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Mini-review

How the niche regulates hematopoietic stem cells

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ABSTRACT

The hematopoietic stem cell (HSC) forms all types of blood cells of the hematopoietic system. In the adult, HSC are mainly quiescent, being mostly in G0/G1 phase of cell cycle during steady-state conditions. However, during hematopoietic stress, the stem cells respond quickly to regenerate the damaged hematopoietic system. To understand how environmental signals affect HSC and its progeny, it is essential to know the lineage relationships and transcriptional mechanisms controlling self-renewal, proliferation and differentiation. Because of the high possible output of blood cells from a single HSC, a tight regulation of these processes is extremely important. An essential component for this control is the marrow microenvironment, in this context also referred to as the HSC niche. The niche is heterogeneous and regulates stem cell metabolism through both surface-bound and soluble factors. Several signaling pathways have been shown to take part in these regulation processes, with Notch and especially Wnt signaling being the best studied ones. Dysregulation of the niche, for instance by environmental exposure, has recently been shown to lead to hematopoietic abnormalities. Thus, to understand the effect of the environment on hematopoiesis, it is of importance to study both HSC, its direct progeny and the cellular components of the niche. Detailed knowledge of the regulatory mechanisms operating between hematopoietic cells and their direct surroundings facilitates the study of how such signaling may be disrupted by environmental exposure.

Contents

1. Introduction

The hematopoietic system is what makes up all of the blood cells in the body, be it white leuko- and lymphocytes or red blood cells. These cells are required for a multitude of tasks, such as protection from infections, removal of damaged tissue, but also to transport vital molecules such as oxygen to where it is needed throughout the body. Most of these hematopoietic cells have a limited life span and since there is a continuous need of cells to perform these tasks

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throughout life, a system to continuously replenish their numbers is required for the organism to survive.

At the centre of this complex developmental process sits the hematopoietic stem cell (HSC), which, in the adult mammalian, primarily resides in the bone marrow (BM). This cell is unique among hematopoietic cells by having the potential to give rise to all the cells in the hematopoietic system and at the same time be capable of self-renewal. Self-renewal is an important cellular event, which means a cell can divide while maintaining at least one daughter cell in the undifferentiated stem cell-like state. Due to this capacity, HSC can generate an entire hematopoietic system from just a single cell and maintain hematopoiesis for the lifetime of the individual [1]. Since HSC reside in the bone marrow, the current idea is that the bone marrow microenvironment, or so-called niche, plays an important role in the regulation of self-renewal and differentiation of HSC. The microenvironment is the collective concept for the different types of cells and structures surrounding the bone, which regulates the fate of hematopoietic cells through direct or indirect means, facilitating a stable generation of all the blood cells needed in a steady-state situation. But, the microenvironment also adapts in times of hematopoietic stress. A failure to maintain a strict regulation of the hematopoietic cells can lead to a variety of malignancies such as different types of leukemia, the most common forms of cancer in humans.

In this review, we will not directly involve ourselves with the toxicology of the hematopoietic system. Rather, we will give an overview of which processes might be sensitive to environmental exposure to toxic substances during hematopoietic development as well as provide some mechanistic background information. In particular, we will focus on the hematopoietic niche and how dysregulation of this niche may affect hematopoiesis.

2. Hematopoietic development

2.1. Embryonic hematopoiesis

In the mouse, the earliest hematopoietic cells found are the primitive, nucleus bearing erythrocytes in the yolk sac at embryonic day 7.5 (E7.5) [2]. At this early stage of development the primitive hematopoietic cells are organized in “blood islands”, which also contain blood vessels. These blood vessels are believed to originate from primitive hemangioblasts, which are capable of producing both hematopoietic and endothelial cells [3]. The molecular mechanisms of blood island formation are, as yet, not elucidated entirely. The basic helix–loop–helix transcription factor Scl (Tal1) is essential for both primitive and later definitive hematopoiesis, and deficiency in either GATA-box-binding transcription factors Gata1 or Gata2 also impairs formation of functional blood islands (reviewed by [4]). Since vascularisation is important for hemangioblasts to develop, molecules involved in vascular development, such as Kdr (also known as Flk1, Vegfr2), are required in the developing embryo for this early hematopoietic differentiation to occur [5]. After the emergence of primitive hematopoiesis in the yolk sac, a second wave of definitive hematopoiesis can be detected around the stage where circulation starts (E8.25). There is now evidence supporting the notion that precursors of definitive cells emerge in the yolk sac, which subsequently seed the embryo proper [6]. The first definitive HSC that can regenerate hematopoiesis in adult recipients can be detected in the aorta–gonads–mesonephros (AGM) region [7]. The role of core-binding transcription factor Runx1 in the emergence of the definitive HSC has been firmly established [8]. These first HSCs appear in the aorta subregion of the ventral AGM [9], possibly as a product of hemogenic endothelium [10–12]. Only slightly later in development, HSC are also detectable in the placenta [13,14], circulation and yolk sac of the embryo and subsequently the number of HSC in the fetal liver starts to rise [15]. Besides Runx1, other transcription factors may play additional roles in the development of definitive hematopoiesis. For instance, the mixed leukemia gene (Mll) [16], Meis1 [17], and the Notch pathway factor Rbpj [18], all frequently found to be involved in dysregulation of adult leukemias, may be important as well. Until birth, the fetal liver is the main hematopoietic organ. From the fetal liver, HSC migrate and colonize the bone marrow (BM) just prior to birth. From birth and onwards, the bone marrow is the primary site of adult hematopoiesis.

Recently, it was demonstrated that besides the transition from primitive to definitive hematopoiesis, a second event is the switch from fetal to adult hematopoiesis: the fetal program (high proliferative capacity) remained until about 3–4 weeks after birth, and then switched to the adult program where HSC are quiescent and mainly in G0/G1 of cell cycle [19]. Another study revealed a possible candidate to identify the switch from embryonic to adult hematopoiesis; the transcriptional regulator Sox17, which is clearly expressed in fetal HSC but not in adult HSC more than 4 weeks after birth in mice [20]. Indeed, a conditional knockout of Sox17 has severe effects on fetal, actively cycling HSC but does not seem to affect adult, quiescent HSC [20].

2.2. The adult mouse hematopoietic hierarchy

After the switch to the adult hematopoietic program, the HSC mainly resides in the bone marrow. Since the number of HSC is relatively small to the vast number of cells needed each day in the living organism, the entire proliferation and hematopoietic maturation process is tightly regulated. To understand these mechanisms, and to understand how these mechanisms can be disturbed by environmental cues, the precise description of all cell types involved and their lineage relationships facilitates the exact pinpointing of changes in the regulation of their proliferation and differentiation.

The adult definitive hematopoietic hierarchy consists of a chain of progressively maturing hematopoietic cells culminating with the mature red and white blood cells mainly found in the circulation, but also in other hematopoietic tissues: spleen, thymus, and lymph nodes. In the mouse, this hierarchy has been described in such detail that single stem cells can be isolated and their behavior studied. Thus, the hematopoietic system is an excellent model to study changes in stem cell regulation caused by environmental cues.

The characterization and isolation of different hematopoietic subsets is usually performed using flow cytometry. HSC have been phenotypically described by the absence of surface expression of lineage markers (Lin−) and the presence of both Ly-6A/E (Sca-1) and Kit [21]. Further improvements of this phenotype facilitate the isolation of single true HSC transplanted. Among those are the recognition that HSC do not express Cd34 [22], Flk2/Flt3 [23], or Cd48 (Slamf2), but do express Cd150 (Slamf1) [24] (Fig. 1A), and the EPC receptor (Procr) [25,26]. A summary of markers used to distinguish the earliest HSC from their more mature counterparts is given in Table 1. These HSC divide and mature into different cell subsets which first become positive for Cd34, Flk2 and Cd48, and after a number of further differentiation steps then form the two basic mature blood cell types: myeloid and lymphoid cells. The differentiation of these two major lineages is thought to separate quite early in the maturation hierarchy at the multipotent progenitor (MPP) stage into interleukin 7 receptor (Il7r)-expressing common lymphoid progenitors (CLP) [27] and common myeloid progenitors (CMP) [28] (reviewed in [29]). These CMP will then further differentiate into granulocyte–monocyte progenitors (GMP) and megakaryocyte–erythroid progenitors (MEP). This hypothesis of the hematopoietic hierarchy assumes that the lymphoid system is completely separated from the myeloid system (Fig. 1B). How-

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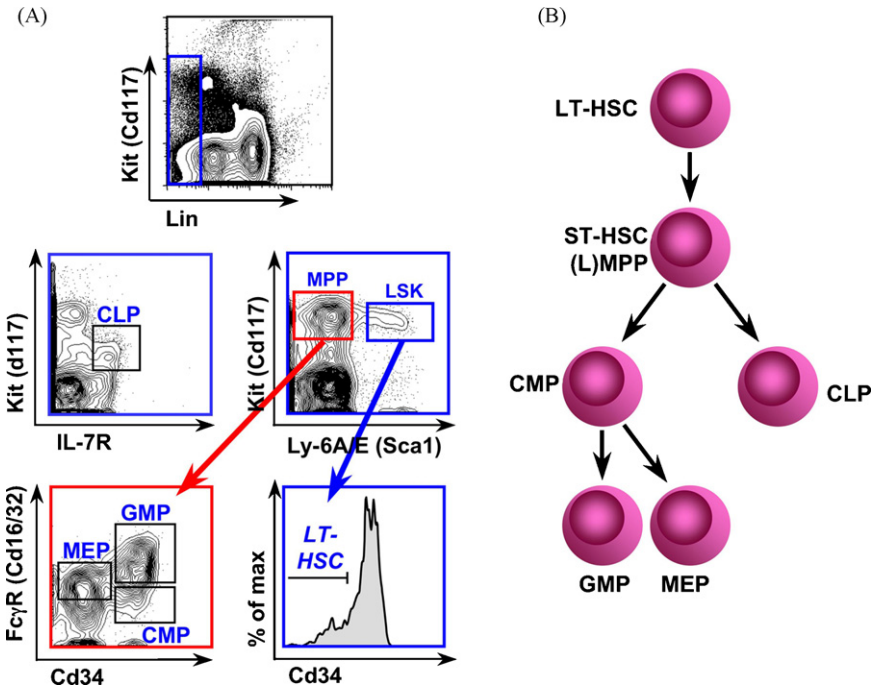

Fig. 1. The hematopoietic hierarchy in the adult mouse. The figure shows the different dot plots obtained by phenotypical analysis of whole bone marrow cells using flow cytometry. In A, the breakdown of different subpopulations is shown as described in detail in [98]. In B, the most likely lineage relationships between the cells in A is shown in a small diagram. Abbreviations: HSC: hematopoietic stem cell (LT: long-term; ST: short-term); MPP: multipotent progenitor; LMPP: lympho-myeloid potential progenitor; CMP: common myeloid progenitor; CLP: common lymphoid progenitor; GMP: granulocyte–monocyte progenitor; and MEP: megakaryocyte–erythrocyte progenitor.

ever, recent evidence suggests that this separation may not be as absolute as thought earlier, since under some special conditions, early lymphoid cells retain their ability to give rise to myeloid lineage cells. This has been observed both for B lymphoid cells [30] as well as T lymphoid cells [31,32]. Such early lineage infidelity may have clinical significance, since it has been shown that early B cell precursors can give rise to myeloid leukemia in CALM-AF10 (Picalm–Mllt10) transformed marrow cells [33].

Despite the uncertainties in early lineage diversification, transcriptional regulation of HSC self-renewal and lineage specification

Table 1
Summary of antibodies used to distinguish different subsets of hematopoietic cells.

Marker	Alternative name	Expressed by	Comments	References
Cd3		Most T cells	Used in lineage cocktail	[111]
Cd4		Subsets of T cells		[112]
Cd5	Ly-1	Most T cells	Used in lineage cocktail	[113]
Cd8		Subsets of T cells		[112]
Cd11b	Mac1	Mostly myeloid cells but also some lymphoid	Used in lineage cocktail	[112]
Cd16/32	FcgrII/III		Used to distinguish different myeloid progenitor subpopulations	[28]
Cd34	Mucosialin	Endothelial cells, some hematopoietic progenitor cells	HSCs are negative or low in expression	[22]
Cd45R	B220	Mostly B cells	Used in lineage cocktail	[114]
Cd48	Slamf2	Many hematopoietic cells, multilineage marker	HSCs are negative or low in expression	[24]
Cd71	Transferrin receptor	Erythroid cell subpopulation separation, dividing cells	Used for erythoid cell subpopulations	[115]
Cd90	Thy1.1	Hematopoietic stem cells and thymocytes	HSC are “low” in expression	[112,116]
Cd117	Kit tyrosine kinase receptor	Hematopoietic stem/progenitor cells and mast cells	HSCs are positive	[21]
Cd127	Il7r	Variations of B and T cells	HSCs are negative, used to sort out CLPs from Lin-cells	[28]
Cd135	Flk2/Flt3 tyrosine kinase receptor	Hematopoietic progenitors lacking erythroid and megakaryocytic potential	HSCs are negative	[117]
Cd150	Slamf1	B and T cells	Upregulated when cells are activated. HSC are positive	[24,116]
Cd161	NK1.1, Klrb1c	Natural killer cell lineage		[118]
Cd201	Epcr, Procr	Endothelial cells and early hematopoietic cells	HSC are positive	[25]
Gr1	Ly-6G	Granulocytes and monocytes	Used in lineage cocktail	[112]
Ter119	Ly76	Erythroid cells	Used in lineage cocktail	[119]
Sca1	Ly6A/E	Hematopoietic stem/progenitor cells and some myeloid and lymphoid cells	HSCs are positive	[112]

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are slowly being uncovered. The previously mentioned transcription factors Runx1 and Scl (Tal1) are both important to maintain the number of HSC, whereas other factors, like Sfpi1 (Pu.1) and Gata1 may be involved in lineage specification [34,35]. One thing that is clear is that HSC reside in the bone marrow as quiescent cells and lineage specification largely takes place within this tissue as well.

3. The hematopoietic stem cell niche

In adults, normal hematopoiesis takes place in the bone marrow. Schofield was the first to formulate that "the stem cell is seen in association with other cells which determine its behaviour" [36]. This notion, that the stem cells fate is determined by surrounding cell structures, is nowadays referred to as the stem cell microenvironment, or the stem cell niche [37–39]. In other organisms, such as *Drosophila* fruit flies [40], the existence of germ cell niches have been well-established. In these germ cell niches, stem cells are propagated by asymmetric cell divisions, where a dividing stem cell gives rise to a niche-attached stem cell and a progenitor cell [41]. The attractiveness of the idea that in the adult hematopoietic system, similar niches exist where stem cells self-renew has spurned many investigators to find the exact location of the niche and define its cellular components.

What is now known is that the most immature HSCs reside most likely near the endosteal region of trabecular bone [42,43]. However, the search for the exact location of the niche and the cell types involved is still not resolved completely. The endosteal region is actively recruiting HSC, probably by secreting factors like the chemokine Sdf1. Within hours after intravenous transplantation, HSC localize within microns of the endosteal surface, though only a small percentage of cells will localize directly adjacent to the osteoblasts [44,45]. Two types of niches have been described: the endosteal niche, where the HSC remain close to osteoblasts of trabecular bone and a perivascular niche, where the stem cells are closer to vascular endothelium in marrow sinuses [46]. Whether these are factually different niches, or whether the two niches are one and the same, remains subject to speculation [39].

Another area of intense investigation revolves about the question how the niche directs self-renewal and differentiation of HSC. Most studies have focused on integral parts of the niche, the osteoblasts and bone marrow stromal cells. It has already been shown that these cells can secrete factors such as G-CSF, GM-CSF, Kitl (stem cell factor, SCF), IL-6 and SDF1 (CXCL12) which influences hematopoietic cell fate both in vitro and in vivo [47–50]. Using the knowledge of which secreted factors are generated by stromal cells, have so far not led to stroma-free culture conditions of HSC expansion. The reason for that might be that stromal activation after environmental insult may be required for short-term HSC expansion. However, the factors governing a return to G0/G1, a prerequisite for long-term maintenance of HSC, are unknown at present. Also, after insult, HSC may be released from the "maintenance niche" and move closer to the "expansion niche" where proliferation and differentiation takes place [44,45]. The idea that HSC are, in fact, subject to the influence of different cellular environments, each with different functional relevance, has received impetus by observations that activated (leukemic) cells, can displace quiescent HSC, thereby dysregulating their proliferative behavior [51].

Thus, in vivo imaging suggests that HSC may occupy several different niches in the bone marrow, depending on the activity of the HSC or its direct progeny at a given time. The picture of the niche, as first formulated by Schofield, has now become focused on the endosteal surface of trabecular bone, where both endosteal and vascular niches may exist.

3.1. Microenvironment-dependent signals which regulate hematopoiesis

It has been shown that most HSC remain quiescent (i.e. in G0/G1 phase of the cell cycle) at any given time [52]. But, HSC will rapidly respond to hematopoietic stress induced by disturbances of the hematopoietic system. Homeostasis thus depends on a tightly regulated balance between self-renewal, proliferation, and differentiation of HSC and its daughter cells. In order to keep this homeostasis, mechanisms have to be in place to insure that HSC return to quiescence with the help of several signaling molecules from a number of different biological pathways. Several pathways have, in fact, been studied for their role in niche–HSC in these activating and de-activating regulatory mechanisms, including the Tie2/Ang1–Cdh2/Myc axis, Bmp/Tgf signaling, Cxcl12/Cxcr4 signaling, hedgehog and Notch signaling, as well as Wingless (Wnt) signaling.

Examples of gene products involved in niche–HSC interaction are Tie2 and its ligand Ang1, which are both required to maintain quiescence of HSC at the endosteal interface [53]. One target of Tie2 signaling, Cdh2 (N-cadherin), has also been implicated in niche–HSC interactions and seemed to be involved in possible asymmetric cell divisions [54]. The central role of N-cadherin could, however, not be confirmed in mice deficient in N-cadherin, since bone marrow cellularity, progenitor activity, HSC function or numbers are unchanged by the absence of N-cadherin [55]. A second pathway involved in stem cell regulation is the Bmp–Tgf pathway. It has been long since known that Bmp4 is not only involved in the hematopoietic specification of embryonic stem cells [56]. But, Bmp4 has also been implicated in stromal cell regulation of embryonic definitive HSC [57] as well as adult HSC in vivo [58]. The responsible Bmp receptor has not yet been identified, but a good candidate is Bmpr1a which has now been found to be strongly expressed by osteoblasts, and its deficiency decreases the number of transplantable HSC [43]. A third pathway of niche–HSC regulation may include stromal derived factor 1 (Sdf1, Cxcl12) and its receptor Cxcr4 [59]. Cxcl12 (Sdf1) is produced by stromal cells in the niche and Cxcr4 is strongly expressed on the earliest HSC. Sdf1 is a chemokine which is thought to be involved in regulating the number of HSC in the circulation [60,61], primarily by regulating the attachment of HSC to the niche through Mmp9- and Kit-dependent proteolytic release [62]. By releasing Cxcr4 expressing cells, not only is their trafficking disturbed, but the released HSC also change their cell cycling activity, suggesting that Cxcr4 may be involved in maintaining HSC quiescence [63]. A fourth pathway is the hedgehog (Hh) signaling pathway, which is governed by the signaling intermediate smoothened (Smo). Like in the case of N-cadherin, however, hedgehog signaling does not seem to be involved in the maintenance of HSC in Smo-deficient mice [64,65]. Two pathways we will discuss in more detail: the Notch and Wnt pathways. Current evidence suggests, that these two pathways find themselves very often collaborating with the other mechanisms described previously as well as with each other. The Notch and Wnt pathways may therefore form a possible interface in niche-mediated regulation of early hematopoiesis.

3.1.1. Notch signaling

In experiments designed to find out the role of Notch signaling in hematopoiesis, it was shown that overexpression of the active intracellular Notch1 domain increased self-renewal of LSK (lineage^{neg} Sca1^{pos} c-Kit^{pos}) cells [66]. Furthermore, the interaction between the Notch ligand Jagged1 and Notch1 impairs differentiation both in vitro [67,68], and in vivo [68]. Similarly, ectopic expression of Dll4 in stromal cells will increase human progenitor cell maintenance in vitro [69] It was later also shown that Notch1 is expressed by HSC. Interestingly, Notch signaling intermediates,

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like Notch1, Notch3, and its ligands Jagged1 and Dll1, are expressed by osteoblasts [42,70], suggesting Notch-mediated HSC–niche crosstalk. Experiments with conditional knockout mouse models using floxed Jagged1 or Notch1 mice or deficiency of Notch signaling through overexpression of a dominant-negative variant of the central Notch intermediate mastermind-like 1 (Maml1) indicate, however, that signaling through this receptor–ligand pair is not necessary for maintenance of HSC and hematopoiesis under steady-state conditions [71,72]. Thus, the exact role of Notch1 signaling, or the role of other Notch receptors (particularly Notch3) in microenvironmental regulation of HSC remains unclear. What is clear, is that Notch signaling cooperates with other signaling pathways during hematopoietic regeneration [73]. In particular, crosstalk between Notch and Wnt signaling was shown to occur. Interestingly, though most studies have concentrated on intrinsic HSC signaling, recent evidence shows that Wnt and Notch crosstalk may occur in an extrinsic manner [74], where stroma cells containing activated β-catenin (Ctnnb1) upregulated Notch signaling in hematopoietic cells during stress conditions such as myeloablation. Thus, it seems likely that Notch signaling is important in niche–HSC interactions, particularly during hematopoietic regeneration.

3.1.2. *Wnt signaling*

Members of the Wingless (Wnt) family of lipid-modified proteins have been investigated best in hematopoiesis [73,75]. The Frizzled (Fzd) receptors act as Wnt receptors which activate downstream signaling in the Ctnnb1-dependent canonical and non-canonical pathways. Canonical Fzd receptors associate with the Lrp5/6 co-receptors, and propagate signals through catenins, to activate Tcf/Lef transcription complexes. This transcriptional complex targets transcription of specific genes, including Myc, Spp1, Socs2, P2ry14 and Ccnd1 [76]. The level of Ctnnb1 is regulated through the proteome. In non-canonical Wnt signaling Fzds and non-related Ryk or Ror receptor tyrosine kinases activate calmodulin/Ca^{2+}- or Rho-dependent responses. These pathways regulate a different set of Wnt targets, such as Pparg and Pcdh8 [77]. Also, there is interaction between non-canonical and canonical pathways, as non-canonical Ca^{2+}-dependent signals inhibits catenin stability through Camk2-mediated activation of Nemo-like kinase (Nlk) and subsequent phosphorylation of Ctnnb1, which is then degraded [78].

Several components of the Wnt signaling machinery have been shown to play a role in HSC self-renewal. Both canonical as well as non-canonical pathways seem to be involved, since the canonical ligand Wnt3a intrinsically promotes self-renewal [79]. On the other hand, the non-canonical ligand Wnt5a has been shown to extrinsically promote self-renewal, but, paradoxically enough, by inhibiting canonical signaling [80,81]. The mechanistic basis for the balance between canonical or non-canonical pathways is not fully understood. It is likely that the numerous Wnt-signaling inhibitors (Dickkopf homolog (Dkk), Wnt inhibitory factor (Wif) or secreted frizzled-related protein (Sfrp), or other Wnt antagonists, such as Kremen, Ctgf, Cyr61, Sost and Sostdc1) are modulating Wnt signaling. Interestingly, some of these also directly stimulate certain Fzds independent of Wnt factors. For example, Sfrp1 directly activates Fzd2 [82], as well as Fzd4, and Fzd7 [83] but can also interact with Wnt5a [84].

This balance and feedback mechanisms between canonical and non-canonical Wnt signaling, suggests that Ctnnb1 is the primary regulatory target of Wnt signaling. However, overexpression or stabilization of Ctnnb1 results in expansion of the HSC pool, but, at the same time, the loss of myelopoiesis is due to a differentiation block [85,86], suggesting that Ctnnb1 promotes self-renewal and/or inhibits differentiation. Surprisingly, conditional deletion of Ctnnb1 or both Ctnnb1 and plakoglobin (γ-catenin, Jup) does not affect the repopulating ability of HSC [87–89]. Thus, it appears that β-catenin does not have intrinsic effects on HSC maintenance and engraftment.

The role of catenin suggests different levels of hematopoietic regulation. Although the above indicates that both β- and γ-catenin are dispensible for normal hematopoiesis, this appears not to be true for leukemic stem cells. Ctnnb1 and other Wnt intermediates are frequently overexpressed in leukemic patient samples [90]. The importance of Ctnnb1 in leukemia is also highlighted by the observations that missplice mutations of its upstream kinase Gsk3b [91], or overexpression of its downstreams mediator Lef1 [92] cause myeloproliferation. In addition, Bcr-Abl1 leukemia requires Ctnnb1 expression [93], probably by conferring self-renewal ability to the mature GMP population [94]. Taken together, current reports suggests that Ctnnb1, and perhaps other catenins, may play different roles in normal as compared to leukemic HSC, where Ctnnb1 is dispensible or redundant for normal HSC but required for leukemic HSC behavior.

The above findings all deal with the possibility of Wnt signals within the stem cells (intrinsic signals). However, there is also data showing that Wnt signaling is important in bone formation and enlarging endosteal surfaces (reviewed by [60]). Several lines of evidence suggests that Wnt signaling in endosteal stromal cells may affect HSC maintenance, not by intrinsic signals, but by signals from the stromal cells (extrinsic signaling). For instance, increased expression of Ctnnb1 in marrow stroma improves HSC maintenance and concomittantly increases HSC engraftment [73,95]. Although the precise mechanism of this effect has not been identified, increased Notch signaling was demonstrated in the HSC cocultured on Ctnnb1-overexpressing stromal cells [73]. Moreover, further evidence comes from mice overexpressing the canonical inhibitor Dkk1 in stromal cells of the niche, the HSC pool is gradually lost [96]. Also, stroma cells from mice deficient in the non-canonical Wnt mediator Nlk were shown to be defective in maintaining hematopoietic progenitors due to extrinsic effects [97]. Finally, our own work indicates that secreted frizzled-related protein 1 (Sfrp1), regulates hemostasis as well as HSC self-renewal in an extrinsic manner. Interestingly, the loss of Sfrp1 in stromal cells was accompanied with a decrease in intracellular beta-catenin levels. Gene-expression studies of these mice showed decreased levels of the Tcf/Lef canonical targets Ccnd1 and Dkk1 HSC and increased expression of Pparg, Hes1, and Runx1 in the more mature MPP [98].

Taken together, Wnt signaling may not be intrinsically involved in the maintenance of normal HSC during hemostasis or self-renewal. However, there is data suggesting that changes of Wnt signaling in endosteal stromal cells affect HSC maintenance through extrinsical mechanisms. Future studies should more clearly define the spider web of interactions that operate in stromal cells and HSC and which, together, are involved in HSC regulation.

4. Dysregulation of the niche may cause hematopoietic abnormalities

Myeloproliferative disease has been shown to be primarily caused by the faulty expression of mutated growth factor receptors or the formation of fusion oncogenes, which cause an intrinsic gain of self-renewal and proliferative capacity. Yet, there are also myeloproliferative conditions where no apparent changes in HSC can be found, such as in myelodysplastic syndromes. Indeed, only recently has it been recognized that changes in the niche may, in fact, cause myeloproliferation. For instance, loss of the NF-κB signaling intermediate Nfkbia (Ikba) causes a stroma-dependent increase in myeloproliferation, which is partly due to increased stromal Jagged1 expression and Notch1 signaling in myelocytes [99]. Another study which points to the Notch pathway are conditional knockouts for the Notch pathway mediator mindbomb

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homolog 1 (Mib1). In these animals, though, suppression of Notch signaling in the microenvironment causes a change in extrinsic cues culminating in myeloproliferation [100], suggesting that upregulating Notch in either HSC or stromal cells may have opposite effects.

Unanticipated was also that deficiency of the cell cycle regulators Rb [101] and Rarg [102] causes a niche-dependent myeloproliferation. In these models, Rb impairs lodgement and homing of HSC, whereas, Rarg disturbs Tnf-mediated signaling.

Lineage decisions are also suspected to be directed by microenvironmental cues. A recent study elegantly showed that certain cytokines direct CMP towards either granulocytes or monocytes [103]. It has been shown that mice deficient in the telomere component Terc show increased stromal production of G-CSF and an increased proportion of Gr1-expressing myelocytes [104], confirming that the niche directs cell fate decisions in the myeloid lineage. It is of interest to note that in disease, the niche may similarly direct the phenotype of myeloproliferative disease. This has been shown to occur in MLL-AF9 expressing cells which form either mixed lymphoid–myeloid leukemia, or myeloid leukemia, depending on the growth factors expressed by the microenvironment [105].

Taken together, these studies show that disruption of the expression of certain genes in the niche may not only cause myeloproliferative disease, but may also direct the lineage fate of HSC development, thereby determining the phenotype of the disease formed from the leukemic stem cell.

5. Summary and conclusions

The regulation of hematopoietic stem cell activity through its surroundings, or niche, is a concept, first proposed in the 70s by Schofield [36]. Investigations into how the components of the niche influence HSC are unravelling the mechanisms involved. The identification of single HSC by their surface phenotype, has facilitated specific studies in lineage relationships and self-renewal of single HSC. It has become clear that the HSC can be found near the endosteal region of the bone possibly in the vicinity of blood vessels. Whether there is a need for direct cell to cell contact between the HCS and its surrounding niche cells, possibly through integrin alpha 4 and alpha 9 mediated interactions [106,107] has still not been resolved decisively. In order to investigate the intricate interplay between niche and HSC, many researchers use cell lines, capable of maintaining HSC activity in vitro, which mimick the niche and serve as homogenous models which can be taken apart in more detail [108–110]. These studies are uncovering possible mechanisms by which the niche regulates self-renewal, quiescence and proliferation of HSC. Furthermore, these studies now allow a modified hypothesis of the cause of myeloproliferation. Whereas it has long since been recognized that intrinsic changes of HSC may cause myeloproliferation (Fig. 2A), it has also become clear that changes induced in the stromal compartment of the niche may also lead to myeloproliferative disease (Fig. 2B). With regard to toxicological research, for instance with regard to benzene toxicity, the mechanisms described above may be involved in exposure-related leukemia. It is of interest to note that enzymes, such as Nqo1, which are involved in benzene detoxification and bioactivation, are, in fact, expressed by bone marrow stromal cells [120]. Whether benzene is, in fact metabolized by marrow stromal cells, or whether stromal cell function is dysregulated by toxic agents such as benzene has, to date, not been investigated. Thus, a deeper understanding of how niche–HSC regulation works, may be of great benefit of uncovering the signaling mechanisms involved in, and design specific therapies for pathological environmental exposure.

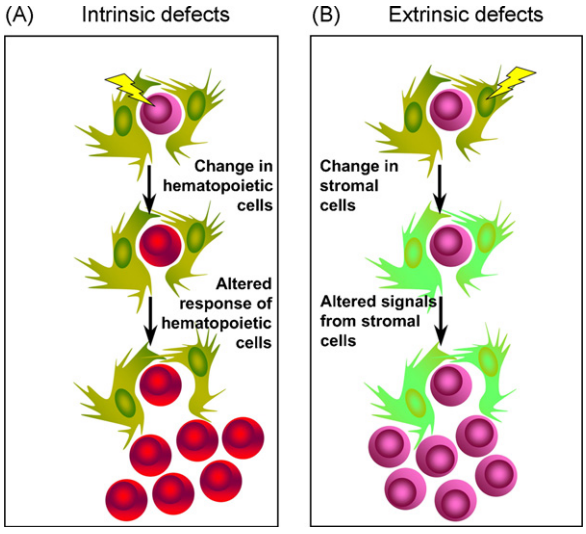

Fig. 2. Different theories of how hematopoietic stem cells could be deregulated after intrinsic (A) or extrinsic damage (B). Damaging factors could for instance be: irradiation, cytotoxic agents, or environmental pollutants (like benzene). In A, these damaging conditions cause intrinsic damage, for instance by inducing DNA breaks or other damage, which results in an intrinsically changed hematopoietic cell. This changed cell does not respond correctly to quiescence-inducing signals from the niche. As a result, the changed HSC will continuously proliferate, which may lead to myeloproliferative disease. In B, the damaging conditions affect the stromal cells. In this scenario the stromal cells are changed and cannot give the HSC the correct signals to keep them quiescent. As in scenario A, the HSC will start to proliferate, which could ultimately result in myeloproliferative disease. Thus, two fundamentally different scenarios lead to the same end-result.

Conflict of interest

None.

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Abbreviation list

AGM: aorta–gonads–mesonephros region
HSC: hematopoietic stem cell
CLP: common lymphoid progenitor
CMP: common myeloid progenitor
G-CSF: granulocyte colony-stimulating factor
GM-CSF: granulocyte–macrophage colony-stimulating factor
GMP: granulocyte–monocyte progenitor
Gr1: granulocyte antigen 1 (product of the Ly6g gene)
IL-6: interleukin 6
LSK: lineage^{neg} Sca1^{pos} c-Kit^{pos}
MEP: megakaryocyte–erythroid progenitor
MPP: multipotent progenitor (lineage^{neg} Sca1^{neg} c-Kit^{pos} cells)
SCF: stem cell factor (product of the Kitl gene)
SDF1: stromal-derived factor 1 (chemokine product of the Cxcl12 gene)

Generic gene names or genes

Abl: v-abl Abelson murine leukemia viral oncogene homolog
Ang1: angiopoietin 1
Bcr: breakpoint cluster region
Bmp4: bone morphogenetic protein 4
Bmpr1a: bone morphogenetic protein receptor, type 1A (also known as Alk3)
Cd34: CD34 antigen
Cd48: CD48 antigen (also known as Slamf2)
Cd150: signaling lymphocytic activation molecule family member 1 (Slamf1)
Cdh2: cadherin 2 (also known as N-cadherin)
Ccnd1: cyclin D1
Ctgf: connective tissue growth factor
Ctnnb1: β-catenin, catenin (cadherin associated protein), beta 1
Cxcl12: chemokine (C–X–C motif) ligand 12
Cxcr4: chemokine (C–X–C motif) receptor 4
Cyr61: cysteine rich protein 61
Dkk1: Dickkopf homolog 1 (*Xenopus laevis*)
Dll4: delta-like 4 (*Drosophila*)
Flk2/Flt3: FMS-like tyrosine kinase 3
Fzd: frizzled homolog (*Drosophila*)
Gata1: GATA binding protein 1
Gata2: GATA binding protein 2
Gsk3b: glycogen synthase kinase 3 beta
Hes1: hairy and enhancer of split 1
Il7r: interleukin 7 receptor
Jup: junction plakoglobin (also known as γ-catenin)
Kdr: kinase insert domain protein receptor (also known as Flk1 and Vegfr2)
Kit: kit oncogene
Kremen: kringle containing transmembrane protein 1
Lef1: lymphoid enhancer binding factor 1
Lrp5/6: low density lipoprotein receptor-related protein 5/6
Ly6a: lymphocyte antigen 6 complex, locus A
Maml1: mastermind like 1 (*Drosophila*)
Meis1: Meis homeobox 1
Mib1: mindbomb homolog 1 (*Drosophila*)
Mll: myeloid/lymphoid or mixed-lineage leukemia 1
Mllt10: myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, *Drosophila*); translocated to, 10 (also known as AF10)
Mmp9: matrix metallopeptidase 9
Myc: myelocytomatosis oncogene
Nfkbia: nuclear factor of kappa light polypeptide gene enhancer in B cell inhibitor, alpha (also known as Ikba)
Nlk: Nemo-like kinase
Notch1: Notch gene homolog 1 (*Drosophila*)
Notch3: Notch gene homolog 3 (*Drosophila*)
P2ry14: purinergic receptor P2Y, G-protein coupled, 14
Picalm: phosphatidylinositol binding clathrin assembly protein (Calm)
Pparg: peroxisome proliferator activated receptor gamma
Procr: protein C receptor, endothelial
Rarg: retinoic acid receptor, gamma
Rb: retinoblastoma 1
Rbpj: recombination signal binding protein for immunoglobulin kappa J region
Ror: receptor tyrosine kinase-like orphan receptor
Runx1: runt related transcription factor 1
Ryk: receptor-like tyrosine kinase
Tal1: T cell acute lymphocytic leukemia 1 (also known as Scl)
Sfpi1: SFFV proviral integration 1
Sfrp: secreted frizzled-related protein
Smo: smoothened
Socs2: suppressor of cytokine signaling 2
Sost: sclerostin
Sostdc1: sclerostin domain containing 1 (also known as Wise or Sostl)
Sox17: SRY-box containing gene 17
Spp1: secreted phosphoprotein 1 (also known as osteopontin)
Terc: telomerase RNA component
Tek: endothelial-specific receptor tyrosine kinase (also known as Tie2)
Tnf: tumor necrosis factor
Wif: Wnt inhibitory factor
Wnt5a: Wingless-related MMTV integration site 5A

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