IN BRIEF

T-CELL ACTIVATION

HS1 functions as an essential actin-regulatory adaptor protein at the immune synapse.

Gomez, T. S. *et al. Immunity* **24**, 741–752 (2006)

Formation of the immunological synapse, which involves actin polymerization and recruitment of signalling molecules, is crucial for T-cell activation. Now, new research has implicated haematopoietic-lineage-cell-specific protein 1 (HS1) as a key regulatory adaptor protein in this process. Using T cells from *Hs1*^{-/-} mice and T cells in which the expression of HS1 is suppressed, the authors showed that HS1 maintains F-actin at the immunological synapse and is required for the organization and maintenance of specific structures that are necessary for conjugate formation. Phosphorylation of HS1, by key signalling molecules in the synapse, is required for actin regulation and is important for the activation of interleukin-2 promoter. This protein is also important for maintaining VAV1, which regulates actin responses, at the synapse. So, HS1 is an actin-regulatory protein that is crucial for T-cell activation.

EVOLUTION

Insect immunity shows specificity in protection upon secondary pathogen exposure.

Sadd, B. M. & Schmid-Hempel, P. *Curr. Biol.* **16**, 1206–1210 (2006)

Immunological memory and specificity characterizes adaptive immunity in vertebrates. Invertebrates can mount an immune response following pathogen exposure, but it was not clear whether this response could be specific. A new study now shows that insects can mount a specific immune response to a previously encountered pathogen. Sadd and Schmid-Hempel tested the immune system of *Bombus terrestris* (the bumblebee) to determine if it could show protection, specificity or both on exposure to bacterial pathogens following previous exposure. The authors found that the immune system of *B. terrestris* responded in a specific manner to previously encountered pathogens, even several weeks after the first exposure, and that this response was functionally protective. So, despite their broad differences, both vertebrate and invertebrate immune systems mount a specific protective response. The authors suggest that similar selective pressures on these different immune systems over evolutionary time might therefore have resulted in comparable solutions.

APOPTOSIS

Gimap4 accelerates T-cell death.

Schnell, S. *et al. Blood* **108**, 591–599 (2006)

By searching for genes that are differentially expressed during T-cell development, the authors of this study identified *Gimap4* (GTPase, immunity-associated protein family member 4). *Gimap4* expression was found to be induced initially during the early stages of T-cell development, turned off during positive selection and re-expressed thereafter, including by mature T cells. Despite this expression pattern, *Gimap4*^{-/-} mice showed no defect in T-cell development. Instead, the authors found that, compared with wild-type cells, cultures of mature T cells from *Gimap4*^{-/-} mice showed increased numbers of apoptotic cells versus dead cells following serum starvation or exposure to other apoptotic triggers. Further studies led the authors to conclude that GIMAP4 acts as an accelerator of the late stages of apoptosis and functions downstream of caspase-3 activation and phosphatidylserine exposure.

REGULATORY T CELLS

In hot pursuit

Despite having been identified more than 10 years ago, CD4⁺CD25⁺ regulatory T (T_{Reg}) cells are still being characterized. Naturally occurring T_{Reg} cells express the transcription factor forkhead box P3 (FOXP3), which has been identified as a major marker and regulator of the development and function of T_{Reg} cells. However, identifying and isolating human T_{Reg} cells for use in functional studies is difficult, because these cells cannot easily be distinguished from activated CD4⁺ non-regulatory T cells. Also, as FOXP3 is an intracellular protein, fixation and permeabilization of the cells is required. Two papers in *The Journal of Experimental Medicine* now report that low surface expression of CD127 (the α -chain of the IL-7 receptor) can be used effectively to identify human T_{Reg} cells.

In an effort to identify new cell-surface markers for human T_{Reg} cells, Liu *et al.* used gene-expression studies to compare two subsets of human T cells: CD4⁺CD25^{hi} T cells and CD4⁺CD25^{lo} T cells. They noted in particular that expression of *CD127* mRNA was inversely correlated with expression of CD25. Subsequent analyses showed that most of the FOXP3⁺ T cells were in the CD127^{low/-} T-cell subset and, further, that the highest levels of FOXP3 expression correlated with the lowest levels of CD127 expression. Using multi-parameter flow cytometry, the authors determined that a broad gating strategy of CD4⁺CD25⁺CD127^{low/-} accounted for ~80% of the FOXP3-expressing T cells. Up to 10% of all the CD4⁺ T cells were identified as potential T_{Reg} cells — a considerably higher percentage than has been shown previously. Liu *et al.* also found that CD127 could be used, independently of CD25, to separate a suppressive T-cell subset, which could be useful in future therapeutic applications. The

authors concluded that using a combination of CD4, CD25 and CD127 results in highly purified T_{Reg}-cell population.

In the second paper, Seddiki *et al.* reasoned that because of the IL-7-dependent and IL-2-independent nature of many non-T_{Reg}-cell subsets, T_{Reg} cells (which require IL-2) might not require IL-7. Using monoclonal antibodies specific for CD4, CD25 (the α -chain of the IL-2 receptor) and CD127, they found that CD127 expression could be used to distinguish two populations of CD4⁺CD25⁺ T cells — a small CD25⁺CD127^{low} population and a much larger CD25⁺CD127^{hi} population. They noted a strong correlation between the number of CD25⁺CD127^{low} T cells and CD25⁺FOXP3⁺ T cells. Interestingly, Seddiki *et al.* saw this correlation in cells that were gated on either CD45RA⁻ or CD45RA⁺ populations, indicating that CD25⁺CD127^{low} T_{Reg} cells can be found within both naive and antigen-experienced T-cell subsets. Finally, the authors looked at the *in vitro* suppressive activity of the T_{Reg}-cell population and found that it was restricted to the CD25⁺CD127^{low} T cells.

Together, these two reports show that human T_{Reg} cells can be identified by their low cell-surface expression of CD127. The ability to selectively enrich these cells for *in vitro* functional studies will hopefully lead to a greater understanding of how they contribute to the immunopathology of disease, and increase the potential of these cells for *in vivo* therapy.

Sharon Ahmad

ORIGINAL RESEARCH PAPERS Liu, W. *et al.* CD127 expression inversely correlates with FoxP3 and suppressive function of human CD4⁺ T reg cells. *J. Exp. Med.* **203**, 1701–1711 (2006) | Seddiki, N. *et al.* Expression of interleukin (IL)-2 and IL-7 receptors discriminates between human regulatory and activated T cells. *J. Exp. Med.* **203**, 1693–1700 (2006)