REVIEW

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Role of the Wnt/β-catenin network in regulating hematopoiesis

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Abstract

The Wnt/β-catenin pathway plays a significant role in several aspects of cell biology, including the stimulation of gene expression, growth, and mobility. Wnt proteins activate at least three cascades: Wnt/β-catenin, Wnt/Ca^{2+}, and planar cell polarity. β-Catenin is not only a very important element of many intracellular signaling pathways, including the Wnt pathway, but it also takes part in creating intercellular adhesive junctions. When overexpressed or mutated it functions as an oncogen. The Wnt/β-catenin signaling pathway has been shown to play an important role in controlling the proliferation, survival, and differentiation of hematopoietic cells. Thus any aberrant signaling through this pathway may have a negative influence on hematopoiesis. Indeed, some recent findings suggest that Wnt/β-catenin signaling is dysregulated in leukemias and lymphomas. All these data position the Wnt/β-catenin signaling network as a critically important regulator of hematopoiesis and justify future efforts to better understand its role in the process of physiological and pathological hematopoiesis. The present review summarizes recent advances in this field.

Key words: Wnt, β-catenin, hematopoiesis, stem cells, tumor cells.

Abbreviations: APC – adenomatous poliposis coli, BFU – base-forming unit, CFU – colony-forming unit, CMP – common myeloid progenitor, CTNNB1 – cadherin-associated protein β-1, Dsh – Dvl-Dishevelled, Fzd – Frizzled, HSC – hematopoietic stem cell, IL – interleukin, LRP – LDL-receptor-related protein, PCP – planar cell polarity, SCF – stem cell factor, sFRP – secreted Frizzled-related protein, TCF – human T-cell factor, LEF – lymphoid enhancer factor, TGF-β – transforming growth factor-β, WIF-1 – Wnt-inhibitory factor 1.

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INTRODUCTION

Wnts are conservative glycoproteins that activate signaling pathways through receptors present on the cell surface, members of the Frizzled (Fzd) and LDL-receptor-related protein (LRP) families. They influence cell differentiation, proliferation, polarization, migration, adhesion, and gene expression [58]. Many elements of the Wnt signaling pathway are crucial during embryogenesis [87]. They also take part in the regeneration of several tissues, such as bone and skin [59, 104]. Wnts activate at least three cascades: Wnt/β-catenin, called the canonical pathway, Wnt/Ca^{2+}, and the establishment of planar cell polarity (PCP) [14, 64]. β-Catenin is a protein that takes part in creating intercellular adhesive junctions. It is also a very important element of many intracellular signaling pathways, including the Wnt signaling pathway [68]. When overexpressed or mutated it works as an oncogen [28]. In the nucleus, β-catenin binds to transcription factors such as human T-cell factor (TCF) and lymphoid enhancer factor (LEF). By stimulating changes in gene expression, β-catenin can enhance cell proliferation and inhibit cell apoptosis [42].

Hematopoiesis is a continuous process in which stem/progenitor cells develop into mature blood cellular components. The Wnt/β-catenin signaling pathway has been shown to play an important role in governing the proliferation, survival, and differentiation of hematopoietic cells [14, 15]. Thus any aberrant signaling through this pathway may have an influence on hematopoiesis. Since most of the data on the role of the Wnt/β-catenin signaling network in hematopoiesis involves research on the canonical pathway, we concentrate on this subject in our review. However, recent findings on the role of Wnt/Ca^{2+} and PCP in hematopoiesis are also included.

Wnt-ACTIVATED PATHWAYS

Wnt is named after the "wingless" type of *Drosophila* with a mutation of the *wg* gene [84] and a mouse study on the protooncogene Int-1 [69, 97]. The family is composed of 19 proteins with molecular weights between 39 and 46 kDa (350-400 amino acids). They are cystein-rich glycosylated short-range ligands (containing 22–25 conservative cysteins) and their function and structure have been the matter of investigation for over 20 years [58].

Wnt/ß-catenin: a canonical pathway

Proteins of the Wnt family participate in several signaling pathways which, by β-catenin-dependent activation of gene expression, stimulate proliferation, adhesion, survival and influence cell fate. They may act through both short- and long-range signaling [16]. Canonical Wnt signaling can be also activated in the absence of β-catenin. Hematopoietic stem cells (HSCs) and mature cells of hematopoietic origin were shown to activate the canonical Wnt pathway in the absence of β-catenin expression [37]. Wnt-activated pathways that exist independently of β-catenin have also been reported. They effect cell behavior and movement and raise the intracellular calcium level. Some of the Wnt family members are designated to act only in the canonical or non-canonical network, while the others can affect both of these pathways [27, 38, 98, 104] (Table 1).

Table 1. Classification of Wnt-activated pathways

Protein			Pathway	
Wnt1, Wnt2, Wnt8, Wnt8b		Wnt3	Wnt/β--catenin	canonical
Wnt4, Wnt5b, Wnt7	Wnt5a, Wnt11, Wnt6		Wnt/Ca^{2+} PCP	non-canonical

Wnt/Ca^{2+} pathway

This β-catenin-independent pathway uses calcium as a messenger to transmit Wnt-mediated signaling from the cell surface to the cytoplasm [46]. Engagement of a Fzd receptor causes an increase in intracellular calcium level and modulation of the calcium-dependent proteins protein kinase C and calmodulin-dependent protein kinase II [33, 48, 49]. This pathway is important during embryogenesis as well as during myoblast development [82, 89].

PCP pathway

This pathway is best known in *Drosophila* and is responsible for cellular morphogenic movement during gastrulation and the planar polarity of the body [100]. PCP involves signaling through small GTPases Rho A, Rac 1, and Cdc42 and through these proteins it might overlap with the Wnt/Ca^{2+}pathway [13, 93, 106]. Some of the Wnts involved in the PCP pathway may inhibit the canonical network [20].

Wnt/G protein-signaling pathway

This is the least well known Wnt pathway that relies on signaling through G proteins and calcium flux [92]. Signaling involves phospholipase C and phosphodiesterases [46]. Similarly to the other two β-catenin-independent pathways, it might be responsible for embryo formation and polarization [46, 74, 91].

β-CATENIN AS A PART OF Wnt SIGNALING

Human β-catenin, also known as Armadillo in *Drosophila* and WRM-1 in *Caenorhabditis elegans*, is a 92-kDa product of the *CTNNB1* gene located on the short arm of chromosome 3. As mentioned earlier, β--catenin is associated with cadherins and it connects cadherins with actin cytoskeleton (through α-catenin), forming adhesive junctions and thus being important for cell migration and adhesion [1, 29, 88] (Fig. 1).

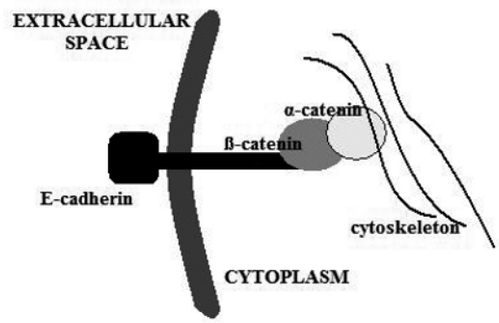

Fig. 1. Intercellular adhesive junction formed by E-cadherin and β-catenin. β-Catenins connect E-cadherins to α-catenins and cytoskeleton.

β-Catenin is situated at the crossroads of the Wnt pathway and a nuclear signaling pathway. When there is no signal from Wnt, β-catenin is restrained in the cytoplasm in a degradation complex with casein kinase 1, adenomatous poliposis coli (APC) protein, axin, and glycogen synthase kinase-3β, which phosphorylates serin and threonin at the N-terminal end of β-catenin and provokes its ubiquination with subsequent proteasomal degradation. Without any stimulation, the cell maintains a low cytoplasmatic level of β-catenin, also by association of the protein with cadherins at the cell membrane. Cadherins compete with APC for interaction with β-catenin [59, 64] and that interlink protects β-catenin from degradation.

Wnt/β-CATENIN PATHWAY REGULATION

There are numerous pathways and factors cooperating with the canonical Wnt signaling pathway. They act

as activators or inhibitors in both extra- and intracellular compartments. A full list of the genes that influence Wnt is published on a web page of Stanford University: http://www.stanford.edu/~rnusse/ wntwindow.html.

Wnts bind to surface proteins belonging to the Fzd family of receptors. To date, ten Fzd receptors have been-identified in humans [8]. They are composed of an N-terminal, a cystein-rich 130-amino-acid α-helix, seven membrane-spanning domains, and a C-terminal tail. Wnt, after binding to Fzd, creates a signaling complex whose activation results in β-catenin stabilization and accumulation. One of the components of this complex, Dishevelled (Dsh or Dsv), mediates axin degradation. As mentioned above, axin is part of β-catenin's degradation complex. Therefore, lack of axin protects β-catenin. The activation of Dsh leads to GSK3β inhibition, which further stabilizes β-catenin. GSK3β can also be inhibited by lithium salts [75]. Frodo and β-arrestin act synergistically with Dsh, whereas Drapper antagonizes their function [7, 59] (Fig. 2).

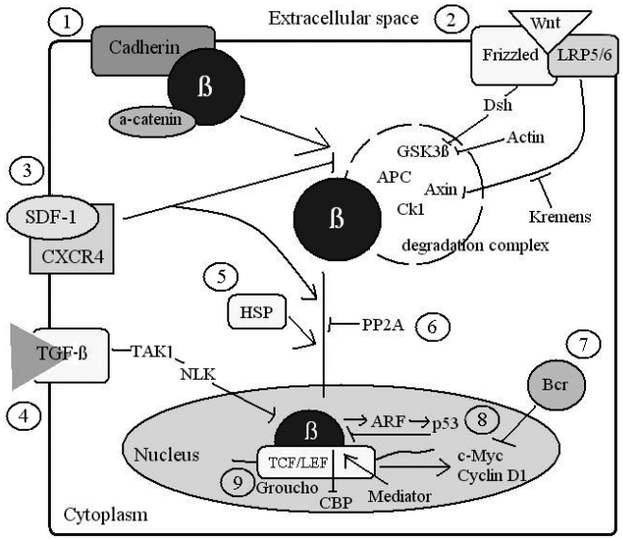

Fig. 2. β-Catenin (abbreviation: β) at the crossroads of many signaling pathways. 1 – Adhesive junction created with cadherins, 2 – signaling through Frizzled receptors and their coreceptors LRP, limitation in the accessibility of LRP5/6 receptors for Wnts through Dickkopfs binding with Kremens, 3 – the influence of the CXCR4-SDF-1 axis; 4 – antagonistic transforming growth factor (TGF)-β acting through TAK1 (TGF-β-activated kinase 1) and NLK (NEMO-like kinase) [34], 5 – participation of β-catenin in the transcription of genes induced by heat shock proteins (HSP), 6 – negative effect of PP2A (protein phosphatase 2A) [109], 7 – Bcr, after forming a complex with β-catenin, decreases the expression of C-Myc [77], 8 – connection with p53 protein, 9 – the intranuclear Tcf/Lef pathway and its regulators. Abbreviations: ARF – alternative reading frame, CBP – CREB-binding protein, CK1 – casein kinase 1, GSK3β – glycogen synthase kinase-3β, SDF-1 – sromal cell-derived factor 1.

LRP5 and LRP6 are coreceptors of the Wnt pathway. Similarly to Dsh, activation of these receptors leads to axin destabilization. Extra- and intracellular proteins, including Dickkopf, secreted Fzd-related proteins (sFRPs), and Wnt-inhibitory factor (WIF)-1, can regulate the binding and activation of these coreceptors. Dickkopf limits the accessibility of LRP5/6 receptors for Wnts by binding them to Kremens and promoting their internalization to the lysosome [4, 104]. The sFRPs are a group of five glycoprotein receptors that bind directly to Wnts and counteract their association with LRP and Fzd [32, 40]. However, sFRPs at low concentrations may also act as carriers for Wnts, supporting their activity [94]. WIF-1, secreted, for example, by tumors and embryonic tissues, binds to Wnts (Wnt1 and Wnt8) and inhibits their signaling [104]. There are data that also suggest a role of Ryk tyrosine kinase receptor in mediating Wnt signaling [9].

Nuclear β-catenin interacts with the members of the TCF and LEF family. Such an interaction activates the transcription of the target genes. TCF and LEF transcription factors possess an HMG-box motif in their structure which enables them to bind to the minor groove of double-stranded DNA (there are about 70 binding sites that have been found so far) [23, 24]. When there is no Wnt stimulation, TCF acts as a repressor, forming a complex with Groucho, CREB-binding protein, carboxy-terminal binding protein, and pontin52 (joins TCF/LEF-β-catenin with tata-box binding protein). Other important proteins cooperating with TCF/LEF through targeting β-catenin to the nucleus are Pygopus and Legless (Bcl9) [15, 47]. The protein Chibby acts conversely, inhibiting binding between TCF/LEF and β-catenin [86]. Nuclear receptors for androgens or vitamins (A or D) compete with TCF/LEF for association with β-catenin [108]. There are also some data indicating that the recently discovered protein Mediator is involved in stimulating the expressions of the target genes in the nucleus in response to Wnt/β-catenin signaling [43] (Fig. 2).

β-Catenin can be also activated independently of Wnt/Fzd signaling by fibroblast growth factor [39], hepatocyte growth factor [57], and urokinase plasminogen activator [30]. Recently, the stromal-derived factor-1/CXCR4 axis has been shown to lead to β-catenin stabilization and its transcriptional activation [52, 54].

Alternative pathways activated by Wnts are regulated independently of β-catenin. In the Wnt/Ca^{2+} pathway, Wnt stimulation increases intracellular Ca^{2+} level, which in turns activates G proteins, decreases the amount of GMP, and activates kinase C [49]. This pathway has a significant influence on cell adhesion and movement during gastrulation [99]. Recent reports indicate that it can also be involved in regulating hematopoiesis; for example, it can inhibit the canonical Wnt pathway during hematopoiesis [65, 66]. In the PCP pathway, Wnt activates Rho/Rac GTPase and Jun-N-terminal sequence kinase, which modulate the organization of the cytoskeleton and influence gene expression [59, 104].

THE INFLUENCE OF β-CATENIN AND Wnt ON PHYSIOLOGICAL HEMATOPOIESIS

During gastrulation, as a result of growth factor activity and intercellular interaction, the endoderm induces the ectoderm to form a mesodermal cell layer. This layer may develop into blood, kidney, muscle cells, and other tissues. Hematopoiesis is a process of forming and differentiating blood cellular components. During the prenatal period it takes place in the yolk sac. In humans from the first to fifth month of fetal life, the main organs responsible for hematopoiesis are the liver, spleen, and lymph nodes. Finally, after the fifth month and after birth, hematopoiesis occurs mainly in red bone marrow in the skull, backbone, sternum, ribs, ilium, and the epiphysis of the long bones [6] (Fig. 3). The myeloid component differentiates in the bone marrow and the lymphoid component in the thymus and peripheral lymphoid organs. All blood cells are produced from self-renewing multipotential HSCs. During maturation, the cells differentiate into the lymphoid or myeloid lineage, losing their multipotentiality and self-renewal ability. These cells enable the bone marrow to regenerate (e.g. after the myeloablation) [61].

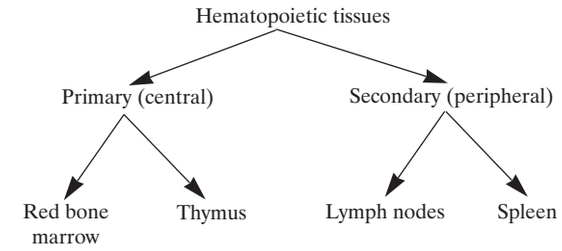

Fig. 3. Classification of blood-forming tissues. Blood-forming tissues can be divided into primary (red bone marrow and thymus) and secondary (lymph nodes and spleen). Primary tissues are responsible for the formation of stem and progenitor cells as well as mature blood cells. Secondary tissues provide a place for blood cell maturation and, during major injury, an additional site of blood cell formation.

HSCs may differentiate into a cell-forming blastic cell colony (CFU-blast), thereafter into the common lymphocyte progenitor, the common myeloid progenitor (CMP) for the erythrocyte, granulocyte, thrombocyte, and monocyte lineages, the progenitor for the erythrocyte lineage (burst-forming unit (BFU)-E), which differentiates into CFU-E, the progenitor for the thrombocyte lineage (CFU-MEG), and the progenitor for the granulocyte and monocyte lineages (CFU-GM), which can differentiate into CFU cells for the granulocyte lineage (CFU-G) or CFU cells for the monocyte lineage (CFU-M) [6] (Fig. 4).

The β-catenin and Wnt pathway have been shown to act as a new group of hematopoietic factors essential in the development of all hematopoietic cells [79] (Fig. 4). Overexpression of Wnts leads to increased proliferation of $CD34^+$ cells [80] and Wnts have been shown to be indispensable in the HSC self-renewal process. They function as hematopoietic growth factors [1]. Recent research has revealed that CFU morphology depends on Wnts. It has also shown that this effect is more significant than those of well-known hematopoietic growth factors such as stem cell factor (SCF) and interleukin (IL)-3. When Wnts act on erythroid or myeloid progenitor cells, the effect is less pronounced than that of SCF, but still stronger than that of IL-3. Wnts have common targets, but often exert contradictory effects [90]. For instance, whereas Wnt10B has an inhibitory effect on BFU-E, Wnt5a and Wnt2b act as activators. However,

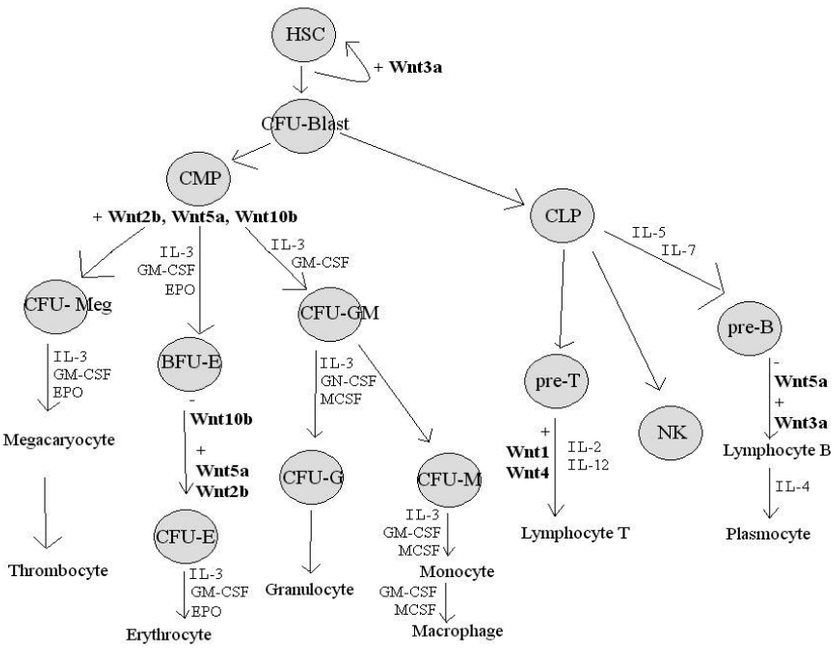

Fig. 4. Hematopoiesis. Successive stages of differentiation into distinct lineages. In addition to known hematopoietic growth factors and cytokines (e.g. GM-CSF, IL-3, EPO, IL-7), Wnts are suggested to play a role as a group of the new hematopoietic growth factors (shown in bold) [1, 2, 15, 80, 95]. Abbreviations: CLP – common lymphocyte progenitor, CSF – colony-stimulating factor, EPO – erythropoietin.

all these factors have identical influence on the development of the CMP. Other proteins of the Wnt pathway, Wnt1 and Wnt4, increase the number of fetal thymocytes [4, 63, 88, 102]. Wnt3a enhances self-renewal of HSCs (it has even been suggested to use this protein as a growth factor in tissue engineering [105]) and is considered to play a crucial role in B lymphocyte development [19]. Wnt5a affects the proliferation of B lymphocytes by inhibiting this process [50]. It is suggested that Wnt5a acts by inhibiting the effect of Wnt3a on HSCs [65]. Wnt2 acts generally as a negative regulator for hematopoiesis and hemangioblast differentiation [101].

Moreover, it has been proved that the expression of the extracellular domain of Fzd inhibits HSC differentiation into T lymphocytes in the fetus [88]. Also, the effects of Wnt signaling are noticeable in mature T lymphocytes, for example influencing the expression of metalloproteinases or regulating T lymphocyte transmigration [107]. The lack of Fzd9 receptor leads to loss of early B-lymphocyte progenitor cells [2]. However, the influence of the Wnt/β-catenin pathway on mature B cells is not so obvious because they do not express TCF/LEF factors [80].

The different action of particular elements of the Wnt signaling pathway is due to the expression of different receptors on the distinct hematopoietic cells. What is more, a particular Wnt protein may bind to different receptors and a particular receptor may interact with various Wnts as ligands, i.e. Fzd1 acts as a receptor for Wnt1, 2, 3A, 5A, and 7A, whereas Wnt 5A may interact not only with Fzd1, but also with Fzd2 [9, 22, 41, 79, 95, 96]. This redundancy is very similar to that observed for chemokine-chemokine receptor interactions [5, 65].

In HSCs engineered to express β-catenin lacking the N-terminal sequence, self-renewal ability is observed with the retention of markers characteristic for the stem cells [79]. Moreover, transduction of HSCs with axin (responsible for β-catenin degradation) reduces growth capability and efficient hematopoiesis [79]. On the other hand, there are data indicating that β-catenin inactivation in HSCs does not decrease their ability to survive, differentiate, or rebuild all hematopoietic lineages [15]. Moreover, two recent papers have shown that overexpression of β-catenin by HSCs leads to their loss and blockade in their differentiation and maturation [44, 83]. However, these studies do not negate the positive impact of the Wnt pathway on hematopoiesis and the possibility of using it to manipulate the hematopoietic system [15]. The lack of β-catenin in thymocytes may be compensated, for example, by plakoglobin [15, 110], whose function in the self-renewal of HSCs has been proved [110]. Both proteins reveal many structural similarities, such as the ability to bind E-cadherin, APC, and axin, possession of an N-terminus phosphorylated by GSK3β, and a C-terminal sequence able to transactivate. On the other hand, the latest reports on β-catenin and γ-catenin double-knockouts show that both of the catenins are dispensable for hematopoiesis [37, 45]. This discrepancy will need further clarification.

Another way of revealing that Wnts have an impact on HSCs was the ectopic expression of inhibitors of the Wnt pathway such as axin and Dickkopf [103]. In this case, abnormalities such as reduced proliferation were observed [78]. Acting on HSCs with the inhibitor of GSK3β (BIO) maintains a non-differentiated phenotype of the stem cells [59].

Hematopoiesis is also regulated by other signaling pathways connected to Wnt. For example, the activation of Wnt in HSCs leads to the increased expression of Hox or Notch, genes involved in the self-renewal of HSCs [73, 103].

THE INFLUENCE OF β-CATENIN AND Wnt ON PATHOLOGICAL HEMATOPOIESIS

Hematopoiesis is controlled by multiple elements. Therefore the process may be disturbed at many stages, which results in abnormalities leading to benign and neoplasmatic diseases. The classification of neoplastic hyperplasias is based on the nomenclature of the particular hematopoietic lineage. They are characterized by diversity in clinical, morphological, and genetic features. World Health Organization discriminates between four groups of neoplasia: myelocytic neoplasms, lymphocytic neoplasms (lymphomas and leukemia), neoplasms of histiocytes and antigen-presenting cells, neoplasms of mastocytes.

In blood neoplasms, transformation can take place at different levels of cell differentiation. For instance, in myeloid leukemia tumorigenesis takes place in HSCs (its progeny retain the ability of multipotential differentiation), whereas in multiple myeloma it is localized to plasmocytes. One of the most basic attributes of malignant processes is the ability of unlimited cell division and self-renewal, which is also characteristic of stem cells. Thus it has been suggested that leukemia may be initiated by the same factors that participate in the proliferation and differentiation of HSCs. Therefore, knowledge about the mechanisms controlling the behavior of stem cells would provide answers to questions concerning the causes and possible therapies of leukemia [72]. These mechanisms are still poorly understood at the molecular level. Numerous pathways are indicated as taking part in the regulation of HSCs, including Hox, Notch, Sonic hedgehog, and Wnt [73].

Studies on the influence of Wnts on hematopoiesis have mainly concentrated on mutations leading to the overexpression or inhibition of various genes and on observing their consequences in the development of the organism. These effects become noticeable in the embryonic period as well as in the adult. In the hematopoietic system, mutations in the Wnt/β-catenin pathway lead to neoplastic diseases (mostly leukemias) as well as to non-neoplastic disorders (immunodeficiency syndromes) [59]. Excessive stimulation of the Wnt cascade is noticeable in the neoplasms of myeloid and lymphoid lineages. Introducing a stable β-catenin form

into CFU-GM leads to regaining a stem-cell phenotype. Blockade of erythrocyte lineage differentiation and lymphocyte development are also observed [44, 83]. Therefore, constitutive activation of β-catenin promotes the expansion of multipotential HSCs and may lead to their transformation [2, 3].

Mutations of Wnts and the related proteins are detected in many hematological patients [103] (Table 2). Proof of a role of Wnt in tumorigenesis is the fact that mutation of Wnt5A results in the development of myeloid leukemia and B-cell lymphoma [50]. Mutations of Wnt16 lead to acute lymphoblastic leukemia [10]. Wnt11 mutations increase the invasiveness of tumor cells [59].

TCF1 mutations or blocking Wnt binding to Fzd disturbs the proliferation and differentiation of thymocytes [88]. Gou et al. [25] have shown that uncensored stabilization of β-catenin stalls the maturation of double-positive thymocytes and predisposes them to transformation. However, upregulation of c-Myc expression is required for final transformation. [71]. *LEF1* mutations increase the apoptosis of pro-B lymphocytes without affecting T lymphocyte survival. Simultaneous abnormalities in the *TCF1* and *LEF1* genes influence both lymphoid lineages [2, 15, 19, 71]. In some neoplasms it may be possible to distinguish between them by taking into consideration the level of some Wnt-related genes. Accordingly, the expression of LEF-1 is higher in chronic lymphocytic leukemia than in B-type non-Hodgkin's lymphoma [31]. A comparison of lymphoma and multiple myeloma reveals an undetectable level of

Table 2. Hematological diseases and mutations in genes related to the Wnt/β-catenin canonical pathway

Hematological disease	Gene	Comments	References
B-ALL	Wnt3a (accumulation)	decreased proliferation of several B-progenitor cell lines	70
	Wnt16	role in leukemia cell survival	10
		Wnt16 activated by E2A-Pbx1 fusion protein mediates autocrine growth of the cells, leads to pre-B ALL development	55
T-ALL	β-catenin	activation of Notch is not necessary for inducing lymphomas by β-catenin	25
CLL-B	LEF-1 (overexpression)	role in the development of leukemia	26
	Wnt3(overexpression)	autocrine stimulation promotes proliferation	31
CLL	Wnt3, Wnt5b, Wnt6, Wnt10a, Wnt14, Wnt16, Fzd3, Lef-1 cyclin D1 (overexpression)	enhanced cell survival, defect in apoptosis	51
MCL	FZD7, LRP5, AXIN1, APC, DVL3, CREBBP, and TCF4 (overexpression)	inactivation of GSK3B by PI3K/AKT or Wnt/β-catenin signaling pathway stabilizes cyclin D1	81
Burkitt lymphoma	Wnt/β-catenin pathway (overactivation)	promotes EBV-mediated malignancy	60
CLL, APL	WIF-1 (methylation)	the lack of Wnts inhibition leads to leukemia development	11, 12
AML	Plakoglobin (overexpression)	leukemia development, enhanced self-renewal, preserved immature phenotype	62
	Wnt1, Wnt2b and LEF-1	decreased progenitor cells apoptosis	85
MDS/AML	SALL4 (constitutive expression)	enhanced Wnt/β-catenin pathway leads to MDS/AML transformation	53
CML	Expression of Bcr-Abl	Bcr but not Bcr-Abl is a tumor suppressor of the Wnt/β-catenin pathway	77
	β-catenin (activation in granulocyte-macrophage progenitors)	enhances self-renewal activity and leads to blast crisis	35
Multiple myeloma	Dkk1	indirect effect: inhibition of osteoblast development	18, 26, 67
	β-catenin (overexpression)	direct effect: the growth of multiple myeloma cells is dependent on Wnt signaling	17

Abbreviations: APC – adenomatous poliposis coli, ALL – acute lymphoblastic leukemia, AML – acute myeloid leukemia, APL – acute promyelocytic leukemia, CLL – chronic lymphocytic leukemia, CML – chronic myelogenous leukemia, Dkk – Dickkopf, LEF – lymphoid enhancer factor, LRP – LDL-receptor-related protein, MCL – mantle cell lymphoma, MDS – myelodysplastic syndrome, WIF-1 – Wnt-inhibitory factor 1.

LRP5/6 in both. This may imply different metastatic potentials of lymphoma and leukemia [76].

CONCLUSION

Recent studies have clearly indicated an important role of the Wnt/β-catenin pathway in normal and pathological hematopoiesis. Considering the processes that are governed by Wnts, it is not surprising that any disturbance in the Wnt pathway may reveal abnormalities in cells and lead to malignant transformations. By deliberate modification of the Wnt pathway and other cooperating signaling pathways it will be possible in the future to influence tumor lesions (e.g. by restraining their progression), develop chemoprevention [14], and facilitate the regeneration of tissues or whole organs [59]. Recent research on the influence of drugs on Wnts and their related factors and pathways includes non-steroidal anti-inflammatory drugs and their analogs R-etodolac [51], Gleevec, and sulindac [36, 77]. Potential therapeutics could also be applied to the process of hematopoiesis. The proposed drugs are mainly antibodies against Wnts [56], short interfering RNA leading to the silencing of incorrect genes [10], and small inhibitors which disturbs the binding between elements of the Wnt pathway, e.g. FJ6, which influences the interaction between Fzd9 and Dsh [21]. Further work is thus needed on new ways of interfering with Wnt signaling that will lead to the future development of new anti-cancer therapies.

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