

Defective checkpoint control in human autoimmunity

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Autoreactive CD4⁺ T cells of both high and low avidity are present in peripheral blood of subjects with autoimmune diabetes, specific for autoantigens including proinsulin and glutamate decarboxylase. Class II tetramer analysis identifies lineage and maturation characteristics which distinguish circulating autoreactive cells in patients from those present in HLA-matched normal controls. Functional analysis and in vivo model studies define three distinct tolerance checkpoints which influence selection and persistence of these cells in the autoimmune setting. Genotypic variation within both patients and controls helps determine which of these tolerance mechanisms predominate, and identifies specific phenotypic traits which suggest alternative approaches to prognosis and therapy.

Relevant 2009 publications:

Concannon P, Rich SS, Nepom GT. Genetics of type 1A diabetes. *N Engl J Med* 360:1646-1654, 2009.

Gebe JA, Yue BB, Unrath KA, Falk BA, Nepom GT. Restricted autoantigen recognition associated with deletional and adaptive regulatory mechanisms. *J Immunol* 183:59-65, 2009.

Long SA, Walker MR, Rieck M, James EA, Kwok WW, Sanda S, Pihoker C, Greenbaum CJ, Nepom GT, Buckner JH. Functional islet-specific Treg can be generated from CD4⁺ CD25⁻ T cells of healthy and type 1 diabetic subjects. *Eur J Immunol* 39:612-620, 2009.