Hamilton Institute

A stochastic T-cell response criterion

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Wednesday, November 23rd, 2011

Abstract:
T-cells sense their environment by means of T-cell receptors (TCRs) on their surface. A T-cell expresses about 30,000 copies of a unique (clonotypic) TCR, whose ligands are complexes composed of a peptide bound to an MHC molecule (pMHC). In vivo, TCR ligands are expressed on the surface of antigen-presenting cells (APCs). In the thymus a variety of professional APCs will subject immature T-cells (or thymocytes) to a "double test'' by displaying a wide range of pMHC complexes, with peptides derived from household proteins (self-peptides). The stochastic nature of gene rearrangements implies that some TCRs will not be able to recognise a self-pMHC ligand (TCRs that are not functional) and that others will recognise it far too well, and thus would give rise to mature T-cells with the potential to generate autoimmune responses. Thus, the need for a double test that will check the functionality of a thymocyte(positive selection) and its state of tolerance, so that it does not recognise self-pMHC complexes with high affinities (negative selection).

This thymic selection process only allows 2-5% of thymocytes to become mature T-cells.We have made use of mathematical modelling to address the following issues: (1) the thymic affinity threshold hypothesis proposed by Palmer and Naeher (Nature Reviews Immunology, 2009) and (2) time is precious for T-cells, so what do TCRs sense (i) equilibrium properties or (ii) stochastic events. We have made use of data from Palmer's group (The Journal of Experimental Medicine, 2007) to compare the equilibrium versus the stochastic hypotheses. Our results indicate that the stochastic hypothesis ties in better with the existing immunological evidence and provides support to the affinity threshold hypothesis. The stochastic model has also been applied to recent two-dimensional binding data by Huang et al. (Nature 2010) and sheds light into 2d versus 3d binding kinetics and T-cell responses.

Venue: Seminar Room, Hamilton Institute, Rye Hall, NUI Maynooth

Time: 1.00pm - 2.00pm

Travel directions are available at www.hamilton.ie

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