The Interaction Between Niche and Hematopoietic Stem Cells

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Abstract Hematopoietic stem cells (HSCs) are one of the somatic stem cells that have the ability to regenerate the entire blood system in a hierarchical way for the duration of an adult life. HSCs reside in the bone marrow niche which contain different cells and molecules that regulate the balance of HSC dormancy and activation. Here, we describe the interaction between HSCs and their niche, in particularly the involvement of some signaling pathway. Insights into the hematopoietic microenvironment will help to obtain a better understanding of normal hematopoiesis and how environmental factors affect these processes.

Keywords HSCs · Microenvironment · Signaling pathway

Introduction

Self-renewal is an important feature of HSCs, which means that HSCs can divide while maintaining at least one daughter cell in the undifferentiated state. Because of this capacity, HSCs can generate the entire hematopoietic system from just a single cell and maintain hematopoiesis for the lifetime of an individual. It's known that the bone marrow microenvironment, or so-called niche, plays an

important role in the regulation of self-renewal and differentiation of HSCs. Thus, in this review, we will focus on the interaction between HSCs and its niche, especially the signaling pathways.

The Hematopoietic Stem Cells Niche

Fate of HSCs is not only controlled by itself, but also by the microenvironment. Schofield was the first to propose that HSCs was in association with other cells which determine their behavior [1–4]. Such a niche composed of specialized cells capable of supporting stem cells.

HSCs could physically anchor to supporting cells, which secrete molecules necessary for HSCs behavior. In the *Drosophila* ovary, somatic cap cells anchor to germline stem cells and then stimulate bone morphogenetic protein (BMP) signalling pathway, which is capable of reprogramming cells to become stem cells [5]. Identification of HSCs remains elusive, in part because of the complex niche, and in part because of the difficulty in identifying cell surface markers of HSCs in vivo.

The bone marrow endosteum and sinusoids are the two predominant niches for HSCs. Many studies suggested that the bone marrow endosteum was the major HSC niche [6–8]. In this review, we will focus on the two hematopoietic niche and elucidate the cross-talk between niche and HSCs.

Endosteal Niche

The endosteum is a layer of connective tissue consisting mainly of osteoprogenitor cells and their progeny such as osteoblasts and osteoclasts. Osteoblasts, the bone-forming cells, which work in tandem with osteoclasts in the process of osteogenesis, are essential components of this niche [9]. They are transient cells that actively provide mineralization

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during bone development and replace lost bone tissues in adults. Previous studies have clearly shown direct associations between osteoblasts and HSCs.

It's reported that activation of osteoblastic cells resulted in an increase in HSCs frequency, while osteoblastic destruction resulted in loss of HSCs. Nevertheless, an expansion in the osteoblast number requires other factors in the HSCs pool. Some of these factors can be expressed by osteoblasts in vitro, such as CXCL12, stem cell factor (SCF) and angiopoietin-1(Ang-1). More recently, osteoclast impairment will induce osteoblast to differentiation which lead to HSCs localization in the BM of a mouse model [10].

However, the osteoblastic niche theory was challenged by studies showing that osteoblasts depleted by biglycan (*Bgn*) deficiency or osteoblastic cells depleted by treatment with ganciclovir had no effect on HSCs frequency [11].

Sinusoidal Niche

Bone marrow sinusoids are thin walled vessels which serve as the medium for blood cells. A broad range of cells, including adventitial reticular cells, perivascular stromal cells, mesenchymal stromal cells (MSCs), and neurons, form sinusoids niche which can regulate behavior of HSCs. These cells secrete a range of cytokines, such as SCF, CXCL12, and alkaline phosphatase to support the maintenance of HSCs. Ding and his colleague showed that sinusoidal endothelium and perivascular stromal cells, but not osteoblasts, directly responsible for the expression of SCF further attracted HSCs to sinusoidal niche and their deletion resulted in decreased hematopoiesis [12]. Indeed, because of hematopoietic deficiencies, SCF knockout embryos died.

Signaling Pathway

A number of signaling pathways have been identified to be important for HSC behavior, including Hedgehog, Wnt, Notch, SDF-1 (CXCL12)/CXCR4 and Tie2/Ang-1 signaling pathways [13]. This review will focus on the signaling pathways associated with HSCs. (Fig. 1).

Notch Signaling Pathway

It regulates the transcription of multiple genes which are related with HSC maintenance and self-renewal.

There are four different Notch receptors (Notch1–4) in mammals; Notch1 and Notch2 are the most similar to the *Drosophila* homolog. Notch is a single transmembrane protein composed of an extracellular domain with variable number of epidermal growth factor (EGF)-like repeats and an intracellular domain containing seven ankyrin-like

Fig. 1 Activation of signalling pathways regulates behavior of HSCs. A number of signaling pathways have been identified to be important for HSC behavior, such as self-renewal, differentiation and quiescence

repeats, nuclear localization signals, and a transactivation domain. There are at least five Notch ligands in mammals: three orthologs of the *Drosophila* Delta (Delta or Delta-like [Dll] 1, 3, and 4) and two of the *Drosophila* Serrate (Jagged1 and Jagged2) [14–17]. In general, Notch binds to one of its ligands, which is located in the adjacent cell and then results in two sequential proteolytic cleavages of the receptor. The latter involves the release of the intracellular part of Notch receptor, which is Notch1 intracellular domain (NICD). It transfers into the nucleus and then associates with recombination signal binding protein-Jkappa (RBP-J, which also known as CSL for the different ortholog proteins: CBF1, Suppressor of Hairless, and Lag1) and the coactivator Mastermind (Mam) to activate specific transcription. Notch pathway participates in the transcriptional regulation of multiple genes, some of which are context-dependent. However, the most important Notch functions have been associated with the regulation of the *Hes* or *Hes*-related (*Hrt*) family of genes [18]. All these genes encode for basic helix-loop-helix (HLH) proteins which function as inhibitors of cell differentiation (Fig. 2).

Studies used transgenic mice carrying dominant negative forms of *Jagged1* or *Notch1* or *Notch2*-deficient mice show that Notch pathway is indispensable for maintenance of adult HSCs under physiologic and homeostatic conditions [19, 20]. Besides, Notch pathway influences the kinetics of LT-HSC recovery after injury [21, 22].

Fig. 2 The Notch signalling pathway. Notch binds to one of its ligands and then results in two sequential proteolytic cleavages of the receptor. The latter involves the release of the intracellular part of Notch receptor, which is NICD. It transfers into the nucleus and then associates with RBP-J and the MAM to activate specific transcription. Notch pathway participates in the transcriptional regulation of multiple genes

Wnt Signaling Pathway

The roles of Wnt pathway in hematopoietic stem cell self-renewal or lineage specific differentiation are manifold.

Recent evidence strongly suggests that Wnt signaling has an important regulatory role in HSCs during both fetal and adult development [23, 24]. Wnt proteins represent a family of secreted signaling molecules that are expressed in diverse tissues. Wnt pathway activates by binding to two types of receptor molecules. One is the Frizzled family of seven-pass transmembrane proteins, which contain a cysteine-rich extracellular domain that binds to Wnt proteins. The other is a subset of the low-density lipoprotein receptor-related protein (or the LRP) family, especially, LRP-5 and LRP-6. It was demonstrated that both LRP-5/6 and Frizzled are required to activate functionally the downstream components of the canonical pathway. By now we know there are 19 secreted Wnt ligand glycoproteins, 10 Frizzled receptors, and 2 LRP coreceptors [25–27]. At least three different Wnt pathways are currently recognized: the canonical Wnt pathway, the non-canonical Wnt pathway and the planar cell polarity (PCP) pathway.

Wnt ligands bind to the Frizzled and Lrp5/6 receptors, activating downstream signaling. The membrane proteins zinc and ring finger 3 (Znrf3) and ring finger 43 (Rnf43) are ubiquitin ligases that continually down-regulate Frizzleds through ubiquitination. Binding of R-spondins to Znrf3 and Rnf43 and the leucine-rich repeat-containing G-protein-coupled receptor 4/5/6 (Lgr4/5/6) relieves Znrf3 and Rnf43 activity, thus stabilizing Frizzleds. Binding of

Wnt to its receptors induces the association of Axin with phosphorylated LRP [28, 29]. The destruction complex falls apart, and β -catenin is stabilized, subsequently binding T cell factor (TCF) in the nucleus to up-regulate target genes, including Axin2 and Lgr5 (Fig. 3).

Fig. 3 The canonical Wnt signalling pathway. Wnt ligands bind to the Frizzled and Lrp5/6 receptors, activating downstream signaling. Binding of Wnt to its receptors induces the association of Axin with phosphorylated LRP. The destruction complex falls apart, and β -catenin is stabilized, subsequently binding TCF in the nucleus to up-regulate target genes, including Axin2 and Lgr5

The roles of Wnt pathway in hematopoietic stem cell self-renewal or lineage specific differentiation are manifold; therefore, Wnt signals have found practical use in manipulating hematopoietic stem cell developmental programs in vitro. From a pragmatic perspective, because wnt induces hematopoietic stem cell self-renewal in certain organs, it enables the in vitro propagation of such cells. For example, mammary gland stem cells can be expanded in vitro in the presence of wnt protein and retain their ability to reconstitute the entire mammary organ after transplantation [23].

Hedgehog Signaling Pathway

Hh pathway regulates the transcription of target genes which affect the proliferation, self-renewal, quiescence and differentiation of HSC.

The Hedgehog (Hh) pathway is also a highly conserved developmental pathway which regulates the proliferation, self-renewal, and differentiation of cells during development [30]. It is typically active during development, but silenced in adult tissues, except tissue regeneration and injury repair. Hh pathway has been closely associated with cell cycle regulation and is implicated both in specification of hematopoiesis during embryogenesis and proliferation of establishing HSCs in adulthood. Three distinct ligands, Sonic (Shh), Indian (Ihh) and Desert (Dhh) Hedgehog exist in humans. Upon ligand binding to the receptor patched (Ptc), inhibition of smoothened (Smo) receptor is relieved. Smo then activates members of the Gli family of zinc-finger transcription factors, which translocate to the nucleus to regulate the transcription of Hh target genes including Gli1, Gli2, Ptch which affect cell proliferation and survival.

Hedgehog pathway acts as a negative regulator of the HSC quiescence. It has demonstrated that constitutive activation of the Hh signaling pathway in Ptc heterozygous (Ptc-1+/-) mice resulted in induction of cell cycling and expansion of primitive bone marrow hematopoietic cells. Furthermore, the common downstream positive effector of Hh signaling, Gli1, has been shown to play a critical role in normal and stress hematopoiesis. However, in some studies the conditional loss of Smo within adult HSCs is dispensable for hematopoiesis. These conflicts might be due to the difference between the mouse model and the conditional system used to impair Hh signaling [31].

Tie2/Ang-1 Signaling Pathway

It mainly plays role in the maintenance of HSCs.

The tight adhesive binding of osteoblastic cells to HSCs via the Angiopoetin-1 (Ang-1) ligand and Tie2 receptor,

respectively allows for a specific population of HSCs to maintain quiescence even in the presence of mobilizing factors such as G-CSF [17]. Although Ang-1 is abundant in a number of cells within the niche, it is produced by osteoblastic cells, and its stimulation triggers maintenance of the long-term repopulating HSCs. Similarly, THPO is produced by osteoblastic cells, and the THPO receptor is found in a quiescent population of LT-HSCs, and these quiescent stem cells are found adhering to THPO+ osteoblastic cells. Stimulation of this pathway increases the number of quiescent HSCs, while inhibition of this pathway leads to a decrease in LT-HSC frequency.

Interaction Between Niche and HSCs in Clinical Significance

There are increasing evidence for the important roles of the interaction between niche and HSCs on controlling the behavior of malignant hematological diseases [32].

When the niche is altered, normal HSCs may become to malignant cells. For instance, acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) are the consequence of stepwise genetic alterations that confer both proliferative and survival advantage, as well as self-renewal to the malignant cells.

Ga-Young Lee's recent study on AML patients shows that the MSCs are altered during leukemic conditions in a clinical course dependent manner. We all know that MSCs is one of the ingredient of niche, which can regulate the behavior of HSCs. These cells secrete a range of cytokines to support the maintenance of HSCs. When the MSCs are altered, HSCs will become to malignant cells, which we call leukemic stem cells (LSCs). LSCs blasts cause reprogramming of transcriptomes of MSCs and remodel the cross-talk in niche, which leads to normal primitive hematopoietic cells suppression and leukemogenesis [33].

There are plenty of data show that the MDS niche is clearly perturbed when compared to the normal niche [34]. The fact that stromal cells in MDS patients often harbor different genomic mutations than their hematopoietic counterparts [35]. When the normal niche is changed, the function of HSCs will be broken. So, the normal HSCs defection can induce bone marrow failure and dysplastic hematopoiesis [36].

HSCs effectively and continuously renew all different hematopoietic lineages [37]. Bone marrow hematopoietic stem cells transplantation (HSCT) restore hematopoiesis, which is an important treatment for patients suffering from hematological disorders, including leukemia, MDS, and aplastic anemia in adults and children [38]. HSCT can alter the niche of patient and use the ability of normal HSCs to self-renew and differentiate [39, 40].

Conclusion

Understanding the signaling pathways that determine HSCs fate is important for the success of a wide array of medicinal applications. These include HSCs transplantation and cancer treatments, and may help refresh treatments strategies for auto-immune diseases as well as viral and bacterial infections.

These investigations reveal the complexity of pathways and protein networks, which determine the HSC's ends in self-renewal, differentiation, and quiescence. Studies have strikingly demonstrated that at times one pathway is involved in all three fates of the HSCs, leading to the assertion that the physiological condition advancing toward the HSC's final fate does not reside in a single route, but within a complex of interactions between several signaling pathways, and within a web of protein clusters. To date, we know that, downstream to activated receptors, protein clusters, which contain kinases, phosphatases, and adaptor proteins, are formed in order to activate transcription factors and sets of genes, which will govern the HSC's fate.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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