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Myelopoiesis embraces its inner weakness

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Abstract

The ability to expand and contract populations of myeloid and lymphoid cells during emergency hematopoiesis helps shape the immune response. The expression of intracellular and soluble forms of osteopontin regulates apoptosis thresholds differently in myeloid cells and lymphoid cells to counter infection.

Enhanced recruitment of neutrophils during infection with the Gram-negative intracellular pathogen *Rickettsia tsutsugamushi* is correlated with poor outcome¹. Here, quality, not just quantity, is important in host resistance to this pathogen. Genetic mapping of loci encoding products that control resistance to *R. tsutsugamushi* has identified a region encoding the phosphoglycyl-coprotein osteopontin (OPN)². Although it was originally identified in bone, OPN influences many aspects of immune responses, including Toll-like receptor-induced cytokine production by macrophages and dendritic cells (DCs)³ and T cell polarization^{3,4}. In the current issue of *Nature Immunology*, a study by Kanayama *et al.* casts new light on the role of OPN in emergency hematopoiesis and how the intracellular form of OPN (iOPN) shapes the inflammatory response⁵.

The supply of myeloid and lymphoid cells during inflammatory responses is tightly regulated to meet the demands of the host: with too few myeloid cells, infections might not be controlled; with too many myeloid cells, exacerbated inflammatory responses, collateral tissue damage and chronic inflammation might be initiated. Not only is the supply of immune cells regulated, but also the balance of myeloid subsets and lymphoid subsets is exquisitely regulated. Numerous stimuli influence the myeloid and lymphoid progenitor-cell compartments. A multitude of hematopoietic growth factors and inflammatory cytokines coordinate with intracellular signal transducers and negative regulators of signal transduction to control the proliferation, differentiation and survival of cells of the myeloid and lymphoid lineages. Emergency myelopoiesis, the process that generates mature myeloid cells, is a feature of the response to infection and inflammatory stimuli and the physiological response to myeloablation. Tailoring emergency myelopoiesis to meet the demands of the bone

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marrow and the demands of the immune response requires constant sensing of peripheral cues in the bone marrow to adjust the output of myeloid cells from the progenitor-cell compartment.

Kanayama *et al.* show how iOPN and secreted OPN (sOPN) can have opposing effects on myeloid and lymphoid progenitor cells during emergency hematopoiesis⁵. The Hippo signaling pathway controls cell proliferation and organ size, but its role in hematopoiesis has remained uncertain. Kanayama *et al.* now demonstrate that E-cadherin-Hippo signaling is important for controlling the cell-density-dependent regulation of OPN expression⁵. At a high density of granulocyte- macrophage progenitors (GMPs) in the bone marrow, E-cadherin-Hippo signaling drives iOPN expression in GMPs to limit the expansion of the myeloid pool (Fig. 1). The nature of the *in vivo* interactions between GMPs and mature hematopoietic or bone-marrow-niche cell types (for example, E-cadherin signaling) are not studied here, but the results suggests that Hippo signaling in GMPs that is dependent on the density of bone marrow cells has a central role in limiting emergency myelopoiesis via iOPN. Hematopoietic growth factors and inflammatory cytokines, such as GM-CSF and TNF, are also shown to induce OPN expression and might provide direct feedback to the myeloid compartment to restrict further expansion when an inflammatory response has been initiated. In contrast to GM-CSF and TNF, signaling by the interferons IFN- α and IFN- β via their receptor IFNAR has been shown to suppress OPN expression in DCs in the periphery, but it is not known if these effects extend to hematopoietic stem cells and progenitor cells⁴. Constitutive and inducible patterns of OPN expression have also been described in DCs (both conventional DCs and plasmacytoid DCs), macrophages, T cells and natural killer cells, as well as in nonhematopoietic cells, including epithelial cells, osteoblasts, fibroblasts, smooth-muscle cells and endothelial cells^{6,7}.

By generating mice that express only iOPN, Kanayama *et al.* show that restriction of myelopoiesis can be attributed to iOPN during emergency hematopoiesis, whereas sOPN, but not iOPN, seems to promote the population expansion of common lymphoid progenitors⁵. They find substantial induction of sOPN and iOPN in T cells after activation, suggestive of a role for OPN isoforms in the resolution phase of effector T cell responses. In precursors of myeloid cells, iOPN suppresses the expression of *Birc5*, which encodes the anti- apoptotic factor survivin, and thereby establishes an appropriate threshold for apoptosis (Fig. 1). Whether survivin is the main target of iOPN needs further study and potentially needs to be considered in the context of published studies showing that OPN induces the anti-apoptotic factor Bcl-x_L and promotes the survival of CD8+ T cells⁸. Such studies suggest that the induction of Bcl-x_L by sOPN might also underlie the population expansion of lymphoid cells in transplantation recipients. Published work has indicated that inhibition of OPN prevents CD8+ T cell-mediated graft-versus-host disease by inducing the apoptosis of donor-derived CD8+ T cells⁸. OPN levels are elevated in autoimmune-prone *MRL-lpr* (faslpr) mice and in the serum of patients with autoimmune lymphoproliferative syndrome^{9,10}. Kanayama *et al.* also show that autoimmune colitis in mice is driven by T cell- derived sOPN⁵. The pathological features of T cell-mediated colitis (thickened mucosa, loss of goblet cells and infiltration of inflammatory cells) are not alleviated by the expression of iOPN, in further support of the proposal of this unique role for sOPN in the survival of T cells among differentiated lymphoid cells in the periphery. These data provide

further support for the use of OPN-neutralizing therapy for some autoimmune patients, because pharmacological inhibition of sOPN would be predicted to impair the survival of activated T cells but would not influence the iOPN-mediated regulation of myeloid-cell production.

OPN contributes to the defense against infection with a low dose of *Candida albicans* but not against infection with a medium dose of this pathogen¹¹. In the current study, to focus on emergency granulopoiesis, Kanayama *et al.* assess responses to a high dose of *C. albicans* in the acute phase of infection⁵. In mice, OPN deficiency affords protection from acute infection with a high dose of *C. albicans*; this might be a consequence of the elevated expansion of the myeloid cell pool in these mice (discussed above). These data suggest that during infection with a low dose of *C. albicans*, iOPN is needed to restrict the inflammatory response to prevent collateral tissue damage, while during infection with a high dose of this pathogen, when presumably large numbers of myeloid cells need to be mobilized, expression of iOPN and its consequent inhibition of myelopoiesis is detrimental to the host. Further work is needed to understand the contribution of iOPN to fungal load and mortality and to understand the influence of OPN during infection with different strains and doses of *C. albicans*. The ability of sOPN to regulate the myeloid-progenitor-cell compartment cannot be completely discounted, given the negative regulatory effects of sOPN on the viability of hematopoietic stem and progenitor cells shown in published studies¹². OPN expression controls the release of lactate dehydrogenase during *C. albicans* infection and is indicative of cell damage, such as systemic apoptosis or a non-apoptotic lytic form of cell death.

The role of cell death during emergency hematopoiesis has come into focus in recent years. Apoptosis, as well as the regulated non-apoptotic forms of cell death (necroptosis and pyroptosis), can influence hematopoiesis following infection or in the setting of bone-marrow transplantation¹³. The demonstration that annexin V staining of hematopoietic stem and progenitor cells is diminished in the absence of OPN following transplantation or infection might also be consistent with descriptions of annexin V staining of cells undergoing non-apoptotic cell death^{14,15}. iOPN and sOPN might also regulate the expression of regulators of these non-apoptotic forms of cell death, in addition to that of genes encoding apoptotic molecules such as survivin and Bcl-x_L.

iOPN and sOPN coordinately shape emergency hematopoiesis via actions on hematopoietic cells and the bone-marrow niche¹². Competitive chimeric animals and adoptive transfer of iOPN-expressing cells will be needed in the future to understand the source and function of sOPN and iOPN isoforms in the bone marrow during emergency hematopoiesis. The contrasting effects of iOPN and sOPN on cell-survival pathways in myeloid progenitor cells and peripheral lymphoid cells suggest that unique apoptosis pathways are engaged by these OPN isoforms. iOPN-expressing mice will be key to understanding how iOPN and sOPN influence the survival of other immune cells and the factors that control the expression, localization and signal transduction of OPN and the degradation of OPN protein.

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Figure 1. iOPN shapes emergency myelopoiesis.

iOPN suppresses myelopoiesis by responding to cell- density cues from the E-cadherin-Hippo signaling pathway. The expression of iOPN in GMPs regulates the level of survivin to establish apoptosis signaling thresholds during emergency myelopoiesis. BM, bone marrow; Mono, monocyte; PMN, polymorphonuclear cell.