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Review Article

Parallels between immune driven-hematopoiesis and T cell activation: 3 signals that relay inflammatory stress to the bone marrow

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ABSTRACT

Quiescence, self-renewal, lineage commitment and differentiation of hematopoietic stem cells (HSCs) towards fully mature blood cells are a complex process that involves both intrinsic and extrinsic signals. During steady-state conditions, most hematopoietic signals are provided by various resident cells inside the bone marrow (BM), which establish the HSC micro-environment. However, upon infection, the hematopoietic process is also affected by pathogens and activated immune cells, which illustrates an effective feedback mechanism to hematopoietic stem and progenitor cells (HSPCs) *via* immune-mediated signals. Here, we review the impact of pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), costimulatory molecules and pro-inflammatory cytokines on the quiescence, proliferation and differentiation of HSCs and more committed progenitors. As modulation of HSPC function *via* these immune-mediated signals holds an interesting parallel with the "three-signal-model" described for the activation and differentiation of naïve T-cells, we propose a novel "three-signal" concept for immune-driven hematopoiesis. In this model, the recognition of PAMPs and DAMPs will activate HSCs and induce proliferation, while costimulatory molecules and pro-inflammatory cytokines confer a second and third signal, respectively, which further regulate expansion, lineage commitment and differentiation of HSPCs. We review the impact of inflammatory stress on hematopoiesis along these three signals and we discuss whether they act independently from each other or that concurrence of these signals is important for an adequate response of HSPCs upon infection.

Contents

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Introduction

Hematopoiesis is the delicate process of development, production and specialization of blood cells in the BM. All hematopoietic lineages find their origin in one population of common progenitor cells, the hematopoietic stem cells (HSCs). HSC behavior was initially thought to be stochastic and independent of extrinsic factors, but findings from the last 2 decades revived Schofield's niche concept, and highlight the importance of the microenvironment in regulating plasticity of hematopoiesis [1,2]. Schofield described the niche for HSCs as an anatomical location that affects stem cell number and behavior by inducing self-renewal in proximity of this location or inducing differentiation at a distance [3]. The HSC niche, which comprises both hematopoietic and non-hematopoietic cells, does not only provide anatomical space for HSCs, but also supplies HSCs with signals for their maintenance, quiescence, self-renewal, proliferation and differentiation [2,4]. Besides the presence of HSC niches there are several other hematopoietic niches that harbor distinct hematopoietic progenitors with either full or restricted hematopoietic capacities [5,6].

Several types of niche cells control the maintenance and function of the hematopoietic stem and progenitor cells (HSPCs) through cell–cell interaction and/or the production of essential soluble factors, such as chemokines and growth factors [2,4]. This is the case for the steady-state situation, but it is less clear how the hematopoietic process is regulated during cellular stress situations, like anemia and inflammation, when hematopoietic output needs to be adjusted in order to cope with the body's altered needs. Adaptation of hematopoiesis during inflammation was first considered to be mainly regulated by systemic changes in hematopoietic cytokine levels, but evidence is accumulating that pathogens and activated immune cells can also directly influence HSPCs inside the BM [7,8]. Immune-mediated feedback signals can thereby quickly adjust the output of hematopoietic progenitors to generate specific offspring required for fighting the invading pathogen or to cope with the loss of specific blood cells. It is therefore of interest that BM not only serves as the primary site for hematopoiesis, but also acts as a microenvironment where immune cells can be activated or recruited to during immune activation [9–12]. Moreover, innate and adaptive immune cells that reside in the BM are generally found in close proximity of HSPCs and largely rely on the same retention factors as HSPCs [13,14]. Here we will review how inflammatory stress signals can modify the function of HSPCs and thereby modulate BM output.

Parallels between differentiation of T cells and HSPCs: introducing a three-signal model

HSPCs are not only regulated by intrinsic stimuli from the niche, but also express pathogen recognition receptors (PRRs), costimulatory receptors and pro-inflammatory cytokine receptors that allow HSPCs to respond to infection and inflammation. All three types of inflammatory receptors have been well characterized in guiding adaptive immune responses against an invading pathogen and it is intriguing to realize that the same molecules also enable the hematopoietic system to respond to the infection. In fact, this inflammatory parallel can even be taken one step further, as modulation of HSPC function through these pro-inflammatory molecules shows a striking analogy with the "three-signal model" described for T cell activation. In this concept, naïve T cells rely for their full effector cell formation on three distinct signals that are induced by dendritic cells (DCs) (Fig. 1) [15]. The *first* signal in this model is provided when the highly specific T cell receptor (TCR) interacts with its cognate antigen peptide presented by major histocompatibility complex (MHC) molecules on DCs, leading to activation of the T cell. Co-stimulatory molecules expressed by DCs provide a *second* signal that drives survival, proliferation and differentiation of T cells during their activation. The *third* signal skews the differentiation towards a particular type of effector T cell and is provided by cytokines derived from the activated DC [15]. We realized that hematopoietic lineage commitment during immune activation has a striking analogy with these three steps involved in T cell activation, as differentiation of quiescent HSCs first requires activation, while costimulatory molecules and inflammatory cytokines further drive the lineage commitment and differentiation (Fig. 1). We here explore immune-driven hematopoiesis along this three-signal model and discuss the inflammatory signals that, independently or in synergy with each other, are capable of regulating HSPC proliferation, lineage commitment and differentiation

Signal 1: activation

T cells are able to recognize an invading pathogen when their unique TCR interacts with a cognate peptide–MHC complex presented by DCs, which elicits Signal 1 and induces T cell activation [15]. HSPCs obviously do not express TCRs, but they are able to respond to an infection and become activated upon recognition of pathogen-associated molecular patterns (PAMPs) through expression of PRRs. HSPCs express Toll-like receptor (TLR) 2, 3, 4, 7 and 9 (reviewed in [8]), which allows them to respond to various bacterial products. Injection of mice with LPS, a TLR4-ligand, activates quiescent HSCs and turns them into self-renewing and proliferating HSCs. Whereas lineage restriction is not altered in LPS-stimulated HSCs, it does impair their repopulation capacity [16,17]. Furthermore, triggering of TLR2 and TLR4 on HSPCs induces proliferation and myeloid differentiation, whereas stimulation of granulocyte–monocyte progenitors (GMPs) drives their development towards monocytes and macrophages, and common lymphoid progenitors (CLPs) towards DCs at the expense of B-cell differentiation [18]. Interestingly, stimulation of HSPCs through TLR4 even induces the production of various pro-inflammatory cytokines by these cells, which is enhanced when TLR2 is also triggered [19]. The production of TLR-induced IL-6 is particularly relevant in this respect, as it induces myelopoiesis and HSPC proliferation in a paracrine manner and mediates myeloid recovery