An Oncogenic Hub: β-Catenin as a Molecular Target for Cancer Therapeutics

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Abstract The Wnt/β-catenin signaling pathway plays diverse roles in embryonic development and in maintenance of organs and tissues in adults. Activation of this signaling cascade inhibits degradation of the pivotal component β-catenin, which in turn stimulates transcription of downstream target genes. Over the past two decades, intensive worldwide investigations have yielded considerable progress toward understanding the cellular and molecular mechanisms of Wnt signaling and its involvement in the pathogenesis of a range of human diseases. Remarkably, β-catenin signaling is aberrantly activated in greater than 70% of colorectal cancers and to a lesser extent in other tumor types, promoting cancer cell proliferation, survival and migration. Accordingly, β-catenin has gained recognition as an enticing molecular target for cancer therapeutics. Disruption of protein–protein interactions essential for β-catenin activity holds immense promise for the development of novel anti-cancer drugs. In this review, we focus on the regulation of β-catenin-dependent transcriptional activation and discuss potential therapeutic opportunities to block this signaling pathway in cancer.

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1 Introduction

β-Catenin (Armadillo in Drosophila) is a multifunctional protein involved in both cell–cell adhesion and Wnt signaling. As an essential co-activator downstream of Wnt signaling, β-catenin regulates many biological processes essential for proper embryonic development and adult homeostasis. Once abnormally activated in adult tissues, however, β-catenin could contribute to the onset of tumorigenesis or accelerate tumor growth. In recent years, a variety of novel β-catenin interactors has been identified, highlighting β-catenin’s role as the hub of a very complex network of protein–protein interactions that fine-tune its transcriptional activity. These molecular interactions, therefore, represent attractive targets for pharmacological intervention. Here, we provide an overview of β-catenin signaling in tumor formation, summarize recent advances in pharmacological strategies to inhibit β-catenin transcriptional output and explore new opportunities for drug discovery in targeting oncogenic β-catenin.

2 The Wnt/β-Catenin Signaling Pathway

Intracellular signaling by the Wnt family of secreted cysteine-rich glycoproteins plays critical roles in normal embryonic development and adult homeostasis (Cadigan and Nusse 1997; Miller 2002; Wodarz and Nusse 1998). This pathway is highly conserved among the animal kingdom. There are 19 members of the Wnt gene family in mammals, which are expressed in a spatially and temporally restricted manner in embryos and in adults. Mutational analyses of Wnt genes in mice have demonstrated diverse roles in axis formation, brain development, pattern formation and organogenesis (Uusitalo et al. 1999; van Amerongen and Berns 2006). More recently, dysregulation of Wnt signaling has been linked to a range of human diseases, especially cancer (Clevers 2006b; Moon et al. 2004; Nusse 2005).

These Wnts signal through distinct intracellular pathways that are broadly categorized as either “canonical” or “non-canonical” Wnt pathways. The best understood canonical pathway utilizes nuclear β-catenin as an ultimate effector, leading to changes in gene expression that regulates cell proliferation, differentiation and survival, etc. In contrast, non-canonical pathways signal via a β-catenin-independent mechanism, generally resulting in changes in cell polarity and movement (Katoh 2005; Kohn and Moon 2005; Veeman et al. 2003).

A simplified model of the Wnt/β-catenin pathway is represented in Fig. 1. β-Catenin is the key component in this cascade, acting as a transcriptional co-activator. In the absence of a Wnt ligand, the cytosolic pool of β-catenin is continuously degraded by the action of a large protein complex called the “destruction complex” (Kimelman and Xu 2006). In this complex, the tumor suppressors Axin and adenomatous polyposis coli (APC) function as scaffold proteins that facilitate sequential phosphorylation of β-catenin at the N-terminus by casein kinase Iα (CKIα) and