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Signalling networks in focus

Wnt signaling from membrane to nucleus: β-catenin caught in a loop

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ABSTRACT

β-catenin is the central nuclear effector of the Wnt signaling pathway, and regulates other cellular processes including cell adhesion. Wnt stimulation of cells culminates in the nuclear translocation of β-catenin and transcriptional activation of target genes that function during both normal and malignant development. Constitutive activation of the Wnt pathway leads to inappropriate nuclear accumulation of β-catenin and gene transactivation, an important step in cancer progression. This has generated interest in the mechanisms regulating β-catenin nuclear accumulation and retention. Here we discuss recent advances in understanding feedback loops that trap β-catenin in the nucleus and provide potential insights into Wnt signaling and the development of anti-cancer drugs.

1. Signaling network facts

- β-Catenin is a central mediator of the Wnt signaling pathway and controls the transcription of genes during both normal and malignant development.
- Nuclear localization of β-catenin is crucial to its role in Wnt signaling and cancer.
- β-catenin is retained in the nucleus through a LEF-1 dependent feedback loop which increases its concentration in the nucleus and overall transcriptional activity.
- Inhibition of Wnt/β-catenin signaling is a potential strategy for cancer therapy.
- Further information on Wnt signaling can be found at http://www.stanford.edu/group/nusselab/cgi-bin/wnt/.

2. Introduction

β-catenin is a member of the Armadillo (Arm) family and contains a central 12 Arm repeat domain (Fig. 1a) (Sharma et al., 2012), which acts as a platform for multiple protein interactions (Fig. 1a) giving rise to diverse cellular functions ranging from cell:cell adhesion at the plasma membrane to transcriptional activation in the nucleus (MacDonald et al., 2009). β-catenin was first identified at *adherens* junctions where it links cadherins with the cytoskeleton to regulate the response to cell adhesion. In addition a small yet dynamic pool of β-catenin shuttles rapidly between the cytoplasm and nucleus (MacDonald et al., 2009) and is responsible for transducing canonical Wnt signals from plasma membrane to the nucleus. Nuclear β-catenin is a hallmark of Wnt signaling and regulates diverse cellular processes in multiple cell types including stem cells (Tanaka et al., 2011) and neurons (Misztal et al., 2011). Deregulation of the Wnt pathway generates excessive nuclear β-catenin and inappropriate activation of Wnt target genes, leading to multiple diseases including cancer (MacDonald et al., 2009). The Wnt pathway is regulated by feedback loops both upstream at the membrane (Tanaka et al., 2011) and downstream in the nucleus. In this review we briefly outline the function of β-catenin as a central effector of the Wnt signaling pathway and focus on how its nuclear accrual is regulated through nuclear retention mechanisms including a LEF-1 positive feedback loop, and the impact on malignant transformation.

3. Functions

3.1. Wnt/β-catenin signaling pathway

The canonical Wnt/β-catenin signaling pathway is conserved in evolution and controls processes including cellular proliferation, differentiation, motility, tissue maintenance (MacDonald et al., 2009), and cell fate specification and maintenance of pluripotency (Tanaka et al., 2011). Wnts are glycoprotein ligands of the Frizzled family of transmembrane receptors that modulate signaling to the nucleus through β-catenin (MacDonald et al., 2009). In the absence of Wnt signaling, β-catenin protein is maintained at low levels through degradation, predominantly by a multiprotein destruction complex comprising factors including tumor

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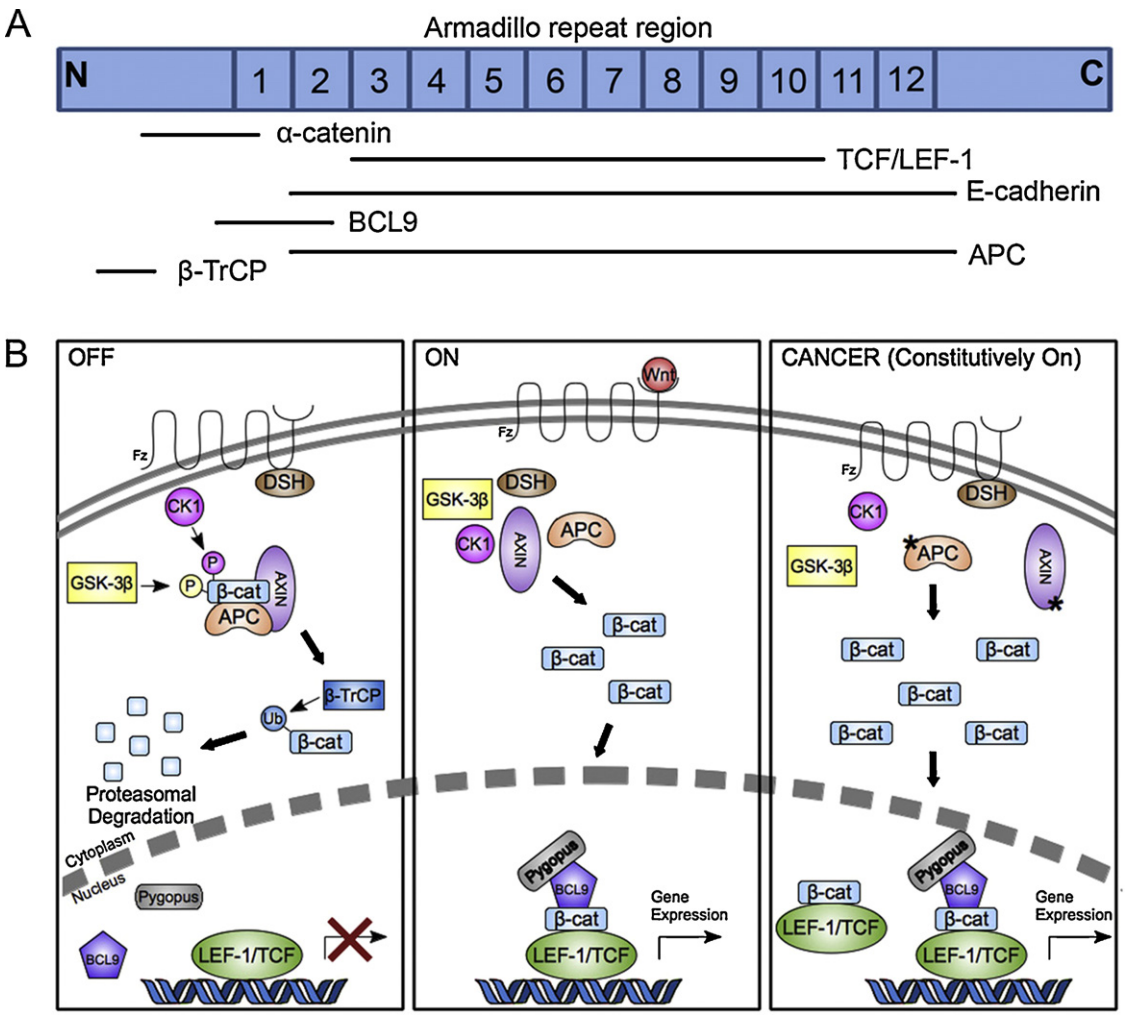

Fig. 1. (a) Schematic diagram of β-catenin protein with binding sites. E-cadherin, LEF/TCF, APC and axin all compete for binding within the armadillo repeat region of β-catenin. (b) Overview of the Wnt/β-catenin signaling pathway. (i) *Wnt off*: In the absence of Wnt signaling, β-catenin is degraded by a multi-protein destruction complex comprising APC, axin, CK1 and GSK-3β. N-terminal phosphorylation of β-catenin by this complex triggers β-TrCP mediated ubiquitination and proteasomal degradation. (ii) *Wnt on*: The binding of Wnt ligand to Frizzled receptors at the plasma membrane lead to disassembly of the destruction complex, and stabilization of β-catenin which accumulates and translocates to the nucleus where it interacts with members of the TCF/LEF-1 family. In the nucleus, β-catenin recruits nuclear co-activators (e.g. BCL9 and pygopus) and converts TCF proteins into potent transcriptional activators to drive the transcription of target genes. (iii) *Cancer*: Mutations (*) in destruction complex members (APC and axin) or β-catenin itself results in a constitutively active pathway. β-catenin is no longer degraded by the destruction complex and accumulates in the nucleus to high levels, driving gene transcription. Fz, frizzled receptor; APC, adenomatous polyposis coli; CK1, casein kinase 1; GSK-3β, glycogen synthase kinase 3-β, β-TrCP; β-transducin repeat-containing protein; P, phosphorylation; Ub, ubiquitin; TCF, T-cell factor; LEF-1, lymphoid enhancer factor 1; BCL9, B-cell lymphoma 9.

suppressors adenomatous polyposis coli (APC) and axin, and the kinases casein kinase 1 (CK1) and glycogen synthase kinase 3-β (GSK-3β) (Fig. 1b). APC recruits β-catenin to the destruction complex where it is phosphorylated at N-terminal serine and threonine residues by CK1 and GSK-3β, marking it for ubiquitination and subsequent proteasomal degradation. In the presence of Wnt signaling, GSK-3β becomes inactivated (MacDonald et al., 2009) and β-catenin is stabilized in a hypo-phosphorylated form that translocates to the nucleus to bind members of the T cell factor family of high motility group (HMG) proteins including LEF-1 (lymphoid enhancer factor 1), TCF-1 (T-cell factor), TCF-3 and TCF-4 (Fig. 1b). In conjunction with nuclear coactivators (B-cell lymphoma 9, pygopus, cyclin dependent kinase 8 (Najdi et al., 2011)), β-catenin and TCFs form transcriptional complexes that activate specific Wnt target genes (MacDonald et al., 2009; Tanaka et al., 2011). The Wnt/β-catenin pathway is activated by loss of function mutations in APC, axin and GSK-3β or gain of function mutations in β-catenin (MacDonald et al., 2009), stimulating transcription of cancer-associated genes including cyclin D1, c-myc and urokinase plasminogen activator (Hiendlmeyer et al., 2004, Brabletz et al., 2001) in colon cancer and up-regulation of glutamine metabolism genes such as glutamine synthetase in hepatocellular carcinoma (Cadoret et al., 2002; Loeppen et al., 2002). A non-canonical Wnt activation pathway also exists (Najdi et al., 2011). The mechanisms that regulate nuclear β-catenin levels after Wnt signaling are therefore important for its pro-active role in cancer.

3.2. Nuclear retention of β-catenin

Immunohistochemical studies revealed a positive correlation between nuclear β-catenin and advancing stages of human colorectal carcinogenesis (Wong et al., 2004). Moreover, nuclear β-catenin has been detected at the invasive front of mesenchyme-like tumors (Brabletz et al., 2001) and colorectal adenomas (Hao et al., 2001). It was earlier hypothesized that Wnt-induced nuclear β-catenin accumulation was likely due to decreased nuclear export (Wiechens and Fagotto, 2001) and retention of β-catenin (Rosin-Arbesfeld et al., 2000).

All four members of the TCF family (LEF-1, TCF-1, TCF-3 and TCF-4) contribute to the Wnt-induced nuclear localization of