Title

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Journal

WNT SIGNALING IN HEALTH AND DISEASE, 153(CA Cancer J Clin 66 1 2016)

ISSN

1877-1173

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Publication Date

2018

DOI

10.1016/bs.pmbts.2017.11.002

Peer reviewed

HHS Public Access

Author manuscript

Prog Mol Biol Transl Sci. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

Prog Mol Biol Transl Sci. 2018 January ; 153: 321–341. doi:10.1016/bs.pmbts.2017.11.002.

Wnt Signaling in Hematological Malignancies

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Abstract

Leukemia and lymphoma are a wide encompassing term for a diverse set of blood malignancies that affect people of all ages and result in approximately 23,000 deaths in the United States per year (Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7–30.). Hematopoietic stem cells (HSCs) are tissue-specific stem cells at the apex of the hierarchy that gives rise to all of the terminally differentiated blood cells, through progressively restricted progenitor populations, a process that is known to be Wnt-responsive. In particular, the progenitor populations are subject to uncontrolled expansion during oncogenic processes, namely the common myeloid progenitor and common lymphoid progenitor, as well as the myeloblast and lymphoblast. Unregulated growth of these cell-types leads to mainly three types of blood cancers (i.e., leukemia, lymphoma, and myeloma), which frequently exhibit deregulation of the Wnt signaling pathway. Generally, leukemia is caused by the expansion of myeloid progenitors, leading to an overproduction of white blood cells; as such, patients are unable to make sufficient numbers of red blood cells and platelets. Likewise, an overproduction of lymphocytes leads to clogging of the lymph system and impairment of the immune system in lymphomas. Finally, cancer of the plasma cells in the blood is called myeloma, which also leads to immune system failure. Within each of these three types of blood cancers, there are multiple subtypes, usually characterized by their timeline of onset and their cell type of origin. Of these, 85% of leukemias are encompassed by the four most common diseases, that is, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), and chronic lymphocytic leukemia (CLL); AML accounts for the majority of leukemia-related deaths (Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7–30.). Through understanding how HSCs are normally developed and maintained, we can understand how the normal functions of these pathways are disrupted during blood cancer progression; the Wnt pathway is important in regulation of both normal and malignant hematopoiesis. In this chapter, we will discuss the role of Wnt signaling in normal and aberrant hematopoiesis. Our understanding the relationship between Wnt and HSCs will provide novel insights into therapeutic targets.

1. HEMATOPOIETIC STEM CELL (HSC) DEVELOPMENT

The development of hematopoietic stem cells (HSCs) is a dynamic process, involving migration through several niches in distinct anatomical locations. The first long-term bona

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fide HSCs arise directly from specialized hemogenic endothelium in all species examined to date, in a process known as the endothelial-to-hematopoietic transition.[1] As this transition occurs, HSCs begin to express markers of hematopoietic fate, such as the transcriptional regulator *Runx1*.[2,3] In mammals, the first HSCs arise from the aorta, umbilical artery, and vitelline artery in the midgestation embryo[1,4,5] (around embryonic day 10 in mouse). These later migrate to the fetal liver, and finally the bone marrow, where HSCs are maintained throughout the lifespan of the animal.[6] It is thought that at each of these progressive locations, the HSCs receive induction cues, such as FGF, Notch, and Wnt, which are important for their maturation and function.[7] During this dynamic developmental process, these HSCs are subject to inputs from various surrounding niches and a variety of developmental signaling pathways, reviewed elsewhere.[8–10] These early inputs give rise to later HSC function, and disruption of these cues fundamentally alter the identity and behavior of these cells.[11,12] The final result of these developmental cues are long-term HSCs (LT-HSCs), housed in the bone marrow; these lie at the apex of the hematopoietic hierarchy, seeding the entire blood system for the duration of the organism's life.

2. HSC HOMEOSTASIS

LT-HSCs are defined by their ability to repopulate the hematopoietic system of an organism for a long duration.[13] In the bone marrow, these are largely quiescent, but give rise to a subpopulation of short-term HSCs (ST-HSCs), which are limited in their capacity for self-renewal and are able to repopulate an organism only for a few weeks.[14] HSCs in turn give rise to the lineage restricted common progenitors of the myeloid and lymphoid fates, which together can differentiate into all mature blood cells.[15,16] (Fig. 1). Recent single-cell analyses have indicated that all of these progenitor types have low levels of coexpression of multiple lineages, suggesting overlapping cell fates at the transcriptional level, and that these fate decisions are rather plastic.[17] Additionally, HSCs with long-term single lineage reconstitution fate have been identified, suggesting that the binary lineage tree of hematopoietic fate is more flexible than previously established.[18] It is through careful regulation of inductive cues that HSCs are able to self-renew and differentiate into the full complement of blood. Disruption of these regulatory cues can accordingly result in cancers of the blood, and our understanding of these cues during normal hematopoiesis will be critical to determining how they are coopted during oncogenesis.

Our understanding of the native processes governing hematopoietic homeostasis has been hindered by technical difficulties, including the relative rarity of these cells in vivo, where it is estimated that HSCs form approximately 1/20,000 nucleated hematopoietic cells.[14] As a result, it has been difficult to elucidate the molecular mechanisms governing their homeostasis, as purification of a large enough number of cells for analysis is challenging. It is apparent that HSCs receive both cell-intrinsic and -extrinsic cues to govern their maintenance reviewed in Ref. 19. In the bone marrow, HSCs reside in close proximity to endothelial cells, osteoblasts, and mesenchymal stem cells, which are proposed to supply the niche cues governing self-renewal and differentiation[20] (Fig. 1), though this is incompletely understood. Among others, the Wnt signaling cascade is known to play important roles in these processes.

3. WNT SIGNALING

Wnt genes encode lipid-modified, secreted signaling molecules, which regulate a diverse set of developmental and homeostatic programs, ranging from axial patterning to stem cell identity and self-renewal reviewed in Ref. 21.[22–24] Their broad range of effects are in part due to the complex genetic nature of these factors with 19 independent Wnt genes in the mammalian genome and multiple genes encoding structurally and functionally distinct receptors, including Frizzled (Fzd), lipoprotein related protein (Lrp), receptor tyrosine kinase-like orphan receptor (Ror), and receptor-like tyrosine kinase (Ryk). Activation of the Wnt signaling cascade has been loosely grouped into either the canonical (β-catenin dependent) or noncanonical (β-catenin independent) pathways, though it is important to note that these pathways do not necessarily work independently or in opposition to each other. Furthermore, a given Wnt may activate distinct signaling cascades depending on expression of downstream signaling components.[21,25–29]

In the absence of Wnt signals (Fig. 2), the DNA binding proteins of the lymphoid enhancing factor (LEF)/T-cell factor (TCF) family recruit corepressors, such as Groucho/transducing-like enhancer (GRG/TLE) and CtBP1, to silence expression of Wnt target genes. The transcriptional activator β-catenin is constitutively tagged for proteasomal degradation by the so-called destruction complex, consisting in part of GSK3β, APC, and Axin. In the presence of a Wnt ligand, Fzd receptors and Lrp coreceptors oligomerize at the membrane, leading to dissociation/relocation of the destruction complex, thus releasing β-catenin from proteasomal targeting and allowing it to enter the nucleus where it displaces GRG/TLE from LEF/TCF and activates expression of Wnt target genes.[30] Activation of this arm of the Wnt signal often leads to maintenance or specification of cell fate (e.g., stem cell self-renewal or differentiation).[21] Wnt signaling can be modulated with secreted negative regulators; such as secreted frizzed-related proteins (SFRP),[31] which are hypothesized to sequester the Wnt ligand; Notum,[32–34] which inactivates Wnt through deacylation; and Dickkopf (Dkk), which bind Lrp to prevent oligomerization with Fzd.[35]

The β-catenin independent pathways remain poorly understood. In its downstream signal, there are a variety of effectors, including RhoA, JNK, and calcium influx pathways[21,36–38] (Fig. 2). Different arms of this cascade can proceed with or without a Fzd receptor, and use different coreceptors, such as Ror and Ryk.[27,39] The result of activation of these pathways is often polarization of the cell for division, migration or extension, or even the polarization of whole tissues (i.e., planar cell polarity).[21] However, there is also evidence for β-catenin independent Wnt signaling in cell fate specification,[40] indicating that these seemingly distinct pathways have overlapping functions and are possibly tightly integrated.

4. WNT IN HSC DEVELOPMENT AND HOMEOSTASIS

The role of Wnt in HSC development and homeostasis has been intensely debated by the field, in part due to conflicting data in the literature.[41] Furthermore, the genetic complexity of the ligands and receptors, as well as the dynamic nature of HSC development, including the multiple cell types involved in self-renewal and differentiation lends itself to a complex series of inputs. In particular, harnessing the particular intricacies of timing and signal

dosage may be the key to unlocking our understanding of Wnt in HSC ontogeny and maintenance.

Almost all *Wnts* and *Fzds* are expressed, at least to some degree, in the various hematopoietic sites during development,[42] indicating a potential role for these during HSC ontogeny; however, the specific requirements, if any, for these are only beginning to be elucidated. For example, a role for Wnt16 in the specification of HSCs in zebrafish has been established,[40] whereas Wnt5a seems to regulate lymphopoiesis.[43,44] In addition, a requirement for Wnt9a in the intraaortic amplification of HSCs was recently shown.[45] The specific requirements for Fzd receptors is less clear, potentially due to functional redundancy, or our incomplete understanding of Wnt-Fzd specificity requirements. It is known that Fzd9 is required for lymphoid development and maturation, for example, but its potential role in the HSC itself is unclear.[46]

The expression of Wnt components in the adult bone marrow are only slightly more refined, with a handful of these being expressed in putative HSC niche cells: osteoblasts, vascular cells, and mesenchymal stem cells.[47–51] Wnt function dependent on β-catenin in HSCs is driven through LEF/TCF DNA elements, as in other cells.[52] Accordingly, conditional deletion of β-catenin in the hematopoietic population impairs the long-term self-renewal[53] and regenerative capacities of HSCs.[54] Amplification of the Wnt signal, through viral expression of a constitutively active β-catenin results in increased numbers of HSCs in vitro and conversely, inhibition of Wnt signaling through viral expression of *Axin2* or addition of a soluble form of a Fzd ligand binding domain results in loss of HSC reconstitution in vivo, [52,55] potentially due to premature differentiation. Early work showed contradictory evidence for the role of Wnt/β-catenin signaling in the HSC system: loss of Wnt function through Wnt3a deletion,[56] β-catenin mutation,[53] or overexpression of the antagonist Dkk1[57] depleted the HSC pool in vivo, whereas activation of Wnt signaling through stabilized forms of β-catenin or the Wnt target prostaglandin E2, resulted in increased HSC number.[58,59] However, others observed a depletion of the progenitor pool upon β-catenin overexpression. [60,61] These contradictions are likely explained by dosage-dependent effects of Wnt signaling on different populations of blood cells[62]; using an allelic series of APC mutants, it was possible to show that a low level of Wnt signaling maintains a proliferative HSC phenotype, whereas a high level of Wnt activation resulted in total impairment of repopulation capacity and exhaustion of the stem cell pool.[62]

There is also evidence for specific function of Wnt ligands in adult HSCs. For example, *Wnt3a*, *Wnt5a*, and *Wnt10b* are all expressed in the bone marrow niche; interestingly, expression of *Wnt10b* is upregulated in response to injury to drive proliferation of bone marrow hematopoietic cells.[63] Fzd receptors likely play specific roles in the adult niche. For example, Fzd8 regulates the long-term quiescence of HSCs by regulating the noncanonical downstream calcium pathway.[64] HSCs from mice deficient in the β-catenin independent receptor *Ryk* have reduced quiescence, decreased self-renewal, and increased apoptosis.[65] During HSC ageing, there is a shift from β-catenin dependent to independent Wnt signaling, which seems to underlie the loss of self-renewal and lineage skewing seen in aged HSCs.[66] Altogether, these studies indicate that a careful balance of Wnt signals is required to regulate HSC specification, amplification, homeostasis and ageing. These effects of Wnt on normal

HSCs are often hijacked in cancer processes, including the establishment and progression of blood cancers (Table 1).

5. WNT SIGNALING IN LEUKEMIA

The balance of self-renewal and differentiation in HSCs is critical to survival of an organism. For a cancer to progress, there must be a sustained increase in proliferation and also a block in differentiation. As such, mutations affecting cell identity or proliferation, such as *FLT3*, *TP53*, *RUNX1*, and *KMT2A* are commonly found in leukemias.[69] In addition to these mutations, chromosomal translocations, especially affecting chromatin modulators, such as *MLLT3-KMT2A*, *BCR-ABL*, and *RUNX1-MECOM* are associated with, and are sometimes sufficient to cause leukemia.[69,70] Differences in genetic causes for leukemias also give rise to cancers with different mechanisms of action, prognostic outcomes, and treatment regimes, making it crucial for us to understand the molecular cues driving these events to derive effective treatments.

In different subsets of leukemias, *WNT* expression and signaling in the bone marrow microenvironment are perturbed, often in the absence of a direct mutation in *WNT* component genes. For example, in chronic lymphocytic leukemia (CLL) B-cells, the WNT signal and expression of *WNT3* and the transcription factor *LEF1* are amplified compared to normal B-cells.[71] In addition, WNT3, WNT4, WNT5B, WNT6, WNT7B, WNT9A, WNT10A, WNT14, and WNT16 are all highly expressed in CLL B-cells.[72,73] Similarly, in E2A-Pbx1 acute lymphoblastic leukemia (ALL) cells, *WNT16* is robustly expressed, although it can be scarcely detected in normal pre-B cells; this expression is dependent on E2A-Pbx1, suggesting that Wnt activation occurs downstream of this translocation.[74] Expression of other leukemic translocation products also induces the expression of WNT components in hematopoietic cell lines.[75]

There is potential for therapeutic targeting of WNT in leukemias. The β-catenin independent coreceptor ROR1 is expressed in CLL leukemic cells, but not nonleukemic leukocytes, allowing for targeting of these cells with an anti-ROR1 monoclonal antibody (mAb, also known as cirmtuzumab).[76] High levels of ROR1 are associated with an accelerated form of CLL.[77] Addition of Wnt5a enhances the proliferation and migration of CLL cells through RhoA/Rac1; this effect can be blocked with cirmtuzumab,[78] and cannot be achieved in non-ROR1 expressing leukemic cells.[77] Clinically, combining cirmtuzumab with a B-cell receptor blocking agent is significantly more effective at clearing leukemic cells in vivo than either drug in isolation.[79] Taken together, these studies indicate how WNT targeting can be used to kill leukemic cells.

On the other hand, not all WNT activation is detrimental. For example, mice hemizygous for Wnt5a, which regulates the calcium signaling cascade, have enhanced B-cell proliferation and develop spontaneous myeloid leukemia and B-cell lymphomas, possibly because Wnt5a antagonizes the β-catenin signal.[44,80] In fact, WNT5A has tumor suppressing activity as loss of function mutations and/or loss of expression are found in a majority of primary human leukemia cells,[44] suggesting that this relief of β-catenin signaling repression may be necessary for some leukemias to progress. In another instance, exogenous Wnt3a reduced

the proliferative capacity of B-cells in vitro[81]; however, this may be due to the dosage-dependent effects of Wnt on HSCs.

Many upstream regulators of Wnt signaling, such as members of the *Dickkopf* (*Dkk*) or *SFRP* families have been reported to be transcriptionally silenced due to promoter hypermethylation in human samples,[82–86] thereby presumably elevating endogenous Wnt signaling activity, which may promote proliferation and oncogenic transformation. In RUNX1-ETO mediated (acute myeloid leukemia) AML, decreased expression of *SFRP1* results from direct transcriptional repression from the *RUNX1-ETO* gene product, and leads to an increase in Wnt activation.[87] Although these are classically thought to be negative regulators of the Wnt signal, this is not always the case. This decrease in antagonist expression actually seems to have a positive effect on patient survival in *BCR-ABL* ALL,[88] suggesting that SFRPs may act to activate the WNT signal in leukemic cells. SFRPs have been suggested to act as carrier proteins for WNTs in other systems, acting to expand the range of the WNT signal, which may also play a role in leukemia.[89] Taken together, these studies exemplify that Wnt signaling is ectopically activated in many subsets of leukemia, leading to increased proliferative and self-renewal capacities of the leukemic stem cells.

Some leukemic stem cells are dependent on Wnt for self-renewal and/or survival. For example, β-catenin enhances the self-renewal and proliferation capacity of *BCR-ABL* chronic myeloid leukemia (CML) cells, which also show an increase in β-catenin signaling during their expansion; this effect is lost when the Wnt signal is dampened with AXIN overexpression.[90] This Wnt-mediated self-renewal is due to a splicing defect in *GSK3*β, which impairs its ability to bind AXIN, and target β-catenin for degradation.[90,91] Furthermore, mouse *BCR-ABL* CML cells refractory to standard treatment are dependent on β-catenin, indicating a potential role for Wnt in the evolution of these types of hematological malignancies.[92] This dependence on β-catenin for cancer progression is not limited to CML; it is also seen in subsets of AML,[93] CLL,[71] and ALL.[94,95] In addition, Wnt is also known to synergize with other leukemic mutations in mouse models, immortalized cells, and patient samples,[96–100] likely due to the increased WNT signal resulting from aberrant transgenes. Finally, the dependence of leukemic stem cells on Wnt is not limited to the β-catenin pathway, as *BCR-ABL* CML cells also rely on the Wnt-mediated calcium pathway for survival[101]; inhibition of numerous components of Wnt/Ca^{2+}/NFAT sensitizes cells to BCR-ABL inhibition. Altogether, these studies point to WNT as a potential therapeutic target; however, consideration of the effective dosage of the WNT signal and the particular cascade affected must be carefully considered.

6. WNT SIGNALING IN LYMPHOMA

Lymphomas are blood cancers that arise in the lymph nodes, as opposed to leukemias that mainly arise in the bone marrow. There are many diseases that fall under the umbrella term of lymphoma, including Hodgkin's Lymphoma, Mantle Cell Lymphoma (MCL), and Burkitt's lymphoma, to name a few. As these cancers arise in a plethora of anatomical locations, it has been difficult to discern the molecular cues regulating their initiation and progression. It is known that lymphomas differ in the genetic causes and also their activation of, and reliance on, WNT signaling. For example, patient samples of many different types of

lymphoma have differentially increased levels of nuclear (active) β-catenin, but the majority of these do not contain mutations in APC or β-catenin,[102–105] suggesting that activation of the pathway is induced by autocrine or paracrine cues. β-Catenin independent signaling has also been proposed to play a role in anaplastic large cell lymphoma, although the extent to which this applies to other lymphomas is unclear.[106]

Many WNT components are found to be dysregulated in various types of lymphoma. For example, MCL is associated with a chromosomal translocation, which leads to an increase in expression of the context-dependent Wnt target gene *cyclinD1*, which is not sufficient to drive lymphoma on its own.[107,108] A microarray study compared gene expression in MCL cells and naïve B-cells (their wild-type counterparts), and found that several WNT pathway components, including *TCF7*, *FZD7*, *LRP5*, *AXIN1*, *APC*, *DVL3* were upregulated in MCL cells, indicating a potential requirement for WNT signaling in the disease progression.[109] Furthermore, MCL cells frequently show inactivation of GSK3β, which leads to an increase in nuclear β-catenin.[110] These studies fall in line with the general paradigm that an increase in the canonical arm of the Wnt signal leads to an increase in tumorigenicity.

Other lymphomas also have dysregulated Wnt; for example, there is evidence for overexpression of the transcription factors TCF1 and LEF1 in subset of T-cell lymphomas and small B-cell lymphomas.[111,112] This upregulation also occurs in lymphomas that are chemoresistant,[113] suggesting that WNT could be involved in the evolution of these cancer stem cells (the slow-dividing cells that initiate tumors) as well. It is worthy of note that TCF1 has also been implicated as a tumor suppressor since 50% of $Tcf1^{-/-}$ mice spontaneously develop thymic tumors.[114] The authors suggest that this may be due to TCF/LEF1 specific functions in this process, mainly TCF1 directly inhibiting *LEF1* transcription and leading to an overall increase in the Wnt signal. Like in leukemia, the absence of Wnt5a, which is thought to antagonize the β-catenin signal, can lead to cancer. Speaking to this, loss of heterozygosity in $Wnt5a^{+/-}$ mice develop B-cell lymphomas that are clonal in origin.[44] These studies also highlight the importance of Wnt signaling as an initiating event in lymphoma, which has also been proposed based on expression studies in humans.[115] However, the reliance of cancer stem cells on Wnt in lymphomas is less clear than that of leukemic stem cells. In a mouse model of lymphoma, which develops to 100% penetrance in all lymphoid organs, the disease is reliant on upregulation of the Wnt signal,[116] demonstrating that at least some lymphoma cancer cells are reliant on Wnt for survival. Finally, different WNTs also differentially affect these cancer cells. For example, a recent study highlights that WNT5A is a motility factor in Hodgkin's lymphoma; addition of WNT5A increases the motility of Hodgkin's lymphoma cells in culture, however, neither WNT10A and WNT10B nor WNT16 are able to elicit the same response.[117] Developing a clear understanding of how different Wnts affect downstream pathways in these diseases will be crucial toward developing therapeutic interventions for patients.

7. WNT SIGNALING IN MYELOMA

Myeloma encompasses cancers of the plasma cells, of which multiple myeloma (MM) is the most common and is characterized by an accumulation of plasma cells in the bone marrow. WNT activation in the absence of β-catenin or APC mutation has been observed in multiple

myelomas cells, which were dependent on this signal for continued growth.[118] In fact, treatment of these with the compound PKF115-584 (which targets the β-catenin/TCF complex) results in cytotoxicity of primary patient MM cells and established cell lines, without effect on normal plasma cells.[119] *Wnt2b*, *Wnt5a*, *Wnt7a*, *Wnt10b*, *Wnt11*, and *Wnt16* are all expressed in MM cell lines[120]; however, it is worthy of noting that cell-autonomous Wnts are not necessarily involved in MM and the effects may not be limited to these particular Wnts. There is some evidence for sensitizing MM cells to autocrine and paracrine Wnt signals from the bone marrow niche.[121] In addition to the β-catenin dependent signal, Wnt3a is able to induce the RhoA signal in MM cells, including changes in cytoskeleton and morphology, indicative of an effect on planar cell polarity.[122] These alterations lead to an increase in the migration and invasion ability of these cells, and similar effects can be achieved using Wnt1 or Wnt4; these effects are dependent on the RhoA arm of Wnt signaling.[120] These data support roles for both β-catenin dependent and independent WNT signaling in MM cells.

MM leads to the osteolytic bone disease, resulting from the destruction of bone (osteoclast induction) and repression of its repair (osteoblast suppression). These in turn lead to further bone marrow niche dysfunction and these effects are also in part due to loss of Wnt regulation. For example, the WNT inhibitors SFRP2 and DKK1 are secreted by several MM cell lines, as well as primary patient cells.[123] SFRP2 inhibits bone mineralization in vitro,[124] and both *Dkk1* and *SFRP2* expression are associated with advanced destructive bone lesions in patient samples.[123,124] In addition, soluble Dkk1 can inhibit the differentiation of osteoblasts in vitro, suggesting that inhibition of Wnt through these soluble factors can inhibit bone formation and repair.[123,125] Severe combined immunodeficient (SCID) mice implanted with MM tumor cells spontaneously develop a loss in bone mineral density, which can be overcome with anti-Dkk1 antibody treatment; this is due to increased levels of osteoblasts and decreased osteoclasts, leading to an overall induction in bone density.[126–128] In addition to its role in MM initiation, MM tumor progression during chemoresistance involves the adhesion of MM cells to the bone marrow stroma, where expression of Wnt3 correlates with increased adhesion, likely progressing through the RhoA signaling cascade.[129] Taken altogether, these data point to the importance in Wnt regulating the interplay between MM and bone homeostasis, which when disrupted leads to osteolytic bone disease.

8. CONCLUSIONS AND PERSPECTIVES

The link between aberrant WNT signaling and many cancers is well established. However, in the case of blood malignancies, this requirement has been less clear, possibly due to the dosage-dependent effects of WNT on the stem cell niche and the dynamic nature of blood development and homeostasis. These studies together show that WNT plays a role in leukemias and lymphomas. Of note, these observations indicate a potential role for planar cell polarity in the pathogenesis of MM. Planar cell polarity has largely been studied in the context of whole tissue polarity, in contrast to the single cell nature of the blood; however, the involvement of the RhoA arm of Wnt signaling in MM suggests that this may be a mechanism exploited by tumorigenic single cells as well. One study has also pointed to a role for planar cell polarity in CLL.[130] Further studies will reveal the involvement of Wnt/planar cell polarity in tumorigenesis of hematopoietic cells. In addition to the roles described

earlier, aberrant WNT seems to be a common mechanism for drug resistance in leukemia and lymphoma,[131–133] suggesting that these tumors may be "WNT addicted." In one example, pretreatment of purified patient ALL blasts to suppress the WNT signal was sufficient to restore chemosensitivity in relapsed patient cell lines,[134] an indication of one potential therapeutic avenue targeting WNT. A thorough understanding of how WNT regulates normal and malignant hematopoiesis will be key to future therapeutic interventions.

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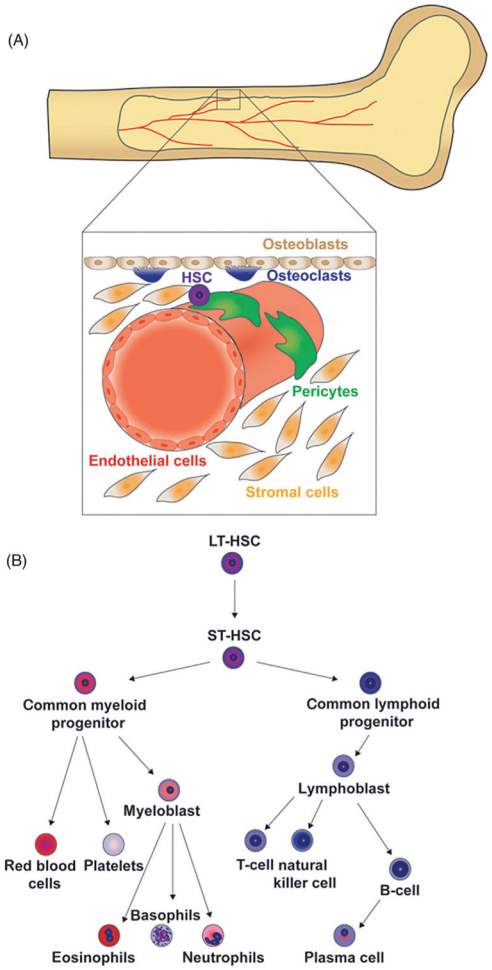

Fig. 1.

Adults hematopoietic stem cells (HSCs) reside in the bone marrow. (A) The marrow of long bones is the niche for homeostasis of HSCs, where they reside in close proximity to many cell types. For example, the blood vessels, which carry circulating HSCs and their progeny; the bone-building osteoblasts; the bone-degrading osteoclasts; the supportive pericytes, and other bone marrow stromal cells. (B) In the niche, the quiescent long-term (LT) HSCs give rise to short-term (ST) HSCs, which in turn can gives rise to the common myeloid or lymphoid progenitors, which can differentiate into all cell types of the blood, and many cells from the immune system.

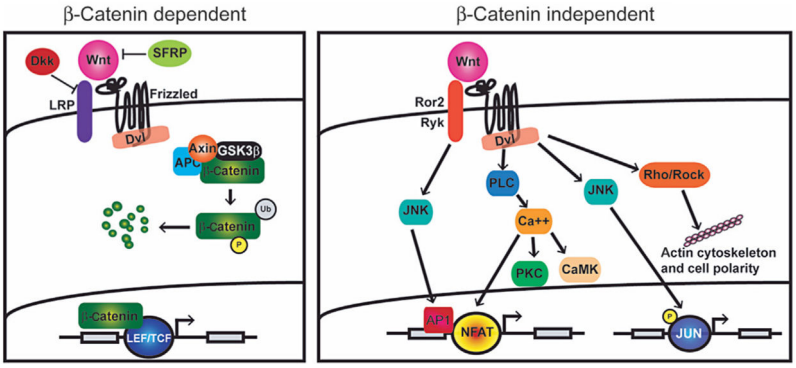

Fig. 2.

Wnt signaling pathways. Schematic representations of the β-catenin dependent and independent Wnt signaling cascades. In the β-catenin dependent cascade, Wnt-Fzd-LRP interaction culminates in the nuclear translocation of β-catenin to bind lymphoid enhancing factor (LEF)/T-cell factor (TCF) transcription factors and drive gene expression. In the β-catenin independent pathway, there are several arms of signaling. For instance, Wnt–Fzd interaction leads to either Rho/Rock or Rac/JNK signaling, culminating in changes in the actin cytoskeleton or gene expression, respectively. Alternatively, WNT-Fzd-Ror2/Ryk interaction lead to changes in intracellular Ca++ levels, which affect protein kinase C (PKC), calmodullin-dependent protein kinase (CaMK) signaling cascades, or NFAT/AP1 driven gene expression changes. *Dkk*, Dickkopf; *Fzd*, Frizzled; *LRP*, lipoprotein related protein; *Ryk*, receptor-like tyrosine kinase; *SFRP*, secreted frizzed-related proteins.

Table 1

Known Wnt and Fzd Knockdown and Knockout (KO) Phenotypes in HSCs.

Genes	Knockdown or Knockout Phenotypes	References
Wnt1	Decreased number of thymocytes; some functional redundancy with Wnt4 (mouse KO)	67
Wnt3a	Homozygous mutants are lethal at E12.5; loss of HSCs and progenitors and impairment of long-term engraftment (mouse KO)	56
Wnt4	Decreased number of thymocytes; some functional redundancy with Wnt1 (mouse KO)	67
Wnt5a	Increased B-cells (mouse KO, cell culture model)	43,44
Wnt9a	Decreased intraaortic expansion of HSCs and progenitors (zebrafish knockdown and KO)	45
Wnt16	Loss of HSC specification (zebrafish knockdown)	40
Fzd5	Extraembryonic vascular development is abnormal (mouse KO)	68
Fzd9	Decreased B-cells (mouse KO)	46

HSC, Hematopoietic stem cell.