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28

Dysregulation of Wnt Signaling in Breast Cancer

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1. Introduction

The Wnt signaling pathway is a significant pathway that consists of two sub-categories: (1) the canonical Wnt/β-catenin signaling pathway and (2) the non-canonical Wnt signaling pathway. A well-programmed crosstalk exists between canonical and non-canonical Wnt pathways, which enable them to regulate stem cell renewal, cell proliferation, migration, and differentiation. Wnt signals are transduced via the interaction between cell surface receptors and secreted Wnt ligands and Wnt agonists, which subsequently activate downstream proteins that regulate cytoskeletal rearrangement, transcription, and cell cycle. Aberrant Wnt signaling is involved in the development of a variety of cancers, including breast cancer.

Breast cancer is the most invasive form of cancer in women and is the second leading cause of death in women in industrialized nations. Three distinct biomarkers including the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER-2) are used to determine breast cancer therapy (Nguyen et al., 2010). Anti-ER and HER2 therapies have benefitted a subset of breast cancer patients (Carter et al., 1992; Arteaga, 2003). However, the genetic diversity of this disease varies greatly in that the pathological hallmarks are distinct in each case. Recent discoveries in stem cell research have shown that breast cancer stem cells may be responsible for the aggressiveness of some breast cancers and may contribute to their resistance to chemotherapy and radiation treatment (Diehn et al., 2009; Li et al., 2008b). Wnt signaling is important in stem cell biology and can lead to tumor formation when aberrantly activated. Therefore, it is essential to understand the intrinsic mechanisms of the Wnt signaling pathway to elucidate candidate proteins within this pathway that may serve as potential targets for breast cancer therapy.

2. The Wnt signaling pathways

At the heart of the canonical Wnt pathway is the stabilization of cytosolic β-catenin, which enters the nucleus and activates Wnt target genes by binding to transcription factors of the T-cell factor and the lymphoid enhancing factor (TCF/LEF) family (Kohn and Moon, 2005; McDonald et al., 2009). Wnts are secreted glycoproteins that can bind to low-density lipoprotein receptor-related protein 5 (LRP5) or LRP6 and seven transmembrane receptors

of the Frizzled (Fz) family. In the absence of Wnt ligands, β-catenin is phosphorylated by a multi-protein complex that marks it for ubiquitination and degradation by the proteasome (Fig. 1A). This β-catenin degradation complex contains the adenomatous polyposis coli (APC) tumor suppressor, the scaffold protein Axin, the glycogen synthase kinase 3β (GSK3β), and the casein kinase 1 (Ck1). The action of this complex is inhibited upon binding of Wnt to its receptors (Fig. 1B). A variety of Wnt/β-catenin target genes have been identified, which include those that regulate cell proliferation, embryonic developmental and tumor progression (Kohn and Moon, 2005; McDonald et al., 2009).

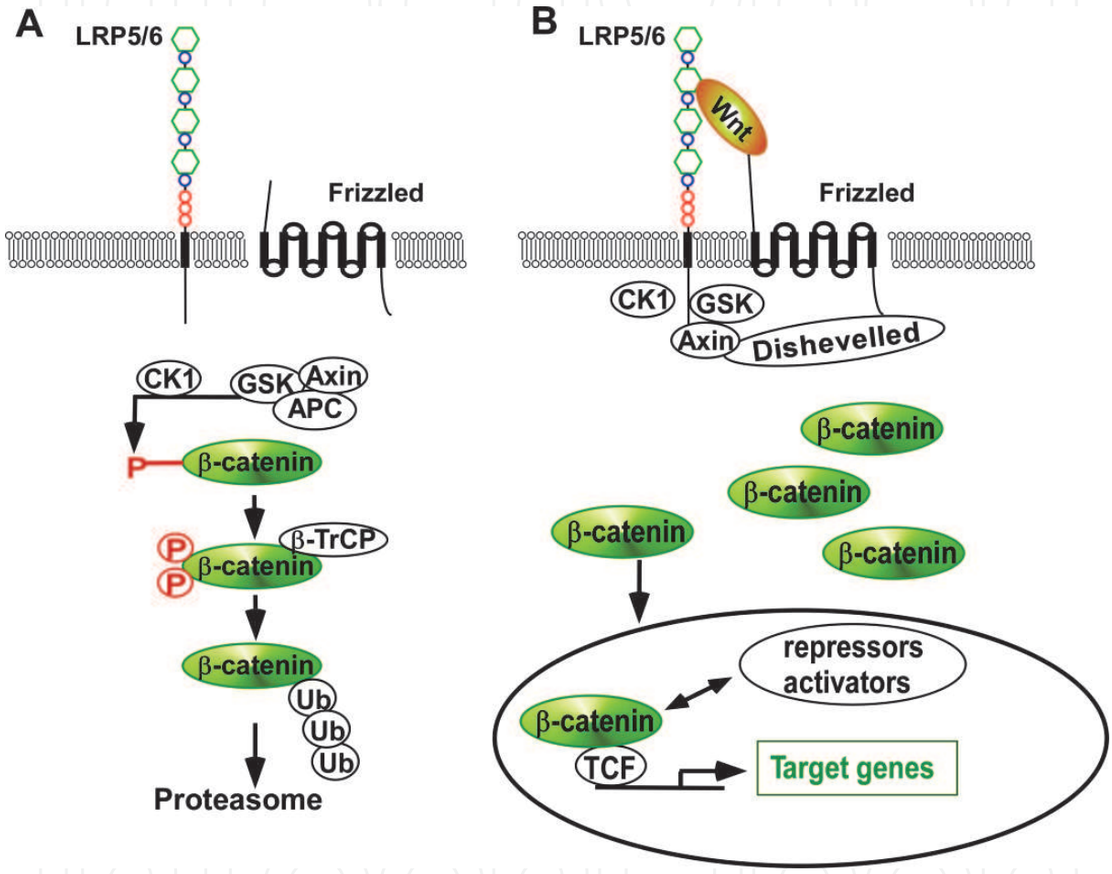


Fig. 1. The canonical Wnt signaling cascade, simplified. (A) In the absence of interaction between Wnts and receptors, β-catenin levels are efficiently regulated by a complex containing APC, axin, and GSK3β. This complex promotes phosphorylation of β-catenin by Ck1 and GSK3β. Phosphorylated β-catenin becomes multi-ubiquitinated (Ub) and subsequently degraded by the 26S proteasome. (B) In the presence of Wnts, phosphorylation and degradation of β-catenin are blocked which allows the association of β-catenin with TCF transcription factors. The TCF:β-catenin complexes bind to DNA and activate Wnt target genes together with various transcriptional repressors or activators.

The non-canonical Wnt signaling pathway, which operates independently of downstream β-catenin activation, consists of the Wnt/Ca^{2+}, Wnt/Planar Cell Polarity (PCP), and Wnt/ROR2 pathway. There are several excellent reviews that discuss the non-canonical Wnt signaling pathway extensively (Kohn and Moon, 2005; Siefert and Mlodzik, 2007; Wang and Nathans,

2007b; Schulte, 2010). The Wnt/Ca^{2+} and the Wnt/PCP pathways are activated via the interaction of Wnt5a and Wnt11 with their Fz co-receptor. This interaction elicits downstream increases in intracellular Ca^{2+} flux (Wnt/Ca^{2+}) and Dishevelled (Dvl)-mediated downstream activation of Rac, Rho, and Jun N-terminal kinase (Wnt/PCP), which ultimately regulate cell motility and orientation. The Wnt/ROR2 pathway requires the interaction of Wnt-5a with ROR2, which activates downstream signaling events that regulate cell motility. Some non-canonical Wnt signaling pathways, including the Wnt/ Ca^{2+} and the Wnt/ROR2 pathways, antagonize canonical Wnt signaling (discussed in more detail below).

2.1 Wnt receptors frizzled protein and LRP5/6

The frizzled (Fz) gene product, originally discovered in *D. melanogaster,* is required for the development of cuticle wing hairs (Vinson and Adler, 1987; Vinson et al., 1989). The Fz receptor consists of 10 mammalian isoforms that contain an N-terminal signal peptide, an extracellular cysteine-rich domain (CRD), a seven-pass transmembrane domain, and an intracellular C-terminal domain, which contains the KTxxxW motif. The CRD of the Fz receptor interacts with the homologous CRD of Wnt proteins (Schulte, 2010). The Fz receptor also interacts with R-spondin (Kazanankaya et al., 2004; Kim et al., 2005; Nam et al., 2006; Wei et al., 2007), Norrin (Smallwood et al., 2007), and secreted frizzled-related proteins (Rattner et al., 1997; Kawano and Kypta, 2003; Bafico et al., 1999). The Fz receptor transduces Wnt signals in a solitary manner or through collaboration with other co-receptors. The Fz receptor forms a ternary complex with Wnt and LRP5/6 to activate the canonical Wnt signaling pathway, which activates β-catenin transcriptional activity (Tamai et al., 2000; Wehrli et al., 2000).

Experiments performed in Drosophila (Wehrli et al., 2000), Xenopus (Tamai et al., 2000) and mice (Pinson et al., 2000) demonstrated that LRP5/6 (termed Arrow in Drosophila) acts as a co-receptor for Wnts, which interact with both Fz and LRP5/6 to activate the canonical Wnt signaling pathway. LRP5/6 appears to transduce the Wnt/β-catenin signal by binding and recruiting Axin to the cell membrane (Mao et al., 2001a; Tolwinski et al., 2003; Liu et al., 2003; Tamai et al., 2004). It has been demonstrated that a PPSPXS motif, which is reiterated five times in the LRP6 intracellular domain and is conserved between LRP5, LRP6, and their Drosophila homolog, Arrow, is sequentially phosphorylated by GSK3β and CK1 upon Wnt stimulation (Tamai et al., 2004, Brennan et al., 2004; Zeng et al., 2005; Davidson et al., 2005). Phosphorylation of the PPSPXS motif provides a docking site for Axin binding (Tamai et al., 2004; Brennan et al., 2004; Zeng et al., 2005; Davidson et al., 2005).

LRP5 and LRP6 are two members of the expanding low density lipoprotein receptor (LDLR) family. The mesoderm development protein (Mesd) and the receptor associated protein (RAP) are two specialized molecular chaperones for members of the LDLR family. Mesd is particularly important for the Wnt co-receptors LRP5 and LRP6, while RAP is critical for other members of the LDLR family such as LRP1 and LRP2 (Culi and Mann, 2003; Hsieh et al., 2003; Culi et al., 2004; Li et al., 2005c; Koduri et al., 2007; Li et al., 2006a). Mesd was discovered due to its requirement for the folding of LRP5 and LRP6 (Culi and Mann, 2003; Hsieh et al., 2003). In mice, the consequences of Mesd deficiency resemble what is seen in Wnt3-deficient mutants (Hsieh et al., 2003). Similar to other ER chaperones, Mesd also carries an endoplasmic reticulum (ER) retention signal (KDEL in Drosophila, REDL in mammals) at its carboxyl terminus and localizes to the ER (Culi and Mann, 2003). All members of the LDLR family have at least one six-bladed β-propeller domain, which is followed by an epidermal growth factor (EGF) repeat (Bu, 2009). Mesd is specifically

required for the maturation of these β-propeller/EGF modules through the secretory pathway (Culi et al., 2004). In the absence of Mesd, LRP5 and LRP6 form aggregates in the ER and fail to reach the cell surface (Culi and Mann, 2003; Hsieh et al., 2003; Culi et al., 2004; Li et al., 2005c; Koduri et al., 2007; Li et al., 2006a).

LRP5/6 does not contain CRD domains, but Wnt binds to their β-propeller domains, which are sufficient to transduce Wnt signals (Hey et al., 1998; Liu et al., 2009; Bourhis et al., 2010). Although controversial, the receptor tyrosine kinase-like orphan receptors, ROR1/2 and RYK, can autonomously transduce Wnt signals or serve as co-receptors with Fz to transduce Wnt signals. Similar to the Fz receptor, ROR1/2 possesses a CRD that binds to Wnt proteins, which stimulate receptor dimerization and subsequent activation (Liu et al., 2008; Minami et al., 2010). ROR2 forms a complex with Fz, Wnt, and Cthrci, a Wnt co-factor, to activate the Wnt/Planar Cell Polarity pathway (Yamamoto et al., 2008). Conversely, another study showed that ROR2 cooperates with Fz2 to mediate Wnt-3a-induced β-catenin activation (Li et al., 2008a). Similar to the ROR1/2 kinase, the RYK tyrosine kinase can form a complex with Fz and Wnt-3a to activate downstream β-catenin signaling (Lu et al., 2004) or it can interact with Wnt-5a independent of Fz cooperation to activate non-canonical Wnt signaling (Li et al., 2009). These results suggest that the Fz receptor can act autonomously or in cooperation with other receptors to regulate canonical and non-canonical Wnt signaling pathways.

2.2 Wnt agonists

The mammalian proto-oncogene *int-1* and its *D. melanogaster* counterpart, w*ingless*, were discovered prior to the Fz receptors (Nusse and Varmus, 1982; Cabrera et al., 1987; Rijseuijk et al., 1987). The nomenclature was later changed to Wnt, which is an acronym derived from *wingless* and *int-1* (Nusse et al., 1991). Wnts are highly conserved secreted glycoproteins that regulate cell growth and homeostasis in a variety of organ systems. This family of proteins consists of 19 cysteine-rich members that serve as ligands for the Fz receptor (Schulte, 2010). Members of this family can be classified based on their ability to transform epithelial cells. For example, Wnt-1, Wnt-2, Wnt-3, and Wnt-3a are considered to be transforming Wnts; Wnt-6 and Wnt-7a are weakly transforming Wnts; Wnt-4, Wnt-5a, Wnt-5b, and Wnt-7b are non-transforming Wnts (Shimizu et al., 1997). Wnt proteins are palmitoylated (Takada et al., 2006) prior to secretion from the cell via the Wntless/Evi seven-pass transmembrane protein (Banziger et al., 2006; Bartscherer et al., 2006). Following secretion from cells, Wnt proteins interact with the CRD of 10 known mammalian Fz receptors (Schulte, 2010) as well as the extracellular domain of the LRP5/6 receptor (Pinson et al., 2000; Tamai et al., 2000; Wehrli et al., 2000) to activate the canonical Wnt/β-catenin signaling pathway. Wnt proteins also activate non-canonical Wnt signaling via their interaction with Fz (Schulte, 2010), ROR1/2 (Liu et al., 2008; Minami et al., 2010; Li et al., 2008a; Yamamoto et al., 2008), and RYK (Lu et al., 2004; Li et al., 2009). The interaction of Wnt proteins with these receptors enables them to regulate a variety of cellular events including differentiation, proliferation, migration, and tumorigenesis.

R-spondins

R-spondins (Rspo) are a family of secreted proteins that activate Wnt/β-catenin signaling. This family consists of four members (Rspo1-4) that share 40-60% homology and are structural similar (Kazanskaya et al., 2004). Rspo proteins contain a signal peptide at the N-terminus, which is followed by a highly conserved CRD and a thrombospondin motif. The

C-terminus is of varying length between the different isoforms of Rspo proteins, but it is positively charged (Kim et al., 2006). Rspo proteins are expressed simultaneously with Wnt proteins during mouse development, suggesting that they may play an important role in facilitating Wnt/β-catenin signaling (Nam et al., 2006). The action of Rspo proteins on Wnt/β-catenin signaling requires Wnt receptors Fz and LRP5/6; however, the direct binding between Rspo and LRP5/6 is still controversial (Kazanankaya et al., 2004; Kim et al., 2005; Nam et al., 2006; Wei et al., 2007; Li et al. 2010). Furthermore, unlike the Wnt ligands, Rspo proteins do not form a ternary complex with Fz and LRP6 (Nam et al., 2006), suggesting that the mechanistic action of Rspo on Wnt/β-catenin signaling activation is not identical to that of Wnt. One plausible mechanism is that Rspo blocks Dkk1-mediated antagonization of Wnt/β-catenin signaling by interfering with the interaction of Dkk1 with the Kremen and LRP6 receptors (Kim et al., 2008).

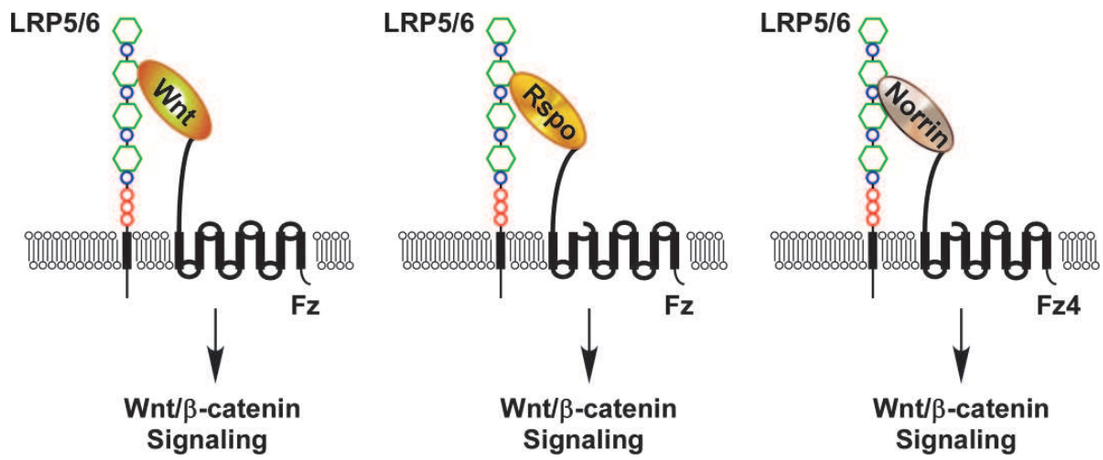


Fig. 2. Secreted Wnt agonists. Wnts are the primary agonists of Wnt/β-catenin signaling by binding to LRP5/6 and Fz to form a complex with LRP5/6 and Fz. Both Rspos and Norrin may act similarly to Wnt, but Norrin specifically binds to Fz4.

Norrin

Norrie disease is a severe X-linked trait that causes impaired retinal development. The clinical features of this malady include blindness, mental retardation, deafness, microcephaly, and hypogonadism (Hendrickx and Leyns, 2008). Mutations in the Norrie disease protein (Norrin) contribute to the pathology of this disease (Berger et al., 1992; Chen et al., 1992). Norrin specifically interacts with the CRD of Fzd4 and the extracellular domain of LRP5/6 receptors, which activates Wnt/β-catenin signaling (Xu et al., 2004; Smallwood et al., 2007). These findings are interesting because Norrin does not share any structural homology with Wnts (Xu et al., 2004). These results are evident of the diverse and complex nature of the regulation of Wnt signaling to promote development and tumor progression.

2.2.1 Wnt antagonists

Dickkopf

Dickkopf (Dkk; German, big head, stubborn) proteins are a family of secreted glycoproteins that function as regulators of Wnt signaling. Dkks consists of four isoforms in vertebrates

(Dkk1-4). Dkk1, 2, and 4 contain a Dkk_N domain (also known as CRD1) near the N-terminus and a colipase fold (also known as CRD2) near the C-terminus. Dkk3 also contains a Dkk_N domain, but the N-terminal soggy domain and the C-terminal colipase fold flank the Dkk_N domain (Niehrs, 2006). The colipase fold is necessary for Dkk1, Dkk2, and Dkk4 to inhibit Wnt signaling (Brott and Sokol, 2002; Li et al., 2002; Mao and Niehrs, 2003). The structural divergence of Dkk3 from the other three Dkk family members is a contributing factor to its functional divergence (Glinka et al., 1998; Krupnik et al., 1999; Mao et al., 2001b). Dkk1 functions solely as an inhibitor of canonical Wnt signaling (Glinka et al., 1998). Dkk1 antagonizes Wnt/β-catenin signaling by binding directly to the YWTD type β-propeller domain of LRP6 and prevents Fz-LRP6 complex formation in response to Wnt. Furthermore, Dkk1 interacts with another transmembrane protein, Kremen. The LRP6-Dkk1-Kremen complex is internalized, thus removing LRP6 from the cell surface (Bafico et al., 2001; Mao et al., 2001b; Semenov et al., 2001; Davidson et al., 2002; Mao et al., 2002; Mao and Niehrs, 2003). Dkk2 can activate Wnt/β-catenin signaling by interacting with Fz (Wu et al., 2000) or LRP6 (Brott and Sokol, 2002). Conversely, depending on the cell type, Dkk2 can inhibit Wnt-Fz-mediated β-catenin activation in the absence of LRP5/6 (Wu et al., 2000; Li et al., 2002; Mao and Niehrs, 2003; Caricasole et al., 2003). Furthermore, Dkk2 can inhibit LRP6 mediated Wnt/β-catenin signaling in the presence of the Kremen2 receptor by inducing the internalization of LRP6 (Mao and Niehrs, 2003). The dichotomy between Dkk1 and Dkk2 regulation of canonical Wnt signaling is due to the structure and function of the two CRDs of Dkk1 and Dkk2. The colipase fold of Dkk1 and Dkk2 can activate LRP6-mediated β-catenin activation, and the Dkk_N domain inhibits the action of the colipase fold of Dkk1, but is neutral on Dkk2 (Li et al., 2002; Brott and Sokol, 2002). Therefore, the structural divergence of the Dkk family of proteins enables them to regulate Wnt/β-catenin signaling differentially.

Schlerostin

Schlerosteosis is an autosomal recessive disorder that causes severe skeletal outgrowth in the skull and mandible. Mutations in the schlersotin (SOST) gene, which is located on chromosome 17q11.2, contribute to the pathology of this disease (Balemans et al., 2001; Brunkow et al., 2001). The SOST gene encodes a 24 kDa secreted glycoprotein that contains a cysteine knot-like domain (Balemans et al., 2001; Brunkow et al., 2001). SOST binds to LRP5/6 and inhibits the interaction of Wnts with LRP5/6, thus inhibiting Wnt/β-catenin signaling (Li et al., 2005b; Ott et al., 2005; Semenov et al., 2005; Semenov and He, 2006). Furthermore, SOST fails to interact with LRP5 carrying the G170V mutation, which is observed in patients with high bone density (Ellies et al., 2006; Semenov and He, 2006).

Secreted frizzled-related proteins

The secreted frizzled related proteins (sFRPs) are soluble secreted proteins (sFRP1-5) that interact with Wnt and Fz proteins, which prevent the binding of Wnts to the Fz receptors. The sFRPs are structurally related to the Wnt-binding domain of the Fz receptor in that their N-terminal domain, which contains the CRD, shares 30-50% sequence homology with that of the Fz receptors (Rattner et al., 1997; Kawano and Kypta, 2003). sFRPs antagonize Wnt signaling by interacting with Wnt ligands via the CRD (Lin `et al., 1997). Furthermore, Uren et al. (2000) showed that mutations in the CRD of sFRP1 abrogate its interaction with *Drosophila* Wg. The same group also showed that the C-terminal domain of sFRP1 interacts with Wnt proteins and that low and high levels of sFRP1 potentiates and inhibits Wg

signaling, respectively (Uren et al., 2000). sFRP1 can dimerize or interact with the Fz receptor to form a non-functional complex (Bafico et al., 1999), suggesting that the mechanistic actions of sFRP-induced inhibition of Wnt signaling are broad.

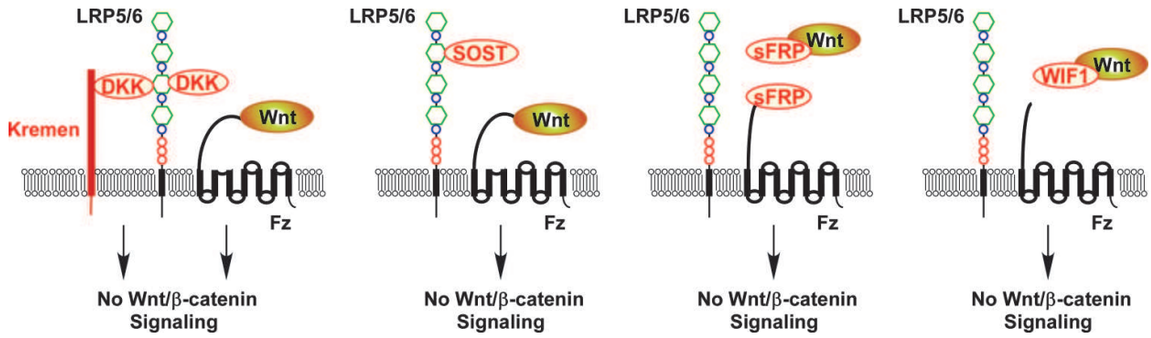


Fig. 3. Secreted Wnt antagonists. By binding to LRP5 or LRP6, Dkk and Sclerostin disrupt Wnt-induced Fz-Wnt-LRP complex and inhibit Wnt/β-catenin signaling. Furthermore, Dkk interacts with another transmembrane protein, Kremen. The LRP-Dkk-Kremen complex is internalized, thus removing LRP5/6 from the cell surface. WIF1 and sFRPs function as inhibitors of Wnt/β-catenin signaling by directly binding to Wnt or both Wnt and Fz.

Wnt inhibitory factor-1

Wnt inhibitory factor-1 (WIF1), another secreted protein that binds to Wnt ligands, is highly conserved in vertebrates, and it was originally discovered as an expressed tag from the human retina (Hsieh et al., 1999). WIF1 consists of an N-terminal signal sequence, a unique WIF domain, and five EGF-like repeats (Hsieh et al., 1999). WIF1 is structurally related to the extracellular domain of RYK (Patthy, 2000; Liepinsh et al., 2006). WIF1 can directly bind Wnt proteins to inhibit Wnt/β-catenin signaling (Hsieh et al., 1999). Furthermore, WIF1 can inhibit Wnt-3a-mediated β-catenin/TCF/LEF transcriptional activity (Surmann-Schmitt et al., 2009) and regulate its own expression through a negative feedback mechanism (Licchesi et al., 2010).

3. Dysregulation of Wnt signaling in breast cancer

Although genetic mutations of APC or β-catenin are rarely observed in certain cancers (e.g. breast cancer), there is compelling evidence that implicates aberrant Wnt/β-catenin signaling in breast cancer development. For example, only 6% of breast tumors contain mutations in the APC gene (Jonsson et al., 2000), which is mutated or deleted in 80% of colon tumors (Kinzler and Vogelstein, 1996). No mutations occur in the amino terminal of β-catenin, which contains the CK1 and GSK3β phosphorylation sites (Jonsson et al., 2000). However, elevated β-catenin expression in breast cancer tissue correlates with a decreased survival rate of breast cancer patients (Jonsson et al., 2000; Dolled-Filhart et al., 2006; Lopez-Knowles et al., 2010; Zardawi et al., 2009; Khramtsov et al., 2010). Cyclin D1 levels are also elevated in 50% of patients with breast cancer (Gillet et al., 1994; Bartkova et al., 1994). Indeed, the cyclin D1 promoter region contains a TCF4-binding site, which is regulated by β-catenin (Tetsu and McCormick, 1999; Shtutman et al., 1999). Elevated β-catenin expression

(not due to CTNNB1 activating mutations) and activation is also associated with triple-negative breast cancer and poor clinical prognosis (Geyer et al., 2011). Since elevated expression of β-catenin and subsequent aberrant activation of Wnt/β-catenin signaling in breast cancer development is not due to genetic mutations in APC and β-catenin, dysregulation of this pathway likely occurs at the cell surface or at the level of epigenetic regulation.

3.1 Wnt agonists in mammary gland development and breast cancer

There is compelling evidence that Wnt ligands are involved in the activation of the canonical Wnt signaling pathway during breast cancer development. Wnt1 and Wnt2, the founding members of the Wnt gene family (Nusse and Varmus, 1982; Peters et al., 1983), are tumorigenic. Furthermore, fusion of the Wnt1 allele with the MMTV long terminal repeat and subsequent generation of MMTV-Wnt1 transgenic mice causes mammary gland hyperplasia and increases adenocarcinomas in mice (Tsukamoto et al., 1988). The transforming capability of Wnt genes in mammary epithelial cells is also increased following the insertion of the MMTV (Blasband et al., 1992; Wong et al., 1994). Additionally, the upregulation and transforming capability of several Wnt genes occur in human primary tumors (Dale et al., 1996; Lejeune et al., 1995; Bui et al., 1997). Recently, Oloumi et al. (2010) reported that the rate of mammary tumor growth is significantly increased in Wnt1 and integrin-linked kinase double transgenic mice. Moreover, crosstalk between the Wnt1 and integrin-liked kinase pathways upregulate FOXA1 and estrogen receptor transcription factors, which accelerate breast cancer development (Oloumi et al., 2010). These results implicate Wnt1 in breast cancer development and suggest that Wnt1 may serve as a potential therapeutic target to combat certain forms of breast cancer. Indeed, RNA inhibition of Wnt1 mRNA expression or inhibition of Wnt1 with an anti-Wnt1 antibody induces apoptosis in a variety of cancer cell lines (e.g. breast cancer) that overexpress Wnt1 (He et al., 2004). Other Wnt proteins, including Wnt10b and Wnt11, are also implicated in breast cancer tumorigenesis. A previous study showed that Wnt10b overexpression induced by the MMTV promoter facilitates mammary gland development and tumor formation in male and female mice (Lane and Leder, 1997). A recent study also showed that the estrogen-related receptor-α and β-catenin synergistically induce the expression of Wnt11, which facilitates breast cancer migration (Dwyer et al., 2010). This study is compelling because it suggests that combinational therapy could utilize synthetic drugs to target the estrogen-related receptor-α/β-catenin complex and antibodies to target Wnt11 in order to treat estrogen-dependent breast cancer.

Increasing evidence suggests that non-canonical Wnt signaling also plays a role in mammary gland and breast cancer development. Roarty and Serra (2007) showed that Wnt-5a is necessary for normal ductal extension and branching. According to previous studies, Wnt-5a activates the Wnt/Ca^{2+} signaling pathway, which antagonizes canonical Wnt signaling by inhibiting the downstream transcriptional activity of β-catenin (Ishitani et al., 2003; Topol et al., 2003; Nemeth et al., 2007). However, a previous study also showed that Wnt-5a can inhibit or activate β-catenin transcriptional activity (Mikels and Nusse, 2006). This dichotomy is likely due to the availability of cell surface receptors in different cell types. Although controversial, most studies suggest that Wnt-5a likely acts as a tumor suppressor. In one study, Wnt-5a mRNA levels are upregulated 10- and 4-fold in benign and invasive tumors, respectively, compared to that in normal breast tissue (Lejeune et al., 1995).

It is possible that Wnt-5a may facilitate breast cancer tumorigenesis in a subset of breast cancers given that Wnt-5a can also activate canonical Wnt signaling and that its mRNA levels are increased in some breast tumors. However, several studies have shown that Wnt-5a levels are low in breast cancer tumors and that low Wnt-5a expression may serve as a prognostic indicator of shorter survival rates in some breast cancer patients (Jonsson et al., 2002; Dejmek et al., 2005; Leris et al., 2005). Furthermore, loss of Wnt-5a in normal mouse mammary glands increases canonical Wnt signaling and stimulates mammary tumorigenesis (Roarty et al., 2009). These results suggest that Wnt-5a is generally anti-tumorigenic and can be supported by previous studies, which showed that Wnt-5a enhances β-catenin/E-cadherin complex formation via a Ca^{2+}-dependent mechanism in human breast epithelial cells (Medrek et al., 2009) and that low Wnt-5a expression enhances migration of ductal breast epithelial cells (Jonsson and Andersson, 2001).

Although there is no direct evidence that implicates Norrin in breast cancer tumorigenesis, there is some evidence that suggests that some members of the R-spondin family of proteins may be involved in the pathogenesis of breast cancer and other forms of cancer. For example, MMTV increases R-spo2 expression in mouse mammary tumors following its insertion into the Int7 locus (Lowther et al., 2005), therefore, implicating hRspo2 in mammary tumorigenesis.

3.2 Wnt receptors in mammary gland development and breast cancer

The Wnt co-receptor, LRP5, plays an important role in mammary gland development and in breast cancer. Loss of LRP5 delays mammary gland development and mouse mammary tumor virus (MMTV)-Wnt1-induced tumor formation in mice (Lindvall et al., 2006). Furthermore, a truncated form of LRP5 (LRP5Δ), which is expressed in breast tumors and breast cancer cell lines, could be implicated in mammary gland tumorigenesis (Bjorklund et al., 2009). LRP6 also plays a pivotal role in mammary gland development and breast cancer. Mammary gland development and MMTV-Wnt1-induced mammary tumorigenesis are delayed in $LRP6^{+/-}$ mice (Lindvall et al., 2009). LRP6 expression is also upregulated in basal-like human breast cancer samples (Lindvall et al., 2009). MMTV constructs are also utilized to assess the role of Wnt receptors in mammary development and breast cancer. In fact, MMTV-LRP6 transgenic mice develop hyperplasia in their mammary glands due to LRP6-mediated Wnt/β-catenin signaling (Zhang et al., 2010). LRP6 expression is also upregulated in a variety of human breast cancer cell lines, including the basal-like cell line, MDA-MB-231 (Liu et al., 2010). Transcriptional knockdown of LRP6 mRNA in MDA-MB-231 cells significantly decreases Wnt signaling, cell proliferation, and tumor growth in SCID mouse models. Furthermore, *in vivo* administration of an LRP6 antagonist, Mesd, markedly suppressed growth of MMTV-Wnt1 tumors without causing undesirable side effects (Liu et al., 2010). These results suggest that LRP5 and LRP6 are involved in breast cancer development and that these receptors can serve as therapeutic targets for the treatment of breast cancer.

The other Wnt co-receptor, Fz, is also involved in the development of breast cancer. Previously, Saitoh et al. (2002) showed that Fz10 and Wnt2 mRNAs are synchronously upregulated by β-estradiol treatment in human breast cancer MCF-7 cells, suggesting that increased Fz10 and Wnt2 expression might stimulate breast cancer production. A subsequent study discovered that Fz1 and Fz2 levels are upregulated in advanced infiltrating ductal breast carcinoma (Milovanovic et al., 2004). Furthermore, Benhaj et al.

(2006) showed that most of the Fz receptors, except Fz9 and Fz10, are expressed in human mammary epithelial cells and most breast cancer cell lines. A recent study discovered that thiazolidinediones, which possess antitumor effects in breast cancer cells, abrogate Wnt/β-catenin signaling by negatively regulating the expression of the Wnt co-receptors, Fz1 and LRP6, in human breast cancer MDA-MB-231 and T47D cells (Wang et al., 2009). Another study showed that the anti-helminthic drug, niclosamide, targets the Fz1 receptor by inducing its internalization through endocytosis, which subsequently inhibits Wnt/β-catenin signaling (Chen et al., 2009). Overall, these results suggest that the Fz receptor may also serve as a potential target for breast cancer therapy.

3.3 Inactivation of Wnt antagonists in breast cancer

Mounting evidence suggests that the frequent occurrence of epigenetic silencing of tumor suppressor genes augments the development and progression of cancer (Ting et al., 2006). Epigenetic silencing of genes occurs via hypermethylation of CpG dinucleotides in promoter regions of genes or histone modifications (Veeck and Esteller, 2010). For example, sFRP1 mRNA is absent in invasive breast carcinomas (Suzuki et al., 2008; Ugolini et al., 1999, 2001). This is likely due to the hypermethylation of the promoter region of sFRP1 in breast carcinomas (Lo et al., 2006; Veeck et al., 2006). The promoter regions of sFRP2 and sFRP5 are also hypermethylated at a higher frequency than sFRP1 or Dkk1 in several breast cancer cell lines (Suzuki et al., 2008). Furthermore, transcriptional knockdown of sFRP1 robustly increases Wnt signaling in breast cancer cells (Suzuki et al., 2008). A recent study showed that stable overexpression of sFRP1 in human breast cancer MDA-MB-231 cells blocks canonical Wnt signaling with ensuing decreases in cell proliferation and suppression of tumor growth and metastasis in xenograft mouse models (Matsuda et al., 2009). These results suggest that sFRP1 and sFRP5 expression is essential to suppress tumor growth and metastasis. Indeed, sFRP1 hypermethylation in breast cancer tissue is associated with decreased patient survival (Veeck et al., 2006; Veeck et al., 2008). Promoter hypermethylation of sFRP2 also occurs frequently in breast cancer, but it is not associated with patient clinical outcomes (Veeck et al., 2008). Interestingly, sFRP2 is highly expressed in canine mammary tumors and tumor cell lines (Lee et al., 2003, 2004) and its levels correlate with those of β-catenin; however, there is no correlation between the levels of sFRP2 or β-catenin with that of cyclin D1. These results suggest, in part, that sFRP2 may serve as a diagnostic marker for breast cancer in humans and dogs, although the mechanistic action of increased sFRP2 expression in canine mammary tumors remains to be elucidated. Another Wnt antagonist, WIF1, is also reduced in 60% of breast carcinomas (Wissmann et al., 2003). A subsequent study supports the previous finding showing that WIF1 downregulation via hypermethylation of its promoter occurs frequently in breast cancer (Ai et al., 2006). Overall, these studies suggest that epigenetic silencing of Wnt antagonists may be a cause for aberrant Wnt/β-catenin signaling, which ultimately results in the development and progression of breast cancer.

3.4 Dkk1 in breast cancer osteolytic bone metastasis

Bone is an active tissue maintained by a balance of cellular activities. The osteoblasts are responsible for bone formation. Osteoblasts synthesize and secrete most proteins of the bone extracellular matrix (ECM) and express proteins that are necessary and sufficient to induce mineralization of the ECM. The osteoclasts are multinucleated cells responsible for bone

resorption. Importantly, the differentiation of osteoclasts is regulated by osteoblasts (Karsenty et al., 2002). Receptor activator of NF-kappaB ligand (RANKL) and macrophage-colony-stimulating factor (M-CSF), both of which are expressed by osteoblastic cells, promote osteoclast differentiation through interaction with their cognate signaling receptors (RANK and c-fms, respectively) (Lacey et al., 1998; Yasuda et al., 1998). This process is regulated by a variety of factors that are produced by osteoblasts, stromal cells, fibroblasts, and lymphocytes. Critically, the secreted decoy receptor of RANKL, osteoprotegerin (OPG), binds to and inhibits the activity of RANKL. OPG inhibits osteoclast formation both *in vitro* and *in vivo* (Simonet et al., 1997). The requirement for RANKL, RANK and OPG in the control of osteoclast formation is well established (Suda et al., 1999).

In recent years, Wnt/β-catenin signaling has been shown to play a substantial role in the control of bone development and remodeling (for review, see Krishnan et al., 2006). Analyses of patients with the *LRP5/6* gene mutations and *LRP5/6* knockout mice revealed that the Wnt coreceptors LRP5 and LRP6 play a pivotal role in bone metabolism (Boyden et al., 2002; Gong et al., 2001; Little et al., 2002; Van Wesenbeeck et al., 2003; Ai et al., 2005; Kato et al., 2002; Fujino et al., 2003; Kelly et al., 2004; van Meurs et al., 2006; Holmen et al., 2004; Kokubu et al., 2004). Loss-of-function mutations of human *LRP5* are associated with the recessive disorder osteoporosis-pseudoglioma syndrome, whereas gain-of-function mutations of human *LRP5* (e.g., G171V) reduce binding affinity of LRP5 for DKK1 and cause high bone mass (HBM) diseases (Boyden et al., 2002; Gong et al., 2001; Little et al., 2002; Van Wesenbeeck et al., 2003; Ai et al., 2005). Direct roles of Wnt/β-catenin signaling in the regulation of bone formation and bone mass are further supported by animal model studies by altered expression of Wnt/β-catenin signaling inhibitors (Bodine et al., 2004; Li et al., 2006b; Morvan et al., 2006; Wang et al., 2007a; Yu et al., 2005). Wnt proteins have also been shown to be important for osteoblastogenesis and bone formation (Zhang et al., 2004; Li et al., 2005a; Bennett et al., 2005). Furthermore, modulation of Wnt/β-catenin signaling in mesenchymal progenitors and osteoblasts reveals that this pathway controls osteoblast differentiation and is critical for bone homeostasis during postnatal life (Day et al., 2005; Glass et al., 2005; Hill et al., 2005; Holmen et al., 2005; Hu et al., 2005). Using a multipotent mesenchymal cell line, OPG expression was found to be upregulated by Wnt/β-catenin signaling in an in vitro screen for Wnt-regulated genes (Jackson et al., 2005). Moreover, cellular and molecular studies demonstrated that OPG is a direct target gene of the β-catenin-TCF complex in osteoblasts (Glass et al., 2005).

Bone metastasis is a frequent complication of cancer. Several tumors show a particular predilection for metastasis to bone, including breast, prostate, and lung cancer and multiple myeloma (Yoneda et al., 1998; Mundy, 2002; Roodman, 2004; Kozlow and Guise, 2005). In the case of breast cancer, up to 70% of patients with advanced disease develop osteolytic bone metastases, which are a common cause of morbidity and sometimes mortality (Yoneda, 1998). Tumor cells, osteoblasts, osteoclasts, and bone matrix are the four components of a vicious cycle necessary for the initiation and development of bone metastases. Cancer cells are known to produce a variety of stimulators of bone resorption, such as parathyroid hormone related protein (PTHrP) and transforming growth factor (TGF-β). The secretion of some but not all of these factors by cancer cells regulates RANKL and OPG expression in osteoblasts. RANKL stimulates osteoclastic bone resorption by binding to its receptor RANK on osteoclast precursors, while OPG is the secreted decoy receptor of RANKL, and binds to and inhibits the activity of RANKL (Yoneda et al., 1998; Mundy, 2002; Roodman, 2004; Kozlow and Guise, 2005).

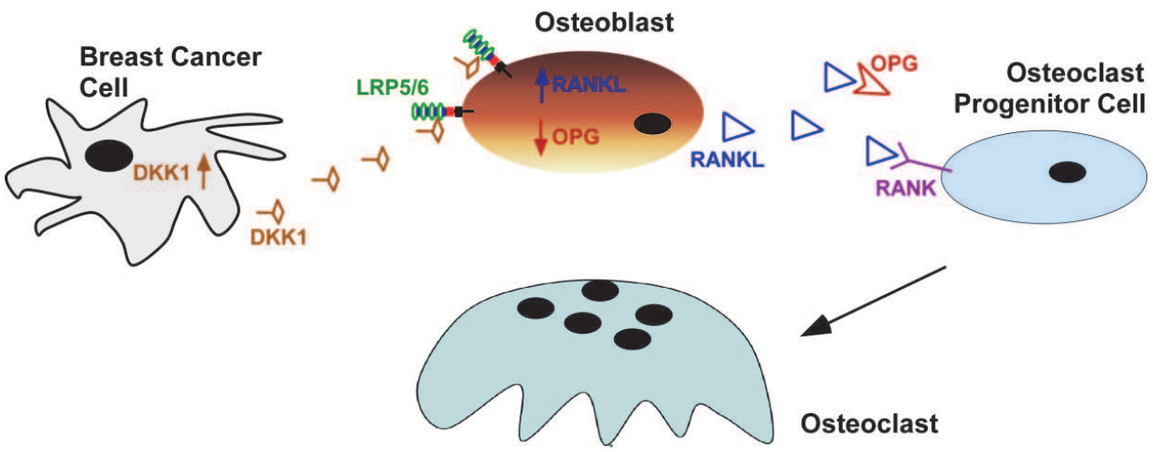


Fig. 4. Model depicting the roles of breast cancer cell-produced DKK1 on osteoclast formation. DKK1 is a Wnt/β-catenin signaling target gene in breast cancer cells. Breast cancer cells with overactivated Wnt/β-catenin signaling produce DKK1. DKK1 secreted by tumor cells blocks Wnt/β-catenin signaling in osteoblasts in a paracrine fashion, resulting in increases RANKL and decreases OPG activity. By decreasing the ratio of OPG to RANKL, DKK1 promotes osteoclastogenesis.

As described above, DKK1 is a specific antagonist of the Wnt/β-catenin signaling pathway. Interestingly, studies also suggested that DKK1 is a direct downstream target of Wnt/β-catenin signaling (Niida et al., 2004; Gonzalez-Sancho et al., 2005; Chamorro et al., 2005). Activation of Wnt/β-catenin signaling by Wnt1 or ectopic expression of active β-catenin, TCF4 or LRP6 mutants induces transcription of the human *Dkk1* gene in several cell line models *in vitro*. Multiple β-catenin/TCF4 binding sites in the *Dkk1* gene promoter region contribute to this activation (Niida et al., 2004; Gonzalez-Sancho et al., 2005; Chamorro et al., 2005). Furthermore, as mentioned above, aberrant Wnt/β-catenin signaling is involved in breast cancer development and progression. Indeed, Dkk1 is highly expressed in several breast cancer cell lines, including the MDA-MB-231 (osteolytic) and MCF-7 (osteolytic and osteoblastic) cell lines (Forget et al., 2007; Pinzone et al., 2009; Bu et al., 2008). Additionally, serum Dkk1 levels were elevated in patients with metastasized breast cancer in the bone compared to patients who were in complete remission (Voorzanger-Rousselot et al., 2007). Dkk1-mediated bone metastasis in breast cancer patients is likely to occur as a result of Dkk1 acting as a molecular switch, which decreases osteoblastogenesis and increases osteolysis (Fig. 4). The mechanistic actions of Dkk1-mediated bone metastasis in breast cancer patients is likely due to the ability of Dkk1 to abrogate Wnt/β-catenin signaling in osteoblasts, which causes a significant decrease in OPG and increase in RANKL levels, thus shifting the balance in the OPG:RANKL ratio (Bu et al., 2008). Increases in RANKL promote osteoclastogenesis and thus, metastasis of breast cancer mesenchymal stem cells into the bone (Pinzone et al., 2009).

3.5 Wnt/β-catenin signaling in breast cancer EMT

Cellular diversity is essential for the development and sustenance of eukaryotic organisms. Epithelial and mesenchymal cells represent two phenotypic distinctions of early organisms. Epithelial cells possess tight junctions, gap junctions, E-cadherins, and epithelial integrins, which foster intercellular communication and fusion with other cells

and the extracellular matrix. They also maintain the integrity and regulate the internal environment of an organism (Micalizzi et al., 2010). Mesenchymal cells, which produce the extracellular matrix that supports epithelial cells, are motile compared to their epithelial counterpart (Hay, 2005). Mammalian development is a dynamic process that involves the interconversion between epithelial and mesenchymal cells known as Epithelial-Mesenchymal Transition (EMT) and Mesenchymal-Epithelial Transition (MET) (Micalizzi et al., 2010). The EMT plays a pivotal role in wound healing, fibrosis, and cancer metastasis (Lopez-Novoa and Nieto, 2009). The EMT consists of three types, which include development (type I), fibrosis and wound healing (type II), and cancer (type III) (Kalluri and Weinberg, 2009). Oncogenic EMT is characterized by the loss of the classical epithelial apico-basal polarity, destruction of tight junctions and adherens junctions, and the downregulation of cytokeratins followed by the upregulation of vimentin, a Type III intermediate filament that is expressed in mesenchymal cells (Steinert and Roop, 1988; Ikenouchi et al., 2003; Kokkinos et al., 2007).

Normal epithelial cells are transformed into more invasive mesenchymal cells due to the disintegration of E-cadherin. E-cadherin is a transmembrane glycoprotein that mediates cell-cell contact between epithelial cells. The cytoplasmic domain of E-cadherin interacts with α-, β, and γ-catenin. Under normal cellular conditions, β-catenin forms a complex with E-cadherin to maintain epithelial cell adhesion (Gottardi et al., 2001). However, during epithelial transformation, β-catenin dissociates from the E-cadherin complex and translocates to the nucleus where it synergizes with TCF/LEF1 to induce the expression of downstream target genes (Behrens et al., 1996). The upregulation of β-catenin transcriptional activity induces the expression of vimentin in breast cancer cells, which is a key mediator in EMT (Gilles et al., 2003). The snail and slug zinc-finger transcription factors, which are E-cadherin repressors, are associated with EMT and upregulation of these proteins in breast cancer correlates with poor prognosis of breast cancer patients (Blanco et al., 2002; Moody et al., 2005; Martin et al., 2005). Indeed, aberrant Wnt/β-catenin signaling increases Snail activity (Yook et al., 2006). Other proteins that contribute to the invasive properties of epithelial cells including matrix metalloproteinase-7, CD44, uPAAR, slug, and the γ2 chain of laminin-5 are also downstream target genes of β-catenin (Brabletz et al., 1999; Wielenga et al., 1999; Mann et al., 1999; Hlubek et al., 2001). Overall, dysfunction of the Wnt/β-catenin signaling pathway is intricately involved in regulating the EMT of breast cancer.

3.6 Wnt/β-catenin signaling in breast cancer stem cells

Stem cells are cells that have the capacity to propagate or differentiate into distinct cell types that form mature tissue (Seaberg and Kooy, 2003). Stem cells may lay dormant and accumulate mutations over a long period of time, which ultimately results in the formation of tumors due to aberrant activation of signaling pathways that regulate stem cell continuity and differentiation (Sell, 2004). Previously, stem cells were isolated from human breast cancer tissue, suggesting that cancer stem cells (CSCs) may be involved in the development of breast cancer (Al-Hajj et al., 2003). Breast CSCs are characterized by the expression of cell surface markers including stem cell antigen-1 (Welm et al., 2002), CD44+/CD24-, aldehyde dehydrogenase-1 (ALDH1), ESA, PROCR, CD133, and CXCR4 (Nguyen et al., 2010). Another indicator of breast CSCs is their ability to efflux Hoechst 33342 dye (Alvi et al., 2003; Hirschmann-Jax et al., 2004; Ho et al., 2007). ALDH is a detoxifying enzyme, which oxidizes intracellular aldehydes (Duester, 2000; Magni et al., 1996; Sophos and Vasiliou,

2003; Yoshida et al., 1998). CD44+/CD24- breast CSCs, which express pro-invasive genes, usually display poor prognosis (Sheridan et al., 2006). A recent study showed that metastatic breast cancer in xenograft mouse models display high ALDH1 activity, which may serve as a predictor of poor patient survival (Charafe-Jauffret et al., 2010). Furthermore, breast CSCs positive for ALDH1 but not CD44+/CD24- are resistant to chemotherapy (Tanei et al., 2009), suggesting that ALDH1 expression may be essential for breast CSC propagation and contribute to drug resistance in some breast cancer types. Indeed, ALDH1-positive tumors are more likely to be ER-, PR-, and HER2+ and exhibit poor prognosis (Morimoto et al., 2009). However, the involvement of ALDH1 in breast CSC development is still controversial. One study showed that there is no correlation between ALDH1 expression and ER and PR status and poor patient survival (Restkova et al., 2010). Furthermore, Restkova et al. (2010) showed that ALDH1 is highly expressed in the stroma of breast cancer tumors and is associated with increased survival.

The Wnt/β-catenin signaling pathway plays an important role in stem cell survival by maintaining their continuity and undifferentiated state (Ling et al., 2009). Aberrant Wnt/β-catenin signaling, which may be induced by mutations in the stem cell genome, contributes to the development and progression of breast CSCs. For example, previous studies show that β-catenin positively regulates the expression of CD44 and CD24 (Wielenga et al., 1999, 2000; Shulewitz et al., 2006). Furthermore, increased cytoplasmic and nuclear localization of β-catenin in basal-like breast cancer overlaps with CD44+/CD24- staining, which suggest that CSC populations exist in basal-like/triple negative breast tumors (Khramtsov et al., 2010). The canonical Wnt signaling co-receptor, LRP6 is overexpressed in triple-negative breast cancer (Liu et al., 2010) and facilitates the metastasis of triple-negative breast tumors (DiMeo et al., 2009). Expression of Wnt1 and stabilized β-catenin (ΔN89β-catenin) under the MMTV promoter induces Wnt/β-catenin signaling in distinct progenitor compartments in mouse mammary tumors (Teissedre et al. 2009). Wnt/β-catenin signaling also mediates the radiation resistance of mouse mammary progenitor cells (Chen et al., 2007; Woodward et al., 2007). These results suggest that aberrant Wnt/β-catenin converts normal mammary stem cells into CSCs by altering their self-renewal and differentiation capabilities.

4. Conclusion

Aberrant activation of the Wnt/β-catenin signaling pathway can lead to tumor formation. While genetic mutations of certain intracellular components of the Wnt/β-catenin pathway, such as *APC* and *CTNNB1*, are significant contributing factors for colorectal cancers, they are typically not the predominate mechanism associated with breast cancer. Instead, it is clear that dysregulation of cell surface Wnt/β-catenin signaling components leads to aberrant activation of this pathway in breast cancer. Studies in the past years have demonstrated that Wnt/β-catenin signaling play a critical role in breast development and progression. Therefore, disruption of Wnt/β-catenin signaling at the cell surface represents a great opportunity to develop novel drugs for breast cancer prevention and therapy (Ettenberg et al., 2010; Gong et al., 2010; Liu et al., 2010).

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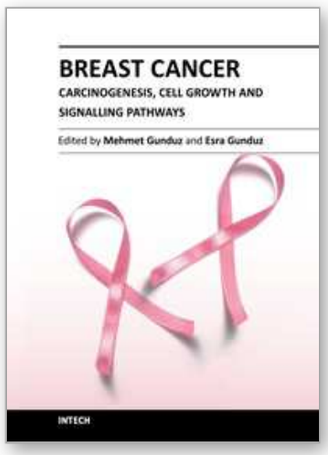
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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various aspects of breast cancer carcinogenesis from clinics to its hormone-based as well as genetic-based etiologies for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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