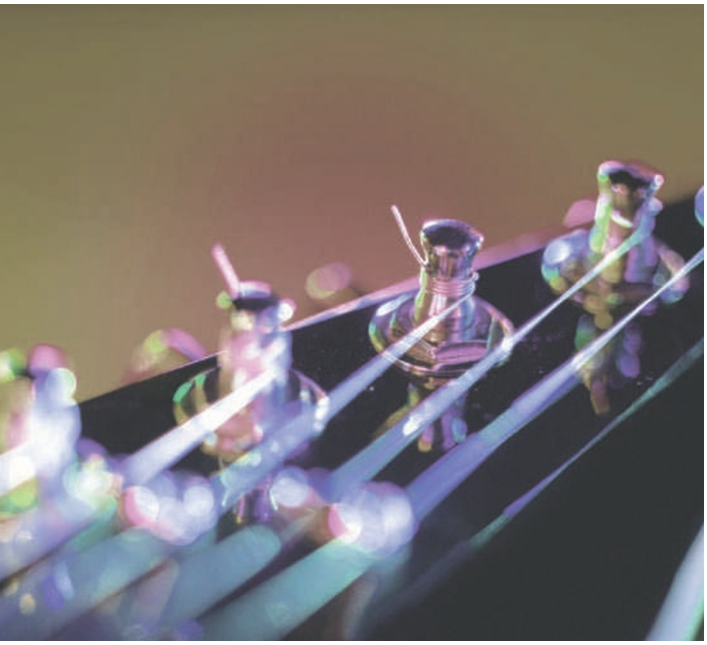
IMMUNE REGULATION

Tightening responses by TIGIT

A new T-cell-expressed regulator of dendritic cells (DCs), termed TIGIT (T-cell immunoreceptor with immunoglobulin and ITIM domains), is described in a paper recently published in *Nature Immunology*.

TIGIT was identified by searching for genes that are expressed by immune cells and that might function as immunomodulatory receptors owing to a protein structure comprising an immunoglobulin domain, a transmembrane region and an immunoreceptor tyrosine-based inhibitory motif (ITIM). Consistent with the search criteria, TIGIT was found to be expressed on the surface of $CD4^+CD25^+$ regulatory T cells, memory T cells and natural killer cells. Its expression was further upregulated by these cell types following activation and could also be detected on naive $CD4^+$ T cells after activation.



Using a TIGIT–Fc fusion protein, the authors then screened a library of secreted proteins for those that bound to TIGIT. Poliovirus receptor (PVR; also known as CD155) was shown to bind TIGIT–Fc with high affinity. PVR belongs to a family of PVR-like proteins (comprising PVRL1–PVRL4, CD96 and CD226), which are known to interact with each other. TIGIT could outcompete CD226 and CD96 binding to PVR, suggesting that TIGIT, CD226 and CD96 share a common binding site on PVR. On the basis of these findings and sequence analysis, the authors suggest that TIGIT belongs to the PVR-like protein family.

So, what is the function of TIGIT? Knockdown of TIGIT expression in primary human T cells by specific RNA-mediated interference had no effect on T-cell proliferation or cytokine production *in vitro*, and exposure of T cells to a TIGIT-specific antibody did not influence their activation. However, when T cells were cultured with autologous DCs, the presence of a TIGIT-specific antibody (which blocks the interaction of TIGIT with its ligand) led to a fourfold increase in interferon-γ (IFNγ) production. Conversely, use of a TIGIT–Fc fusion protein to ligate PVR inhibited IFNγ production by T cells in T-cell–DC co-cultures. This suggested that TIGIT might regulate T-cell responses by interacting with PVR expressed by DCs.

In agreement with this idea, exposure of monocyte-derived DCs (MDDCs) to TIGIT–Fc (or CD226–Fc) resulted in increased production of the immunosuppressive cytokine interleukin-10 (IL-10) and decreased production of IL-12 following stimulation. Further analysis revealed that TIGIT–Fc engagement of PVR on DCs induced the phosphorylation of PVR and the downstream activation of extracellular-signal-regulated kinase (ERK), which is probably involved in the observed effects of PVR ligation on DC cytokine production.

Yu *et al.* then showed that TIGIT–Fc-treated MDDCs, but not control MDDCs, inhibited T-cell proliferation in a mixed lymphocyte response assay and that this suppression was associated with high levels of IL-10. Importantly, the suppressive effects of TIGIT–Fc were confirmed in an *in vivo* delayed-type hypersensitivity (DTH) assay: treatment of wild-type but not $Il10^{-/-}$ mice with TIGIT–Fc reduced DTH responses. Finally, the finding that DCs isolated from TIGIT–Fc-treated mice contained more *Il10* mRNA and less *Il12* mRNA than DCs from control mice is consistent with the idea that TIGIT-mediated modulation of DCs is responsible for the immunosuppressive effects of TIGIT *in vivo*.

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ORIGINAL RESEARCH PAPER Yu, X. *et al.* The surface protein TIGIT suppresses T cell activation by promoting the generation of mature immunoregulatory dendritic cells. *Nature Immunol.* 16 Nov 2008 (doi:10.1038/ni.1674)