BANANASTOCK

IMMUNE REGULATION

Controlling neutrophil plasticity

Recently, neutrophils have been found to have previously unanticipated plasticity, being able to take on either a pro-inflammatory or an anti-inflammatory phenotype. Now, a study in *Nature Immunology* shows that this plasticity is regulated by a systemic acute-phase protein and by invariant natural killer T (iNKT) cells. The authors propose that tumours may exploit the anti-inflammatory properties of neutrophils to limit tumour-specific immune responses.

Cerundolo and colleagues first noticed that the blood of patients with melanomas contained a larger number of neutrophils (defined as $CD11b^{+}CD15^{+}$ cells) than the blood of healthy individuals. Moreover, these neutrophils constitutively produced the anti-inflammatory cytokine interleukin-10 (IL-10) and, unlike neutrophils from healthy individuals, they could suppress the proliferation of tumour-specific $CD8^{+}$ T cells in *in vitro* assays. A search for the factor responsible for this expansion of IL-10-producing neutrophil populations revealed that the factor that was present at the highest concentration in the blood of all of the patients with melanomas was the acute-phase protein serum amyloid A1 (SAA1). The levels of SAA1 positively correlated with the frequency of neutrophils and the stage of disease. Furthermore, when neutrophils from healthy individuals were exposed to SAA1, they secreted IL-10 and gained T cell suppressive activity. This SAA1-dependent secretion of IL-10 could be blocked by antibody specific for the SAA1 receptor formyl peptide receptor 2 (FPR2) and by inhibitors of its downstream protein kinases.

To further investigate the regulation of neutrophil plasticity, the authors turned their attention to iNKT cells, which have been shown to control the activity of some suppressive myeloid cell populations. Neutrophils express both CD40 and CD1d (the restriction element for iNKT cells) and, accordingly, incubation of neutrophils from melanoma patients with iNKT cells promoted the activation and production of interferon-γ by iNKT cells. In turn, IL-10 secretion by neutrophils in these co-cultures was suppressed and instead they secreted the pro-inflammatory cytokine IL-12. Several lines of evidence showed that this crosstalk was dependent on CD40 and CD1d, and was promoted by the presence of SAA1 and the iNKT cell agonist α-galactosylceramide, indicating that iNKT cells provide a negative feedback loop to decrease IL-10 production by neutrophils and limit their anti-inflammatory activities.

This feedback loop was also shown to occur in an *in vivo* setting: mice that lacked NKT cells generated a greater number of IL-10-producing neutrophils following injection of SAA1, and in mixed bone marrow chimeric mice, more CD1d-deficient cells expanded into IL-10-producing suppressive neutrophils than did CD1d-expressing cells.

So, this study identifies a new mechanism for the control of inflammatory processes mediated by SAA1 that results initially in the generation of anti-inflammatory neutrophils and then in a neutrophil–iNKT cell crosstalk that downmodulates the neutrophil suppressive properties. Why this downmodulation does not occur in patients with melanomas requires further investigation.

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ORIGINAL RESEARCH PAPER De Santo, C. *et al.* Invariant NKT cells modulate the suppressive activity of IL-10-secreting neutrophils differentiated with serum amyloid A. *Nature Immunol.* 3 Oct 2010 (doi:10.1038/ni.1942)