Beyond canonical: The Wnt and β-catenin story

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This Editorial Guide uses Wnt-stimulated activation of the transcriptional activity of β-catenin, the canonical Wnt/β-catenin pathway, to illustrate the hazards of limiting research investigation and questions to those that fit the “canonical” view.

It is human nature to look for patterns, assign labels, and establish order to information; signaling researchers are no exception. When thinking about cellular behavior and the molecular networks that control it, these tendencies are both advantageous, by helping us organize and find patterns in information, and disabling, by limiting our thinking and making it difficult to challenge published findings. Signaling researchers and geneticists studying phenotypes associated with mutation of specific genes have often named proteins and their encoding genes by the first identified function, phenotype, or biochemical activity associated with them. Although this can lead to some amusing names, such as “Wingless” for the fly homolog of the family of morphogenetic ligands known in vertebrates as Wnts, it can create confusion and be misleading for future research. A case in point is glycogen synthase kinase 3 (GSK3), which was originally named for its biochemical function in phosphorylating glycogen synthase, a metabolic enzyme involved in converting short polymers of glucose into the polymeric storage form glycogen. Since its discovery in animals in the 1980s and its subsequent discovery in plants, GSK3 has been found to phosphorylate numerous proteins that modulate multiple cellular signaling pathways—for example, the Wnt/β-catenin and Hedgehog pathways—in development, disease, and tissue homeostasis. In the Wnt/β-catenin pathway, GSK3 regulates the steady-state levels and transcriptional activities of β-catenin. Deeper investigation of how GSK3 regulates β-catenin has provided myriad insights into biology, as well as into how terminology and linear thinking can impede scientific progress.

Signaling researchers have tended to apply a linear pathway paradigm often based on the first, and not infrequently or accidentally, the easiest experimentally measured output of the pathway. The Wnt-mediated stabilization of β-catenin is a case in point. Like many proteins, β-catenin has numerous functions. For example, it is a member of a family of proteins that are involved in cell-cell adhesion complexes and named for the Latin word for “chain,” because these proteins were thought to “link” actin to the transmembrane adhesion protein cadherin. Indeed, β-catenin functions in these cell adhesion complexes, not as a signaling protein, but as a structural protein. The low amount of β-catenin that is free in the cytosol is maintained through the constitutive activity of a phosphorylation-dependent destruction complex that contains none other than the β isoform of GSK3 (GSK3β). The presence of some members of the large family of secreted ligands called Wnts inhibits the destruction complex, which stabilizes cytosolic β-catenin. As the amount of cytosolic β-catenin increases, some is transported into the nucleus, where it interacts with other transcription factors, the best characterized of which is the T cell factor/lymphoid enhancer factor (TCF/LEF) family, and regulates gene expression, including genes encoding proteins that are part of the destruction complex. This defines the so-called canonical Wnt/β-catenin pathway. Consequently, the accepted readout of Wnt activity has been defined as activation of β-catenin-dependent transcription, enabling researchers to identify the relevant response elements in the gene promoters and to create highly sensitive reporters to monitor activation of this Wnt/β-catenin pathway. Although this facilitated the discovery of many regulatory components of the Wnt/β-catenin pathway and provided insights into this pathway’s function in development, adult cell homeostasis, and cancer, this narrow view that the Wnt/β-catenin pathway terminates in transcriptional regulation has limited the discovery of other regulatory functions of Wnt ligands, other pathways in which components of the core canonical Wnt/β-catenin pathway function, and other regulators of the transcriptional activity of β-catenin.

A move away from linear concepts of signaling pathways is warranted, not only based on inadequacy in incorporating spatial information but also on the inability to convey dynamics of information flow through the pathway, how the pathway network changes over time, and the difficulty in adequately representing pathway crosstalk. For instance, Wnt/β-catenin signaling interacts with other pathways in context-dependent ways. These include the Jak-STAT (Janus kinase–signal transducer and activator of transcription) cytokine pathway, the TGFβ (transforming growth factor–β) pathway, the DNA damage pathway, and the Hippo pathway. As an example of how the information flow through the pathway changes as a consequence of pathway activity, one of the targets of the Wnt/β-catenin is the gene encoding Axin, which is a protein that is part of the destruction complex. Thus, activity through the pathway ultimately feeds back to limit the pathway’s own activity.

The difficulty in weaning researchers from linear depictions of signaling pathways resembles the struggle of drug addiction—it helps the user avoid and hide from “inconvenient truths.” The “poster child” for such inconvenient truths can readily be found by perusing the past 20 years of Wnt research. Depending on cellular context and the composition and activity of membrane receptors and co-receptors belonging to the Frizzled and LRPS and LRPS6 families, members of the Wnt family can act through β-catenin–independent (that is, noncanonical) pathways that can involve the kinase JNK (c-Jun N-terminal kinase), calcium signals, calcium/calmodulin-dependent protein kinase II (CaMKII), Rac, and protein kinase C (PKC). Not only can these noncanonical Wnt pathways antagonize the canonical Wnt/β-catenin pathway, but they also control cell polarity, cell migration, and synaptic function. The lack of robust assays has hindered the elucidation of the mechanisms of noncanonical Wnt signaling, but the challenge of deciding how to superimpose calcium, PKC, CaMKII, and other entities onto graphical representations of signaling networks should not be accepted as a legitimate reason to avoid including the overwhelming evidence that not all Wnt

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signaling goes through β-catenin and not all β-catenin transcriptional activity depends on Wnt or TCF/LEF.

This idea that signaling proteins have functions beyond those for which they were originally identified and best characterized has led to the need to change our signaling vernacular. There are now “canonical” pathways and “noncanonical” pathways; there are also “moonlighting” functions for proteins, indicating a function divergent from the originally identified one. Maybe a better strategy would be to have more explicit names for pathways, such as the Wnt/β-catenin transcriptional activation pathway (instead of just the Wnt/β-catenin pathway) or the Wnt-calcium pathway or the β-catenin dendrite morphology pathway.

Science Signaling editors have a long-standing interest in fostering the investigation of noncanonical regulatory pathways, pathway crosstalk, and pathway dynamics, as is evident from the many highlights of research on the Wnt pathway in the Archives. Science Signaling remains the place to publish newly identified and unexpected regulators of well-known pathways, which are continuing to be discovered as “unbiased” (or, as we prefer, “untargeted,” because all methods have some form of bias). However, Science Signaling is also the place to publish unanticipated molecular functions of regulatory molecules and unexpected cellular responses to regulation of signaling molecules.

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