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Inflammatory cytokines provide both infection-responsive and developmental signals for blood development: Lessons from the zebrafish

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ABSTRACT

Hematopoietic stem cells (HSCs) are rare, largely dormant, long-lived cells that are capable of establishing and regenerating all mature blood cell lineages throughout the life of the host. Given their therapeutic importance, understanding factors that regulate HSC development and influence HSC proliferation and differentiation is of great interest. Exploring HSC biology through the lens of infection has altered our traditional view of the HSC. The HSC can now be considered a component of the immune response to infection. In response to inflammatory cytokine signaling, HSCs enhance their proliferative state and contribute to the production of in-demand blood cell lineages. Similar cytokine signaling pathways also participate during embryonic HSC production. With its highly conserved hematopoietic system and experimental tractability, the zebrafish model has made significant contributions to the hematopoietic field. In particular, the zebrafish system has been ideally suited to help reveal the molecular and cellular mechanisms underlying HSC development. This review highlights recent zebrafish studies that have uncovered new mechanistic insights into how inflammatory signaling pathways influence HSC behavior during infection and HSC production within the embryo.

1. Introduction

The hematopoietic system is hierarchically organized, with hematopoietic stem cells (HSCs) at the top that undergo limited divisions to either maintain the stem cell pool throughout the life of the host, or give rise to multipotent and lineage-committed hematopoietic progenitor cells that generate all mature blood cell lineages. This hierarchical organization ensures large-scale amplification of mature blood cell types, for example $\sim 3 \times 10^5$ erythrocytes and 3×10^4 leukocytes are generated per second within the adult human hematopoietic system (Takizawa et al., 2012). In addition to maintaining homeostatic numbers of blood cells, this hierarchical organization provides flexibility in cellular output when homeostasis of the blood system is lost. The hematopoietic system has evolved mechanisms to sense when homeostasis is lost and initiate changes in the cells it produces to help restore it. As an example, inflammation or infection has profound effects on bone marrow hematopoiesis, including changes in the production of in-demand blood cell lineages such as neutrophils (Takizawa et al., 2012; King and Goodell, 2011; Baldridge et al., 2011; Manz and Boettcher, 2014). During infection, inflammatory signaling pathways act to alert the blood system. This process involves several cellular components, from peripheral tissue-resident immune cells such as macrophages and non-hematopoietic endothelial cells that act to sense the pathogen, to bone marrow-resident hematopoietic stem and progenitor cells (HSPCs) that respond to signals sent from these pathogen-sensing cells (Manz and Boettcher, 2014; Boettcher et al., 2014). It has been suggested that similar inflammatory signaling pathways also function during early development, when the hematopoietic system is first established (Qiu et al., 1998; Weih et al., 1995; Beg et al., 1995; Orelio et al., 2008; Robin et al., 2006). With their self-renewal and multipotent potential, HSCs are the key component in blood transplantations to treat patients with blood deficiencies (Clapes and Robin, 2012). Given this clinical importance, a thorough understanding of the molecular mechanisms that control HSC development and regulate HSC behavior is necessary to completely unlock their therapeutic potential.

In this review we briefly describe the cellular and molecular mechanisms through which inflammation, and its associated signaling pathways, influences blood development, before highlight-

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ing recent zebrafish studies that have expanded our understanding of this growing field of research. Of particular focus is the influence of inflammatory signaling pathways on the most regenerative cell of the blood system, the HSC.

2. Inflammatory signaling and hematopoiesis

2.1. Emergency granulopoiesis

The hematopoietic system is dynamically responsive to stress and has evolved mechanisms to communicate stress-induced changes in the peripheral blood system back to the bone marrow where cellular output of specific blood cell types is increased to meet the needs to the host. This adaptive type of hematopoiesis is called demand-driven hematopoiesis (Takizawa et al., 2012). Perhaps the best example of this adaptive nature of the hematopoietic system is its response to severe infections. During a local infection, neutrophils migrate to the infection site where they contribute to containing and eliminating the pathogenic challenge through their antibacterial activities. Neutrophilic inflammation then resolves as neutrophils reenter the circulation or undergo apoptosis (Kolaczkowska and Kubes, 2013). If the infection is not contained and spreads systemically there is a higher demand for neutrophils to help clear the spreading infection and to replace those already consumed by infection. This higher demand is met by switching hematopoiesis in the bone marrow from steady-state to emergency granulopoiesis (Manz and Boettcher, 2014). This skewing of hematopoiesis towards granulopoiesis is often at the expense of other lineages, in particular the lymphoid lineage (Takizawa et al., 2012; Manz and Boettcher, 2014).

Broadly speaking the emergency granulopoietic response can be divided into 3 phases: 1, the pathogen needs to be sensed to alert the immune and hematopoietic systems; 2, the sensing of this emergency state needs to be communicated to the bone marrow to initiate enhanced neutrophil production; 3, following clearance of the infection hematopoiesis needs to revert back to steady-state (Manz and Boettcher, 2014). Following systemic spread of bacteria, hematopoietic and non-hematopoietic cells within peripheral tissues and bone marrow likely contribute to pathogen-associated molecular pattern (PAMP) sensing through pattern recognition receptors (PRRs) including the Toll-like receptors (TLRs). Both direct and indirect mechanisms have been proposed to activate the hematopoietic system (Fig. 1). HSPCs could sense PAMPs directly within the bone marrow compartment or hematopoietic (e.g. macrophages) and/or non-hematopoietic cells in peripheral tissues or bone marrow could sense the pathogen and translate this to HSPCs through cytokine signaling (Manz and Boettcher, 2014). A critical cytokine in this process is the granulopoiesis-promoting cytokine granulocyte colony-stimulating factor (G-CSF) (Boettcher et al., 2014; Panopoulos and Watowich, 2008). Recently, the endothelial cell has been revealed as a primary non-hematopoietic cell type that can sense systemic bacterial spread and indirectly translate pathogen sensing to the bone marrow during emergency granulopoiesis (Boettcher et al., 2014). This endothelial cell sensing of systemic bacteria is translated into endothelial cell G-CSF production through cell intrinsic TLR4/myeloid differentiation primary response gene 88 (MyD88) signaling (Boettcher et al., 2014). Another recent mouse study has demonstrated a role for inflammation-induced reactive oxygen species (ROS) production in the bone marrow during emergency granulopoiesis (Kwak et al.,

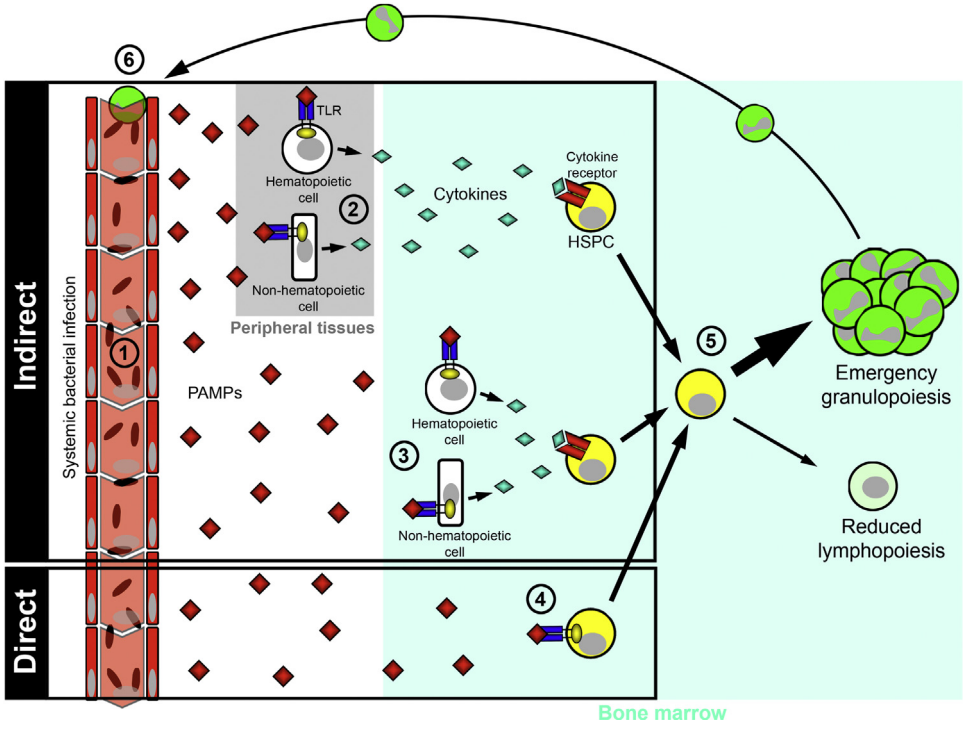

Fig. 1. Schematic illustrating both direct and indirect mechanisms of HSPC activation during emergency granulopoiesis. (1) Locally uncontrolled infection leads to systemic dissemination of bacteria. (2) In peripheral tissues, bacteria-derived pathogen-associated molecular patterns (PAMPs) can stimulate hematopoietic and non-hematopoietic cells (e.g. endothelial cells) expressing PAMP-specific Toll-like receptors (TLRs). This results in the production of cytokines (e.g. G-CSF) that can reach the bone marrow via the circulation and bind cognate receptors on HSPCs. (3) Hematopoietic cells and non-hematopoietic cells (e.g. endothelial cells) within the bone marrow compartment can also sense PAMPs leading to cytokine production that can influence HSPC behavior. (4) HSPCs themselves possess their own pattern recognition receptors that could directly sense PAMPs. (5) Cytokine and/or PAMP stimulation of HSPCs results in their proliferation and enhanced commitment to the granulocytic lineage (emergency granulopoiesis). This enhanced granulopoiesis is at the expense of lymphoid lineage commitment. (6) Increased neutrophil release from the bone marrow contributes to clearing the bacterial challenge. Both direct and indirect mechanisms of HSPC activation most likely contribute to emergency granulopoiesis.