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T CELLS

Lymphoid stroma says NO to activated T cells

The lymph node stroma is composed of non-haematopoietic fibroblastic reticular cells (FRCs) and lymphatic endothelial cells (LECs). These lymphoid stroma cells have been previously reported to present self antigens to naive T cells and establish deletional tolerance. A recent study published in *Nature Immunology* reports that FRCs and LECs also control the proliferation of activated T cells in the lymph nodes.

To investigate the role of FRCs and LECs during an ongoing T cell response in the lymph node, the authors established *in vitro* co-culture assays, in which T cells were stimulated in the presence of FRCs or LECs. Interestingly, both stromal cell populations were shown to inhibit T cell proliferation, and this was independent of the presence of other leukocytes.

So, what mechanisms are involved in the inhibition of T cell proliferation by lymphoid stroma cells? Activated T cells were shown to induce the expression of inducible nitric oxide synthase (iNOS) by lymphoid stroma cells. iNOS catalyses the production of nitric oxide (NO) — which can suppress T cell proliferation — and its expression was required for the suppressive function of FRCs and LECs.

Interestingly, exogenous interferon-γ (IFNγ) was found to induce the upregulation of iNOS expression in lymphoid stroma cells. Moreover, co-culture assays with activated T cells and lymphoid stroma cells that lacked expression of IFNγ or the IFNγ receptor showed that IFNγ secretion by the activated T cells was required for the suppressive function of lymphoid stroma cells.

However, IFNγ does not act alone to induce iNOS-mediated NO production by lymphoid stroma cells, as it increased mRNA but not protein levels of iNOS. In addition, tumour necrosis factor produced by activated T cells and T cell–stromal cell contact were found to be essential for NO production in the co-culture assays.

As T cell proliferation in response to antigen presentation by iNOS-deficient FRCs was comparable to that induced by dendritic cells, the authors sought to confirm their findings *in vivo*, using transgenic mice in which ovalbumin (OVA) expression is restricted to lymph node FRCs (iFABP-tOVA mice). Interestingly, adoptively transferred OVA-specific $CD8^+$ T cells proliferated more in the lymph nodes of iNOS-deficient iFABP-tOVA mice than in the lymph nodes of iNOS-expressing iFABP-tOVA mice.

Thus, lymphoid stroma cells that are in close proximity with activated T cells control T cell proliferation through NO production. This cross-talk may be crucial for the protection of secondary lymphoid organs from unrestricted T cell activation.

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> “lymphoid stroma cells … control T cell proliferation through NO production”

ORIGINAL RESEARCH PAPER Lukacs-Kornek, V. *et al.* Regulated release of nitric oxide by nonhematopoietic stroma controls expansion of the activated T cell pool in lymph nodes. *Nature Immunol.* 18 Sep 2011 (doi:10.1038/ni.2112)