*Review*

# Influencing the Wnt Signaling Pathway in Multiple Myeloma

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**Abstract.** *Recent studies have implicated genetic and epigenetic aberrations resulting in aberrant activation of the Wingless-Int (Wnt) pathway and thus influencing the initiation and progression of multiple myeloma (MM). Of major importance, these findings may lead to novel treatment strategies exploiting targeted modulation of Wnt signaling. This review describes the current status of knowledge concerning the role of Wnt pathway alteration in MM and outlines future lines of research and their clinical perspectives.*

## Multiple Myeloma

Multiple myeloma (MM), a well-known but still incurable disease of the blood, is a hematologic malignancy of B-lymphocytes which is characterized by clinical heterogeneity, such as anemia, bone disease, renal dysfunction and prolonged infections (1-3). In the past, for most patients with MM, chemotherapy with melphalan and prednisone or high dosage chemotherapy with stem-cell transplantation were the only therapeutic options (4, 5). During recent years, major effort has been put into immunotherapeutic approaches for this malignancy (4). Due to high mortality rates and high relapse rates among transplant patients with MM, new therapeutic strategies are required.

In the past few years, major progress has been made in the treatment of MM by introducing novel therapeutic agents such as thalidomide, lenalidomide and bortezomib. In newly diagnosed patients, the combination of lenalidomide and dexamethasone has shown an effective response rate of 91%. Nevertheless, MM remains an incurable disease (6, 7).

The Wingless-Int (Wnt)/β-catenin pathway has been shown to play an important role in the regulation of cell proliferation, differentiation and apoptosis (8-10). Recently, it was demonstrated that the Wnt pathway is aberrantly activated in a considerable fraction of MMs. Thus, Wnt/β-catenin signaling molecules are attractive candidates for developing novel targeted therapies for this disease.

## Wnt Signaling Pathway

Wnt (wingless) proteins constitute a family of cysteine-rich glycosylated proteins that contribute to lymphopoiesis and early stages of both B- and T-cell development (11). They function as extracellular signaling molecules that may activate the Wnt/β-catenin signaling pathway by binding to the extracellular domain of Frizzled receptors. In addition to their extracellular Wnt-binding domain, Frizzled receptors have seven transmembrane-spanning sequences and a *C*-terminal tail. Wnt proteins regulate cell proliferation, cell morphology, cell motility and cell fate. To date, more than 14 Wnt members have been identified in humans and more than 8 mammalian Frizzled genes are known (12). Wnt signaling results in the activation of intracellular signaling cascades which are associated with several forms of cancer (11).

Binding of Wnt to either Frizzled and the low-density lipoprotein receptor-related proteins (LRP) 5 and 6, or to Frizzled protein alone results in the stabilization of β-catenin, the major mediator of canonical Wnt signaling (Figure 1) (13, 14). Frizzled receptors have no enzymatic motifs on their intracellular domains, therefore intracellular signaling molecules have to be recruited or released (12). These are members of the Dishevelled (Dvl) family. Three members of Dvl, including Dvl-1, Dvl-2 and Dvl-3, have been characterized (15). They lack any known enzymatic

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activity but function as molecular adaptors on Frizzled receptors due to their protein-protein interaction domains and/or heterotrimeric G-proteins (12, 14). β-Catenin is associated in a cytoplasmic complex together with the adenomatous polyposis coli (APC) protein, the cytoplasmic serine/threonine kinase glycogen synthase kinase-3β (GSK-3β), and axin (Figure 1) (12, 16). In unstimulated cells, axin in its phosphorylated form is able to bind β-catenin effectively. Upon Wnt signaling, however, axin is dephosphorylated by the protein phosphatase 2A (PP2A). The dephosphorylated form of axin binds β-catenin less efficiently than it does the phosphorylated form, thereby promoting the release of β-catenin (17). A complex of axin with one of the three iso-enzymes of casein kinase I (CKIα, δ or ε) phosphorylates β-catenin on serine 45. This step is independent of GSK-3β and initiates the phosphorylation-degradation cascade of β-catenin. In the subsequent step, β-catenin is phosphorylated at serine 33/37 by GSK-3β (15).

The phosphorylated β-catenin is subsequently recognized by the E3 ubiquitin ligase subunit β-transducin repeat-containing protein (β-TrCP) and thereby targeted for ubiquitination and subsequent degradation by the proteasome (16, 18, 19).

In the presence of Wnt signaling, the phosphorylating activity of GSK-3β is inhibited leading to the stabilization of β-catenin (20). This is mediated by the intracellular protein Dvl through a Frizzled receptor (16). The APC-GSK-3β-Axin activity is dissociated and unphosphorylated β-catenin accumulates in the cytoplasm (16, 20). From there, free β-catenin is able to translocate into the nucleus where it interacts with TCF and LEF transcription factors (20). Dvl not only stabilizes β-catenin in the cytoplasm, but is also required in the nucleus where it interacts between c-Jun and β-catenin, respectively. This mediates the formation of a Dvl–c-Jun-β–catenin-TCF transcriptional complex, binding to the promoter of Wnt target genes (14). For example, β-catenin may stimulate cell-cycle progression and differentiation by Wnt/β-catenin target gene expression of genes, including *c-myc,* cyclin D1 and fibronectin (11, 14).

## β-Catenin

β-Catenin is a 92 kDa protein consisting of several structural domains (Figure 1) (12, 21). The *N*-terminal region mediates binding activity by phosphorylation sites for GSK-3β and β-catenin (12). The central domain contains 13 incomplete conserved Armadillo repeat motifs ('Arm' amino acid repeats) facilitating protein-protein interactions of, *e.g.* cadherins, β-catenin, the APC protein, axin, or lymphoid-enhancing transcription factor (LEF)-1/T cell transcription factor (TCF) (12, 21). A positively charged groove in a superhelix of this central domain is hypothesized to interact with acidic regions of APC, TCF transcription factors and cadherin cell-adhesion molecules (12). The *C*-terminal region encodes a transcriptional transactivation domain. Both the central domain and the *C*-terminal region are involved in the signaling activity of β-catenin (21).

β-Catenin acts as a structural protein at cell–cell adherens junctions where it links cadherins to the actin cytoskeleton (11). In addition to β-catenin, there are two other catenins known as α-catenin and γ-catenin (plakoglobin). β-Catenin associates with E-cadherin and α-catenin, forming a cadherin–catenin protein complex under *in vivo* conditions (21). Furthermore, β-catenin acts as a central molecule in the Wnt pathway, influencing membrane structure and the shape of a cell (11). Thus, β-catenin has a dual cellular function in mediating cell–cell adhesion as well as Wnt signaling (21).

## Wnt Pathway Signaling in MM

MM depends on the bone-marrow microenvironment for growth and survival. The tumor is characterized by extensive bone loss and osteolytic lesions located at sites of medullary plasmacytomas, suggesting that myeloma cells secrete factors that alter the biology of bone remodeling. Wnt signaling is essential for the maintenance of osteoblast and osteoclast homeostasis, and thus, coupled bone turnover (8, 20). Recent data highlight the importance of the local microenvironment in the effect of Wnt signaling on the development of myeloma bone disease and demonstrate that, despite a direct effect on increasing tumor growth at extraosseous sites, increasing Wnt signaling in the bone-marrow microenvironment can prevent the development of myeloma bone disease and inhibit myeloma growth within bone *in vivo* (22).

Emerging evidence suggests that production of Wnt-signaling inhibitors DKK1, sFRP2 and sFRP3 by myeloma cells contributes to the development of osteolytic lesions through the direct suppression of osteoblast differentiation (20, 23). In addition to enhanced osteolysis, MM cells also suppress bone formation, at least in part, through an inhibition of the canonical Wnt pathway by secreting Frizzled-related protein 2 sFRP-2 (24). Recently, a consistent, close correlation between DKK1 expression by myeloma cells and the occurrence of focal osteolytic bone lesions was demonstrated in MM patients. In addition, data was provided for a novel functional link between β-catenin and aurora kinase A, underscoring a critical role of these pathways in disease progression (20, 25).

In contrast, it was shown that bortezomib, a novel drug used to treat MM, induces osteoblast differentiation *via* Wnt-independent activation of the β-catenin/TCF pathway, suggesting that proteasome inhibition therapy of MM may function, in part, by subverting tumor-induced suppression of canonical Wnt signaling in the bone microenvironment (26).

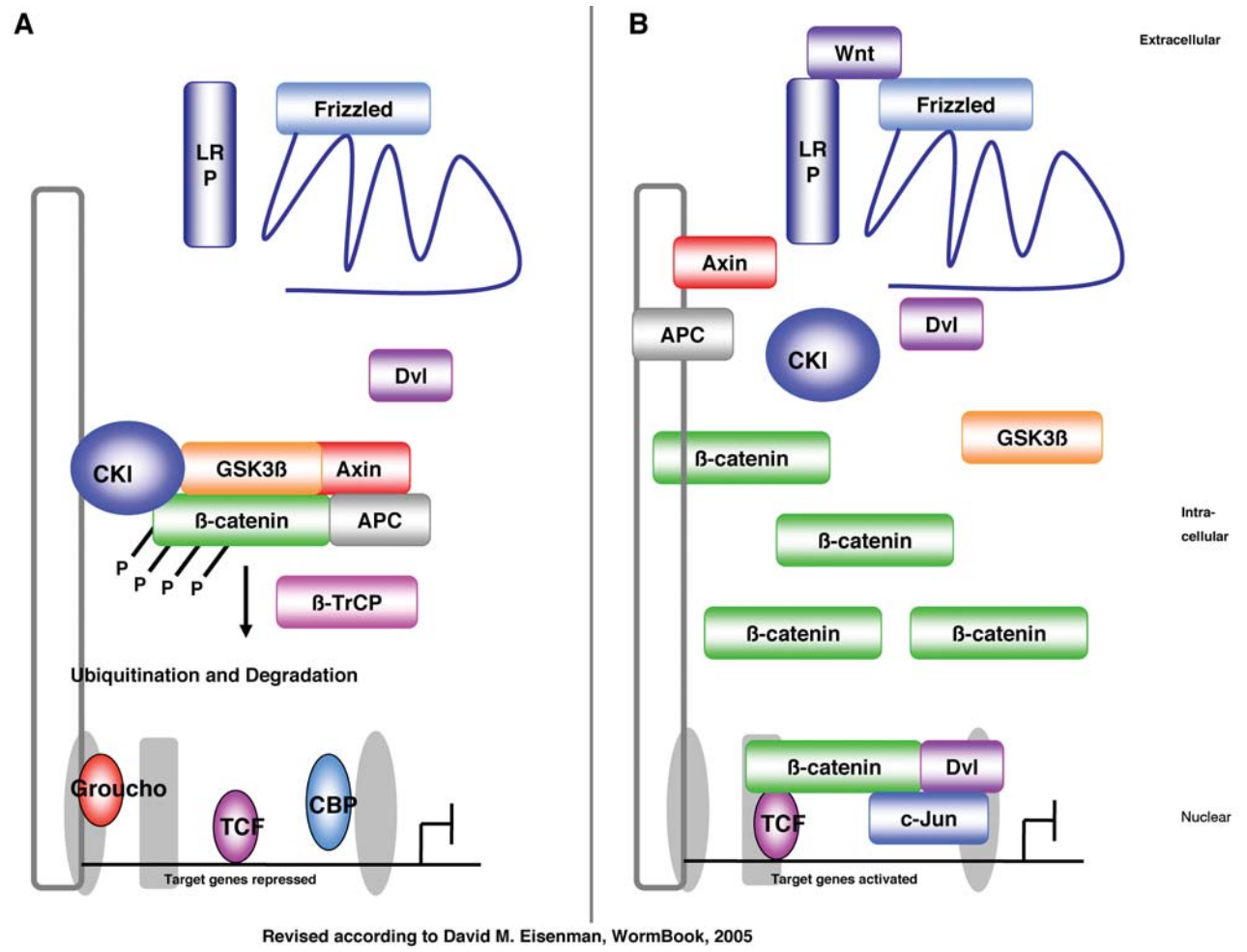


Figure 1. *Schematic overview of the Wnt pathway revised according to David M. Eisenman (43) without (A) and with (B) Wnt activation.*

## DKK1 and MM Bone Disease

DKK1 is a negative regulator of the canonical Wnt signaling pathway. Wnt signaling mediated by LRP5/6 is required for the maintenance of normal bone density in adults. Stimulation of osteoblast differentiation (27, 28), regulation of osteoblast proliferation (17, 29) and apoptosis (16, 30-32) and induction of osteoblast activity (33) are thought to be the main mechanisms by which Wnt signaling increases bone mass due to increased bone formation. In addition, Wnt signaling may also increase bone mass by affecting osteoclast function (33-35) and, thereby, decreasing bone resorption.

When DKK1 is neutralized, the Wnt pathway is activated and Wnt target genes are expressed, leading to activation and differentiation of osteoblastic cells and therefore BHQ880, a human, anti-DKK-1 neutralizing antibody, has the potential to act as a bone anabolic agent and perhaps reduce the incidence of skeletal-related events (36).

MM cells, but not plasma cells, from healthy donors and patients with monoclonal gammopathy of undetermined significance or other plasma cell dyscrasias involving the bone marrow, express the Wnt-signaling antagonist DKK1 (34, 36). Previously, it was reported that secretion of DKK1 by MM cells likely contributes to osteolytic lesions in this disease by inhibiting Wnt signaling. The mechanisms responsible for activation and regulation of DKK1 expression in MM are not yet known (31). DKK1 expression changes may be traced in MM cells to perturbations in the JNK signaling cascade, which is differentially modulated through oxidative stress and interactions between MM cells with osteoclasts *in vitro*. Despite its role as a tumor suppressor and mediator of apoptosis in other cell types including osteoblasts, the data suggest that *DKK1*, a stress-responsive gene in MM, does not mediate apoptotic signaling, is not activated by TP53 and its forced overexpression may not inhibit cell growth or sensitize MM cells to apoptosis

following treatment with thalidomide or lenalidomide (36). Specific strategies to modulate persistent activation of the JNK pathway may be beneficial in preventing disease progression and treating myeloma-associated bone disease by inhibiting DKK1 expression (25). Recent findings suggest DKK1 as a serum biomarker for screening against a variety of cancers, and anti-DKK1 antibodies as potential tools for diagnosis and treatment of cancer (37).

## Targeting the Wnt Pathway in Myeloma

The Wnt/β-catenin pathway has been shown to play an important role in the regulation of cell proliferation, differentiation and apoptosis (8-10). Lymphomas may show aberrant activation of the pathway (20), which therefore represents an attractive candidate for targeted therapeutic intervention in these tumors. More recently, a study investigated the apoptotic effects of ethacrynic acid (EA) and the antifungal agent ciclopiroxolamine (CIC), another drug that inhibits Wnt/β-catenin signaling, on the myeloma cell line OPM-2 (23). EA is already used clinically as a diuretic agent. Glutathione-*S*-transferase (GST), which is overexpressed in human tumors in the form of GST-P, couples glutathione (GSH) with electrophilic compounds and detoxifies the cell (38). GSH acts as a reducing agent and antioxidant. The binding of EA to GSH can enhance the cytotoxicity of chemotherapeutic agents (39). CIC is used topically for the treatment of yeast infections in humans and is degraded by glucoronidation (40). It acts as a chelator of polyvalent metal cations (*e.g.* $Fe^{3+}$ and $Al^{3+}$), resulting in the inhibition of the metal-dependent enzymes in the metabolism of the cell. Furthermore, it blocks the cell cycle near the $G_1$/S phase boundary (40).

Treatment of OPM-2 cells and the three lymphoma cell lines, OCI-LY8-LAM-53, SU-DHL-4 and Raji, led to a significant decrease of viability in these tumor cell lines but not in PBMCs derived from healthy donors (23). These results suggest a selective induction of apoptosis by CIC and EA in lymphoma and myeloma cells.

A recent study used a 96-well plate-based TOPflash reporter system to screen the Gen-plus drug library (Microsource, Gaylordsville, CT, USA), which contained 960 compounds (20). This screen identified EA and CIC as Wnt/β-catenin inhibitors. Given that the canonical Wnt signaling pathway is activated in lymphoma and myeloma cells (20), the study investigated whether EA and CIC may induce apoptosis and reduce the viability of lymphoma and myeloma cell lines. The effect of EA was studied in primary cultures derived from patients with chronic lymphocytic leukemia. Similar data as for cell lines were obtained for primary cells. The study showed a significant induction of apoptosis by CIC and EA in lymphoma and myeloma cells. Taken together with previous results (20), these data suggested that EA and CIC can inhibit Wnt/β-catenin signaling in lymphoma and myeloma cell lines. In addition, EA was also shown to be effective in primary cultures derived from patients with chronic lymphocytic leukemia. These results are in accordance with a recent report (13) that the canonical Wnt signaling pathway is activated in MM through constitutively active β-catenin (23).

Aberrant activation of Wnt/β-catenin signaling promotes the development of several types of cancer. Recently, it was demonstrated that the Wnt pathway is also activated in lymphoma and myeloma (11, 13, 22, 23, 26). Therefore, the Wnt/β-catenin signaling molecules are attractive candidates for the development of targeted therapies in these diseases. To this extent, it was recently confirmed that the diuretic agent EA and the antifungal agent CIC inhibit Wnt/β-catenin signaling (20). Patients with myeloma are currently treated with drugs such as doxorubicin and thalidomide or with novel compounds such as bortezomib and lenalidomide. Recently, these compounds were tested in combination with CIC and EA. CIC, lenalidomide and EA were more effective than thalidomide in decreasing the viability of myeloma cell lines. In addition, EA and CIC decreased the viability of lymphoma cells (20). In OPM-2 cells, the combination of CIC and EA plus bortezomib did not further decrease the viability of OPM cells. Interestingly, the addition of thalidomide and lenalidomide indicated a synergistic effect of these drugs with EA and CIC. Moreover, it was demonstrated that β-catenin expression is down-regulated when CIC and EA are added to lymphoma cells. These results revealed a significant selective induction of apoptosis by CIC and EA in both lymphoma and myeloma cells and suggested a synergistic effect when CIC and EA are combined with thalidomide or lenalidomide in myeloma cells. Interestingly, recently, similar results were obtained using drugs chemically similar to EA and CIC (41, 42).

In conclusion, the Wnt signaling pathway seems to be of major importance in myeloma. Influencing this pathway is a novel treatment strategy and should be investigated in further studies for future clinical use in patients with MM.

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