REGULATORY T CELLS

Suspended license to kill

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A mechanism to explain how $CD4^+CD25^+$ regulatory T (T_{Reg}) cells impair cytotoxic T lymphocyte (CTL) function is reported in *Immunity*. Mempel, Pittet and colleagues used multi-photon intravital microscopy to analyse how CTLs interact with target antigen-presenting cells (APCs) in the presence or absence of activated T_{Reg} cells in the lymph nodes of mice. They found that T_{Reg} cells can selectively interfere with the release of lytic granules by CTLs in a reversible, transforming growth factor-β (TGFβ)-dependent manner.

There is a large body of work highlighting the importance of T_{Reg} cells in the active suppression of the immune system, but there is considerably less evidence about the precise mechanism by which T_{Reg} cells mediate their suppressive effects. T_{Reg} cells have been shown to impair the effector functions of primed CTLs, so the authors investigated several possible mechanisms to explain this impairment, by directly visualizing interactions among CTLs, target APCs and T_{Reg} cells in mouse lymph nodes *in vivo*. They established that suppression of CTL function by T_{Reg} cells can occur exclusively by compromising lytic activity. The clonal expansion, distribution and motility of CTLs, as well as their ability to detect agonist T-cell-receptor ligands on target APCs and to form stable antigen-specific cell–cell conjugates, remained unaffected.

> “T_{Reg} cells can selectively attenuate the cytotoxicity of CTLs”

The lytic activity of CTLs occurs mainly through the calcium-dependent release of specialized lytic lysosomal granules after recognition of antigen at the surface of a target cell. So how is this activity compromised by T_{Reg} cells? The authors found that, although the granule content of CTLs and their expression of lytic effector molecules did not change in the presence of T_{Reg} cells, there was delayed lytic-granule release, which impaired the ability of CTLs to induce target-cell death before the cell–cell conjugates dissociate.

Further investigation showed that suppression of CTL function by T_{Reg} cells was dependent on TGFβ-induced signalling, although Mempel, Pittet and colleagues conceded that other suppressive signals might also be required. They also found that T_{Reg}-cell-mediated suppression of CTLs was reversible, because sustained CTL suppression required the continuous presence of T_{Reg} cells, although prolonged CTL–T_{Reg}-cell contact was not required.

The authors have shown that T_{Reg} cells can selectively attenuate the cytotoxicity of CTLs, seemingly without affecting their priming or differentiation. These findings, they note, could have implications for the design of therapeutic strategies, particularly for those strategies that rely on the modulation of ongoing immune responses.

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ORIGINAL RESEARCH PAPER Mempel, T. R. *et al.* Regulatory T cells reversibly suppress cytotoxic T cell function independent of effector differentiation. *Immunity* **25**, 129–141 (2006)