INFLAMMATION

Mopping up the mess

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As immune responses wind down, leukocytes start to die by apoptosis, and the local milieu switches from being pro-inflammatory to being 'pro-resolution'. A recent report in *Nature Immunology* provides a link between these two events and indicates that apoptotic leukocytes themselves have an active role in resolving inflammation, by functioning as scavengers of pro-inflammatory chemokines.

To assess key events in the resolution of acute inflammation, Serhan and colleagues studied mouse peritonitis that was induced by injection of zymosan A (a cell-wall component of yeast). The authors noted that, 12 hours after the induction of peritonitis, peritoneal exudate from mice that were deficient in CC-chemokine receptor 5 (CCR5) contained greater amounts of the CCR5 ligands CC-chemokine ligand 3 (CCL3) and CCL5 than did exudate from wild-type mice. By contrast, CCR5 deficiency did not prevent the reduction in levels of the pro-inflammatory chemokine CXC-chemokine ligand 12 (CXCL12; which is not a ligand for CCR5) that normally occurs 12 hours after the induction of inflammation. These findings indicated that CCR5 might be involved in the clearance of its pro-inflammatory chemokine ligands during the resolution of inflammation.

Next, the authors asked whether neutrophils that are undergoing apoptosis in the inflamed peritoneal cavity might be involved in the clearance of CCR5 ligands. To address this, the authors transferred apoptotic neutrophils from wild-type or CCR5-deficient mice into the peritoneal cavities of CCR5-deficient mice with peritonitis, then (1 hour later) measured the chemokine levels in the peritoneal exudate. Indeed, the peritoneal exudate of mice that had received wild-type apoptotic neutrophils contained less CCL3 and CCL5, as well as slightly less of the pro-inflammatory cytokine tumour-necrosis factor, than did the exudate of mice that had received CCR5-deficient cells. Moreover, that apoptotic neutrophils have a role in this process was supported by the observation that these cells expressed large amounts of CCR5, particularly at late stages of apoptosis (as determined by positive staining with propidium iodide).

The upregulation of CCR5 expression by neutrophils late in apoptosis was shown to depend on the caspase-mediated pathway of apoptosis and could be prevented by exposure of the cells to the pro-survival factor tumour-necrosis factor. By contrast, exposure to pro-resolution lipid mediators, such as lipoxin A_4 and protectin D1, caused a marked increase in CCR5 expression by apoptotic neutrophils. Interestingly, CCR5 expression by apoptotic neutrophils did not confer chemotactic responsiveness to CCR5 ligands, consistent with a scavenging role for CCR5 on these cells.

Finally, similar observations were made for T cells that were induced to undergo apoptosis by the drug staurosporine or by exposure to CD95 ligand: late in apoptosis, T cells were shown to express large amounts of CCR5 in a caspase-dependent manner. Importantly, CCR5 expressed by T cells at late stages of apoptosis was shown to have a higher affinity for the CCR5 ligand CCL4 than did CCR5 expressed by non-apoptotic cells, indicating that apoptotic T cells might be particularly efficient at sequestering CCR5 ligands.

Together, these results define a new role for apoptotic neutrophils and T cells in shutting down immune responses, by expressing large amounts of CCR5 and mopping up pro-inflammatory chemokines. That these apoptotic, CCR5-expressing chemokine scavengers are ultimately targets of phagocytosis by macrophages completes the steps that are required for the clearance of pro-inflammatory mediators.

Lucy Bird

ORIGINAL RESEARCH PAPER Ariel, A. *et al.* Apoptotic neutrophils and T cells sequester chemokines during immune response resolution through modulation of CCR5 expression. *Nature Immunol.* 1 Oct 2006 (doi:10.1038/ni1392)