CYTOKINES

WSX1 exposed to positive and negative influences

A recent report in *The Journal of Immunology* indicates that expression of the ligand-specific component of the interleukin-27 (IL-27) receptor, WSX1, is differentially regulated after activation of distinct lymphoid-cell populations — WSX1 expression is increased after T-cell activation but decreased after natural killer (NK)-cell or natural killer T (NKT)-cell activation.

Initial reports indicated that the level of mRNA encoding WSX1 was decreased after activation of naive $CD4^+$ T cells and that WSX1-deficient mice were more susceptible to infection with intracellular pathogens. Therefore, it was proposed that IL-27 is an important factor for the activation of naive $CD4^+$ T cells to mediate type 1 immunity. However, subsequent studies showed that IL-27 was an inhibitor of effector T cells: WSX1-deficient mice infected with *Toxoplasma gondii* generated an appropriate immune response but succumbed to an inflammatory disease.

So Villarino *et al.* set out to study the level of expression of WSX1 on the lymphoid-cell populations that are known to have a role in controlling infection with *T. gondii*. A significantly lower proportion of NK cells and NKT cells (which are activated during the acute phase of infection) expressed high levels of WSX1 in mice infected with *T. gondii* than in uninfected animals. Furthermore, those cells still expressing high levels of WSX1 retained an unactivated phenotype, indicating that downregulation of WSX1 correlates with cellular activation. By contrast, the proportion of $CD4^+$ and $CD8^+$ T cells (which are required for resistance to infection with *T. gondii*) expressing high levels of WSX1 was increased after infection. Furthermore, the $WSX1^{hi}CD4^+$ T cells had an effector phenotype, indicating that WSX1 upregulation correlates with T-cell activation.

Consistent with a role for T-cell activation as a regulator of WSX1 expression, T-cell-receptor crosslinking on $CD4^+$ T cells *in vitro* resulted in increased cell-surface expression of WSX1, although this increase was only transient. Interestingly, upregulation of WSX1 required that the cells entered the cell cycle, but continued cell division was associated with the decrease in WSX1 expression levels. Additional signals that negatively regulate WSX1 expression levels were shown to come from IL-2.

This study indicates that activation of distinct lymphoid cells results in differential regulation of WSX1 expression levels and that both positive and negative signals can regulate this process, both in distinct cell types and within a responding population of cells.

Karen Honey

References and links

ORIGINAL RESEARCH PAPER Villarino, A. V. *et al.* Positive and negative regulation of the IL-27 receptor during lymphoid cell activation. *J. Immunol.* **174**, 7684–7691 (2005)

FURTHER READING Hunter, C. A. *et al.* New IL-12-family members: IL-23 and IL-27, cytokines with divergent functions. *Nature Rev. Immunol.* **5**, 521–531 (2005)

IN BRIEF

STRUCTURE

Signaling conformations of the tall cytokine receptor gp130 when in complex with IL-6 and IL-6 receptor.

Skiniotis, G. *et al. Nature Struct. Mol. Biol.* 15 May 2005 (doi:10.1038/nsmb941)

Structural analysis of the cytokine-binding domains of gp130 (glycoprotein 130), interleukin-6 (IL-6) and the α-chain of the IL-6 receptor (IL-6Rα) indicated that this trimolecular complex dimerizes for signalling to occur. However, the membrane-proximal domains of gp130 were predicted to extend away from each other, rather than enter the membrane in close proximity as would be expected for signalling to occur. Skiniotis *et al.* visualized the conformation of the extracellular portion of gp130 (the cytokine-binding and membrane-proximal domains) complexed with IL-6 and IL-6Rα and observed that the gp130 molecules are bent such that the membrane-proximal domains interact close to the membrane. The authors suggest that this enables activation of intracellular signalling and that bending of the gp130 molecules might occur as a conformational transition when ligand binds.

DENDRITIC CELLS

Nectin-like protein 2 defines a subset of T-cell zone dendritic cells and is a ligand for class-I-restricted T-cell-associated molecule.

Galibert, L. *et al. J. Biol. Chem.* **280**, 21955–21964 (2005)

Galibert *et al.* set out to identify markers of dendritic cell (DC) subsets that are conserved across species. A single-chain antibody fragment (scFv) that specifically labels human $BDCA3^+$ DCs was isolated using a whole-cell-panning phage-display approach. When expressed as an Fc fusion protein, this scFv also bound mouse splenic $CD11c^+CD11b^-CD8\alpha^+$ DCs. The scFv target was shown to be nectin-like protein 2 (NECL2), and its ligand was identified as class-I-restricted T-cell-associated molecule (CRTAM), which is expressed by activated $CD8^+$ T cells. CRTAM–NECL2 interactions induced increased expression of interleukin-22 mRNA by the activated $CD8^+$ T cells, leading the authors to suggest that this conserved interaction probably contributes to DC–T-cell crosstalk.

LYMPHOCYTE SIGNALLING

Cytokine-driven cell cycling is mediated through Cdc25A.

Khaled, A. R. *et al. J. Cell Biol.* 31 May 2005 (doi:10.1083/jcb.200409099)

Lymphocytes are known to require cytokine-mediated signals, such as those provided by interleukin-7 (IL-7) or IL-3, for both survival and proliferation, but until now, little has been known about the cytokine-driven proliferation pathway. This study shows that cytokine signals are required to prevent p38 mitogen-activated protein kinase (MAPK)-mediated phosphorylation and degradation of the phosphatase CDC25A (cell-division cycle 25A). CDC25A, in turn, dephosphorylates cyclin-dependent kinases such as CDK2, which promotes association with cyclin E, phosphorylation of the cell-cycle inhibitor retinoblastoma-susceptibility protein and entry to the cell cycle. Cytokines, therefore, seem to protect lymphocytes from a stress response that involves activation of the stress kinase p38 MAPK by cytokine withdrawal.