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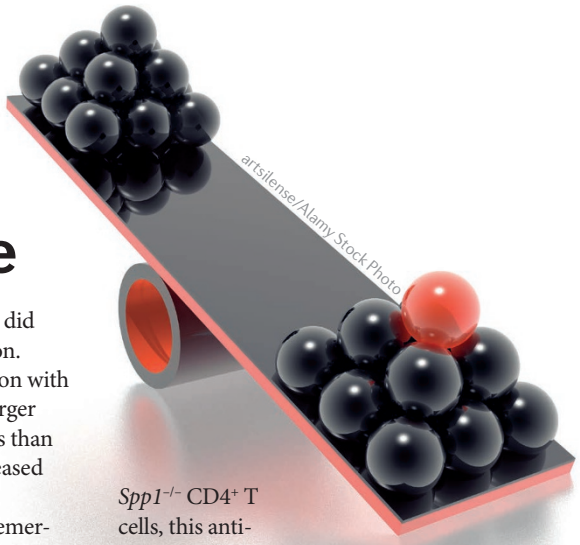
HAEMATOPOIESIS

Osteopontin skews lymphoid–myeloid balance



The balance between the production of myeloid cells and lymphoid cells in the bone marrow is tightly regulated to adapt to demand. For example, after severe infection, inflammation or irradiation, 'emergency myelopoiesis' compensates for the loss of myeloid cells. This study reports distinct roles for different isoforms of osteopontin (OPN) — secreted (sOPN) and intracellular (iOPN) — that together function to skew the balance of haematopoietic cells towards decreased myeloid cell numbers and increased lymphoid cell numbers.

In mixed bone-marrow chimaeras generated by the transfer of wild-type bone marrow and *Spp1*$^{-/-}$ bone marrow (which lacks OPN) into irradiated hosts, the *Spp1*$^{-/-}$ donor cells formed larger populations of myeloid progenitor cells and smaller populations of lymphoid progenitor cells in multiple organs compared with wild-type donor cells. This result indicated that cell-intrinsic OPN expression restricts the emergency myelopoiesis response to irradiation. Similar data were obtained from a model of neutrophil migration from the bone marrow, which was induced by peritoneal injection of thioglycollate. Here, *Spp1*$^{-/-}$ mice had more granulocyte–macrophage progenitors (GMPs) and neutrophils in the bone marrow than did wild-type mice 24 hours after injection. Furthermore, during systemic infection with *Candida albicans*, *Spp1*$^{-/-}$ mice had larger populations of GMPs and neutrophils than did wild-type mice, resulting in decreased fungal load and increased survival.

To investigate how OPN restricts emergency myelopoiesis, the authors showed that *Spp1*$^{-/-}$ multipotent progenitors express higher levels of *Birc5* (which encodes the anti-apoptotic protein survivin) and have increased survival in *ex vivo* assays compared with wild-type progenitors. In irradiated wild-type host mice receiving wild-type donor cells, there was significantly greater apoptosis of myeloid progenitors (but not lymphoid progenitors) than in mice receiving *Spp1*$^{-/-}$ donor cells. Thus, OPN promotes apoptosis of myeloid progenitors. By contrast, OPN was shown to be anti-apoptotic for differentiated lymphoid cells during, for example, chronic lymphopenia-induced proliferation of B and T cells. In a T cell-mediated colitis model, disease severity was reduced in mice receiving *Spp1*$^{-/-}$ donor T cells compared with mice receiving wild-type T cells.

As the addition of recombinant OPN to cell culture partially restored the survival of *Spp1*$^{-/-}$ CD4^{+} T cells, this anti-apoptotic function seems to be mediated by sOPN. The authors generated a mouse strain that expresses iOPN but not sOPN, and used this to confirm that sOPN, not iOPN, protects T cells from apoptosis. However, in various models, it was iOPN that restricted the size of GMP populations, in part through decreased expression of *Birc5*.

In summary, the results show that iOPN and sOPN differentially regulate myeloid progenitors and differentiated lymphoid cells, respectively, through pro- and anti-apoptotic effects. The net result is that OPN functions to restrict emergency myelopoiesis but enhance the response to lymphopenia.

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ORIGINAL ARTICLE Kanayama, M. *et al.* Skewing of the population balance of lymphoid and myeloid cells by secreted and intracellular osteopontin. *Nat. Immunol.* http://dx.doi.org/10.1038/ni.3791 (2017)