The Wnt signaling pathway: The foundation of cell growth, development, and potential therapeutics

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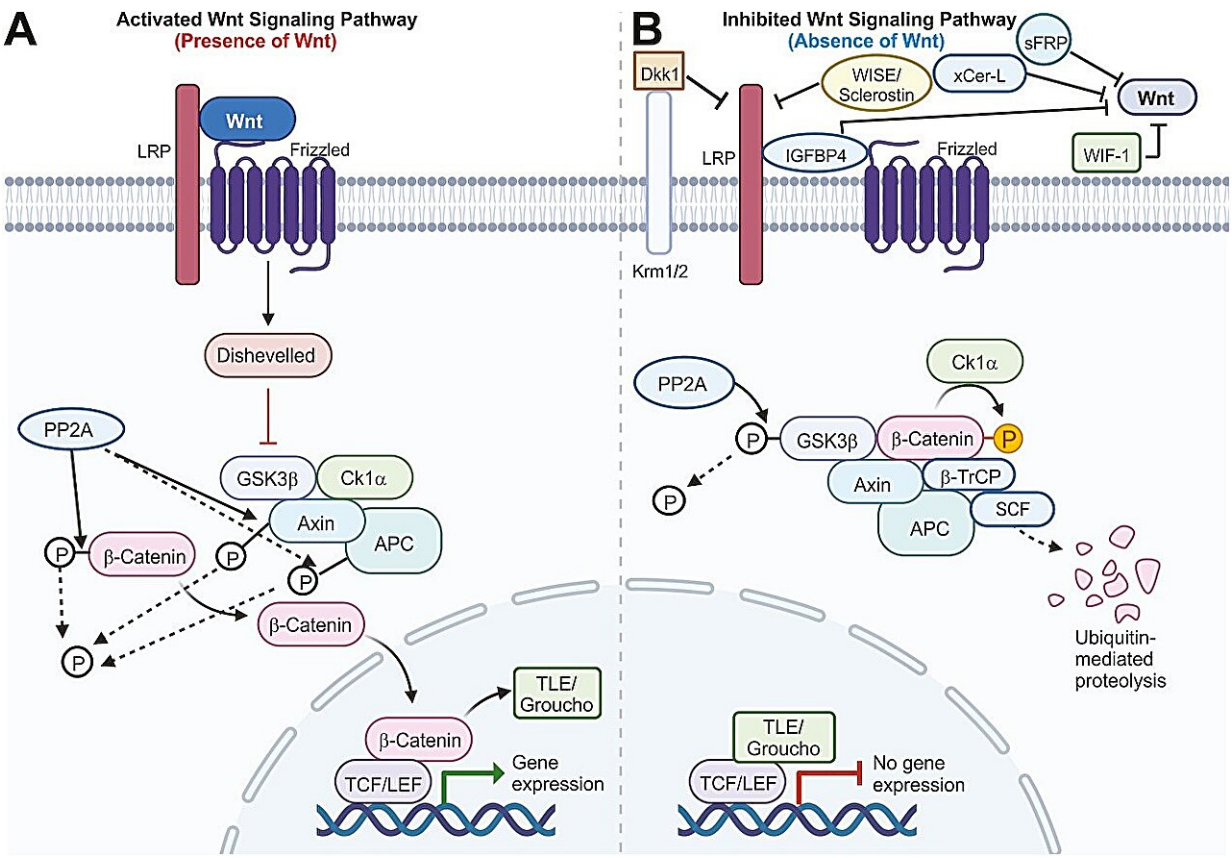


The canonical Wnt signaling pathway. The left panel (A) demonstrates the activated Wnt signaling cascade, while the right side portrays the inhibited Wnt signaling cascade. Wnt binds to the Fz receptor and LRP5/6 co-receptor. This activates Dvl to cause the dissociation of Axin from the destruction complex, causing β-catenin to be stabilized and enter the nucleus. β-Catenin can then displace the inhibitory TLE/Groucho complexes, enabling TCF/LEF to

transcribe the target genes. PP2A can also enhance Wnt signaling by dephosphorylating β-catenin, APC, and Axin. The result is the preservation of β-catenin by preventing ubiquitination and proteasomal breakdown. In the absence of Wnt signaling (B), the destruction complex breaks down β-catenin and inhibits gene transcription. Several other proteins also contribute to the inhibition of Wnt signaling. Dkk1 associates with Krm1 or Krm2 and LRP5/6, causing endocytosis of the LRP5/6 co-receptor. Wise/sclerostin binds to LRP5/6 to inhibit proper Wnt association with the coreceptor. xCer-L and WIF-1 both bind to Wnt ligands to inhibit signaling. IGFBP-4 functions as a competitive inhibitor of Wnt signaling by associating with LRP6 and Fz8, while sFRPs complex with Fz receptors to prevent Wnt ligand binding. The illustration was inspired by and created in BioRender. Credit: Kevin Qin, et al.

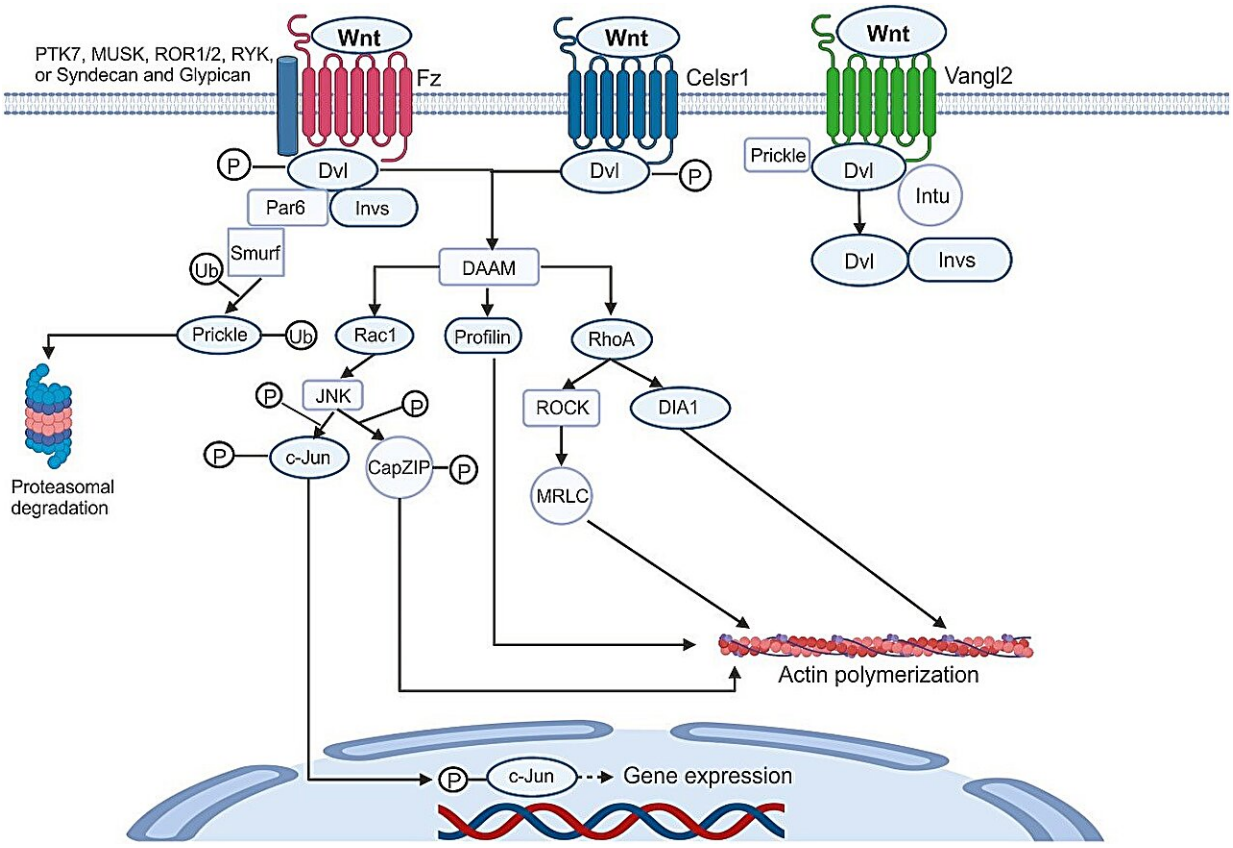
The Wnt signaling pathway, a system present in living organisms, plays a pivotal role in cell growth, differentiation, and migration. It has a long history dating back to 1982, when the first Wnt gene, essential for cellular growth, was discovered. The pathway is initiated by Wnt ligands, a set of 19 glycoproteins that transmit signals through specific receptors and proteins, leading to modifications in gene expression.

In a review published in the journal *Genes & Diseases*, researchers from The University of Chicago Medical Center have not only delved into the history of Wnt signaling, but also examined the different types of Wnt signaling, highlighting the components of each and their interplay with other cellular functions.

The review emphasizes the interactions and overlaps between Wnt signaling and other cellular pathways, showcasing the intricate web of communication within our cells. Wnt signaling serves as a bridge connecting numerous cellular functions, making it integral to overall health. Its mismanagement can result in a multitude of diseases, from cancer to developmental anomalies, underlining the importance of its

precise regulation.

The pathway is so central that deviations can even lead to embryonic fatality. Wnt's widespread involvement in our body's processes makes it an attractive target for therapeutics. Potential treatments focusing on Wnt signaling can address ailments ranging from cancer to heart disease. However, as with any powerful tool, the utilization of these treatments carries inherent risks. Unintended consequences, such as tumor formation or accidental suppression of essential cellular functions, are possible.



The noncanonical Wnt/PCP pathway. The binding of Wnt ligands leads to the phosphorylation of Dvl, which recruits Invs, Par6, and Smurf. Smurf ubiquitinates the inhibitory protein Prickle, targeting it for destruction. Dvl can

then associate with DAAM, activating Rac1, profilin, and RhoA. Rac1 activates JNK, which phosphorylates c-Jun and CapZIP. c-Jun then goes to the nucleus to stimulate gene transcription. RhoA activates ROCK and DIA1, with the latter activating MRLC. CapZIP, MRLC, DIA1, and profilin all stimulate actin polymerization. Celsr1 stimulates Dvl due to Wnt binding like the Fz receptor. Wnt binding to the Vangl2 receptor causes dissociation of Prickle and Intu from Dvl, which can then bind to Invs. The illustration was inspired by and created in BioRender. Credit: Kevin Qin, et al.

While our understanding of Wnt signaling has grown leaps and bounds over the past four decades, mysteries remain. The exact mechanisms by which the 19 Wnt ligands interact with their receptors are not entirely understood. The complete spectrum of pathways influenced by Wnt signaling is yet to be fully mapped. Furthermore, while the components of the Wnt signaling pathway are being deciphered, their full range of functions might still be hidden.

The ultimate goal is to harness the power of the Wnt signaling pathway for therapeutic use, but this requires a deeper understanding and utmost caution. Current treatments, both activators and inhibitors, come with potential risks. Further research aims to ensure the safety of these therapies and expand our understanding, with the hope of capitalizing on the potential benefits of regulating Wnt signaling.

The Wnt signaling pathway, while complex, is undeniably central to many processes in living organisms. The past 40 years have offered a plethora of insights, yet the pathway remains a treasure trove of potential knowledge. As researchers continue to unveil its secrets, there's hope that these findings will catalyze advances in biology, medicine, and overall human well-being.

More information: Kevin Qin et al, Canonical and noncanonical Wnt

signaling: Multilayered mediators, signaling mechanisms and major signaling crosstalk, *Genes & Diseases* (2023). DOI: 10.1016/j.gendis.2023.01.030

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