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MUCOSAL IMMUNOLOGY

# Bewildered progenitors

Chronic inflammation involves aberrant cytokine production by innate immune cells and T cells. Here, Powrie and colleagues report that pro-inflammatory cytokines — including interferon-γ (IFNγ) and granulocyte–macrophage colony-stimulating factor (GM-CSF) — act on haematopoietic stem cells (HSCs) and granulocyte–monocyte progenitors (GMPs) to increase the generation of neutrophils and other inflammatory myeloid cells in mice with interleukin-23 (IL-23)-dependent colitis.

Studies using a mouse model of T cell-dependent colitis (induced by the transfer of $CD25^{-}CD4^{+}$ T cells to *Rag1*$^{-/-}$ mice, which lack mature adaptive immune cells) showed that colitis was associated with high numbers of HSCs and GMPs in the bone marrow. Moreover, the numbers and differentiation capacities of HSCs and GMPs were increased in the spleens of colitic mice compared with control mice or mice that had received co-transferred regulatory T cells. In addition, GMPs emerged in the colon and mesenteric lymph nodes of colitic mice. Thus, intestinal inflammation influences the overall number and differentiation potential of both bone marrow and extramedullary haematopoietic progenitors.

> “targeting cytokine signalling in HSCs and GMPs may be a relevant strategy for the treatment of chronic inflammatory disorders”

So, what drives the accumulation of HSCs and GMPs in the bone marrow and in the periphery of colitic mice? The expression of the colony-stimulating factors G-CSF and GM-CSF was found to be increased in the colons of diseased mice, and treatment of *Rag1*$^{-/-}$ mice with G-CSF or GM-CSF induced expansion of the bone marrow GMP population to levels comparable with those in colitic mice. However, administration of G-CSF or GM-CSF was not sufficient to increase the numbers or differentiation capacities of extramedullary HSCs and GMPs, indicating that local pro-inflammatory cytokines rather than colony-stimulating factors may have a dominant role in extramedullary granulopoiesis during chronic inflammation.

Indeed, HSCs express cytokine receptors, including the receptor for IFNγ, which is produced by colitogenic innate lymphoid cells and T cells in an IL-23-dependent manner. Strikingly, IFNγ blockade reversed the colitis-associated increase in the numbers of bone marrow and splenic HSCs and hampered extramedullary granulopoiesis in a mouse model of T cell-independent colitis. Moreover, in the T cell-dependent colitis model, IFNγ-producing T cells were found to accumulate not only in the spleen and colon, but also in the bone marrow. So, local IFNγ production may promote granulopoiesis directly by sustaining the proliferation and differentiation of HSCs.

Notably, although GM-CSF administration alone was not sufficient to induce extramedullary granulopoiesis, GM-CSF blockade reduced the numbers of splenic and colonic GMPs and decreased the differentiation of these cells into neutrophils in colitic mice. Thus, GM-CSF — which was found to be produced in part by colitogenic T helper 17 cells in an IL-23-dependent manner — acts downstream of the IFNγ-dependent expansion of the HSC population to promote the peripheral accumulation and differentiation of GMPs.

Finally, adoptive transfer of splenic GMPs from colitic mice into *Rag1*$^{-/-}$ recipients confirmed the key role of these progenitor cells in disease pathogenesis. Thus, the authors suggest that targeting cytokine signalling in HSCs and GMPs may be a relevant strategy for the treatment of chronic inflammatory disorders such as inflammatory bowel disease.

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**ORIGINAL RESEARCH PAPER** Griseri, T. *et al.* Dysregulated hematopoietic stem and progenitor cell activity promotes interleukin-23-driven chronic intestinal inflammation. *Immunity* 29 Nov 2012 (doi:10.1016/j.immuni.2012.08.025)