Abstract Osteosarcoma (OS) is the most common primary bone malignancy diagnosed in children and adolescents with a high propensity for local invasion and distant metastasis. Despite current multidisciplinary treatments, there has not been a drastic change in overall prognosis within the last two decades. With current treatments, 60–70% of patients with localized disease survive. Given a propensity of Wnt signaling to control multiple cellular processes, including proliferation, cell fate determination, and differentiation, it is a critical pathway in OS disease progression. At the same time, this pathway is extremely complex with vast arrays of cross-talk. Even though decades of research have linked the role of Wnt to tumorigenesis, there are still outstanding areas that remain poorly understood and even controversial.

C.H. Lin
The Hyundai Cancer Institute, CHOC Children’s Hospital, Orange, CA USA
Department of Orthopaedic Surgery and Chao Family Comprehensive Cancer Center,
University of California, 101 The City Drive South, Irvine, Orange, CA 92868, USA

T. Ji
Department of Orthopaedic Surgery and Chao Family Comprehensive Cancer Center,
University of California, 101 The City Drive South, Irvine, Orange, CA 92868, USA
Musculoskeletal Tumor Center, People’s Hospital, Peking University, Beijing,
People’s Republic of China

C.-F. Chen
Department of Orthopaedic Surgery and Chao Family Comprehensive Cancer Center,
University of California, 101 The City Drive South, Irvine, Orange, CA 92868, USA
Department of Orthopaedics, Therapeutical and Research Center of Musculoskeletal Tumor,
Taipei Veterans General Hospital, Taipei, Taiwan

B.H. Hoang, M.D. (✉)
Department of Orthopaedic Surgery and Chao Family Comprehensive Cancer Center,
University of California, 101 The City Drive South, Irvine, Orange, CA 92868, USA
e-mail: bhhoang@uci.edu

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The canonical Wnt pathway functions to regulate the levels of the transcriptional co-activator β-catenin, which ultimately controls key developmental gene expressions. Given the central role of this mediator, inhibition of Wnt/β-catenin signaling has been investigated as a potential strategy for cancer control. In OS, several secreted protein families modulate the Wnt/β-catenin signaling, including secreted Frizzled-related proteins (sFRPs), Wnt inhibitory protein (WIF), Dickkopf proteins (DKK-1,2,3), sclerostin, and small molecules. This chapter focuses on our current understanding of Wnt/β-catenin signaling in OS, based on recent in vitro and in vivo data. Wnt activates noncanonical signaling pathways as well that are independent of β-catenin which will be discussed. In addition, stem cells and their association with Wnt/β-catenin are important factors to consider. Ultimately, the multiple canonical and noncanonical Wnt/β-catenin agonists and antagonists need to be further explored for potential targeted therapies.

Keywords Osteosarcoma • Wnt • β-Catenin • Dickkopf • Wnt inhibitory protein • Frizzled-related proteins

Introduction

Osteosarcoma is the most common primary bone malignancy which occurs frequently in a bimodal distribution, with peak incidences in the second decade of life and after the age of 60 [1]. With the current multidisciplinary treatments, 60–70 % of patients with localized disease survive [2]. OS has a high tendency for local invasion and early metastasis. Unfortunately, with metastatic disease, the rate of 5-year overall survival is greatly reduced to 20–30 %, and the 5-year event-free survival for patients with relapse is 20 % [3, 4]. Metastasis occurs primarily to the lungs and bones. Even though initial scans may not show evidence of pulmonary disease, it is thought that micrometastasis is extremely common, making it difficult to successfully eradicate this tumor. Despite aggressive efforts to strengthen and modify chemotherapy, the outcome of patients with OS has not significantly improved over the past few decades [5].

The exact molecular mechanism leading to the development of OS is not fully understood. Research endeavors have focused on the Wnt signaling pathway since the discovery of the WNT1 gene (originally named Int-1) in 1982 [6, 7]. The discovery of the Drosophila segment polarity gene Wingless and the mouse proto-oncogene Int-1 initiated the advancement of this signaling pathway now commonly referred to as the canonical Wnt signaling pathway [8]. There are currently 19 Wnt proteins which have been identified in the human genome [9, 10]. A good portion of them are considered target genes of Wnt signaling and play a critical role in development and tumorigenesis [11–15] (see http://www.stanford.edu/group/nusselab/cgi-bin/wnt/). Aberrant signaling by Wnt pathways is linked to a wide spectrum of diseases, including neurodegenerative, bone, cardiovascular, and especially cancer. Notably, colon cancer has been associated with mutations of the
Overview of Wnt/β-Catenin Signaling Pathway and Cancer

The Wnt family is a group of secreted glycolipoproteins that initiate a signaling cascade to direct cell proliferation, cell fate determination, and differentiation in numerous developmental stages, from embryogenesis to adult tissue homeostasis [15, 20–23]. Aberrant Wnt signaling plays a role in multiple cancers, such as colon, gastric, lung, breast, prostate, skin cancers and osteosarcoma [19, 24–28]. Given the power of this central mediator, understanding the mechanisms to inhibit the Wnt/β--catenin signaling pathway is a potential strategy for cancer therapy.

In order to understand this pathway, the components of the signaling system are important to grasp. In a non-proliferative state, there is an absence or inhibition of Wnt, which enables the cytoplasmic β-catenin to form a complex with multiple entities, including Axin, adenomatous polyposis coli gene product (APC), casein kinase 1 (CK1), and glycogen synthase kinase 3β (GSK3β) [9, 20, 21, 29, 30] (see Fig. 1). Once this complex forms, CK1 and GSK3β act in conjunction to phosphorylate β-catenin, which is then recognized by the β-Trcp, an E3 ubiquitin ligase subunit. β-Trcp targets β-catenin for proteasomal degradation.

When the signaling cascade is “on,” in the presence of Wnt, binding to targeted receptors, comprising Frizzleds (seven-span transmembrane receptor proteins)/low-density lipoprotein receptor-related protein 5 and 6 (single-span transmembrane coreceptor proteins) and cytoplasmic disheveled (Dvl), causes phosphorylation of the complex, leading to inhibition of GSK3β. This creates a cytoplasmic accumulation of non-phosphorylated β-catenin, inhibiting its degradation and promoting translocation to the nucleus. Within the nucleus, it creates a complex with transcription factors, including T-cell transcription factor (TCF) and lymphoid enhancer-binding factor (LEF), and transcriptional co-activators, causing transcriptional activity of multiple downstream target oncogenes, such as c-myc, cyclin-D1, and Axin2, thus enhancing cellular proliferation [9, 20]. Other secreted factors, such as WIF-1 and Frzb/sFRP3 inhibit Wnt binding to frizzled receptors, and Dickkopf (Dkk) proteins antagonize the Wnt/LRP interaction. Wnt antagonists will be further explained in the latter part of the chapter.

The Wnt pathway has been extensively studied in colon cancer. Mutation of the APC gene leads to the activation of the Wnt pathway via stabilization of the β-catenin. This pathway was first associated with cancer development when it was discovered to be activated in both inherited familial adenomatous polyposis (FAP) and colorectal cancer. Approximately 90% of sporadic colon cancers display mutations in APC leading to aberrant Wnt signaling activity [31, 32]. Since this time, multiple investigators have sought to uncover the role of the Wnt signaling pathway in other malignancies, including OS.
Fig. 1 Overview of Wnt/β-catenin signaling. In the absence or inhibition of Wnt, the cytoplasmic β-catenin forms a complex with Axin, adenomatous polyposis coli (APC), casein kinase 1 (CK1), and glycogen synthase kinase 3β (GSK3β). CK1 and GSK3β phosphorylate β-catenin. β-Trcp (E3 ubiquitin ligase subunit) recognizes this complex and targets β-catenin for proteosomal degradation. In the presence of Wnt binding to targeted receptors frizzleds, low-density lipoprotein receptor-related protein 5 and 6 (LRP 5/6), and disheveled (Dvl), the complex becomes phosphorylated, leading to the inhibition of GSK3β. Cytoplasmic non-phosphorylated β-catenin accumulates, inhibiting its degradation and promoting translocation to the nucleus. A complex with transcription factors, including T-cell transcription factor (TCF), Lymphoid enhancer-binding factor (LEF), and transcriptional co-activators, lead to transcriptional activity of multiple downstream target oncogenes.

**Overview of Wnt/β-Catenin Signaling Pathway and Osteosarcoma**

Clinical tissue samples from osteosarcoma patients have been used to correlate various entities of the Wnt pathway and clinical outcome. In our 2004 study, RNA isolated from fresh-frozen osteosarcoma tissue was used to examine the expression of the Wnt receptor LRP-5 by polymerase chain reaction. LRP-5 RNA expression statistically correlated with worse event-free survival in patients [33, 34], and dominant negative LRP-5 decreased tumorigenicity and metastasis of OS in vivo in nude mice experiments [35]. Furthermore, it appears that blocking Wnt/LRP-5 signaling can reduce tumor invasiveness by reversing the epithelial-to-mesenchymal transition [36].
Role of Wnt Antagonists in Osteosarcoma

Secreted Wnt antagonists have been observed to suppress tumorigenesis and metastatic potential in osteosarcoma. Two types of secreted Wnt antagonists are characterized by their mechanisms of inhibition. The first type directly binds to Wnt ligands, promoting an inhibitory response. Wnt inhibitory factor-1 (WIF-1), sFRP family and Cerberus are examples of Wnt antagonists that bind directly to Wnt ligands and inducing an inhibitory response. The second type of antagonist such as the Dickkopf family and sclerostin inhibit the Wnt pathway by binding to transmembrane receptors, thereby preventing Wnt signaling activation.

The Dickkopf family comprises of four secretory proteins, including Dkk-1, Dkk-2, Dkk-3, and Dkk-4. Human Dkk-1 inhibits Wnt signaling pathway by binding to the transmembrane receptors LRP5/6 [37]. Dickkopf 3(Dkk-3), also known as reduced expression in immortalized cells (REIC), has been shown to impede invasion and motility of osteosarcoma cells [38]. Dkk-3 expression is downregulated in multiple cancer cell lines although its exact oncogenic suppressive mechanism is still unknown. Dkk-3 has been shown to downregulate β-catenin nuclear translocation in OS cells leading to inhibition of downstream LEF/TCF activation [39]. The expression of Dkk-3 and dominant-negative LRP5 mutant in OS cell lines substantially decreases cell invasion and motility. We further demonstrated the ability of Dkk-3 to suppress tumorigenesis and pulmonary metastasis in nude mice via intratibial injection of Dkk-3 transfected OS cells [40].

Frzb, a member of secreted frizzled-related protein (sFRP) family, is another Wnt antagonist that has been associated with cancer. It has an amino-terminal cysteine-rich domain (CRD) that is homologous to the ligand-binding domain of Frizzled [41]. Frzb blocks receptor signaling by primarily binding to the extracellular Wnt ligands, preventing the ligand-receptor interaction [42]. Frzb re-expression has been shown to inhibit tumorigenesis and invasiveness in both prostate and fibrosarcoma cancer cells. In vitro studies demonstrated that Frzb can inhibit c-Met, a Wnt target gene that plays a key role in sarcoma progression [24, 43, 44]. Not only is Frzb expression downregulated in soft tissue sarcomas, but it is also less expressed in OS tissue and cell lines [45]. DeAlmeida et al. demonstrated that a secreted Wnt antagonist comprising of the CRD of Fz8 attached with human IgG showed antitumor activity in a teratocarcinoma animal model [46]. This suggests the possibility of creating antagonist fusion proteins as a potential class of therapeutic agent.

The antagonist Wnt inhibitor factor 1 (WIF-1) is frequently downregulated in cancer cells, including prostate, breast, lung, bladder and in osteosarcoma [47, 48]. This secreted protein comprises of a WIF domain for Wnt binding activity and epidermal growth factor repeats [49]. In various cancers, such as lung, breast, gastric, colorectal, and nasopharyngeal, silencing of the WIF-1 promoter by hypermethylation is associated with Wnt signaling activation [50–54]. Kansara et al. demonstrated that in primary OS, silencing of WIF-1 was also associated with in vivo acceleration of tumorigenesis in mice [55]. Recently, we demonstrated that
re-expressing WIF-1 in OS cells resulted in inhibition of anchorage-independent growth and cellular motility. With elevated WIF-1 expression, proteolytic enzyme matrix metalloproteinases (MMP-9 and MMP-14) were suppressed from degrading extracellular matrix. In vivo, injecting WIF-1 transfected OS cells into nude mice showed reduced tumorigenesis and pulmonary metastasis [48].

Besides naturally occurring antagonists, small molecule Wnt inhibitors are also being explored as a potential means to suppress tumorigenesis. Chen et al. examined several synthetic compounds via high-stringency cell-based screening and discovered two new classes of small molecules that perturb the Wnt pathway. The first class of compound inhibits the membrane-bound acyltransferase Porcupine, which is involved in Wnt protein production. The second class nullifies the destruction of Axin, which are known suppressors of the Wnt/β-catenin signaling pathway [56].

More specifically, it has been shown that OS progression can be affected by small molecule inhibitors that disrupt the Wnt/β-catenin pathway. Previous research on the natural compound curcumin showed an inhibitory effect against β-catenin/Tcf signaling amongst several cancer cell lines [57]. Hallet et al. found that PKIF118-310 (β-catenin/TCF inhibitor II) given to breast tumor-bearing syngeneic mice arrested tumor growth in vivo [58]. In OS, Leow et al. revealed that both curcumin and PKIF118-310 suppressed both intrinsic and activated β-catenin/Tcf transcriptional activities using luciferase reporter assays. They also showed significant reduction of nuclear β-catenin and inhibitory effects on OS cell migration and invasion in a dose-dependent manner. These anticancer effects correlated with decreased expression of downstream targeted oncogenes, such as cyclin D1, c-Myc, and survivin [59]. Other small molecule inhibitors, targeting Met, such as PF2362376 (targeting canine OS cell lines) and STA-1474 (heat-shock protein 90 inhibitor targeting both human and canine OS cell lines) have also shown to decrease proliferation and decrease phosphorylation of both Met and PKB/AKT [60, 61].

Grandy et al. recently revealed another small molecule inhibitor of Wnt via the PDZ domain of dishevelled [62]. Dishevelled (dvl) is an essential component of the Wnt signaling pathway, which transduces Wnt signals from the Frizzled receptor to downstream targeted components. Through structure-based ligand screening and NMR spectroscopy, these investigators were able to discover a small molecule inhibitor (3289-8625) with an affinity to the PDZ domain of dvl. It was shown to suppress the tumorigenesis of prostate cancer PC-3 cells, decrease Wnt signaling in the hyaloid vessel system, and may prove to have similar affects in OS cells.

Sclerostin is yet another glycoprotein that is known to antagonize the Wnt/β-catenin signaling in osteoblasts by binding to LRP5/LRP6 and subsequently inhibiting osteoblast differentiation, activity, and survival [63, 64]. The SOST gene encodes for sclerostin, and its inhibition has been an area of interest for treatment of osteoporosis [65, 66].
Controversy of Inactivity of Wnt/β-Catenin Pathway in High-Grade OS

There is some controversy over the impact of Wnt/β-catenin pathway in high-grade osteosarcoma. Unlike previous data, Cai, et al. in 2010 published results suggesting that loss of Wnt/β-catenin pathway activity may contribute to osteosarcoma proliferation [67]. Nuclear β-catenin rather than cytoplasmic β-catenin was examined in osteosarcoma biopsies/cell lines and osteoblastomas by immunohistochemistry. Nuclear β-catenin was not detected in 90% of the OS biopsies and cell lines and the rest of the cases showed weak nuclear staining. After treating OS cells with GSK3β inhibitor (Wnt pathway activator), immunofluorescence β-catenin nuclear staining was positive in all cell lines and cellular proliferation rates were reduced. These investigators noted that only nuclear staining, and not membranous/cytoplasmic staining of β-catenin, can determine the degree of Wnt activity, since it is within the nucleus that transcription occurs for target gene expression. On the contrary, other groups such as Goentoro et al. demonstrated that the fold change, and not absolute level of β-catenin, determines the impact of Wnt activity and transcriptional changes [68]. With limitations of in vitro models, the theory from Cai et al. has yet to be proven within the context of an in vivo environment.

Targeting Noncanonical Wnt Pathways (β-Catenin-Independent Pathways)

Besides the canonical pathway, Wnt has been known to affect β-catenin-independent pathways as well, including Wnt/calcium, Wnt/Rho GTPase, and Wnt/JNK pathways [10]. Over the past two decades, more noncanonical Wnt pathways have been described, although they are less understood and are initiated by Wnt/FRZ signaling, rather than β-catenin transcriptional function. These signals are transduced via Frizzled family receptors and co-receptors ROR2 and RYK [69]. In the Wnt/calcium pathway, Wnt5a/FRZ-2 modulates the calcium-sensitive proteins, calcium/calmodulin-dependent kinase II and protein kinase C, thus increasing the intracellular calcium flux [70]. Wnt/FRZ activates cyclic GMP-specific phosphodiesterase (PDE6) leading to depletion of cellular cGMP and inactivation of protein kinase G (PKG), and subsequently causing increase intracellular calcium concentration. The calcium-dependent effector molecules of this pathway are Nemo-like kinase (NLK) and nuclear factor of activated T cells (NFAT). The NLK inhibits TCF/β-catenin signaling via phosphorylation of TCF/LEF family transcription factors, while the NFAT inhibits ventral patterning in Xenopus, respectively [71–73].

The Wnt/planar cell polarity (PCP) pathway, consisting of Wnt5a and Wnt11, initiates signaling through its interaction with frizzled (Fz), activating dishevelled (Dvl) and forming Dvl/effector complexes [71, 74, 75]. The Dvl downstream
PATHWAY, INCLUDING BOTH RAS HOMOLOG GENE FAMILY A (RHOA) AND JUN KINASE (JNK),
REGULATES ACTIN CYTOSKELETON, CELL MOBILITY, AND ADHESION [9, 76]. IT IMPACTS TEMPORAL
AND SPATIAL CONTROL OF EMBRYONIC DEVELOPMENT SEEN IN BOTH XENOPUS EMBRYOS AND
CUTICULAR HAIRS IN DROSOPHILA.

THE JNK PATHWAY IS ALSO A MEDIATOR OF NONCANONICAL WNT SIGNALING WHICH IS
ACTIVATED VIA WNT-ROR2 SIGNALING. BY USING siRNA TO SUPPRESS WNT5A OR ROR2,
ENOMOTO ET AL. DEMONSTRATED REDUCED INVASIVENESS AND INVADOPODIA FORMATION IN
OS CELLS [77].

WNT/B-CATENIN SIGNALING AND STEM CELLS

THE WNT/β-CATENIN PATHWAY NOT ONLY HAS A ROLE IN TUMORIGENESIS BUT HAS ALSO BEEN
SUGGESTED TO EXERT DIVERSE REGULATORY EFFECTS ON CANCER STEM CELLS (CSC) [78]. STEM
CELLS IN GENERAL ARE DEFINED AS HAVING THE ABILITY TO SELF-RENEW ALONG WITH CREATING
SPECIALIZED CELLS. SEVERAL GROUPS OF INVESTIGATORS HAVE EXAMINED THE WNT PATHWAY
AND ITS EFFECTS ON SPECIFIC STEM CELL FUNCTIONS [6]. AS EARLY AS THE 1990S, KORINEK
ET AL. DEMONSTRATED THE ASSOCIATION BETWEEN MUTATED TCF4 AND SUBSEQUENT DEPLE-
TION OF INTESTINAL STEM CELLS. STUDIES ON THE ROLE OF STEM CELLS IN HAIR FOLLICLE FORM-
ATION HAVE SUGGESTED THAT WNT INHIBITORS PLAY A PROMINENT ROLE IN REGULATING THE STEM
CELL MICROENVIRONMENTS [79]. THE TRANSGENIC OVEREXPRESSION OF LEF1 RESULTED IN NOT
ONLY FOLLICLE STEM CELL GROWTH BUT ALSO DIFFERENTIATION OF THE HAIR LINEAGE [80].

IN OS CELL LINES, TIRINO ET AL. IDENTIFIED A SUBPOPULATION OF CD133+ CELLS WITH
SELF-RENEWAL PROPERTIES, HIGHER PROLIFERATION, SPHERICAL FORMATION, AND EXPRESSION
OF THE STEM CELL-ASSOCIATED GENE OCT3/4 [81]. IN ADDITION, ELEVATED ALDEHYDE DEHYDRO-
GENASE (ALDH) ACTIVITY IN NORMAL STEM CELLS AND SOLID TUMOR CSC HAS LED TO THE USE
OF ALDH AS A MEANS OF IDENTIFYING CSC IN SARCOMAS. WANG ET AL. FOUND THAT OS CELL
LINES CONTAINING A SUBPOPULATION OF CELLS WITH HIGH ALDH ACTIVITY POSSESS INCREASED
TUMORIGENIC CAPACITY, PROLIFERATIVE CAPACITIES, SELF-RENEWAL, AND EXPRESSION OF STEM
CELL MARKERS [82].

THERAPY AGAINST WNT TARGET GENES IN OSTEOSARCOMA

GIVEN AN ABUNDANCE OF DATA SUGGESTING WNT/β-CATENIN INVOLVEMENT IN TUMORIGENESIS,
 THERE IS A NEED TO DISCOVER WAYS TO MITIGATE THE WNT TRANSCRIPTIONAL ACTIVATION [29, 83].
SEVERAL STRATEGIES HAVE BEEN PROPOSED TO EXPLOIT THE WNT PATHWAY FOR CANCER THERAPY
[22, 84, 85]. THE CHALLENGE TO SOME OF THESE STRATEGIES IS THAT THE WNT PATHWAY IS A
VAST NETWORK THAT ALSO REGULATES NORMAL CELL FUNCTIONS, TISSUE REGENERATION, AND STEM
CELL DIFFERENTIATION. DEPENDING ON HOW THIS PATHWAY IS TARGETED (EXTRACELLULAR,
CYTOPLASMIC, NUCLEAR), DETRIMENTAL SIDE EFFECTS MAY BE INCURRED.

TARGETING THE WNT/β-CATENIN SIGNALING AT THE EXTRACELLULAR LEVEL IS A STRATEGY THAT
FOCUSES ON SECRETED WNT ANTAGONISTS, INCLUDING WIF-1, DKK, AND sFRPs. RESTORING
the expression of these antagonists in the antagonist-deficient tumors may prove to be helpful in reducing the proliferation of OS cells. Another strategy that simulates the mechanisms of Wnt antagonists is to create anti-Wnt monoclonal antibodies that can induce apoptosis of OS cells by blocking Wnt-Frizzled interaction. Therapeutic monoclonal antibodies against Wnt-1 and Wnt-2 have demonstrated inhibition of Wnt signaling and suppression of tumor growth in hepatocellular carcinoma and melanoma, respectively [86, 87]. This model can also be explored and potentially replicated for OS. Besides the extracellular level, we can aim to target the cytoplasmic components, such as β-catenin-binding domain of APC, for tumor suppression. Shih et al. showed that in colon cancer cells, re-expression of a recombinant adenovirus with APC (with known β-catenin binding repeats) can inhibit nuclear translocation of β-catenin as well as β-catenin/Tcf-mediated transactivation [88]. At the nuclear level, targeting the β-catenin/Tcf transcriptional activity along with key downstream mediators, such as c-Myc, cyclin D1, survivin, needs to be further explored. In OS, the hepatocyte growth factor receptor c-Met is another Wnt target gene that is frequently overexpressed. Recent evidence suggests that c-Met can transform normal human osteoblasts into OS cells [44]. Therefore, c-Met is a candidate Wnt-related gene that can explored for OS therapeutics.

Nonsteroidal anti-inflammatory drugs (NSAIDS) have been studied and thought to impact the Wnt pathway by inhibiting the accumulation of prostaglandin E2, which ultimately decreases degradation of the β-catenin. NSAIDs have mainly shown chemopreventative effects against colon cancer [89, 90]. Xia et al. demonstrated the effects of celecoxib (cyclo-oxygenase-2 inhibitor) on inhibiting β-catenin-dependent survival of human OS cell line (MG-63). Not only did β-catenin protein decrease in the cytosol and nucleus following celecoxib treatment, but there was also a significant reduction of the Wnt target gene c-Myc and CCND1 [91]. As mentioned previously, using small molecule inhibitors identified by high-throughput screens can be helpful to make an impact on OS therapy. These inhibitors are known to target β-catenin/TCF antagonists, transcriptional co-activator modulators along with the PDZ domain of Dvl [92].

Conclusion

Given the complexity of the Wnt signaling network, it is not an easy task to determine which group of components is responsible for the interactions that drives OS progression. With a large permutation of Wnt signaling (given 19 human Wnt family members, 11 human Fz receptors, 4 human Dkks, along with multiple regulatory proteins), it is challenging to identify specific combinations of interaction that may be clinically relevant to OS. Although our understanding of the Wnt pathway has improved over the last few decades, there are certainly many regulatory mechanisms yet to be discovered. From this standpoint, the Wnt pathway offers a plethora of targeting potentials for cancer drug development. By understanding the pathophysiology of aberrant Wnt signaling in OS, we are getting closer to designing much more precise and personalized treatment for this disease.
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