T CELLS

Broken synapses in autoimmunity

Self-reactive T cells have a central role in the pathogenesis of numerous autoimmune diseases. Previous studies have identified several unusual structural features of the self-reactive T cell receptor (TCR)–self-peptide–MHC complex. Now, Wucherpfennig and colleagues show that human self-reactive CD4⁺ T cell clones also have an impaired ability to form classical immune synapses.

The immune synapse is a complex ring-like structure that forms at the interface between a T cell and an antigen-presenting cell (APC). Microclusters of TCRs and associated signalling molecules initially form at the periphery of the interface and then move to the central supramolecular activation cluster (cSMAC), where the TCRs are internalized. TCR signalling is initiated in the microclusters and is sustained by the continued formation of new microclusters.

In this study, the authors analyzed immune synapse formation by seven human CD4⁺ T cell clones from patients with relapsing–remitting multiple sclerosis or type 1 diabetes and compared it with that of two T cell clones specific for influenza virus haemagglutinin. Incubation of self-reactive T cells on planar lipid bilayers displaying the adhesion molecule ICAM1 and the appropriate peptide–MHC complex resulted in limited peptide–MHC

complex accumulation in the synapse and impaired cSMAC formation compared with the characteristics of haemagglutinin-specific T cell synapses. However, all the self-reactive T cell clones formed classical immune synapses on lipid bilayers displaying a CD3ε-specific Fab fragment instead of the peptide–MHC complex, indicating that the defective immune synapse formation was intrinsic to TCR recognition of self-peptide–MHC complexes. Further analysis showed that the self-reactive T cells on planar lipid bilayers were also highly motile compared with haemagglutinin-specific T cells.

Despite the lack of classical immune synapse formation, the self-reactive T cell clones proliferated, mobilized Ca²⁺ and produced interleukin-2 in response to their cognate peptide. Furthermore, some peripheral microclusters containing phosphorylated CD3ζ and the TCR signalling molecule SLP76 formed in response to stimulation by self-peptide–MHC complexes, even though very little accumulation of peptide–MHC complexes was observed. However, most of the clones had a low TCR affinity for self-peptide–MHC complexes, as only one self-reactive T cell clone was

stained by a relevant peptide–MHC tetramer. Indeed, the on-rate of TCR binding to peptide–MHC complexes for the three self-reactive T cell clones that were analyzed was approximately tenfold lower than that of the haemagglutinin-specific T cell clones, although the off-rates were similar. This suggests that the altered synapse formation observed in the self-reactive T cells was due to a slow on-rate (and resulting low affinity) of TCR binding to self-peptide–MHC complexes.

So, TCR signalling and effector functions can occur in self-reactive T cells even in the absence of classical immune synapse formation. The authors suggest that the impaired immune synapse formation by self-reactive T cells may facilitate escape from negative selection in the thymus, where the expression of self antigens is very low. However, the large quantities of self antigens in the target organs of autoimmune disease may be sufficient to activate self-reactive T cells, despite the lack of classical immune synapse formation.

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ORIGINAL RESEARCH PAPER Schubert, D. A. et al. Self-reactive human CD4 T cell clones form unusual immunological synapses. *J. Exp. Med.* 6 Feb 2012 (doi:10.1084/jem.20111485)

FURTHER READING Dustin, M. L. & Depoil, D. New insights into the T cell synapse from single molecule techniques. *Nature Rev. Immunol.* **11**, 672–684 (2011)