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Review Article

Hematopoietic stem cells: interplay with immunity

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Abstract: Ample evidence indicated that hematopoietic stem cells (HSCs) receive signaling from infection or other immune responses to adjust their differentiation and self-renewal. More recent reports also suggested that, while the bone marrow microenvironment or niche may provide the immune privilege for HSCs, HSCs can present surface immune inhibitors *per se* to suppress innate immunity and adaptive immunity to evade potential immune surveillance and attack. These findings support the hypothesis that HSCs are capable of interacting with the immune system as signal "receivers" and signal "providers". On the one hand, HSCs are capable of directly sensing the signals from the immune system through their surface receptors to modulate their self-renewal and differentiation ("in" signaling); on the other hand, HSCs display surface immune inhibitory molecules to evade the attack from the innate and adaptive immune systems ("out" signaling). The continuing investigation of the interplay between HSCs and immunity may lead to the open-up of a new research filed – the immunology of stem cells.

Keywords: Hematopoietic stem cells, immunity, immune privilege, CD47, CD274, LILRB2, PIR-B, immune inhibitory receptors, infection, inflammation

Introduction

Hematopoietic stem cells (HSCs) are responsible for the daily production of all the lineages of blood cells in the body and have been widely used in transplantation to treat patients with leukemia, lymphoma, some solid cancers, and autoimmune diseases [1]. The balance between different cell fates—quiescence, self-renewal, differentiation, apoptosis, and migration—determines the number and function of HSCs [1]. In nature HSCs are an essential part of the immune system by production of different types of immune cells. The bone marrow microenvironment or niche provides an immune-privileged site for HSCs [2]. This is opposite to the situation of pluripotent stem cells, which are not immune privileged [3, 4]. Deeper than that, recent evidence suggests that HSCs *per se* express surface molecules mediating "in" signaling and "out" signaling that directly dialogs with the immune system. For the "in" signaling, the stimulatory signals originated from infection and inflammation activate HSCs and induce differentiation through surface receptors including toll-like receptors (TLRs), tumor necrosis factor α (TNFα) receptor, interferon (IFN) receptors, and others (see review by Goodell's group [5]). Our most recent study also suggests that there exists inhibitory "in" signaling that decreases differentiation and potential exhaustion of stemness of HSCs so that the stem cell potential is reserved [6]. On the other hand, the "out" signaling, mediated by surface immune inhibitory molecules such as CD47 and CD274, inhibits attack from the innate and adaptive immune responses, respectively [7, 8]. The "out" signaling enables HSCs to gain regulatable "immune privilege" that is to a certain extent similar to that of mesenchymal stem cells and amnion stem cells [9]. We propose that the co-existence of both types of signaling ensures the balance of cell fates of HSCs. This review focuses on recent progress suggesting how HSCs interact with the immune system through these "in" and "out" signaling.

"In" signaling

HSC activation by the immune system through stimulatory receptors: While HSCs are resistant to direct infection by pathogens ([10-12]; we

speculate that the "out" signaling of HSCs may prevent these cells from direct infection, see below), it is also clear that HSCs can directly respond to pathogen-specific infection through systematic cytokine stimulation from both innate and adaptive immune signals. Several classes of stimulatory signaling receptors expressed on HSCs that bind to cytokines or infectious ligands directly participate in the infection response: IFN receptors [12-14], TNFα receptor [15-17], and TLRs [18-20] (reviewed by Goodell's group [21]). In general, the infection or inflammatory signals activate HSCs so that HSCs produce more immune effector cells to counteract the initial infection. Meanwhile this process may chronically lead to accelerated differentiation at the expense of loss of HSC potency [12]. The aberrant IFN and TNF signaling are associated with myelodysplastic syndrome and bone marrow failure [21]. Therefore, HSCs are naturally activated to proliferate by the "in" signaling to combat infection and inflammation.

Immune inhibitory receptors on stem cells: In addition to the above stimulatory receptors, we predicted that other immune-related surface signaling receptors also regulate the cell fates of HSCs. Most recently, we demonstrated that inhibitory receptors LILRB2 and PIR-B are expressed on the surface of human and mouse HSCs respectively [6]. We found that these receptors bind to ligands Angiopoietin-like proteins (Angptls) [22-24], to inhibit differentiation and support self-renewal of stem cells [6].

Multiple types of ligands of LILRB2 and PIR-B were identified. In addition to binding to Angptls, LILRB2 or PIR-B has been known to bind to other ligands including various MHC class I molecules (MHCI) [25] and myelin inhibitors [26]. As reported by Takai's group, in general an inhibitory receptor may bind to its membrane-bound ligand in *trans* (in which the ligand is expressed on another cells) or in *cis* (in which the ligand is expressed by the same cells that express the receptor) [27]. Because Angptls are abundantly expressed by many types of cells including those from endocrine organs [28] and potential BM niche (endothelium and adipocytes [23, 28]), and can be induced by hypoxia [28], these secreted factors may have important direct and indirect effects on the activities of HSCs and perhaps other stem cells *in vivo* through possible *trans*- interaction. To support this view, we demonstrated that Angptl3 expressed by the bone marrow vascular cells supports HSC activity [23]. Importantly, Angptls are also highly expressed by HSCs *per se* [23, 29]. It is therefore possible that a *cis*-interaction between Angptls and LILRB2 occurs on HSCs. Future investigations are needed to clarify and study the biological significance of this *cis*-interaction.

Similarly, both *cis* and *trans* interactions were reported to exist between MHCI and LILRB2/PIR-B. The development of osteoclasts is regulated by *cis* interaction between PIR-B and MHCI as determined by fluorescence resonance energy transfer analysis [30]. The *cis* interaction between PIR-B and MHCI was also identified to occur on B cells, dendritic cells, and mast cells [31, 32]. Similarly, LILRB2 are able to *cis* interact with MHCI on human basophilic leukemia KU812 cells [27]. On the other hand, PIR-B on dendritic cells and MHCI on $CD8^+$ T cells were found to interact in *trans* at the immunological synapse [31]. Since both HSCs and other somatic cells express MHCI [8], it will be interesting to test whether the *cis* and *trans* interactions between inhibitory receptors and MHCI exist on HSCs *per se* and between HSCs and regulatory or niche cells.

While the LILRB/PIR-B receptors were reported to suppress activation of differentiated immune cells and inhibit neurite outgrowth of neural cells [26, 27], they support HSC repopulation and inhibit differentiation of leukemia stem cells [6]. This result suggests the importance of these "inhibitory receptors" in maintenance of stemness of stem cells. In contrast to the "stimulatory receptors" such as IFN receptors or TLRs that activate and induce differentiation of HSCs upon infection, LILRB2 or PIR-B may respond to niche- or chronic inflammation- produced Angptls and protects HSCs from excessive activation and exhaustion. We suspect that adult stem cells and cancer cells likely require both stimulatory receptors and inhibitory receptors to maintain the balance of their cell fates.

Interaction between stimulatory receptors and inhibitory receptors: The counterregulatory roles of immune inhibitory receptors and stimulatory receptors expressed on the same cells were reported in many studies. While both PIR-B (the inhibitory receptor) and c-Kit (the

stimulating receptor) are expressed on mast cells, their co-ligation inhibited SCF-induced mast cell responses [33]. Similarly, c-Kit mediated inflammatory reactions are also counterregulated by the inhibitory receptor LILRB4 [34]. The TCR mediated T cell activation is counterregulated by another inhibitory receptor LILRB1 [35]. Because LILRB2/PIR-B and c-Kit are expressed on the same HSCs [6], it is possible that the counterregulation between these immune inhibitory receptors and stimulatory receptors exists on HSCs and is important to balance the cell fates of stem cells.

Another example of interaction between immune inhibitory receptors and stimulatory receptors is the interplay between PIR-B and a Toll-like receptor (TLR9) [27]. After the components of invaded bacteria or virus bind TLR9 in B cells, TLR9-initiated Lyn activation stimulates the phosphorylation of PIR-B, leading to enhanced SHP-1 recruitment to PIR-B. The recruited SHP-1 dephosphorylates the TLR9 downstream kinase Btk, which then attenuates the immune activation that otherwise may produce overreactive antibodies. This counterregulation of TLR signaling by inhibitory receptor PIR-B is important to prevent the potential harmful consequence of autoreactive antibodies in immune cells [27]. Again, because both PIR-B and several TLRs are expressed on HSCs [6, 18, 36], it is to be determined whether these two types of receptors have important counterregulatory interactions that balance the cell fates of stem cells.

"Out" signaling

HSCs are immune protected by bone marrow microenvironment: In vivo, stromal cells and other cells form a complex microenvironment for HSCs that controls their multiple cell fates, including quiescence, apoptosis, and migration as well as the cell divisions that lead to formation either of daughter HSCs or of lineage-committed progenitors that are capable of limited proliferation. Currently, we know of the existence of several types of cells that form bone marrow HSC microenvironment or niches [37]. The endosteal HSC niche contains osteoblasts as the main supportive cell type for maintenance of hematopoiesis [38, 39]. The vascular HSC niche is mainly composed of sinusoidal endothelial cells [40]. More recently, it was suggested that these two types of cells may establish a compound niche [41, 42]. In addition, SDF-1 abundant reticular (CAR) cells [43], CD146-expressing subendothelial stromal [44], Nestin$^+$ mesenchymal stem cells [45], macrophages [46, 47], and the sympathetic nervous system [48] have also been demonstrated to represent components of HSC niches [37].

HSCs may indirectly interact with the immune system through their microenvironment or niche. HSC mobilization can be contributed by the suppression of CXC-chemokine ligand 12 (CXCL12) production by osteoblasts in the bone marrow [49], and by complement cascade activation through granulocyte egress [50]. A recent elegant study by Fujisaki et al. using high-resolution *in vivo* imaging demonstrated that regulatory T cells (Treg) colocalize with HSCs in the endosteal area in the bone marrow to protect HSCs from immune attack [2]. IL-10 produced by these Treg cells plays an essential role in this immune protection. This is functionally similar to the reported Treg recruitment to the cancer microenvironment [51]. These findings suggest that the HSC niche not only specifies an environment to control the cell fates of HSCs, but it may also provide an immune-privileged site for HSCs [2].

HSCs are capable of regulating their own "immune privilege": While the niche offers protection for HSCs from immune attack, HSCs are capable of migrating in and out of the niche [52], which drastically increases the possibility that they will interact with the immune system. It is evident that HSCs outside of the niche apparently are resistant to pathogen infection [10, 11].

HSCs are capable of protecting themselves from innate macrophage phagocytosis [7]. CD47, also known as integrin-associated protein, binds to SIRPa on macrophages and inhibits its phagocytosis. Weissman's group showed that CD47 is expressed on freshly isolated bone marrow HSCs at a relatively low level, implying a slim possibility of the potential interaction between HSCs and the innate immune system at the bone marrow niche. When HSCs are activated by potent inflammatory signals and mobilize into circulation, the CD47 level is dramatically upregulated on the surface of HSCs [53]. Similarly, CD47 is also upregulated on a variety types of blood cancer and solid cancer cells [54]. It was suggested that the

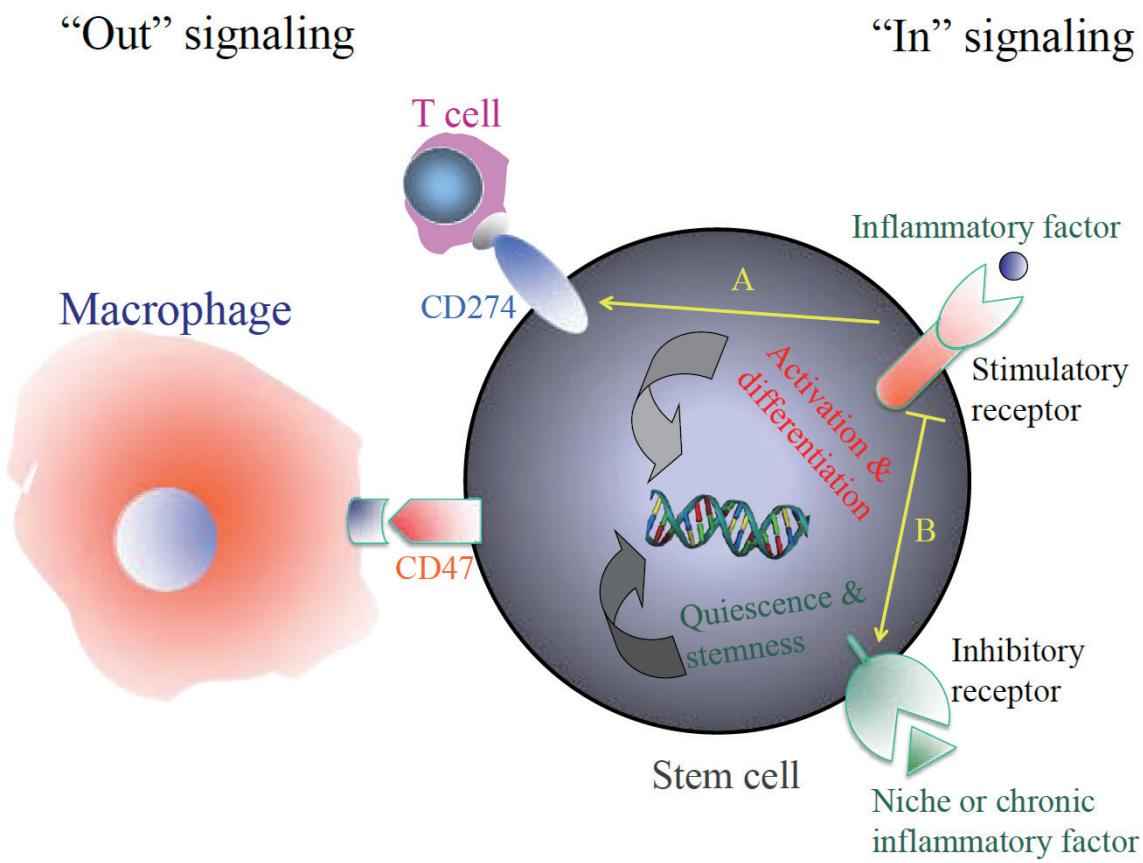

Figure 1. A model of the interplay between HSCs and the immune system. HSCs express surface immune molecules for "in" signaling and "out" signaling that directly dialog with the immune system. While the "out" signaling, mediated by surface molecules such as CD47 and CD274, inhibits attack from the innate immunity and adaptive immunity responses, respectively, the stimulatory "in" signaling from infection and inflammation activates HSCs and induces differentiation through surface receptors including TLRs, TNFα receptor, IFN receptors, and others. There also may exist the inhibitory "in" signaling that decreases differentiation and reserves the stemness of HSCs in response to niche or chronic inflammatory cues. In the indicated process A, stimulatory 'in" signals induces upregulation of the "out" signaling by CD274. In the indicated process B, stimulatory receptor signaling activates inhibitory receptor signaling, which in turn represses the stimulatory receptor signaling. The co-existence of "in" and "out" signaling and their interaction ensure the balance of cell fates of HSCs.

increased expression of CD47 on the surface of mobilized HSCs and cancer cells protects these cells from phagocytosis by macrophages [54].

In addition to evading the potential attack from the innate immune system, HSCs are also able to protect themselves against the adaptive immune system. CD274 (B7-H1 or PD-L1) is a member of the B7 family that is expressed on dendritic cells, activated immune cells, and parenchymal cells under certain condition and on cells in immune-privileged sites such as eyes and placenta where it inhibits T cell or innate activation [55, 56]. CD274 is also selectively expressed by various cellular components in the tumor microenvironment, where it inhibits tumor-specific T-cell immunity by inducing T cell apoptosis and delaying rejection [55].

We recently provided evidence demonstrating that HSCs possess the ability to regulate their surface expression of CD274 in order to evade the rejection by the acquired immune system [8]. We showed that CD274, similar to CD47, is expressed low on freshly isolated bone marrow HSCs *in vivo* [8]. Surprisingly, after *in vitro* culture, HSCs upregulate the surface expression of CD274 at least 10-fold, which efficiently inhibits host T cell proliferation upon allograft transplantation [8]. These observations clearly indicate that *ex vivo* culture significantly modulates the immunogenicity of stem cells. Fiorina et al. demonstrated that CD274 is upregulated

on mouse splenic $Lin^{-}Kit^{+}$ hematopoietic cells after the treatment of an antagonist of chemokine CXCR4 [57], suggesting that the CD274 level on phenotypic hematopoietic progenitors can be increased upon mobilization. Whether the expression of CD274 on primitive and functional HSCs or blood cancer cells can be physiologically regulated *in vivo* and its biological significance warrants further investigation. Practically, the future identification of potentially additional immune molecules whose alterations can regulate allograft acceptance will enable the complete resolution of the issue of immune rejection in allogeneic transplantation.

Therefore, in striking contrast to pluripotent stem cells, HSCs have modulatable immune privilege that can overcome allogeneic immune barrier, and HSCs can directly suppress the adaptive immunity.

Interaction between "in" and "out" signaling

It is known that the expression of surface immune inhibitor CD274 can be induced or maintained by proliferating signals [8], especially interferon−γ (IFNγ) [55]. This upregulation of CD274 expression has been reported to occur in various types of cells including cancer cells and HSCs [8, 55]. These findings lead us to hypothesize that "in" signaling (such as that is mediated by IFN receptor) can regulate the output of the "out" signaling (such as CD274's immune inhibitory activity) in stem cells. This is reasonable because normally HSCs are immune privileged in their bone marrow niche; only after HSCs sense the immune signals through the "in" signaling pathway, they can initiate responses to enhance their "out" signaling to protect themselves. Further studies are needed to investigate the details of mechanisms by which the CD274 expression is upregulated, and whether other molecules in "out" signaling are also controlled by similar activities.

In addition to acting as a ligand to inhibit T cell responses, CD274 can also function as a receptor to transmit signals into T cells and cancer cells [58, 59]. It is possible that this reverse signaling from the "out" signaling may have regulatory roles in the balance of self-renewal, differentiation, and other cell fates of HSCs.

Model of the interplay between HSCs and the immune system

Based on these recent progress and a previous model [60], we propose a new model for the interaction between HSCs and the immune system. Within the niche, HSCs are protected by Treg and other niche cells from potential immune attack. Outside the niche, HSCs are capable of directly interacting with the immune system through surface immune molecules for "out" signaling and "in" signaling (**Figure 1**).

The "out" signaling is mediated by factors such as CD47 and CD274 that inhibit attack from the innate immunity and adaptive immunity responses, respectively. Based on the results discussed here, we hypothesize that homeostatic HSCs express low levels of surface immune suppressors, and the levels of these suppressors can be induced by stress or immune signals. These immune suppressors may thus modulate HSC immunogenicity and, therefore, contribute to the "immune privilege" of HSCs. This regulatable "immune privilege" should be advantageous to HSCs as it should allow these important stem cells to rapidly adjust to altered environmental conditions or protect them from excessive immune activation/inflammation or potential autoimmune disorders.

The stimulatory "in" signaling activates HSCs and induces differentiation through surface receptors including TLRs, TNFα receptor, IFN receptors, and others. The net outcome of the activating "in" signaling is to produce immune effector cells that counteract the initial infection. Nevertheless, because adult stem cells only have limited division capacity, a chronic activating signaling may result in eventual decrease of stemness. Therefore the activating "in" signaling may be counter-balanced by the environmental cues within the stem cell niche or from chronic inflammation that activate the surface inhibitory receptors (such as LILRB2 and PIR-B), which inhibit differentiation and maintain the quiescence and stemness of HSCs. In addition, the stimulating "in" signaling may also directly activate the signaling of immune inhibitory receptors in the cytosol. The co-existence of both types of signals, which may regulate each other, ensures a balance of cell fates for HSCs. We speculate that an imbalance will lead to either total differentiation

(exhaustion, if stimulatory signals dominate) or apoptosis (if inhibitory signals dominate).

As we hypothesize, there may exist interaction between the "in" and "out" signaling. It is reasonable to speculate that the "in" signaling that is able to sense the immune cues should upregulate the "out" signaling that protects the stem cells from a potential immune surveillance and attack. Moreover, this "out" signaling may also reversely regulate the cell fates of stem cells through the cytosolic signaling domains of the immune surface suppressors such as CD274.

The continuing investigation of how stem cells interact with the immune system may open up a new scientific field - the immunology of stem cells. We speculate that a common mechanism exists for regulation of immune signals in some other types of stem cells. It will be interesting to study the immunology of stem cells by investigating the roles of surface immune molecules and receptors on pluripotent stem cells, other adult stem cells, and cancer stem cells.

Open questions

The following questions must be addressed to provide new insights into the understanding of immunology of stem cells:

1) What are the respective roles of *trans*- and *cis*- interactions between immune surface molecules and their ligands to control the cell fates of stem cells?

2) How do immune inhibitory receptors and stimulatory receptors work together to regulate the cell fates of stem cells?

3) How is the expression of immune surface molecules regulated *in vivo*?

4) What is the connection between the "in" signaling and "out" signaling? Can "in" signaling modulate the type and magnitude of "out" signaling and vice versa? Can a surface signaling molecule serve both the "in" and "out" signaling?

5) What are the expression and functions of surface immune molecules and receptors on stem cells other than HSCs?

6) Does the aberrant immune property of stem cells cause diseases/cancer?

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Conflict of interest statement

The author declares no conflicts of interests.

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