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T-CELL SIGNALLING

A chicken or egg situation

Which comes first, the immunological synapse or T-cell receptor signalling? Current dogma dictates that signalling in T cells, and therefore T-cell activation, is a consequence of the formation of the immunological synapse — where a T cell contacts an antigen-presenting cell (APC) — which serves to cluster T-cell receptors (TCRs). But, a report by Andrey Shaw's group challenges this model by presenting data that indicate that TCR-mediated signalling occurs before mature synapses form.

Shaw and colleagues set out to determine exactly where the interaction between TCRs and the antigenic peptide–MHC complexes of the APC occurs. They did this by spinning together antigenic-peptide-containing APCs and T cells, then analysing the localization of TCRs in the conjugates. TCRs of T cells that were studied after a short spinning time (2–15 minutes) were detected at the edges of the immunological synapses, but later (after 15 minutes), became concentrated in the centre. However, after 1 hour, no TCRs were found in the synapse. Changes in the staining pattern for the integrin leukocyte function-associated antigen 1 (LFA1) confirmed that the synapse progressed from an immature (at 15 minutes) to a mature (30 minutes) state during this procedure.

So, if the TCRs disappear from the mature synapse, what happens to TCR-mediated signalling? To address this issue, the authors studied the localization of active Lck and ZAP70

(ζ -chain-associated protein kinase, 70 kDa) — two tyrosine kinases that are crucial in TCR signalling — in the conjugated cells. The results showed that phosphorylated Lck and ZAP70 were only found at the edges of immature synapses and could not be detected in mature synapses, which indicates that TCR-mediated signalling occurs well before the mature synapse has formed.

To investigate whether naive T cells could be efficiently activated by this seemingly short duration of TCR-mediated signalling, T cells that had been allowed to conjugate with APCs for defined lengths of time were analysed for cell-cycle progression. The authors found that T cells only divided after they had interacted with APCs for a minimum of 2 hours. These findings contrast with previous results, which indicated that only long periods of TCR signalling (up to 20

hours) can activate T cells. It is unclear at present what happens in the period after TCR signalling is attenuated, and before T cells commit to divide, but other signalling pathways might have important roles.

So, what is the function of the immunological synapse if not to cluster TCRs? Although there are several hypotheses — for example, involvement in polarized secretion, activation of other signalling pathways or endocytosis of TCRs — this is now the million-dollar question.

Katrin Bussell, Associate Editor,
Nature Reviews Molecular Cell Biology

References and links

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WEB SITES

Andrey Shaw's lab:
<http://pathbox.wustl.edu/~shawlab/>
Encyclopedia of Life Sciences: <http://www.els.net>
antigen-presenting cell