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Review article

Secreted frizzled-related protein 2-mediated cancer events: Friend or foe?

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ABSTRACT

Secreted frizzled-related protein (SFRP)2, an identified member of the SFRPs family of molecules, is often methylated in human cancers and its down-regulation is closely related to Wnt signaling activity and tumor progression. Although the blocker of the Wnt signaling has not been fully used in clinical trial, interest has been further enhanced by the realization of SFRPs' potential as targets to modulate Wnt signaling and cancer cell growth. Emerging evidence showed that SFRP2 was an anti-oncogene, however, a steady flow of research has indicated that it may also have tumor promotion effects in some cancer types. Furthermore, SFRP2 methylation was shown to accelerate cancer cell invasion and growth in tumor progression. In this review, we define recent understanding of the diverse roles of SFRP2 in tumorigenesis, and it might promote the development of novel drugs for curing cancer by targeting SFRP2.

Contents

Introduction

Wnt signaling plays a vital function in a variey of biological processes including cell proliferation, cell differentiation, and cell migration [1–3]. Wnt signaling pathways are conventionally divided into the β-catenin-dependent canonical and the β-catenin-independent non-canonical pathways, which the latter consists of the Wnt/Ca^{2+} pathway and the planar-cell-polarity (PCR)-like pathway [4]. It has recently been indicated that non-canonical Wnt pathways could even antagonize the canonical Wnt pathway [5]. The primary effectors of the Wnt signaling pathway are the Wnt ligands and Frizzled (Fz) receptors [6]. There

Abbreviations: BPH, benign prostate hyperplasia; CRD, cysteine-rich domain; DKKs, Dickkopfs; DNMTs, DNA methyltransferases; Fz, Frizzled; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LC, liver cirrhosis; LRP-5/6, low-density lipoprotein receptor-related proteins-5/6; NTR, netrin-related motif; PCR, planar-cell-polarity; SFRP, secreted frizzled-related protein; WIF, Wnt inhibitory factor; Wg, wingless.

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are 19 known human Wnt proteins and 10 known Fz receptors, which are 7-transmembrane-span proteins in human [7]. Wnt proteins are a family of secreted glycol-proteins that bond to cell surface receptor-Fz proteins and low-density lipoprotein receptor-related proteins (LRP) −5/6, which transduce a signal to the Axin complex that inhibits the combination of β-catenin and GSK-3β, and suppresses phosphorylation and degradation of β-catenin. Accumulation of β-catenin allows it to translocate to the nucleus, thereby activating the canonical Wnt pathway [8] (Fig. 1). Activation of the non-canonical Wnt pathway may only link with the binding of Wnt to Fz receptors with no need for LRP5/6 [9,10] (Fig. 1). Increasing numbers of studies have indicated that the abnormal activation of the Wnt signaling pathway is related to tumorigenesis [11,12]. Therefore, inhibition of Wnt signaling by using Wnt antagonists is a potential target to treat cancer.

Wnt antagonists traditionally can be divided into two functional classes: the SFRP classes can bind to both the Fz receptors and Wnt proteins to inhibit both the canonical and non-canonical Wnt pathway, while the Dickkopfs (DKKs) classes can interact with Wnt co-receptors LRP-5/6 to block only the canonical Wnt pathway [13]. The SFRP classes include the SFRPs family (SFRP 1–5), Wnt inhibitory factor (WIF)-1, and Cerberus, while the DKKs classes contain members of the DKKs family. In the presence of the SFRPs family, canonical and non-canonical Wnt signaling are inhibited as SFRPs can bind to both Wnt proteins and Fz receptors, causing formation of Axin complex and phosphorylation of β-catenin, priming it for proteosomal degradation [14] (Fig. 2). The mini-review emphasizes recent progress in our study of the SFRPs family, especially secreted frizzled-related protein (SFRP2) since SFRP2 has received much attention in the progress of tumorigenesis.

Biology of SFRP2

SFRP2, a secreted glycoprotein, are considered to be a Wnt antagonist that regulates the Wnt signaling pathway [15]. It is approximately 300 amino acids in lenth. with the N-terminal consisting of signal peptides and a frizzled-like cysteine-rich domain (CRD), and the C-terminal including a hydrophilic heparin-binding region and a netrin-related motif (NTR) defined by six cysteine residues that form three disulfide bridges [16]. SFRP2 can compete with the Fz receptors to interact with Wnt proteins due to its CRD domain consisting of 10 conserved cysteine residues and possessing a similar sequence to the CRD domain of the Fz receptors on the extracellular part [17,18]. However, SFRP2 is different from the Fz receptors since it lacks transmembrane and cytosolic domains [19] (Fig. 3). Further evidences indicate that SFRP2 is able to inhibit the Wnt-induced increases in the levels of free β-catenin and influence cell cycle process and tumor cell proliferation [20,21]. Thus, SFRP2 is recognized as an antagonist to the Wnt signaling and a novel molecule of tumor suppressors.

An increasing number of studies have indicated a decrease of SFRP2 in a variety of cancers [22,23]. However, there appear some opposite reports about the antagonistic role of SFRP2. They found that the up-regulation of SFRP2 expression was related to tumorigenesis and SFRP2 may strengthen diffusion and availability of Wnt proteins, leading to canonical Wnt signaling activation and tumorigenesis [24–26]. Thus, the molecular mechanisms that

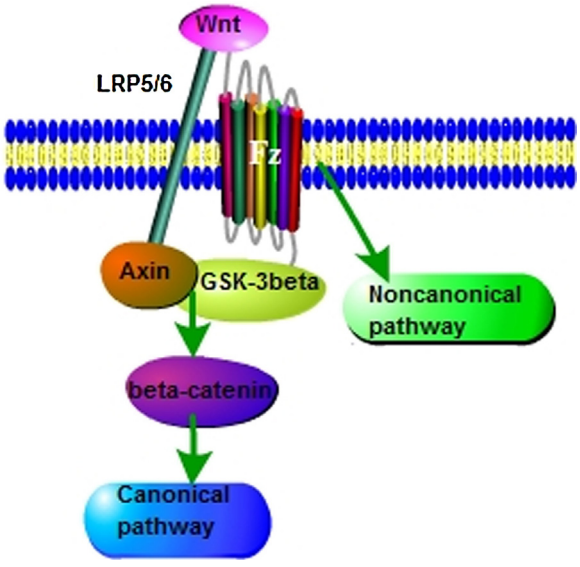

Fig. 1. Activation of Wnt signaling. Activation of the canonical Wnt pathway is initiated when secreted Wnt proteins interact with Frizzled and LRP5/6 on the cell membrane, a signal will transduce to the Axin complex. The process can destroy the combination of β-catenin and GSK-3β, and suppresses phosphorylation and degradation of β-catenin. Activation of the non-canonical Wnt pathway is only linked with the binding of Wnt to Fz, with no need for LRP5/6.

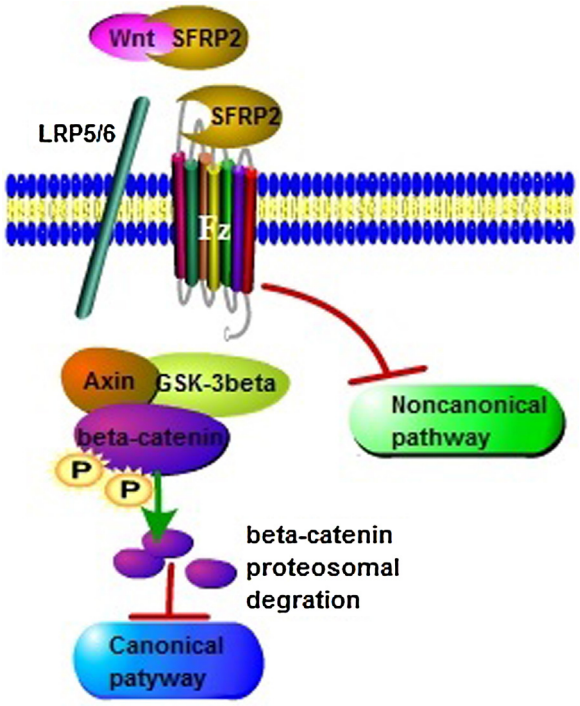

Fig. 2. Regulation of Wnt signaling by SFRP2. SFRP2 can interact with both the Fz receptors and Wnt proteins to inhibit both the canonical and non-canonical Wnt pathway.

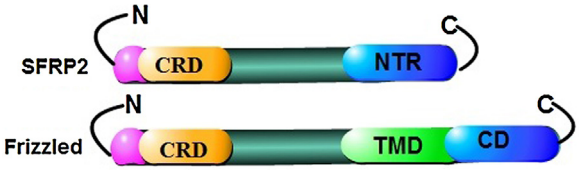

Fig. 3. The structures of SFRP2 protein and Frizzled receptors. SFRP2 is related to Fz receptors in the CRD (Cysteine-rich domain). NTR, netrin-related motif; CD, cytoplasmic domain; TMD, transmembrane domain. Signal peptides are shown as amaranthine.