Review Article
The role of Wnt/β-catenin signaling pathway in the pathogenesis and treatment of multiple myeloma (review)

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Abstract: Multiple myeloma (MM) is a refractory hematological malignancy characterized by aberrant accumulation of plasma cells. Patients with MM are susceptible to becoming resistant to chemotherapy, eventually leading to relapse. Progression of MM is largely dependent on the bone marrow microenvironment. Stromal cells in the bone marrow microenvironment secrete Wnt ligands to activate Wnt signaling in MM, which is mediated through the transcription regulator β-catenin. In addition, Wnt/β-catenin pathway encourages osteoblast differentiation and bone formation, dysregulation of which is responsible for proliferation and drug resistance of MM cells. As a result, direct inhibition or silencing of β-catenin or associated genes in the Wnt/β-catenin pathway has been proposed to be an effective therapeutic anti-MM strategy. However, the underlying regulatory mechanism of the Wnt/β-catenin pathway in MM remains to be fully elucidated. Herein, we summarized research advances on the specific genes and molecular biology process of Wnt/β-catenin pathway involved in tumorigenesis of MM, as well as the interaction with bone marrow microenvironment. Additionally, comprehensive summaries of drugs or small molecule inhibitors acting on Wnt/β-catenin pathway and targeting MM were introduced. This review intends to provide an overview of theoretical supports for novel Wnt/β-catenin pathway based treatment strategies in MM.

Keywords: Multiple myeloma, Wnt/β-catenin pathway, bone marrow microenvironment, osteoblasts, targeted therapy, drugs or small-molecule inhibitors

Introduction

Multiple myeloma (MM) is an aggressive neoplasm of clonal plasma cells, which is also the second most common hematological malignancy worldwide [1]. MM represents about 10% of all hematological tumors and typically occurs in the elderly, with an average age of over 70 years [2]. Since MM can adversely affect the function of different organs like bone marrow and kidney, it is associated with high rates of morbidity and frequently has a fatal outcome [1]. In addition, this disease is accompanied with a number of complications, including anemia, bone marrow (BM) failure, bleeding disorders, hypercalcemia related to excessive bone conversion, renal insufficiency, impaired immunological function, and neurological and cardiovascular complications [3]. Current treatment

modalities for MM, including immunoregulatory agents, proteasome inhibitors and histone deacetylase inhibitors, have all been tested in clinical trials. Although advances in the development of MM treatment strategies have improved the survival rates of patients with MM, MM remains an incurable disease, with a median survival time of 6-7 years [4]. Therefore, the research focus has been shifted to exploring novel therapeutic strategies, which have been previously exploited in clinical trials. Over the past decade, a number of novel MM treatment strategies, such as chimeric antigen receptor T-cell therapy and targeting B-cell mature antigens, have been reported to confer clinical benefits [5]. In addition, the use of isatuximab, daratumumab and monoclonal antibodies against the CD38 receptor has been revealed to be promising approaches to the

treatment of MM [6, 7]. However, due to multi-drug resistance and drug-related adverse reactions, alternative treatment options for refractory MM are needed.

Wnt is a family of cysteine-rich glycoproteins that function as ligands and are responsible for cell fate determination during embryogenesis, hematopoiesis and development [8]. The Wnt signaling pathway comprises two pathways: The canonical, which is dependent on β-catenin, and the noncanonical, which is independent of β-catenin [9]. β-catenin is the mammalian homologue of the drosophila *armadillo* gene, which exerts regulatory effects on gene transcription and intercellular adhesion [10]. Biochemical regulation of the canonical Wnt signaling pathway on cellular functions is mainly mediated by altering β-catenin protein levels and its intracellular localization [11]. A number of studies have reported that the canonical Wnt pathway is a receptor-mediated signal transduction network, which plays a critical role in a multitude of cancers [11, 12]. Mutations or activation of pivotal components of the Wnt/β-catenin pathway have been frequently associated with tumorigenesis and drug resistance [13-16]. At present, targeting the Wnt/β-catenin pathway has been attracting the attention of researchers and is becoming a topic of interest with regard to cell physiology regulation. However, there remains a lack of sufficient mechanistic data on the Wnt/β-catenin pathway in MM.

MM is considered to be an oncogene-addicted cancer. In view of the reported regulatory role of the Wnt/β-catenin pathway in tumors, we will focus on the molecular mechanisms involved in the regulation of MM pathophysiology by the Wnt/β-catenin pathway. Moreover, compounds that can interfere with the Wnt/β-catenin pathway and have been demonstrated to serve as attractive candidates for MM treatment will be described and summarized. The aim of the present review was to provide information on the novel approaches aimed at targeting the Wnt/β-catenin pathway to manage this incurable disease.

Molecular mechanism underlying Wnt/β-catenin activation during carcinogenesis

Accumulating evidence suggests that the Wnt/β-catenin pathway is closely associated with embryonic development and tissue homeostasis [10]. Dysfunctions in this pathway can result in a broad range of diseases in humans, such as obesity [17] and cancer [8]. β-catenin is an important component of Wnt signaling that is normally under regulation by a multi-protein degradation complex [9]. The molecular mechanism underlying this pathway has been extensively studied [19]. When Wnt signaling is not activated, cytoplasmic β-catenin protein is typically degraded by the Axin complex, which consists of adenomatous polyposis coli, casein kinase 1, glycogen synthase kinase 3 (GSK3) and Axin [18]. In this complex, GSK3 serves as the control center by phosphorylating β-catenin, resulting in its recognition by E3 ubiquitin ligase and subsequent ubiquitination prior to proteasomal degradation [19]. In this manner, the continuous degradation of β-catenin results in the repression of Wnt signaling. When Wnt signaling is activated, the Wnt ligand binds to its co-receptor Frizzled (FZD) and low-density lipoprotein receptor-related protein 5/6 (LRP5/6), facilitating the recruitment of the Axin complex to the receptors [20]. This, in turn, inhibits the GSK3-mediated phosphorylation of β-catenin, which allows it to enter the nucleus. There, β-catenin serves as a multifunctional protein, which can bind to T-cell factor (TCF)/lymphoid enhancement factor (LEF), thereby activating the transcription of multiple target genes, the majority of which are oncogenes, including cyclinD1 (CCND1), c-Myc, PDK, MTC-1, matrix metalloproteinase (MMP) 7, cyclooxygenase-2 and Axin-2 (**Figure 1**) [21, 22]. In summary, a subgroup of Wnt ligands can trigger a cascade of intracellular events that results in the stabilization of β-catenin in the cytosol, which promotes its translocation into the nucleus to induce oncogenic gene transcription.

Aberrant activation of the Wnt/β-catenin pathway has been shown to contribute to carcinogenesis and tumor progression in a variety of cancer types, including breast [23], prostate, colorectal, liver, ovarian, lung [24] and pancreatic cancer [8, 9, 25-34], in addition to MM [35]. For instance, GSK3 phosphorylation and β-catenin expression was reported to be downregulated by knocking down MM SET domain-containing protein expression [23]. Therefore, the expression of downstream targets cyclinD1 and MMP9 were significantly reduced, resulting
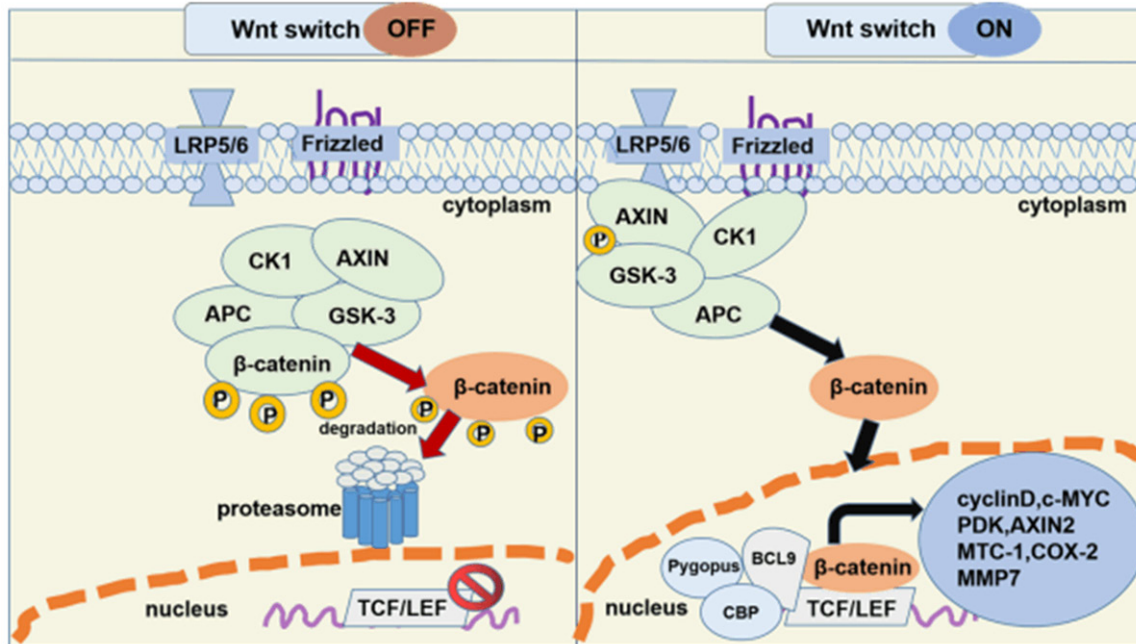
Figure 1. Schematic representation of the molecular mechanism of Wnt/β-catenin pathway. When the Wnt switch is off, β-catenin is continuously phosphorylated by a complex of Axin, CK1, GSK-3 and APC, which is subsequently identified, ubiquitinated and degraded by the proteasome. When the Wnt switch is turned on, the formation of the destruction complex is disrupted. Then, stabilization and nuclear translocation of non-phosphorylated β-catenin binds to the co-receptor LRP5/6 and FZD, further activating TCF/LEF transcription. Upon cooperation with TCL/LEF complex and its co-transcriptional activators like BCL9, CBP and pygopus, β-catenin initiates the transcription of Wnt target genes including *cyclinD1*, *c-MYC*, *PDK*, *Axin2*, *MTC-1*, *COX-2* and *MMP7*.

in the inhibition of breast cancer cell proliferation [23]. It has been previously documented that mutations in components that participate in the Wnt/β-catenin pathway can lead to the formation of prostate ducts in the fetus, which can initiate prostate cancer development [25]. As a consequence, targeting Wnt/β-catenin signaling has been implicated in preventing the development of prostate cancer [25]. In addition, activation of the Wnt/β-catenin pathway has been reported to be positively correlated with the occurrence of liver cancer [36]. Recombinant sFz7 peptide, the extracellular domain of Frizzled-7 receptor (FZD7), has been shown to suppress Wnt activation in liver cancer, thereby contributing to the inhibition of liver cancer cell proliferation [36]. These observations suggest that dysregulation of the Wnt/β-catenin pathway can induce tumorigenic phenotypes and promote tumor progression. Since it is a subtype of hematological malignancy, dysregulation of the hematopoietic process has been associated with MM progression. Hematopoiesis is a process in which hematopoietic stem cells (HSCs) and hematopoietic

progenitor cells differentiate into mature hematopoietic cells [37]. It has been previously reported that mice expressing stabilized β-catenin exhibited HSCs with poorly differentiated phenotypes, resulting in hematopoietic reconstitution failure [37]. Therefore, Wnt signaling plays a pivotal role in the regulation of hematopoiesis. Hematopoiesis is regulated by extracellular factors, including Wnt ligands, agonists and antagonists, receptors expressed on the cell surface, signaling constituents expressed in the cytosol and the BM microenvironment [38]. In the context of MM, it has been shown that the bidirectional communication between MM cells and the BM microenvironment can play an important role in MM pathogenesis by facilitating the growth of MM tumors [39]. Compared with the effect of the Wnt/β-catenin pathway on other tumor types, Wnt antagonists secreted by MM cells have been found to affect the BM to regulate osteoblastic differentiation, which can lead to osteolytic lesions [40]. This finding has led to the role of the Wnt/β-catenin pathway in MM becoming the focus of research.
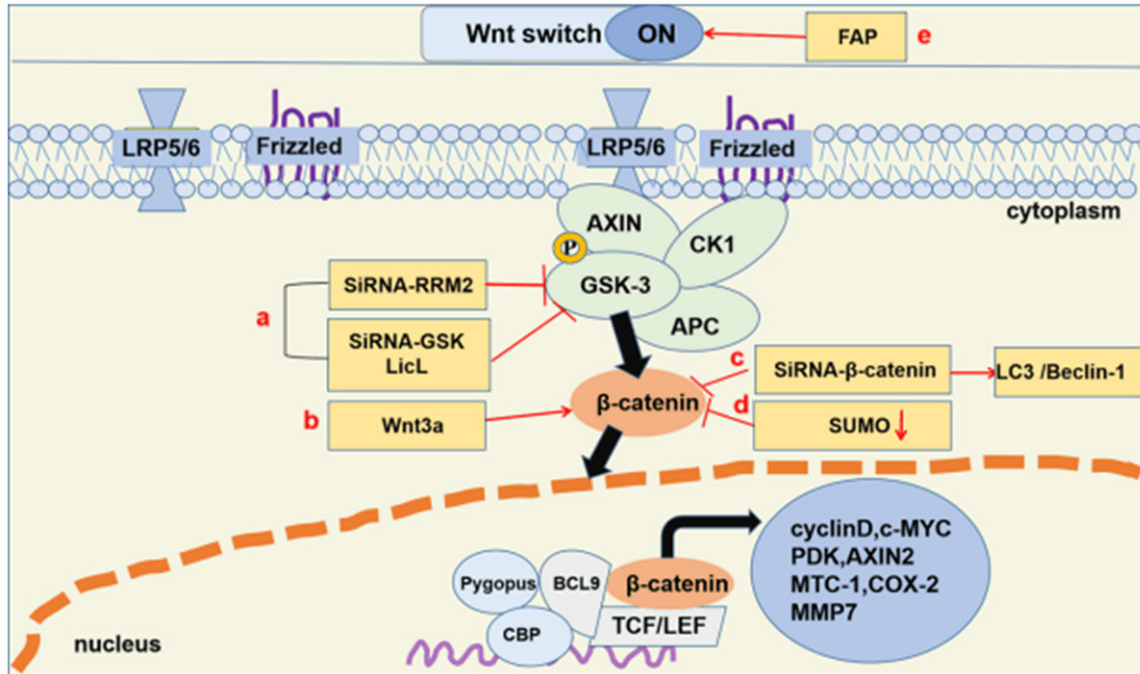
Figure 2. The vital molecules involved in the regulation of Wnt/β-catenin pathway in MM. Multiple components involved in Wnt/β-catenin pathway play different regulatory roles: a. Direct silencing of GSK-3 by siRNA or inhibition by lithium chloride or down-regulation of RRM2 can attenuate the pathway; b. Wnt3a is able to activate β-catenin into nucleus; c. Direct silencing of β-catenin by siRNA induces the secretion of autophagy related factors LC3 and Beclin-1 in cells; d. Interference with SUMO induces degradation of β-catenin; e. The upregulation of FAP may indirectly activate the pathway.

Specific components regulated by the Wnt/β-catenin pathway are associated with the occurrence and development of MM

The majority of cases of MM exhibit hallmarks of constitutive Wnt signaling activation in the absence of receptor stimulation [40]. This suggests that autocrine Wnt signaling may be driving this phenomenon [40]. As one of the core Wnt pathway components, amplification of β-catenin has been frequently found in MM plasma cells [41]. In addition, a previous study identified the Wnt/β-catenin pathway to be a signaling route that MM cells use to accelerate proliferation, since it can also confer self-renewal properties onto hematopoietic stem cells [40]. Therefore, this pathway can be used as an oncogenic indicator of MM cell proliferation. Collectively, currently available experimental evidence suggests that stimulation of Wnt signaling by using Wnt3a, lithium chloride [42], the constitutively active S33Y β-catenin mutant or the disruption of β-catenin/TCF activity by TCF4 can all affect MM proliferation on different levels (mRNA/epigenetic/protein) (**Figure 2**) [43]. Many proteins involved in Wnt/β-catenin pathway have been reported to exert notable effects on the regulation of MM physiology, including a range of Wnt ligands, β-catenin, GSK-3 and B-cell lymphoma 9 (BCL9).

Wnt ligands

Clinically, novel molecularly targeted drugs for the treatment of MM are required, since most patients with MM will ultimately develop drug resistance [44]. One of the mechanisms underlying the acquisition of drug resistance is the adhesion of MM cells to the BM matrix [45]. It was suggested that the cross-talk of cells with the extracellular matrix via integrins can regulate Wnt-1 expression, such that the Wnt-dependent signaling pathway can in turn control fibronectin expression, which alters the adhesive properties of leukemic cells to govern the degree of chemosensitivity [46]. In addition, Wnt3, which is a secreted glycoprotein that belongs to a large family of Wnt ligands, has been found to be highly expressed in human BM cells [47], which may be one of the causes of lenalidomide resistance. In particular, Wnt3-mediated signaling may serve as a

Table 1. Drugs, small molecular compounds and siRNAs that target Wnt/β-catenin pathway in MM

Name	Target/sequences
Bortezomib	GSK-3
FH535	β-catenin/T-cell factor (TCF)
iCRT-3,5	β-catenin
AV-65	β-catenin
Sdx-308	unknown
SAH-BCL9B	β-catenin/BCL9 interaction
PKF115-584	β-catenin/T-cell factor (TCF)
ICG-001	β-catenin/CBP interaction
BC2059	β-catenin
KY-05009	TCF4/TINK/β-catenin interaction
Go-203	TCF4/MUC1-C/β-catenin interaction
Pyrvinium pamoate	casein kinase 1α
Ilimaquinone	β-catenin
Ethylsmenoquinone	β-catenin
Deferasirox	GSK3β
SB216763/SB415286	GSK/ATP
siRNA-β-catenin	siA: CCGGGCTTGGAATGAGACTGCTGATCTCGAGATCAGCAGTCTCATTCCAAGCTTTTT
	siB: CCGGCCGCATGGAAGAAATAGTTGAACTCGAGTTCAACTATTTCTTCCATGCGTTTTT
	siC: CCGGAGGTGCTATCTGTCTGCTCTACTCGAGTAGAGCAGACAGATAGCACCTTTTTT
siRNA-GSK-3β	GAUCAUUUGGUGUGGUAUA; GCUAGAUCACUGUAACAUA; GUUCCGAAGUUUAGCCUAU; GCACCAGAGUUGAUCUUUG
siRNA-RRM2	sc-36338A: sense 5'-CGAUGGCAUAGUAAAUGAAtt-3 and antisense 5'-UUCAUUUACUAUGCCAUCGtt-3
	sc-36338B: sense 5'-CACCAUGAAUUGUCCGUAAtt-3 and antisense 5'-UUACGGACAAUUCAUGGUGtt-3
	sc-36338C: sense 5'-CAAGGAGCUUCUUAAGUUAtt-3 and antisense 5'-UAACUUAAGAAGCUCCUUGtt-3

molecular target for potentially weakening drug resistance of lenalidomide and enhancing bone resorption in MM [48].

β-catenin

β-catenin is a downstream target of the Wnt signaling pathway that serves a central role in Wnt signaling. Silencing of β-catenin expression by small interfering (si)RNA transfection has been found to result in a significant increase in autophagy markers LC3 or Beclin-1, thereby activating the mitochondrial apoptosis pathway (**Figure 2**; **Table 1**) [49]. Both *in vitro* and *in vivo* evidence suggested that the overexpression of β-catenin is positively associated with autophagy and apoptosis in MM cells. siRNA/collagen complex of β-catenin was found to slowly diffuse into the MM tumor after administration, inhibiting its growth in a mouse model [50]. In addition, a previous study revealed a new method of promoting the ubiquitylation and subsequent proteasome-mediated degradation of β-catenin [51]. This was achieved by knocking down small ubiquitin-like modifier expression using siRNA, which attenuated the proliferation of MM cells (**Figure 2**) [51].

GSK-3

GSK-3 is a pleiotropic serine-threonine kinase with two major isoforms, GSK-3α and GSK-3β [52]. In the Wnt signaling pathway, it regulates phosphorylation of β-catenin to promote proteasome-mediated degradation, which plays a decisive role in controlling the transcriptional activity of β-catenin [52]. Activation of Wnt signaling blocks GSK-3 activity, leading to the accumulation of β-catenin in the nucleus to activate the transcription of target genes. It has been previously found that the functional signature of lithium chloride-activated Wnt/β-catenin signaling is typified by inhibition of GSK-3β activity (**Figure 2**) [53]. Yao *et al.* [54] previously found that lithium chloride can promote the apoptosis of MM cells and overcome resistance to bortezomib by targeting GSK-3 to activate Wnt/β-catenin signaling, highlighting its antagonistic role in MM progression. In particular, knocking down the expression of various isoforms of GSK-3 using siRNAs has been demonstrated to reduce MM cell proliferation (**Figure 2**). Genetic targeting of the *GSK-3α* gene has been shown to enhance MM cell toxicity induced by bortezomib, while knocking down *GSK-3β* expression hindered the activity

of MM cells (**Table 1**) [52]. This suggests that GSK-3α and β have distinct functional roles in regulating MM cell survival and sensitivity to proteasome inhibitors. Therefore, inhibiting the activity of GSK-3 may be a feasible treatment strategy for MM.

BCL9

The transcriptional activity of β-catenin largely depends on BCL9 and pygopus family PHD finger, which are co-activators of Wnt/β-catenin-mediated transcription [55]. BCL9 promotes the transcriptional activity of β-catenin of a subset of Wnt target genes by direct binding [56]. Therefore, it may be hypothesized that the transcriptional activity of β-catenin would be suppressed in response to the downregulation of BCL9. Indeed, targeting BCL9 has been proposed to be a novel form of therapy for the treatment of MM driven by aberrant Wnt signaling [56]. Abolishing the oncogenic activity of BCL9 can impair the proliferation of MM cells (**Figure 2**) [57]. Short hairpin RNA-induced disruption of the BCL9 gene has also been shown to suppress the expression of the downstream genes, including *c-MYC*, *CCND1*, *CD44* and vascular endothelial growth factor, which are involved in the Wnt/β-catenin pathway in MM cell lines [56]. Interfering with the interaction between BCL9 and β-catenin by using a small-molecule compound mimicking the BCL9 HD2 domain was therefore proposed as a result of this finding [58]. microRNAs (miRs) may also play an important role in the treatment of MM. The binding of BCL9 to β-catenin may be blocked by upregulating the expression of miRs in the miR-30-5p family (**Figure 2**), which reduced the expression of downstream target genes of β-catenin and inhibited MM cell proliferation [59]. These findings suggest that pharmacological targeting of the BCL9-β-catenin interface may serve as another therapeutic option for MM.

Other signaling components

FAP is a member of the serine protease family that possesses gelatinase and type I collagenase activities [60]. It has been documented that FAP expression is associated with adverse clinicopathological outcomes in a number of human malignancies [60]. It was previously found that upregulation of FAP expression protected MM cells from bortezomib-induced apoptosis, possibly through the Wnt/β-catenin pathway (**Figure 2**) [61]. It has also been reported that erythrocyte protein band 4.1-like 4a (Nbl4) is a target gene of the Wnt/β-catenin pathway, which belongs to a member of the protein 4.1R, ezrin, radixin, and moesin protein superfamily. The abnormal high expression of Nbl4 predicted favorable survival outcomes of patients with MM [62]. By contrast, knocking down ribonucleotide reductase M2 (RRM2) expression has also been proposed to be a novel strategy for treating MM, as RRM2 can significantly increase the phosphorylation of GSK-3β, thereby downregulating the expression levels of c-MYC and cyclinD1 (**Figure 2**) [63]. Another previous study found that the inhibitory effect of Traf2- and Nck-interacting kinase (TNIK) on Wnt signal transduction plays an important role in inducing MM apoptosis [64]. Therefore, inhibition of Wnt signaling involving TNIK may become an effective therapeutic strategy for MM [65]. In addition, a novel SRY-box transcription factor 5 subtype was found to upregulate the expression of β-catenin protein levels, which promoted the proliferation of malignant B cells [66]. A previous study revealed a potential role of syndecan-1 as a regulator of growth factor/cytokine binding and signaling by modifying its heparan sulfate chains, which was identified to be a key component of the Wnt signalosome in MM cells. It can bind Wnt and R-spondins to enhance Wnt/β-catenin signaling and, in turn, MM cell proliferation [67].

Furthermore, it should be noted that various specific genes have been reported to be involved in inhibiting the Wnt/β-catenin pathway. Promoter methylation and subsequent downregulation of protocadherin 10 (PCDH10) expression has been found in a variety of cancers [68]. Since PCDH10 is a tumor suppressor gene, its overexpression can inhibit the nuclear translocation of β-catenin and reduce the transcriptional activity of TCF, which may prove to be another preclinical research direction for the treatment of MM [68]. In addition, a common genomic aberration in the gene encoding the deubiquitinase CYLD in MM has been reported to negatively regulate the Wnt/β-catenin pathway [69].

Previous studies have revealed the specific functional roles of the components in the Wnt/β-catenin pathway in MM, which suggested
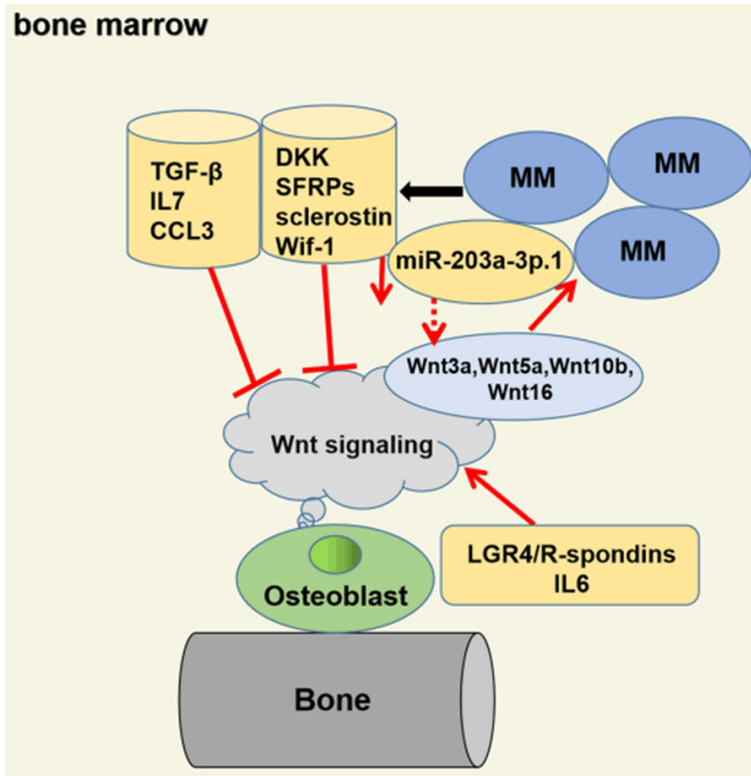
Figure 3. Wnt/β-catenin pathway is closely related to myeloma microenvironment. The activation of Wnt signaling in osteoblasts regulates the interaction of multiple cell growth factors (Wnt3a, Wnt5a, Wnt10b, Wnt16 and IL-6) with the bone marrow microenvironment. DKK protein, SFRPs, sclerosin and Wif1 secreted by MM cells antagonize Wnt signal. Identically, other molecules, such as TGF-β, IL-7 and CCL3, also block Wnt signaling. LGR4/R-spondings can activate Wnt signal via protecting LGR4-expressing MM cells against secreted Wnt antagonists.

that Wnt/β-catenin signaling may play a regulatory role in the development of MM. However, the precise underlying mechanism remains to be fully investigated.

Relationship between the Wnt/β-catenin pathway and BM microenvironment in MM

MM is frequently characterized by osteolytic bone lesions, where osteoblast function is impaired following extensive MM cell infiltration of the BM [4]. It has been hypothesized that the oncogenic proliferation of MM cells can be supported by the tumor microenvironment. Indeed, the BM microenvironment appears to particularly favor MM cell adhesion, which plays a key role in the proliferation, differentiation and apoptosis of MM cells and contributes to tumor growth [70]. It is becoming increasingly evident that the imbalance between osteoblast-mediated bone formation and osteoclast-mediated bone resorp-

tion in the BM microenvironment may create conditions that promote the development of MM, forming a crucial part of the "MM niche" [70, 71]. A number of studies have revealed that the Wnt/β-catenin pathway is important for healthy bone development and formation [71]. Canonical Wnt signaling primarily takes part in the regulation of osteoblast development by promoting osteoblast proliferation, differentiation and survival (**Figure 3**) [72]. The proliferation of MM cells in the BM is maintained by the interaction between multiple growth factors and the BM microenvironment.

Ligands that have been reported to be secreted by BM stromal cells, including Wnt3a, Wnt5a, Wnt10b and Wnt16, can increase the proliferative and self-renewal capacities of hematopoietic stem cells (**Figure 3**) [50, 73]. In addition, a previous gene expression analysis discovered the expression of a diverse range of Wnts, including Wnt3, 4, 5a, 5b, 6, 7, 8a, 10a, 10b, 11, 14 and 16, in primary MM, most of which exert well-characterized functions mediated through β-catenin [40]. The Wnt3a ligand can activate the transcriptional activity of TCFs in osteoclasts. TCFs, such as TCF1, TCF3, TCF4 and LEF1, can promote the expression of a wide variety of downstream genes [74, 75]. These genes are also highly expressed in primary osteoclasts of patients with MM, which exhibit oncogenic potential [74, 75]. Several studies have reported that Wnt7b and Wnt10b can activate mammalian target of rapamycin complex 2 in osteoblastic cells, which facilitates the osteoanabolic function of sclerostin (scl) neutralization [76]. In addition, Wnt16 was shown to initiate β-catenin activation, which enhances oleate oxidation during bone development [77].

Previous studies found that the Wnt signaling pathway can promote the differentiation of osteoblasts, in addition to the formation and

absorption of osteoclasts via mutations in Wnt receptors, such as LRP5, LRP6 and FZD [78]. LRP5 was first independently identified in 1998 as a novel gene expressed in osteoblasts. At present, LRP5 is considered to be a regulator of the proliferation and functional lifespan of osteoblasts, where it enhances the efficiency of Wnt signal transduction [79]. LRP6 is recognized to be a mammalian Wnt signaling molecule, which shares 71% amino acid sequence homology with LRP5 and plays an important role in skeletal development [79]. The mechanism of signal transduction following LRP6 activation by Wnt in osteoblasts may differ from that of LRP5, since LRP6 markedly activated Wnt3a-mediated signaling and LRP5 slightly affected this signaling pathway in osteoblasts [79]. Since FZDs interact with Wnts through a cysteine-rich domain on the extracellular surface, they are widely considered as cell surface receptors for Wnts. Following engagement by Wnt ligands, FZDs may participate in a feedback mechanism to mediate Wnt signaling in osteoblasts [77]. In addition, receptor tyrosine kinase-like orphan receptor 2 (ROR2) has also been reported to belong to the Wnt5a receptor family, which is highly expressed in MM cells and participates in promoting the pathophysiology of MM-induced bone disease. Interactions between MM cells and the surrounding BM can be facilitated, at least in part, by ROR2, which induced apoptosis and markedly inhibited MM progression [80].

In addition, bone cells secrete a variety of Wnt inhibitors, including Dickkopf (DKK) protein, soluble brittle related protein (sFRPs) and scl. It has been previously demonstrated that DKK1 and several sFRPs, including sFRP-1, sFRP-2, sFRP-3 and sFRP-4, in addition to Wnt inhibitory factor 1, can antagonize the Wnt-1/Wnt-3a signaling pathway in the BM microenvironment (**Figure 3**) [4, 81, 82]. DKK1 and sFRPs, serving as Wnt inhibitors, both contribute to osteolytic bone disease by blocking osteoblast differentiation [83, 84]. MM-triggered bone disease has been shown to be associated with high expression levels of DKK1. Specifically, overexpression of DKK1 has been shown to inhibit Wnt signaling whilst positively regulating receptor activator of nuclear factor κB ligand (RANKL) and negatively regulating osteoprotegerin expression, thereby preventing osteoblastic differentiation in mesenchymal stem cells [85].

The mRNA expression levels of the DKK1-binding receptor LRP5/6 and the single-pass transmembrane proteins Kremen1/2 were found to be higher in mesenchymal stem cells of patients with MM, which formed a ternary complex and interacted with DKK1. This process can enhance the endocytosis and removal of LRP5/6 from the cell membrane, leading to the reduction of Wnt signaling, thereby favoring systemic osteolytic bone damage [86]. Results from another previous study suggest that the inhibition of Wnt ligand binding to FZD using sFRP-1 reduced β-catenin stabilization, inhibited β-catenin/TCF-regulated transcription and suppressed the expansion of several human MM cell lines [40]. Therefore, these observations suggest that DKK1 and sFRP-1 produced by MM cells can dampen osteoblast differentiation in the BM microenvironment. The application of DKK antibodies has been proposed to improve bone synthesis because they can trigger the activation of Wnt/β-catenin signaling [48]. In addition, osteoblast-derived R-spondins can potentiate Wnt/β-catenin signaling further by interacting synergistically with leucine-rich repeat-containing G protein-coupled receptor 4 (LGR4). It has been previously shown that LGR4 is unique in MM plasma cells. Once activated, MM cells can hijack R-spondins produced by pre-osteoblasts in the BM niche, leading to enhanced auto- and paracrine Wnt signaling [87]. Consequently, the LGR4/R-spondin axis was hypothesized to be a driver of oncogenic Wnt/β-catenin signaling, where its aberrant activation results in the epigenetic loss of sFRPs and DKK1, natural suppressors of the Wnt pathway, during advanced MM (**Figure 3**) [87]. Alternatively, runt-related transcription factor 2 (Runx2) is another bone-specific transcription factor, which upregulates Akt/β-catenin/Survivin signaling and promotes the secretion of RANKL, a critical stimulator of osteoclast differentiation, thereby contributing to the aggressive phenotype of MM (**Figure 3**) [35, 88].

Scl is a natural inhibitor of the Wnt/β-catenin pathway, which is a product of the *sost* gene and is primarily expressed by mature osteocytes. Scl blocks the Wnt/β-catenin signaling pathway via binding to LRP4/5/6 to regulate bone formation and resorption [89]. Previous studies have found that increased Scl levels in the MM BM microenvironment can directly

inhibit osteoclast differentiation by targeting the Wnt/β-catenin pathway [90-92]. The anti-Scl antibody (Scl-Ab) has been demonstrated to reduce the expression of RANKL and directly inhibit osteoclast precursor differentiation by suppressing Wnt/β-catenin signal transduction [93]. However, due to the insufficient number of *in vivo* studies on the effects of Scl-Ab, it was tested in combination with proteasome inhibitors to improve the osteolytic lesions induced by MM cells [94]. Other osteoblast inhibitors, including transforming growth factor-β, hepatocyte growth factor activator A, interleukin (IL)-7, C-C motif chemokine ligand 3 and tumor necrosis factor-α, can also exert inhibitory effects on the Wnt/β-catenin signaling pathway in MM (**Figure 3**) [95, 96].

In addition, several miRs have previously emerged as key regulators of bone development and regeneration by targeting the Wnt/β-catenin pathway. In particular, miR-203a-3p.1 was found to regulate the osteogenic differentiation of (MM)-mesenchymal stem cells by targeting the Wnt3a/β-catenin signaling pathway (**Figure 3**) [85]. In addition, cyclophilin A secreted by endothelial cells in the BM has been previously revealed to be a new transcriptional target of the Wnt/β-catenin/BCL9 pathway [57]. Cyclophilin A can form a complex with its receptor CD147, also known as basigin, to promote BM colonization and MM cell proliferation [57]. In MM, enhanced expression of miR-342 and miR-363 can significantly reduce the expression of Runx2, which in turn suppressed the expression of DKK1 and RANKL to inhibit the expression of β-catenin and GSK-3β, thereby reducing osteolysis [35].

To summarize, targeting the canonical Wnt signaling in the BM microenvironment is of potential therapeutic value for bone diseases associated with MM [93, 97].

Drugs or small-molecule inhibitors targeting Wnt/β-catenin pathway in MM

Since Wnt/β-catenin pathway activation is mostly dependent on ligand binding, this pathway can be targeted by drugs specific for its receptors on the cell membrane. Consequently, a series of drugs targeting the Wnt/β-catenin pathway cascade in MM have been designed for clinical and pre-clinical testing. Clinically, proteasome inhibitors and immunoregulatory

drugs have been extensively applied for the treatment of MM, including bortezomib, ixazomib [98], lenalidomide and thalidomide [99]. Furthermore, advancements in molecular biology have opened new drug discovery avenues. Indeed, a wide spectrum of therapeutic agents or small-molecule inhibitors targeting the Wnt/β-catenin pathway have been explored over the past decade, some of which have been proposed to be potentially novel treatment options for MM. In this section, we summarize the potential role of some of these drugs in regulating bone metabolism in MM via targeting the Wnt/β-catenin pathway.

Proteasome inhibitors

Proteasome inhibitors have been used extensively for clinical application since the ubiquitin-proteasome pathway has been widely reported to be important for regulating bone metabolism in MM [98]. Bortezomib is a first-generation proteasome inhibitor that has been utilized as an effective agent for the treatment of MM, which induces GSK-3 activation and nuclear translocation (**Table 1**) [52]. In addition, Carfilzomib can activate Wnt-independent β-catenin/TCF signaling by suppressing proteasome-mediated β-catenin degradation without the need for Wnt ligands, FZD receptors or LRP5/6 co-receptors, which promoted the differentiation of mesenchymal stem cells into osteoblasts [100]. Ixazomib has been approved as the first orally-administered proteasome inhibitor for the treatment of MM. Ixazomib can promote β-catenin translocation and separate parathyroid hormone (PTH) receptor from β-catenin at the plasma membrane, which enhances PTH-stimulated GSK-3β phosphorylation and cAMP generation. Therefore, osteoblast differentiation is promoted by ixazomib by activating β-catenin/TCF signal transduction downstream of cAMP signaling in osteoblasts [98]. Preclinical studies on the activity of MLN2238, which is a hydrolyzed product of the oral proteasome inhibitor MLN9708, showed that it could promote osteoblast differentiation, inhibit osteoclast absorption and MM cell proliferation by activating TCF4/β-catenin signaling in the BM microenvironment [101].

Immunomodulatory drugs

Lenalidomide is an important immunomodulatory drug that has been used for the treatment

of recurrent MM. Recurrent MM is a particularly resistant phenotype of MM clinically, and is associated with the expression levels of CD44 surface receptors. CD44 is a glycosylated class-I transmembrane protein that has been found to be overexpressed on the surface of various solid tumors [102]. It can regulate a number of cellular processes and promote resistance to several forms of multiple chemotherapy [102, 103]. In particular, CD44 is the target of Wnt/β-catenin signaling, which functions as a mediator of cell adhesion-mediated drug resistance in MM cells by binding to the glycosaminoglycan hyaluronan (HA) [104]. Targeting CD44 using monoclonal antibodies, free HA or knocking out the *CD44* gene was observed to result in enhanced lenalidomide sensitization and reversal of drug resistance [70]. Furthermore, the novel β-catenin/TCF antagonist FH535, IL-6 and all-trans retinoic acid (ATRA) have all been shown to enhance the toxicity of lenalidomide in MM cells. FH535 was found to function through the tankyrase 1/2 enzymes, whilst ATRA improved sensitivity to lenalidomide by downregulating the total expression levels of β-catenin and CD44 (**Table 1**) [105]. MM cells develop resistance to lenalidomide by decreasing the expression of casein kinase 1 whilst enhancing the phosphorylation of GSK3 to activate the transcriptional activity of TCF/LEF, which upregulates β-catenin activity and cyclinD1 and c-MYC transcription. When β-catenin expression or activity was reduced through transfection with siRNA or shRNA or inhibitors, the sensitivity of MM to lenalidomide was increased [48]. Despite the reported pleiotropic anti-MM effects of the aforementioned drugs, only a selected number of patients achieve complete remission due to drug resistance after prolonged treatment. Therefore, there is an urgent demand for developing novel therapeutic agents targeting the biology of MM.

Small-molecule inhibitors and antibodies

Previous studies have shown that various small-molecule compounds can directly target Wnt/β-catenin pathway. A number of studies were previously performed to assess the effects of active β-catenin-regulated transcription (iCRT) compounds, including oxazole (iCRT-3) and thiazole (iCRT-5), on MM cells. They were found to diminish the activity of β-catenin and reduce the levels of β-catenin in the nucleus to inhibit MM cell proliferation [106]. These effects were found to be independent of the expression of DKK1, an upstream component of the Wnt pathway, suggesting that iCRT3 and iCRT5 specifically target β-catenin (**Table 1**) [106]. In addition, another previous study also performed high-throughput screening to search for small molecules that may be used to treat MM, resulting in the discovery of AV-65 [107]. AV-65 was found to repress MM growth by inducing the apoptosis pathway, which was proposed to be due to reduced β-catenin protein expression levels and diminished TCF transcriptional activity, leading to the reduction of c-MYC, cyclinD1 and survivin expression (**Table 1**) [107]. Similarly, sdx-308 was also demonstrated to be toxic to MM cells by inhibiting the Wnt/β-catenin pathway (**Table 1**) [108]. The small-molecule compounds SAH-BCL9B [59] and PKF115-584 [109] can also suppress the activity of the Wnt/β-catenin pathway to impair the proliferation and migration of MM cells. Specifically, PKF115-584, screened out using high throughput enzyme-linked immunosorbent assay, prevented β-catenin/TCF transcription complex formation and downregulated the expression of Wnt target genes, which resulted in the inhibition of MM cell proliferation without affecting normal plasma cells [73] (**Table 1**). In addition, we previously found a synergistic anti-MM activity of PKF115-584 in combination with proteasome inhibitors [73]. Small-molecule GSK-3 inhibitors, such as SB216763 and SB415286, have also been found to enhance bortezomib-induced MM cytotoxicity through accumulation of β-catenin and nuclear ERK1/2 phosphorylation, which triggered MM cell cycle arrest and apoptosis (**Table 1**) [52]. Another novel pharmacological inhibitor, ICG-001, was found to specifically bind to the transcriptional coactivator CREB binding protein (CBP), which then blocked the interaction between CBP and β-catenin in MM cells, thereby repressing β-catenin/TCF-mediated transcription (**Figure 1**; **Table 1**). Additionally, ICG-001 also reduced the resistance of MM cells to Adriamycin and melphalan [110]. Other small-molecule compounds, including IWR-1 and XAV939, have been found to inhibit the proliferation of MM cells by indirectly affecting the Wnt/β-catenin pathway [58].

It should be emphasized that gene-specific inhibitors can also halt the proliferation of MM cells by targeting the Wnt/β-catenin pathway. A novel β-catenin inhibitor, BC2059, which is an anthracene-9,10-dione dioxime compound [2-(3R,5S)-3,5dimethylpiperdin-1ylsulfonyl-7-(3S,5R)-3,5-dimethylpiperidin-1-ylsulfonyl], was able to block the interaction between β-catenin and transducin β-like protein 1, in addition to its associate transducin β-like 1 X-linked receptor [111]. This prevented the recruitment of β-catenin to the Wnt target gene promoter [111]. Consequently, the transcription activity of the TCF complex and target gene expression, such as Axin-2, were diminished (**Table 1**) [111]. Furthermore, this study also provided a rationale for using the interaction of β-catenin with other proteins as a druggable target, as exemplified by the use of BC2059 in this case, since it displayed synergism with bortezomib to inhibit proliferation and induce apoptosis in MM cells, with fewer side effects [111]. GSK126 is another highly selective inhibitor that inhibits enhancer of zeste 2 polycomb repressive complex 2 subunit methyltransferase activity, which has been previously reported to be a key epigenetic regulator of the Wnt/β-catenin pathway in MM [112]. Findings from *in vitro* studies showed that GSK126 can reduce the expression levels of β-catenin, its downstream targets c-MYC and LEF1, in addition to its upstream component disheveled 2/3 [112]. GSK126 can also induce apoptosis in MM cells, either as a single agent or in combination with bortezomib [112]. As a result, the application of GSK126 has entered the first phase of clinical trials [112]. Previous experimental evidence suggested that the combined treatment of the TNIK inhibitor KY-05009 and the receptor tyrosine kinase inhibitor dovitinib synergistically downregulated the expression of TNIK in MM cells, which interfered with the interaction among TCF4, TNIK and β-catenin to reduce TCF4 phosphorylation (**Table 1**). As a result, the expression of Wnt target genes, including *CCND1*, Axin-2, *ZCHC12* and *TCF7*, was suppressed [65]. Crucially, such a combination has also been observed to inhibit IL-6-mediated proliferation of MM cells [65]. A large number of *in vitro* and *in vivo* studies have been performed to assess the effects of targeting DKK1 and Scl, both of which can promote the formation of osteoblasts. PTH 1-34 (teriparatide) has been shown to increase bone density by inhibiting DKK1 and Sclerostin [113]. In addition, the anti-Scl antibodies romosozumab, blosozumab and BPS804 have also been revealed to increase osteoblast numbers and bone formation whilst alleviating osteolytic bone lesions [114-116]. Combined application of the anti-sclerostin antibody with the proteasome inhibitor carfilzomib resulted in enhanced anti-MM activity. However, the long-term use of these drugs may result in side effects, including excessive bone growth and other bone complications [117]. Therefore, their potential clinical application requires further study.

Bruton tyrosine kinase (BTK) has emerged as a novel therapeutic target in MM stem cells, since the overexpression of BTK facilitated the Wnt/β-catenin/Nanog signaling axis by combining with the NANOG promoter, which accelerated tumor growth [118]. CGI1746 is a second-generation BTK inhibitor that exhibited prominent therapeutic effects against MM by overcoming primary and acquired resistance [118]. Mucin 1 (MUC1) is a transmembrane oncogenic protein that has been reported to drive MYC signaling in MM cells by stabilizing β-catenin to activate the Wnt/β-catenin signaling pathway [119]. Combined treatment with the MUC1-C inhibitor Go-203 [(R) 9-cqcrrkn] and lenalidomide was found to induce apoptosis in MM cells in response to drug resistance. Go-203 is a cell-penetrating peptide inhibitor of MUC1-C copolymerization, which inhibits the interaction between MUC1-C and β-catenin/TCF4 (**Table 1**) [120]. This, in turn, disrupts the redox signaling equilibrium and inhibits the expression of Wnt target genes, including *MYC* and *CD44*, to ultimately reduce the resistance of MM to lenalidomide [120].

Other drugs

A number of other drugs have been found to significantly regulate the Wnt/β-catenin pathway to impede the proliferation of MM cells. Pyrvinium pamoate (PP), which is also marketed as Povan or Vanquin, is an oral anti-helminthic drug that was approved by the U.S. food and drug administration [121]. The mechanism of action of PP in MM was found to be inhibition of the Wnt/β-catenin pathway by activating casein kinase 1α whilst promoting the degradation of β-catenin (**Table 1**), thereby triggering

apoptosis [121]. In addition, S9-phosphorylated GSK3, which is inactive, was found to be degraded by PP, whilst the levels of Y216-phosphorylated GSK3, which is active, remained unchanged. This leads to the down-regulation of the expression of the target genes Axin-2, *MYC* and *CCND1*. PP can also target the Wnt/β-catenin pathway by reducing the stability of β-catenin and Axin in the cytoplasm, along with Pygopus and TCF/LEF1 in the nucleus [121]. Synergism between PP and bortezomib has also been reported to induce MM cell death, supporting its potential application in a future clinical trial setting [99]. Ilimaquinone and ethylsmenoquinone are sesquiterpenoid quinone compounds that can be isolated from the marine sponge [122]. Both ilimaquinone and ethylsmenoquinone were demonstrated to exert inhibitory effects on β-catenin-mediated transcription after Wnt3a treatment by promoting β-catenin degradation (**Table 1**), thereby downregulating *CCND1*, *c-MYC* and Axin-2 expression in MM cells [122]. In addition, the iron chelator deferasirox, which is normally used as an oral medication for patients undergoing blood transfusion, has been shown to inhibit the growth of MM tumors *in vivo* and *in vitro* [123]. Mechanistically, deferasirox was found to be a Wnt inhibitor, which accelerated the degradation of β-catenin by activating GSK3β (**Table 1**) [123].

In conclusion, the aforementioned data collectively described a number of novel small molecules and peptides that can either sequester components of the Wnt signaling pathway, block Wnt receptor activity, or target the expression of genes involved in the Wnt/β-catenin pathway. It is hoped that this will lay a solid foundation for the initiation of future clinical trials using some of these compounds, which have the potential for the development of attractive therapeutic strategies against MM.

Conclusions

To conclude, the Wnt/β-catenin signaling pathway is of great importance in the pathogenesis of MM, such that blocking the Wnt/β-catenin signaling pathway in MM may contribute to improving patient outcomes. Additionally, assessment of specific genotypes among individuals as part of a personalized treatment approach may not only increase the safety and efficacy of drugs that target the Wnt/β-catenin pathway, but can also be applied to predict the disease outcome in MM.

Disclosure of conflict of interest

None.

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