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REVIEW

Interferon and tumor necrosis factor as humoral mechanisms coupling hematopoietic activity to inflammation and injury

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ABSTRACT

Enhanced hematopoiesis accompanies systemic responses to injury and infection. Tumor necrosis factor (TNF) produced by injured cells and interferons (IFNs) secreted by inflammatory cells is a co-product of the process of clearance of debris and removal of still viable but dysfunctional cells. Concomitantly, these cytokines induce hematopoietic stem and progenitor cell (HSPC) activity as an intrinsic component of the systemic response. The proposed scenario includes induction of HSPC activity by type I (IFNα/β) and II (IFNγ) receptors within the quiescent bone marrow niches rendering progenitors responsive to additional signals. TNFα converges as a non-selective stimulant of HSPC activity and both cytokines synergize with other growth factors in promoting differentiation. These physiological signaling pathways of stress hematopoiesis occur quite frequent and do not cause HSPC extinction. The proposed role of IFNs and TNFs in stress hematopoiesis commends revision of their alleged involvement in bone marrow failure syndromes.

1. Introduction

The complex and delicate balance between quiescence and extinction by differentiation of hematopoietic stem and progenitor cells (HSPCs) is maintained by specific molecular configurations and extrinsic signals from the surrounding microenvironments. Units of regeneration in the hematopoietic system are endowed with inherent patterns of gene expression regulated at the transcriptional level that on the one hand prevent extinction by apoptosis and incidental induction of differentiation, and on the other hand make them sensitive to external signals. Cycling fetal hematopoietic progenitors are stabilized in a state of mitotic quiescence within the bone marrow in the early post-natal period [1]. Afterwards, signals evolving from specialized subendosteal marrow niches are dominant in preserving functional and mitotic quiescence of progenitors (referred to as quiescent niches) [2]. The state of functional and mitotic quiescence is transient and reversible, with occasional self-renewal [3] or quite frequent cycling [4], associated with vast variations in transcription and phenotype [5] that render progenitors residing in quiescent niches responsive to external stimuli [6]. These activities of progenitors are geographically distinct within the marrow of long bones: quiescent HSPCs reside in niches aligned along the endosteal surface whereas active progenitors switch to niches located in central marrow space [7].

Among numerous critical questions concerning the homeostasis of hematopoietic progenitors in quiescent marrow niches, intensive efforts are directed to decipher the mechanisms of progenitor activation. One of the critical questions is whether differentiation is induced prior to or following egress of progenitors from the quiescent niches. One possible scenario suggests that units of regeneration are induced to differentiate within the subendosteal niches, a process associated with cell cycling and variations in receptor profile that fosters egress from this site of residence. In support of this mechanism is the differential activation of distinct patterns of differentiation in various stages of cell cycle of hematopoietic progenitors [8]. Another scenario suggests that units of regeneration are induced to egress from the niche prior to induction of differentiation and adopt different traits upon engagement of developmental niches in central marrow. Supporting evidence is the observation that HSPCs egress periodically from the marrow niches and resume their residence after circulation in peripheral blood, indicating that transient mobilization is not necessarily associated with differentiation [9].

Here we consider the possible involvement of inflammatory and injury signals in mobilization and functional activation of hematopoietic progenitors under physiological and stress conditions, focusing on the activity of interferons and members of the tumor necrosis factor (TNF) superfamily. Several recent reviews have summarized current knowledge on the involvement of stress signals in hematopoietic progenitor activation [2,10–13]. We discuss the possibility that humoral factors are involved in the process of recruitment and activation of stem and progenitor cells.

2. Interferons as signals associated with inflammation

Interferons (IFNs) are a family of acute phase reactants secreted primarily by immune cells that promote the conversion of naive to

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cytotoxic T cells and amplify their activity. Two types of interferons are classified according to the cognate receptors: IFNα, IFNβ and other isotypes bind type I receptor and IFNγ selectively interacts with type II receptor [14]. Initial *in vitro* studies attributed interferons suppressive effects on hematopoietic progenitors [15–18], although it has been recognized that these cytokines cooperate with other growth factors and chemokines in stimulation of HSPC activity [19–21]. IFNα prompts exit of quiescent progenitors from the Go phase and signaling through the STAT pathway induces gene expression including stem cell antigen (SCA-1) [22]. The versatile activity of IFNα includes phasic exposure that promotes progenitor egress from the dormant state, whereas tonic exposure appears to compromise progenitor activity [22]. Excessive IFNα-dependent activation of progenitors might cause exhaustion, which is prevented by interferon regulatory factor-2 (IRF2), a transcriptional suppressor of type I receptor signaling that modulates the suppressor and stimulatory nature of signal transduction [23]. IFNγ also stimulates the activity of murine hematopoietic progenitors in a STAT-dependent manner [24], evident from persistent stimulation caused by tonic increase in IFNγ levels in response to chronic infections [25] under regulatory activity of IRF1 [26].

Balancing these stimulatory activities of interferons on hematopoietic progenitor proliferation and differentiation in response to viral infections are suppressor activities that prevent detrimental consequences of excessive signaling of these pathways. Inhibitory activities are recognized at several levels. Both type I and II IFN receptors have been associated with preservation of the viability of hematopoietic precursors preventing their extinction without functional inhibition [16,27,28]. Furthermore, IFNα suppresses the development of T and B lymphocytes in the bone marrow [29] and cooperates with Interleukin-7 (IL-7) in regulation of peripheral homeostatic expansion of B lymphocytes [30]. Although IFNγ is a pivotal activator of cytotoxic T cells, it can also mediate negative regulation, possibly to avoid overstimulation of the immune system [31]. Therefore, the role of interferons in fine-tuning of inflammatory reactions and hematopoietic responses includes both stimulatory and inhibitory activities.

3. Tumor necrosis factor family factors associated with injury

Tumor necrosis factor (TNF) superfamily includes receptor/ligand interactions that are involved in physiological homeostasis of hematopoietic and immune systems, with pleiotropic inductive and suppressive activities [32,33]. TNFα has been initially associated with functional suppression of hematopoietic progenitors [15,17,18] however early reports have already demonstrated variability in responses to this cytokine under various experimental conditions [34–36]. This cytokine, however, has many more roles in physiological and stress hematopoiesis, which can be not classified as purely inhibitory or stimulatory [13]. Hematopoietic stem and progenitor cells are inherently resistant to apoptosis due to intrinsic molecular configuration regulated at the transcriptional level [37]. These cells are not unresponsive to TNF family members due to absent or low levels of receptor expression, because the receptors are acutely upregulated in response to stress (*vide infra*). Although apoptotic pathways are well developed in hematopoietic progenitors, dominant transcription and translation of anti-apoptotic factors and the NFκB pathways actively protect cell viability. Sensitivity to apoptosis develops along differentiation of the progenitors and TNF family members become pivotal mediators of negative regulation of mature hematopoietic and immune progeny *via* activation-induced cell death (AICD).

4. Humoral factors in stress hematopoiesis

The physiological sequence of events under stress conditions is initiated by immediate recruitment of the marginal vascular pools of neutrophils mediated by acute stress chemokines and hormones such as cortisol. In parallel, acute inflammatory and injury factors operate at two levels. At first level, differentiated myeloid cells and lymphocytes are mobilized from the bone marrow to peripheral blood [38,39]. For example, TNFα mobilizes immune cells by downregulation of CCL12 [38] similar to the mechanism of mobilization of granulocyte colony stimulating factor (G-CSF) [40]. At the second level, IFN and TNF stimulate the activity of hematopoietic progenitors in the bone marrow to replenish the acute decline in available pools of immune cells. In fact, members of TNF superfamily such as Fas, TNFα and TNF-related apoptosis-inducing ligand (TRAIL), as well as the type I and II IFN receptors trigger trophic signals in most primitive stem and progenitor cells, which are resistant to apoptotic signaling through these receptors [27,28,37,41,42]. The exact signaling pathways dissociating apoptotic and trophic signaling in progenitors and the changes in wiring of these pathways along the differentiation process are yet unknown.

IFN and TNF are non-specific stimulants of hematopoietic progenitors that synergize with other growth factors in recruitment on colony forming units and enhancement of their development. The inductive activities of these cytokines are maximized by cooperation of TNFα with IL-1β and G-CSF and of IFNγ with IL-3 [19–21,38,42]. These cytokines are therefore best viewed as non-specific stimulants that recruit and activate progenitors residing in the quiescent niches rendering them responsive to other growth signals. In this capacity, IFN and TNF participate in awakening of dormant progenitors within the marrow niche [2] and serve as coupling mechanisms between inflammation and injury, and stimulation of hematopoiesis.

Activation of hematopoietic progenitors is associated with wide variations in patterns of expression of intracellular molecules and cell surface receptors. Unlike transient spontaneous mobilization of progenitors that periodically enter peripheral circulation and resume their marrow residence [9], activated progenitors resume activity at sites that encourage proliferation and differentiation [7]. Phenotypic dynamics that modulate progenitor behavior may be rather non-specific and associated with cell cycle [5,6], may result from activation of inherent patterns of gene expression such as NFκB activation by TNFα [13], or mediated by induction of distinct molecules such as SCA-1 by interferons [43,44]. Notably, responses to TNF family members depend on the time of exposure, with differential activation of sets of genes under phasic and tonic stimulation of the NFκB pathways [45,46].

5. Are interferons and TNF family members involved in physiological hematopoiesis?

In differentiated hematopoietic and immune cells, the TNF receptors are ubiquitous negative regulators of expanding clones, controlling the intensity of the immune reaction through AICD [13]. In variance, IFNs stimulate immune cells as a mechanism of amplification of the immune reaction [10–12], although under certain conditions they also restrain immune reactivity [25,29–31]. Despite these differences in distal stages of differentiation, their activity in proximal stages of differentiation is similar: stimulation of hematopoietic stem and progenitor cell activity. The two signaling pathways described above couple hematopoietic activity to inflammation (IFN) and injury (TNF).

The physiological significance of signaling cytokines is questioned by the demonstration that deficient transgenes do not display overt hematopoietic abnormalities, though increased numbers of progenitors might disclose functional deficiency [22,25,47,48]. However, deficiencies in IFNs [25,26,49] and TNFs [48,50,51] result in impaired competitive murine engraftment, assigning these cytokines significant roles in hematopoietic progenitor function. Confounding results showing a competitive advantage of IFNγ-deficient progenitors have been explained on the basis of increased fractions of quiescent cells that correspond to the main engrafting subset [25,52], as also demonstrated for progenitors deficient in the transcriptional repressor IRF2 of type I receptor signaling [22]. Likewise, in contrast to failure of progenitors deficient in TNF receptors to generate durable reconstitution [51], this deficiency has been associated with superior reconstituting activity following whole bone marrow cell transplants [53]. These discrepancies may be related either