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Review

Targeting the Wnt pathway in cancer: The emerging role of Dickkopf-3

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ABSTRACT

Aberrant activation of the Wnt signaling pathway is a major trait of many human cancers. Due to its vast implications in tumorigenesis and progression, the Wnt pathway has attracted considerable attention at several molecular levels, also with respect to developing novel cancer therapeutics. Indeed, research in Wnt biology has recently provided numerous clues, and evidence is accumulating that the secreted Wnt antagonist Dickkopf-related protein 3 (Dkk-3) and its regulators may constitute interesting therapeutic targets in the most important human cancers. Based on the currently available literature, we here review the knowledge on the biological role of Dkk-3 as an antagonist of the Wnt signaling pathway, the involvement of Dkk-3 in several stages of tumor development, the genetic and epigenetic mechanisms disrupting *DKK3* gene function in cancerous cells, and the potential clinical value of Dkk-3 expression/*DKK3* promoter methylation as a biomarker and molecular target in cancer diseases.

In conclusion, Dkk-3 rapidly emerges as a key player in human cancer with auspicious tumor suppressive capacities, most of all affecting apoptosis and proliferation. Its gene expression is frequently downregulated by promoter methylation in almost any solid and hematological tumor entity. Clinically, evidence is accumulating of Dkk-3 being both a potential tumor biomarker and effective anti-cancer agent. Although further research is needed, re-establishing Dkk-3 expression in cancer cells holds promise as novel targeted molecular tumor therapy.

Contents

Abbreviations: aa, amino acids; ALL, acute lymphoblastic leukemia; APC, Adenomatous polyposis coli; CCND1, Cyclin-D1; CGH, comparative genomic hybridization; Cox-2, Cyclooxygenase 2; CpG, cytosine-phosphate-guanine dinucleotide; CTNNB, β-catenin; Cys, cysteine-rich domain; DFS, disease-free survival; *DKK*, Dickkopf (gene); Dkk, Dickkopf (protein); DNMT, DNA methyltransferase; DVL, Dishevelled; ECFC, endothelial colony-forming cells; EMT, epithelial-to-mesenchymal transition; ER, endoplasmatic reticulum; FDA, U.S. Food and Drug Administration; Fz, Frizzled receptor; HDAC, histone deacetylase; HR, hazard ratio; Hsp, Heat-shock protein; HUVEC, human umbilical vein endothelial cells; IL, Interleukin; JNK, c-Jun NH_2-terminal kinase; Krm, Kremen receptor; Lrp, Low-density lipoprotein receptor-related receptor; MBD, methyl-CpG-binding domain protein; MYCN, v-myc myelocytomatosis viral related oncogene, neuroblastoma derived (avian); NHF, normal human fibroblasts; NSCLC, non-small cell lung cancer; OS, overall survival; PCP, planar cell polarity; s.c., subcutaneous; Sfrp, Secreted frizzled-related protein; SGY-1, Soggy; Tcf, T cell factor; Wif-1, Wnt-inhibitory factor-1

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1. Introduction

The Wnt signaling pathway describes a complex network of proteins well known for their roles in embryogenesis and cancer, but also in normal physiological processes in adult tissues, such as homeostasis. In 1982, the term "Wnt" was derived by merging the names of the *Drosophila* segment polarity gene *Wingless* and the mouse mammary tumor virus (*MMTV*) proto-oncogene *Int-1*. It was the seminal finding of Nusse and Varmus [1] that mouse mammary tumorigenesis by *MMTV* is strongly favored through proviral insertion within the *Int-1* locus, which leads to enhanced expression of the *Int-1* gene, later on termed *WNT1*. To date, 19 highly conserved members of the Wnt protein family have been identified, each of which is thought to play a crucial role in cellular and developmental processes, including stem cell homoeostasis, cell fate determination, differentiation, and proliferation (reviewed in: [2,3]).

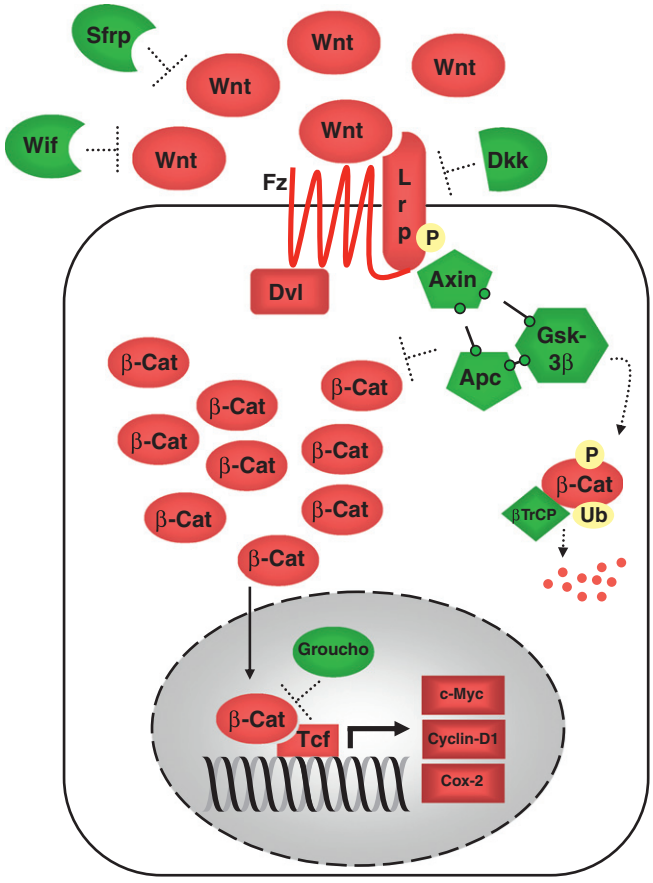

Fig. 1. Active Wnt/β-catenin signaling cascade. Binding of Wnt ligand to a receptor complex of Fz and Lrp stimulates Dvl to bind Fz within the cytoplasmic receptor domain. Following phosphorylation of Lrp, Axin is released from the β-catenin destruction complex (consisting of Axin, Apc and Gsk-3β), diminishing its degradation capacity. β-catenin then accumulates in the cytoplasm and is translocated into the nucleus, where it replaces the transcriptional repressor Groucho from binding to Tcf. The resulting complex of β-catenin and Tcf now acts as a transcriptional activator, initiating expression of target genes such as c-Myc, Cyclin-D1 and Cox-2. Dotted lines indicate conditions in the non-activated signaling cascade: Sfrps and Wif sequester Wnt and prevent its binding to the Fz/Lrp complex; Dkk ligands bind Lrp and force receptor internalization. The active destruction complex phosphorylates and ubiquitinates β-catenin leading to its degradation via the proteasome. Molecules in red color act oncogenic, whereas molecules in green color mediate tumor suppressive effects. β-cat, β-Catenin; βTrCP, beta-transducin repeat containing; Cox-2, Cyclooxygenase 2; Dkk, Dickkopf; Dvl, Dishevelled; Fz, Frizzled 7-transmembrane receptor; Gsk3β, Glycogen-synthetase-kinase-3β; Lrp, Low-density lipoprotein receptor-related protein; P, phosphorylation; Sfrp, Secreted frizzled-related protein; Tcf, T-cell factor; Ub, ubiquitination; Wif, Wnt inhibitory factor.

Secreted Wnt ligands act as pleiotropic growth factors on at least three distinct intracellular signaling cascades: The canonical Wnt/β-catenin pathway, the Wnt/Ca^{2+} pathway and the Wnt/planar cell polarity (PCP) pathway. Best characterized is the Wnt/β-catenin signaling cascade, deregulation of which is implicated in a variety of human cancers and other diseases [4]. To activate this cascade, Wnt ligands bind to their cognate Frizzled (Fz)/Low-density lipoprotein receptor-related protein (Lrp) receptor complex and relay a signal via cytoplasmic transduction intermediates onto β-catenin (Fig. 1). Uncomplexed β-catenin is then translocated from the cytoplasm to the nucleus where it acts as a transcription factor activator, facilitating the expression of various target genes. A number of extracellular Wnt antagonists precisely modulate the activity of this signaling cascade. Members of the Secreted frizzled-related protein (Sfrp) family and Wnt-inhibitory factor-1 (Wif-1) directly sequester Wnt ligands, whereas Dickkopf-related proteins (Dkk) interfere with Lrp and Kremen co-receptors, mediating the internalization of Lrp, thus preventing Wnt from binding a functional receptor complex.

Uncontrolled Wnt signaling has been recognized as an important trait of human cancer. In numerous tumor entities cytoplasmic and nuclear accumulation of β-catenin is a strong indicator of aberrant Wnt pathway activation [5], which is further confirmed by overexpression of Wnt target genes in respective tissues [6,7]. Interestingly, oncogenic disruption of the Wnt pathway is established at different subcellular levels, from deregulated expression patterns of the membranous ligand/receptor/inhibitor complexes to dysfunction of the cytoplasmic signal transducers, or the constitutive activation of the key mediator β-catenin. Extensive research over the last decade has identified numerous Wnt pathway genes as targets of either genetic or epigenetic aberration. In this respect, we here review the current knowledge on the secreted Wnt signaling inhibitor Dickkopf-related protein 3 (Dkk-3), expression of which was found to be frequently downregulated in almost any cancer entity. Lately, Dkk-3 emerged as a potential key player in tumor suppression, and thus may represent an interesting therapeutic target against aberrant Wnt signaling in the treatment of human neoplasia.

2. Structure and function of Dkk-3 protein

2.1. Structural divergence of Dkk-3 within the Dkk protein family

In vertebrates, the family of Dkk proteins comprises four members (Dkk-1 to Dkk-4) and a unique Dkk-3-related protein, termed soggy (DKKL1, or SGY-1). Dkk proteins are secreted glycoproteins with a molecular weight between 25 kDa and 29 kDa (Dkk-1, Dkk-2, and Dkk-4), or 38 kDa (Dkk-3). Besides the N-terminal signal peptide, all Dkk members except SGY-1 share two conserved cysteine-rich domains (CRD), termed Cys1 and Cys2 (Fig. 2), whereas other members of the protein family show only weak amino acid (aa) sequence similarity [8]. Overall sequence homology ranges from 46% to 50% between Dkk-1, Dkk-2 and Dkk-4, and 37% to 40% between Dkk-3 and other Dkk proteins [9]. The N-terminal Cys1 domain is unique to the Dkk family and is not found among other vertebrate proteins. The C-terminal Cys2 domain contains ten cysteine residues which