PHAGOCYTOSIS

Come and get it!

The rapid and efficient removal of apoptotic cells is an important feature of embryonic development, tissue maintenance and wound healing, as well as immune responses. If apoptotic cells are not removed promptly, there is a risk of secondary necrosis and inflammation. But how do phagocytes know where to find dying cells? A study in *Cell* now shows that apoptotic cells, as well as presenting 'eat me' signals on the cell surface, release a chemoattractant that guides phagocytic cells to the site of cell death.

To test the theory that dying apoptotic cells might release attractant signals for phagocytes, Lauber and colleagues assessed the supernatants from cells that had been induced to undergo apoptosis by ultraviolet radiation or pharmacological inducers such as staurosporine. Supernatants from dying cells induced the migration of various monocytic-cell lines in transmigration assays. Supernatant from apoptotic MCF7 breast tumour cells — which are deficient for the pro-apoptotic molecule caspase-3 — induced minimal migration compared with other cell lines. But supernatant from MCF7 cells that stably express caspase-3 did induce migration, and this could be inhibited by treatment with the caspase inhibitor zVAD-fmk, indicating that the process was caspase-3 dependent.

Next, the authors investigated the nature of the chemoattractant signal in the supernatants. Treatment with proteinase K, DNase or RNase had no effect, so the chemoattractant could not be protein, DNA or RNA. The factor could be extracted with chloroform or diethyl ether, indicating that it was a lipid. The authors then tested a series of active phospholipids and found that lysophosphatidylcholine (LPC) and platelet-activating factor (PAF) could neutralize the chemotactic effect when added to the responding cells in transmigration assays, but only LPC could directly induce the migration of monocytes. Injection of supernatants from apoptotic cells into the peritoneum resulted in a greater macrophage infiltration than did administration of supernatant from non-apoptotic cells.

How is LPC generated in dying cells? Further experiments showed that LPC is generated as a result of caspase-3-mediated activation of the calcium-independent phospholipase A2.

This work shows that apoptotic cells attract professional phagocytes by releasing recruitment signals to ensure that dying cells are promptly dealt with and so prevent secondary necrosis.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPER Lauber, K. *et al.* Apoptotic cells induce migration of phagocytes via a caspase-3-mediated release of a lipid attraction signal. *Cell* **113**, 717–730 (2003)

FURTHER READING Savill, J. *et al.* A blast from the past: clearance of apoptotic cells regulates immune responses. *Nature Rev. Immunol.* **2**, 965–975 (2002) | Ravichandran, K. S. "Recruitment signals" from apoptotic cells: invitation to a quiet meal. *Cell* **113**, 817–820 (2003)

IN BRIEF

LYMPHOCYTE MIGRATION

Selective imprinting of gut-homing T cells by Peyer's patch dendritic cells.

Mora, J. R. *et al. Nature* **424**, 88–93 (2003)

The capacity of activated effector and memory T cells to migrate preferentially to tissues that are connected to the lymphoid organs in which they first encountered antigen has been known for some time. But how is this homing ability conferred on the T cells? For gut-homing T cells, von Andrian and colleagues now show that Peyer's-patch dendritic cells (DCs) are the cells that confer this homing capacity. Only DCs from the Peyer's patches could induce high levels of expression of the integrin $\alpha4\beta7$ and the chemokine receptor CCR9, which are essential for homing of T cells to the small intestine. Whether this imprinting is an instructive or selective process remains to be determined.

TUMOUR IMMUNOLOGY

Stat5 synergizes with T cell receptor/antigen stimulation in the development of lymphoblastic lymphoma.

Kelly, J. A. *et al. J. Exp. Med.* **198**, 79–89 (2003)

This study shows the oncogenic potential of dysregulated expression of STAT5a or STAT5b. Signal transducer and activator of transcription (STAT) proteins are important components of many signalling pathways that are induced by cytokines and growth factors, and they have also been implicated in oncogenesis. In this study, Kelly *et al.* investigated the effect of overexpression of non-activated Stat5a or Stat5b in the lymphoid compartment. Expression of a *Stat5a* or *Stat5b* transgene resulted in the development of thymic T-cell lymphoblastic lymphomas. The rate of malignant transformation was increased by antigenic or adjuvant stimuli, or by the introduction of T-cell receptor transgenes.

T-CELL DEVELOPMENT

The Runx1 transcription factor inhibits the differentiation of naive CD4$^+$ T cells into the T_H2 lineage by repressing *GATA3* expression.

Komine, O. *et al. J. Exp. Med.* **198**, 51–61 (2003)

The transcription factor RUNX1 (also known as acute myelogenous leukaemia protein 1, AML1) is involved in the control of haematopoiesis and in leukaemogenesis. The differentiation of naive CD4$^+$ T cells into T helper (T_H) cells is controlled by a combination of transcription factors and here, the authors investigated the role of RUNX1 in this process. Naive CD4$^+$ T cells from transgenic mice that express a dominant interfering form of Runx1 showed enhanced production of the T_H2-type cytokine interleukin-4 and enhanced T_H2-cell development. By contrast, overexpression of Runx1 blocked the development of naive CD4$^+$ T cells into T_H2 cells and inhibited the expression of the transcription factor GATA3. So, by inhibiting GATA3 expression, RUNX1 acts as a negative regulator of T_H2-cell differentiation.

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