Biochemical and Molecular Signaling of the Canonical Wnt Pathway

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Letter to the Editor

The canonical Wnt pathway plays an important role in numerous cell processes, such as embryogenesis, cell proliferation, self-renewal of stem cells, myogenesis, and adipogenesis [1]. This pathway is mediated by specific factors called Wnt proteins, which act as chemical mediators controlling the development of different types of cells [2,3]. Wnt proteins are structurally different from other proteins, in that they have a fatty acid chain bound covalently at their N-terminal region [4]. The Wnt pathway is regulated by another protein, beta-catenin (β-cat). It is known that β-cat activates the transcription of more than 60 different genes [1].

In epithelial cells, most of the β-cat protein is found at cellular adherens junctions, which are associated with transmembrane adhesion proteins known as E-cadherins. At these junctions, β-cat assists in connection of E-cadherin with the actin protein present in the cytoskeleton [5]. Any β-cat protein that is not associated with E-cadherins is rapidly degraded in the cytoplasm of both epithelial and non-epithelial cells by a degradation complex [6].

Several molecules participate in the mechanism underlying canonical Wnt signaling, as shown in Table 1. When Wnt proteins bind to their receptors, a conformational change occurs in both transmembrane receptors, which exposes the phosphorylation domains in the tail of the LRP5/6 receptor in the cytoplasm. This biochemical

and molecular signal recruits the Dvl-3 protein, disrupting the β-cat degradation complex [7]. Subsequently, the GSK-3β and CK1 proteins are attracted by the LRP5/6 receptor tail to phosphorylate its domain [8]. Due to the decomposition of the β-cat degradation complex, β-cat protein is not degraded, resulting in an increase in the level of this protein in the cytoplasm and its migration into the nucleus [9]. In the nucleus, β-cat recruits co-activators, such as Legless and Pygopus, to form a transcriptional complex with other factors, that is, TCF-4/LEF1, that were previously inactivated by the Groucho (Grg) protein [7]. The formation and activity of this transcriptional complex are β-cat dependent. The β-cat protein disrupts Grg, activating the transcriptional complex and causing the transcription of target genes, such as those that inhibit the differentiation of pre-adipocytes or adipogenesis [10]. This mechanism is illustrated in Figure 1.

Furthermore, parallel mechanisms involved in the activation of these target genes have been described. The testosterone hormone stimulates the interaction of the β-cat/androgen receptor located in the cytosol. This complex then migrates to the nucleus to activate the transcription of target genes. This mechanism inhibits adipogenesis by suppressing lipoprotein lipase activity and downregulating mRNA transcription and protein expression of key transcriptional adipogenesis factors [10,11]. Another molecule, TNFα, enters the cell by binding to its receptor TNF receptor 1 (TNFR1). TNFα stabilizes the free β-cat in the cytoplasm, allowing β-cat translocation into the nucleus to activate the

Protein	Characteristic/function	Reference
Axin	Degradation complex molecule (DCM). Interacts with LRP5/6, contributing to β-cat stabilization.	[14]
Casein Kinase 1 (CK1)	DCM. Phosphorylates the amino terminal region of β-cat, serine residue (Ser45), preparing it for the second phosphorylation by the enzyme GSK-3β.	[14-16]
Glycogen Synthase Kinase 3β (GSK-3β)	β-cat phosphorylation at Ser33, Ser37, and Thr41 for recognition by F-box and β-TrCP proteins.	[14,17]
SCFp-TRCP-ubiquitin ligase	Ubiquitination of β-cat for its degradation in the proteasome.	[15]
Frizzled (FZD) and LRP5/6 proteins	Important in Wnt mechanism. Transmembrane receptors with an extracellular N-terminal cysteine-rich domain (CRD).	[3]
β-catenin	Transcriptional co-activator in the Wnt pathway. Adherens junction components involved in cell-cell adhesion. Interacts with the transcriptional factors (TCF family) in the nucleus and regulates gene expression.	[17,18]
Adenomatous polyposis coli (APC)	Regulation of β-cat turnover. Scaffold function. Facilitates β-cat phosphorylation by GSK-3 at the β-cat N-terminal domain.	[14,15]
SCF-E3 (SCF)	Binds to phosphorylated β-cat and ubiquitinates this molecule.	[14]
Disabled-2 (Dab2 or DOC-2)	Regulation of the Wnt signaling pathway interacting with Dvl-3 and Axin.	[19]
Pygopus (Pygo)	Required for the transcriptional regulation of β-cat via its association with Legless/BCL9 cofactor.	[20]
Legless (Lgs)	Acts as an adapter between β-cat and Pygopus proteins	[21]

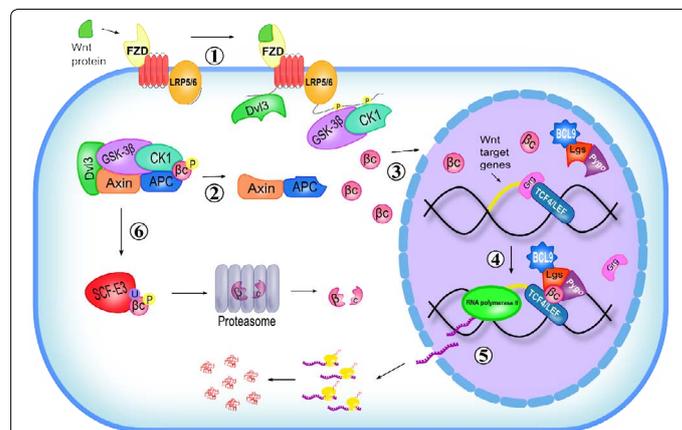**Table 1:** Examples of proteins involved in the Wnt pathway.

Figure 1: Canonical Wnt pathway mechanism in the activation of target genes.

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transcription of downstream genes [10]. Binding of insulin hormone to its receptor (insulin receptor, INS) also increases free β-cat levels [12], however the mechanism underlying this is unclear. Thus, mechanisms that prevent the degradation of β-cat enable the maintenance of a high concentration of this signal protein in the cytoplasm, resulting in its translocation into the nucleus to coactivate the transcription of target genes [13].

In conclusion, the relevance of the canonical Wnt pathway in cellular biochemical and molecular signaling is unquestionable. Further studies are required to elucidate the mechanisms by which this pathway regulates the expression of target genes that control metabolism.

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