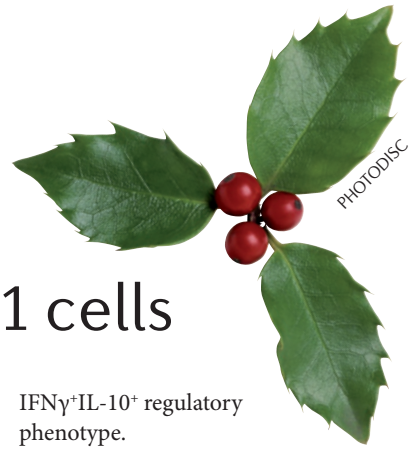

T CELL RESPONSES

Jagged gives an edge to T_H1 cells

> a role for jagged–CD46 interactions in regulating human T_H1 cell responses

The complement and Notch systems have well-appreciated roles in innate immunity and immune cell development, respectively. A recent study in *Nature Immunology* suggests that crosstalk between these two systems also regulates adaptive T cell responses in humans.

CD46 (also known as membrane cofactor protein) protects host cells from complement-mediated damage by binding to and promoting the inactivation of complement components C3b and C4b. There is also evidence that CD46 regulates the induction of T helper 1 (T_H1) cells in humans and their subsequent switching to an interferon-γ (IFNγ)$^+$ and interleukin-10 (IL-10)$^+$ phenotype and then to an IL-10$^+$ regulatory phenotype. The authors suspected that an alternative ligand for CD46 may exist, which could explain these complex effects on T_H1 cell responses. Indeed, initial screens identified the Notch ligand jagged 1 as a ligand for CD46.

They next explored whether CD46–jagged 1 interactions influence T cell responses. Activation of human T cells with CD3- and CD46-specific antibodies *in vitro* led to their upregulation of Notch 1, Notch 2, jagged 1 and jagged 2, but caused the downregulation of the Notch ligand Delta-like 1 (DLL1) and of CD46 itself. The upregulation of these Notch proteins seems to be crucial for CD46-mediated control of T_H1 cell responses, as blocking Notch signalling pathways prevented CD46 from driving the upregulation of IFNγ by human T_H1 cells and their subsequent switching to an IFNγ$^+$IL-10$^+$ phenotype. Confocal microscopy studies showed that jagged 1 mainly colocalized with CD46 and not with Notch in resting T cells. However, following CD3- and CD46-mediated activation of T cells, ~50% of Notch became associated with jagged 1. This suggests that the sequential engagement of CD46 and then Notch by jagged 1 regulates the upregulation of IFNγ by T_H1 cells and subsequent switching to dual IFNγ and IL-10 production.

To further investigate the importance of this pathway, the authors examined T cells from three patients with mutations in *CD46*. Notably, these patients suffer from recurrent infections. Each patient had normal numbers of B cells, CD4$^+$ T cells and CD8$^+$ T cells. Furthermore, following stimulation *in vitro*, their T cells proliferated normally and differentiated into T_H2-type effectors. However, T cells from two of the patients were unable to differentiate into T_H1-type effector cells. In addition, although T cells from the third patient could differentiate into T_H1-type effectors, they were unable to switch to an IFNγ$^+$IL-10$^+$ regulatory phenotype.

Finally, the authors assessed T cells from four patients with Alagille's syndrome. These individuals have heterozygous mutations in the gene encoding jagged 1 that cause developmental defects. Some patients also suffer from recurrent infections, but the reasons for this have not been understood. Similarly to the T cells from patients with *CD46* mutations, T cells from the patients with Alagille's syndrome showed defective IFNγ induction and were unable to switch to an IFNγ$^+$IL-10$^+$ phenotype. Interestingly, activated T cells from patients with Alagille's syndrome or with *CD46* mutations had deregulated expression of CD127 and CD132; the authors propose that jagged–CD46 interactions may influence T cell signalling in response to IL-2 family members. Taken together, these data describe a role for jagged–CD46 interactions in regulating human T_H1 cell responses and suggest that the failure of this pathway can increase susceptibility to infection.

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