Neutrophils set the bone marrow on fire

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Neutrophils are immune defenders. In this paper, Kawano *et al.* show that, by producing prostaglandin E_2 (PGE_2), they also regulate hematopoietic stem cell mobilization and cause fever [1].

The bone marrow is home to hematopoietic stem and progenitor cells (HSPC) and their descendants. Continued production of all blood lineages requires a structured organization and complex interactions among the many cell types that reside in this organ. Among these cell types, early studies identified osteoblastic cells that line the endosteal surface as important components of the hematopoietic niche, whereas macrophages and other cells of hematopoietic origin have only been recognized as regulators of the bone marrow niche in recent years [2]. Sympathetic nerves and mesenchymal progenitors are also regulators of the HSPC niche, and current efforts in the field aim to understand how all these very different cellular elements coordinate to preserve bone marrow homeostasis.

Transient disorganization of the cellular niche network may be important when the bone marrow needs to supply a surplus of defensive immune cells in response to a stress. For example, during acute infections endothelial cells respond by producing large amounts of the cytokine granulocyte colony-stimulating factor, or G-CSF [3]. On one hand, this cytokine accelerates production of neutrophils (i.e., granulopoiesis), the genuine anti-microbial defenders; on the other hand, G-CSF initiates a cascade of events within the bone marrow that disrupts niche activity and leads to the release of HSPC into the bloodstream. Hematologists appreciated the therapeutic potential of using G-CSF to expand and push HSPC out of the bone marrow for their efficient collection from blood. Indeed, blood obtained from G-CSF-treated donors is nowadays the preferred source of HSPC for transplantation therapy. A surprising side-effect of G-CSF treatment is the appearance of low-grade fever and bone pain that responds to nonsteroid anti-inflammatory drugs (NSAID), which inhibit the prostaglandin synthesis pathway. How G-CSF caused fever was unknown, until now.

While studying the mechanism of fever in experimental models of G-CSF mobilization, Kawano et al. identify a previously unknown molecular and cellular circuitry in the bone marrow that induces the production of PGE_2. This lipid not only caused fever, but also limited the inhibitory effect of G-CSF on the hematopoietic niche.

The authors reasoned that if G-CSF treatment caused a raise in temperature that could be prevented by NSAID, activation of the arachidonic acid cascade and production of pyrogenic prostaglandin E_2 might be involved in the mobilizing effects of the cytokine. They identified the microsomal PGE-1 synthase as a critical mediator of fever in G-CSF-treated mice. Surprisingly, while deficiency in this catalytic enzyme prevented changes in body temperature, it enhanced –rather than prevent- mobilization of HSPC into blood, and these effects required its expression in the transplantable hematopoietic compartment. The authors found, however, that G-CSF did not trigger PGE_2 production by acting directly on hematopoietic cells. How, then, did G-CSF control prostaglandin production?

To search for possible mechanisms the authors revisited their own seminal work from a decade earlier demonstrating that G-CSF stimulates the catecholaminergic tone in the bone marrow [4]. They therefore predicted that catecholamines might be intermediaries needed for PGE_2 production. Indeed, treatment with a β-adrenergic agonist stimulated prostaglandin release by neutrophils, and to a lesser extent by macrophages, in a

process that depended on the β3 adrenergic receptor. The authors went on to demonstrate that if neutrophils were depleted before G-CSF treatment, or if the cells that produce catecholamines were eliminated, then fever disappeared in treated mice.

These findings, however, were at odds with the exaggerated mobilization of HSPC in mice unable to synthesize PGE_2, and suggested that generation of fever and mobilization were antagonistic effects. The response to this puzzle came, again, after revisiting earlier work showing that PGE_2 improves HSPC retention by stimulating osteoblastic cell function through production of osteopontin, an HSPC retention molecule [5]. In agreement with these observations, Kawano et al. found that indeed PGE_2 acts locally in the bone marrow by dramatically increasing osteopontin on pre-osteoblastic cells, through the prostaglandin receptor EP4. Altogether, the data presented in this paper uncovers a signaling network elicited by G-CSF that stimulates catecholamine production, which acts on β3-adrenergic receptors on neutrophils to induce production of PGE_2. This lipid acts locally on niche cells to limit HSPC release, and systemically on the hypothalamus to induce fever (see Figure).

The findings by the Katayama group are important because they provide formal demonstration that neutrophils, which are the most abundant cell type in the bone marrow, are *bona fide* regulators of the HSPC niche. Previous studies had demonstrated that neutrophils can induce local inhibition of niches, or control granulopoiesis from extramedullary tissues [6,7]. The present study, however, is the first to identify a neutrophil-derived product that positively regulates niche cells. Although less abundant, monocytes and macrophages respond in a similar way, thereby reinforcing the notion that innate immunity is an important regulatory network within the marrow. Different from other proposed niche cells, however, neutrophils and other myeloid cells appear to provide a system that better integrates environmental signals for finer regulation of HSPC during stress. The study raises the important question of whether, and if so how, innate immunity regulates stem cell niches in the context of pathological stress (e.g., infection or leukemia).

Finally, it is intriguing that experimental depletion of neutrophils caused mild but significant reductions in body temperature after G-CSF treatment. Because neutrophils are distributed in many more organs than the bone marrow, are can themselves produce not only PGE_2 but also catecholamines [8], it would seem that neutrophils are superbly fitted to regulate core processes, as illustrated here for body temperature and stem cell niches. Clearly, neutrophils are far more than immune defenders.

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Figure legend

Treatment with G-CSF causes mobilization of HSPC and triggers fever. By acting on catecholaminergic cells (nerve cells or other), G-CSF increases the adrenergic tone in the marrow, thereby generating catecholamines that in turn activate neutrophils through the β3 adrenergic receptor (β3R; inset). As a consequence of adrenergic stimulation neutrophils produce PGE_2, which can target osteoblastic cells through the EP4 receptor to promote HSPC retention. Additionally, neutrophil-derived PGE_2 causes fever by systemically acting on the brain.