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Review

Secreted frizzled related proteins: Implications in cancers

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ABSTRACT

The Wnt (wingless-type) signaling pathway plays an important role in embryonic development, tissue homeostasis, and tumor progression becaluse of its effect on cell proliferation, migration, and differentiation. Secreted frizzled-related proteins (SFRPs) are extracellular inhibitors of Wnt signaling that act by binding directly to Wnt ligands or to Frizzled receptors. In recent years, aberrant expression of SFRPs has been reported to be associated with numerous cancers. As gene expression of SFRP members is often lost through promoter hypermethylation, inhibition of methylation through the use of epigenetic modifying agents could renew the expression of SFRP members and further antagonize deleterious Wnt signaling. Several reports have described epigenetic silencing of these Wnt signaling antagonists in various human cancers, suggesting their possible role as tumor suppressors. SFRP family members thus come across as potential tools in combating Wnt-driven tumorigenesis. However, little is known about SFRP family members and their role in different cancers. This review comprehensively covers all the available information on the role of SFRP molecules in various human cancers.

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1. Introduction

Wnt signaling plays an essential role in cell proliferation, patterning, and fate determination during normal developmental processes [1–4]. Wnt signaling pathways are traditionally characterized as β-catenin dependent (canonical) and β-catenin independent (non-canonical) pathways, the latter comprising the non-canonical planar cell polarity and the Wnt/Ca^{2+} pathways. However, it has recently been suggested that there is a degree of overlap and interaction amongst these pathways [5]. Major effectors of the Wnt signaling pathway are the Wnt ligands, which are a large family of secreted glycoproteins that are cysteine-rich and highly hydrophobic, and Frizzled receptors (FZD) that bind to Wnt ligands and initiate Wnt driven signaling. There are 19 known Wnt proteins in mammalian systems along with 10 known human frizzled receptors whose expressions are spatially and temporally regulated during development [6].

1.1. Canonical Wnt signaling pathway

During the inactive 'OFF' state of the canonical pathway, β-catenin is bound by the destruction complex that consists of Axin, adenomatosis polyposis coli (APC), and glycogen synthase kinase-3-β (GSK3β), where phosphorylation by GSK3β primes it for β-transducin repeat-containing protein (β-TrCP) mediated ubiquitylation, followed by proteosomal degradation [7]. Prior to phosphorylation by GSK3β, priming phosphorylation of serine 45 on β-catenin by casein kinase 1 (CK1) is required, where CK1 is bound to axin [8]. Concurrently, transcriptional activity of TCF is inhibited by corepressor Groucho [9]. Upon binding of the Wnt ligand to the FZD membrane receptor protein and low-density lipoprotein receptor-related proteins (LRP-5/6), the canonical Wnt signaling pathway is activated (Fig. 1). This interaction causes Axin and the phosphoprotein disheveled (DVL) to bind to phosphorylated LRP5/6, thus inhibiting the function of the destruction complex, which results in an increased level of stabilized β-catenin in the cytoplasm. β-Catenin then translocates to the nucleus and, in concert with the T-cell factor/lymphocyte enhancer factor (TCF/LEF) family of transcription factors, promotes the expression of Wnt-responsive genes such as *c-myc* [10] and *cyclin D* [11]. The downstream targets of Wnt signaling are involved in cell survival, proliferation, and differentiation, and an aberrant activation of Wnt signaling has been frequently associated with tumorigenesis [12–14]. Inhibition of Wnt signaling has been an area of extensive research as a potential target for cancer therapy. One approach of inhibiting Wnt signaling is through Wnt antagonists that keep Wnt signaling in check. Therefore, a better understanding of these antagonists is imperative in modulating Wnt signaling.

1.2. Non-canonical Wnt signaling pathway

In non-canonical Wnt signaling, Wnts are able to initiate downstream signaling and transcription in a β-catenin independent manner. Two of the more well-characterized mechanisms of the non-canonical Wnt signaling pathways are the planar cell polarity (PCP) pathway and the Wnt/Ca^{2+} pathway. The PCP signaling pathway is essential for regulating cell polarity during morphogenesis via activating JUN-N-terminal kinase (JNK)-dependent transcription factors, through a cascade involving small GTPase RAC1 and RHOA, as well as JNK. PCP is activated often by the Wnt5A ligand, and numerous studies have shown the PCP signaling pathway to antagonize the canonical pathway [15]. In the Wnt/Ca^{2+} pathway, phospholipase C (PLC) is first activated, resulting in the release of intracellular Ca^{2+} stores, which subsequently activates downstream effectors, Ca^{2+} and calmodulin-dependent kinase II (CAMKII), calcineurin, and protein kinase C (PKC), and finally activating the transcriptional regulator Nuclear factor of activated T-cells (NFAT). The Wnt/Ca^{2+} signaling pathway has been found to be associated with SFRP2 during angiogenesis, another hallmark of cancer in breast cancers, via increased expression of NFAT [115].

2. SFRP family of Wnt antagonists

It is suggested that Wnt signaling is regulated by several classes of negative modulators. Wnt antagonists can be divided into 2 classes based on their mechanisms of action [16]. The first class includes the SFRP family, Wnt inhibitory factor (WIF)-1, and Cerberus. Wnt

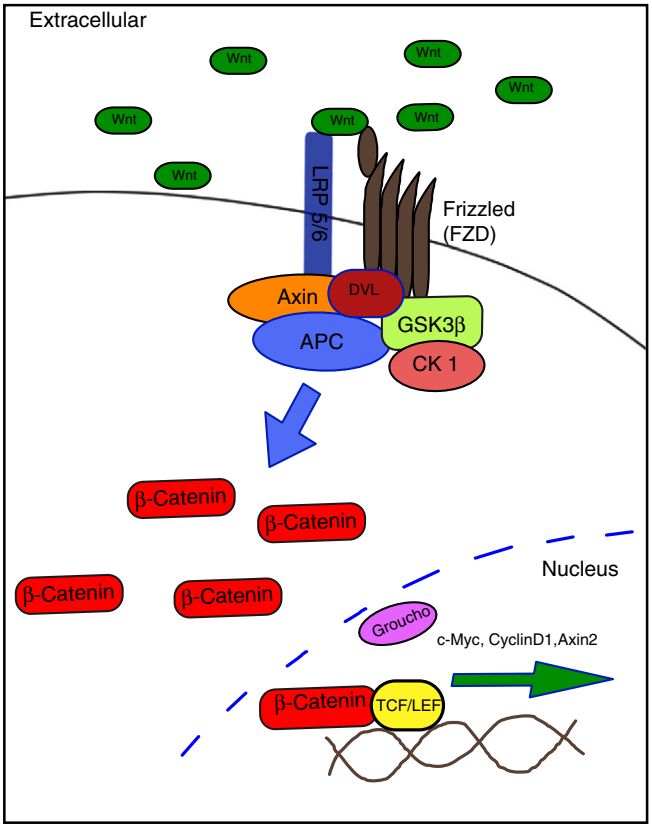

Fig. 1. The canonical Wnt signaling pathway ("ON" State). Binding of secreted Wnt factors to Frizzled receptors on the cell membrane transduces a signal to the Axin complex that inhibits phosphorylation and degradation of β-catenin. β-Catenin then accumulates in the cytoplasm and can translocate to the nucleus, where it interacts with TCF/LEF and other families of transcription factors to regulate expression of target genes.

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