ANTIGEN PROCESSING

Haute couture for peptides

Antigenic peptides to be presented by MHC class I molecules are generated by the proteasome in the cytoplasm and then transported by transporter for antigen processing (TAP) molecules to the endoplasmic reticulum (ER). But, these peptides are not the final products that are presented by MHC class I molecules and, as for the customized fitting of a good suit, they require some careful tailoring at the amino terminus to fit properly into the MHC class I groove. The existence of an aminopeptidase in the ER that is responsible for this final trimming stage has been assumed for some time. Reporting in *Nature*, Serwold and colleagues now describe the isolation and identification of this peptidase, which they have named ERAAP (ER aminopeptidase associated with antigen processing).

ERAAP was isolated from mouse liver and spleen that had been solubilized with detergent and fractionated using ion-exchange chromatography. A single activity peak was identified, which was purified further using chromatographic techniques. Trypsin digestion of the gel-isolated protein, followed by mass spectrometry, gave a peptide fingerprint, which was used to search the databases. This search identified an aminopeptidase, which the authors named ERAAP.

ERAAP co-localizes with the ER markers BiP and gp96. The expression of ERAAP correlates with MHC class I expression in various cell types, and it is upregulated by stimulating cells with interferon-γ, which also upregulates the expression of other molecules in the antigen-processing pathway. The function of ERAAP as a peptide-trimming molecule in the ER was confirmed by knocking down ERAAP expression in antigen-presenting cells (APCs) using small interfering RNA (siRNA) and assessing the effect on the presentation of antigens to T cells. ERAAP expression was reduced by 90% by siRNA treatment, which decreased the expression of surface MHC class I molecules by 20–40% (because empty class I molecules cannot be expressed stably at the cell surface). The expression of two specific MHC class I peptides was inhibited significantly in APCs transfected with mouse siRNA for ERAAP, which confirms the importance of ERAAP for generating these peptides. So, ERAAP connects the peptides that are generated in the cytosol with the peptides that are presented at the cell surface on MHC molecules.

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References and links

ORIGINAL RESEARCH PAPER Serwold, T., Gonzalez, F., Kim, J., Jacob, R. & Shastri, N. ERAAP customizes peptides for MHC class I molecules in the endoplasmic reticulum. *Nature* **419**, 480–483 (2002)

IN BRIEF

CYTOKINES

Macrophage migration inhibitory factor (MIF) plays a pivotal role in immunity against *Salmonella typhimurium*.

Koebernick, H. *et al. Proc. Natl Acad. Sci. USA* **99**, 13681–13686 (2002)

Although the cytokine macrophage migration inhibitory factor (MIF) has many biological functions, its role in bacterial infections is not understood. Here, Koebernick *et al.* investigated the response of *Mif*$^{-/-}$ mice to *Salmonella typhimurium*. *Mif*$^{-/-}$ mice were unable to control this bacterial infection, and they had an impaired T helper 1 (T_H1) response, as indicated by the reduced production of interleukin-12, interferon-γ and tumour-necrosis factor. In addition, increased levels of nitric oxide and corticosteroids were seen. Therefore, MIF promotes T_H1 responses and reduces immunosuppressive stress responses.

THYMIC DEVELOPMENT

Stromal cells provide the matrix for migration of early lymphoid progenitors through the thymic cortex.

Prockop, S. *et al. J. Immunol.* **169**, 4354–4361 (2002)

As thymocytes develop into mature T cells in the thymus, they migrate outwards from the cortex towards the thymic capsule. What controls this directional migration? Adhesion receptors on the migrating lymphoid cells are required, as well as a stable matrix of their ligands. This study investigates the nature of this matrix and indicates that it is cellular rather than extracellular, and includes cytokeratin-positive cortical stromal cells that express the α4-integrin ligand vascular cell adhesion molecule 1, which are crucial for the control of precursor migration.

B-CELL DEVELOPMENT

B cells develop in the zebrafish pancreas.

Danilova, N. & Steiner, L. A. *Proc. Natl Acad. Sci. USA* **99**, 13711–13716 (2002)

In bony fish, T-cell development takes place in the thymus, whereas the pronephros (or head kidney) is thought to be the main site of B-cell development. However, expression of recombination-activating gene 1 (*Rag1*) and *Rag2* is not detected in the zebrafish pronephros until three weeks of life. By contrast, *Rag1/2* expression can be detected in the thymus by day 4. So, is early B-cell development in zebrafish delayed relative to T-cell development, or does it take place at a distinct anatomical site? This study shows that rearrangements of the genes that encode Igμ can be detected in DNA extracted from whole zebrafish as early as day 4 and that *Rag1* is expressed in the pancreas by day 4. Igμ is also expressed in the pancreas from day 10, which confirms that the pancreas is an organ for B-cell development in the zebrafish.