Receptor pre-clustering and T cell responses: insights into molecular mechanisms

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A hallmark of the adaptive immune system is the ability of T cells, making use of the T cell receptors (TCRs) on their surface, to recognise a given agonist peptide-MHC ligand complex (pMHC) with high sensitivity[4]. Some aspects of TCR-pMHC molecular interactions that are of current research interest are the frequency of encounters between T cells and the agonist pMHC, how cell-cell interactions determine the activation of lymphocytes[1], how early interactions change the state of the T cell receptor, what are the mechanisms of modulation of receptor-ligand interactions at cell-cell interfaces, and how protein organisation in the cell membrane (for instance, protein islands or lipid rafts) affect the recognition process[6].

While antigen presenting cells (APCs), such as dendritic cells or B cells, present $10^3 - 10^4$ times more self pMHC than antigenic pMHC, self pMHC ligands by themselves do not usually elicit a T cell response, even though their affinity for TCR$\alpha\beta$ is only 10 times lower than the affinity of the antigenic pMHC[3]. This illustrates how a small difference in affinity results in high specificity, when there is only a few antigenic pMHC molecules in a background of self pMHC ligands[5].

In this poster, we discuss the consequences of TCR pre-clustering in signalling and in distinguishing naive and memory T cell responses. We present some experimentally obtained distributions of TCR clusters for both types of cells (see Fig. 1), and two complementary theoretical models: (i) a simple model of receptor oligomerisation that describes cluster size distributions, and (ii) a generalisation of a novel stochastic T cell response criterion previously used for monomeric interactions[2], to accommodate the hypothesis that the minimum signalling unit is composed of a TCR receptor cluster that is bound by the same cross-linked multivalent ligand (see Fig. 2).

We find that this signalling unit is able to discriminate between agonist and antagonist pMHC ligands, (with greater sensitivity than in the monomeric case), and to explain some of the advantages that higher cluster sizes can provide to memory T cells. The model also points at the need to invoke additional cooperative mechanisms, to explain the experimentally observed role of clustering in T cell responses.

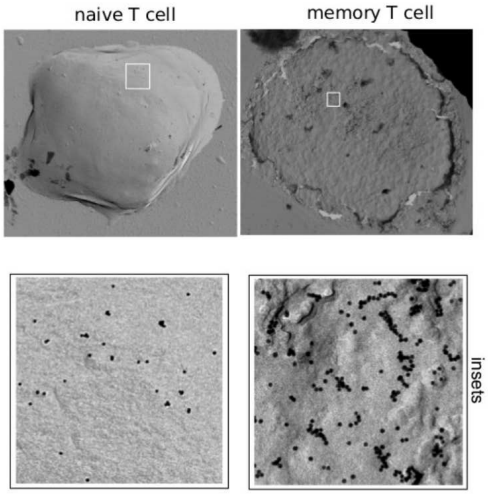

FIG. 1. TCR clusters on the surface of T-cells.

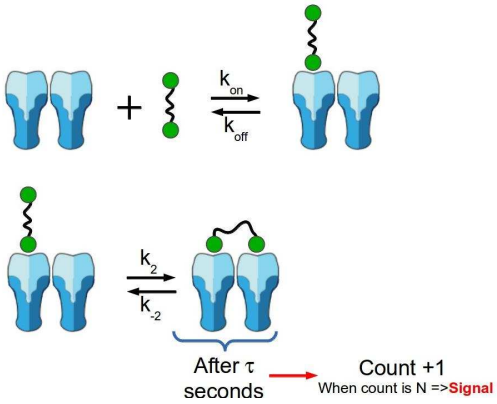

FIG. 2. Reactions involved in the stochastic activation model.

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[1] F D Batista and M L Dustin. *Immunological Reviews*, 251(1):7–12, 2013.

[2] J. Currie, M. Castro, G Lythe, E. Palmer, and C Molina-París. *Journal of The Royal Society Interface*, 9(76):2856–2870, 2012.

[3] M A Daniels, *et al.* *Nature*, 444(7120):724–729, 2006.

[4] J B Huppa and M M Davis. *Nature Reviews Immunology*, 3(12):973–83, December 2003.

[5] S. Valitutti, D. Coombs, and L. Dupré. *FEBS Letters*, 2010.

[6] V. Zarnitsyna and C. Zhu. *Physical Biology*, 9(4):045005, 2012.