Opinion

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Inflammation In HSC Emergence

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ABSTRACT

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Opinion

In our classical view, inflammation is triggered by environmental changes; may it be pathogens or tissue damage. The stimuli activate a complex transcriptional program that is both cell type and stimulus specific. At the cellular level, a complex gene expression programs that include hundreds of genes is activated within minutes after the initial activation through a stimulus [1]. But this response can vary not only between cell types [2], but even within a cell population depending on their niche environment [3]. In response to inflammatory stimuli, several response pathways can be initiated, including signal transducers and activators of transcription (STAT) [4], activator protein 1 (AP-1) [5], the nuclear factor of the κ light chain enhancer of B cells (NF-κB) [6], and interferon regulatory factors (IRFs) [7]. All these triggers have distinct binding specificities and have different receptor – ligand interaction that leads to a specific transcriptional output. For example, cytokines acting primarily through the activation of STAT TFs such as IFN-γ, are in general unable to activate NF-κB and AP-1, which are broadly responsive to a large panel of inflammatory stimuli (stretching from LPS and other microbial products to tumor necrosis factor [TNF]-α) [8]. Inflammation in general, is therefore essential for survival in the adult. Specifically, the blood system responds with cell proliferation, HSC self-renewal and progenitor expansion and differentiation.

Hence, it is all the more striking that these pathways are essential for the HSC generation in the embryo, although the mammalian fetus is protected from pathogens by a robust innate immune system at the maternal/fetal interface [9]. During embryonic development, the first Transplantable HSCs are detected between E10.25-E11.5 in the aorta- gonad and mesophephros region (AGM) [10-12] as residents of Intra-aortic hematopoietic clusters (IAHC) that are closely associated with the ventral wall of the dorsal aorta [13-15]. Although to total number of hematopoietic (cKIT) positive cells in the AGM is believed to total around 600 cells, only a small fraction is HSCs [10,16]. In general, blood cells trans-differentiation of specialized endothelial-like cells that can generate blood, termed hemogenic endothelium (HE), to hematopoietic fate during early development. This process is called endothelial to hematopoietic transition (EHT) [17-24]. All the more, it´s remarkable that IL-1RI, that is a receptor for IL1 and leads to NF-κB and c-Jun N-terminal kinase (JNK) activation [25], is expressed by cells in the E11 aortic endothelial and mesenchymal cells, and at low levels in the IAHC [26].

Upon stimulation with IL1β, AGM explants show higher levels of CXCR4, a chemokine receptor that is specific for stromal cell-derived factor-1(SDF-1) required for homing of hematopoietic cell to their niches. The importance of signaling through IL1R1 was further confirmed in transplantation settings; IL1R1 mutant AGM cells showed reduced HSC activity [26]. In fact, recent reports show a correlation of CXCR4 expression and HSC activity in the AGM [27]. In agreement with these findings, Tnf α and TnfR2 morphant zebrafish embryos have decreased expression of the hematopoietic markers runx1 and cmyb, and a NF κB reporter line confirms its activity within the ventral domain of the aorta [28]. Interestingly, the authors find aberrant notch signaling, eg decreased levels of Jag1a, which is required for IAHC formation [28,29]. In parallel, a study on Tlr4, MyD88 and NF κB, a core of inflammatory signaling axis leading to nuclear p65, came to comparable conclusions; they found decreased numbers of hematopoietic cells in the aorta of these morphants, and established a link to aberrant notch signaling in this study, the authors found a reduced induction of the notch

downstream effectors Hey1/2 and her15.1 [30]. If this lower notch status is due to reduced Jag1a expression as suggested by Espin-Palazon et al. is not known. Interestingly, in the same study, the authors also investigated the HSC activity in the AGM of TLR4 deficient mouse embryos. TLR4 deficient hematopoietic cells in the AGM could generate CFU-C, albeit at a reduced number, but strikingly, almost all HSC activity was diminished in transplantation assays [30]. These studies highlight the high susceptibility of HSC to NF κB signaling, but the HSPCs, the more differentiated cells show a less substantial dependency. Nevertheless, it´s still unclear which target genes are activated by p65 mediated NFkB signaling in HSCs and HSPCs.

In an elegant study by Li et al. the authors subjected E10.5 embryos that express GFP under the Ly6a/Sca1 promoter, a marker of HSPCs, including HSCs, to different cytokines [31]. Here they found moderate increases in Sca1 expression after treatment with IL1β, IL6 and TnfA in the AGM region, but treatment the Inf α4 or Inf γ lead to a huge increase of Sca1 expression in the AGM, including the aorta. The increase in Ly6aGFP+ was due to both, higher expression of Sca1GFP, and enhanced proliferation [31]. In order to determine if there were HSPCs that can receive both Ifnγ and Tnfα simultaneously, combinatorial MO knockdown of Ifnα and Tnfγ was used in zebrafish embryos. Knockdown of both cytokines together caused a greater decrease in hematopoietic gene expression (runx1) in the dorsal aorta than the knockdown of either gene alone, indicating that multiple inflammatory cytokines can cooperate in the formation and expansion of embryonic HSPCs in the absence of pathological stimulation.

Interestingly, blood flow is needed for the expression of ifng1-2, as ifng1-2 was nearly absent from the axial vessels of tnnt2 (silent heart) morphants that don't have a blood circulation [32]. The reason for this curious observation was not further clarified, but recent studies might provide a plausible explanation. Blood flow might be needed to enhance the sources of inflammatory cytokines to the dorsal aorta.

Detailed analysis of the cellular composition of the AGM microenvironment using mass cytometry (CyTOF) revealed the presence of yolk sac derived macrophages closely associated with IAHC [33]. Prior to HSPC generations in the AGM, the yolk sack produces HSC independent blood progenitors, including macrophages that express different receptors to interact with their niche cells, including Cx3cr1 and Csfr1 [34,35]. Time course analysis with a Csf1r:GFP transgenic mouse model that labels Yolk sac derived macrophages, the study elegantly demonstrates their arrival in the AGM from E9.5 and significantly increasing in abundance by E11.5, ie in time for the HSPC and HSC emergence [33]. Cx3cr1, a chemokine receptor was identified on the macrophages, whereas the possible interacting ligand, Cxcl12, was highly expressed by HE cells. Ablation of Cx3cr, or pharmacological of macrophages with BLZ945, an inhibitor of the colony stimulating factor 1 receptor (CSF1R) reduced CFU-C numbers and HSC activity in transplantation assays. The authors further identified a sub-population of macrophages based on their cell surface expression of CD206 that specially upregulate cytokine expression of Tnf, Ccl24, Ccl9, Igf1, Bmp2, Pf4, Ccl2, and Ccl7, Whereas Ifnα, Ifnγ, and IL1β expression was observed in all AGM macrophages [33].

In summary, inflammatory signaling pathways are essential for hematopoiesis in the AGM in general, and most importantly, positively influence HSC activity. There is some evidence that some cells are susceptible to more than on the cytokine stimulus at a time [32]. In summary, during development, inflammatory signaling pathways are activated to establish cell identity. It will be important to study the impact of cytokines individually or combined in different cell populations in order to understand the gene expression changes that they inflict. Perhaps the multitude of single cell data sets on AGM cells can give us more clues. Here, we can readily distinguish between the blood cell types and profile their gene expression for inflammatory signaling members. In fact, several single cell data sets of AGM derived cells showed enrichment of inflammatory signaling pathway activation in HE and IAHC [36-38]. Further, detailed analysis of these data sets can help to improve our understanding of these stimuli in HSC emergence and helps us to improve *in vitro* approaches to generate HSC by artificially fine tuning these cytokines in culture conditions.

Conflict of Interest

No conflict of interest with any institution/organization.

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