor caspase-recruitment domain 11 (CARD11) is required for constitutive NF-κB activation and is mutated in ~10% of patients with ABC DLBCL. Staudt and colleagues found that many patients with wild-type CARD11 have mutated activatory motifs in the B cell receptor (BCR) accessory proteins CD79a and CD79b. This resulted in chronic active BCR signalling and downstream constitutive NF-κB activation. Fluorescence microscopy studies showed that ABC DLBCL cells had prominent BCR clusters, resembling those found in antigen-stimulated normal B cells. Blocking BCR signalling components with kinase inhibitors or RNA interference killed ABC DLBCL cells with wild-type CARD11; this may be a useful strategy for treating patients with these lymphomas.

AUTOIMMUNITY

Negative regulation of autoimmune demyelination by the inhibitory receptor CLM-1

Xi, H. *et al. J. Exp. Med.* 28 Dec 2009 (doi:10.1084/jem.20091508)

Myeloid cells contribute to disease in multiple sclerosis and mouse experimental autoimmune encephalomyelitis (EAE) by destroying myelin sheets and axons, leading to a loss of motor functions. This study identifies CMRF35-like molecule 1 (CLM1), an immunoglobulin family member with an intracellular immunoreceptor tyrosine-based inhibitory motif (ITIM), as a negative regulator of myeloid cells in the central nervous system (CNS). CLM1 was not expressed by resident CNS myeloid cells but was expressed by inflammatory myeloid cell populations that infiltrated the CNS in EAE. CLM1 suppressed the production of pro-inflammatory cytokines and reactive oxygen species by infiltrating myeloid cells, and mice lacking CLM1 showed increased EAE severity. Bone marrow chimera experiments showed that the increased EAE severity in these animals was due to the lack of CLM1 expression by inflammatory bone marrow-derived myeloid cells.