CELL SIGNALLING

Preventing WNT signalling

WNT ligands interact with Frizzled receptors and the WNT co-receptors low-density lipoprotein receptor-related protein 5 (LPR5) and LPR6 to induce β-catenin-dependent canonical WNT signalling. In addition, WNT binding to Frizzled proteins alone initiates non-canonical WNT signalling. Here, Hao *et al.* describe a role for zinc and RING finger 3 (ZNRF3) in the inhibition of both canonical and non-canonical WNT signalling pathways.

ZNRF3 was identified in a screen for β-catenin gene targets that are potentially involved in the negative regulation of WNT signalling. *ZNRF3* encodes an E3 ubiquitin ligase with a transmembrane domain and a cytoplasmic RING finger domain. Overexpression of ZNRF3 suppressed β-catenin-dependent transcription, whereas silencing of *ZNRF3* or overexpression of a dominant-negative form of ZNRF3 that lacked the RING finger domain increased LRP6 and Frizzled levels at the membrane and enhanced β-catenin activation. Notably, ZNRF3 was found to form a complex with Frizzled and LRP6 and to ubiquitylate Frizzled, thereby inducing its degradation. Thus, ZNRF3-mediated inhibition of WNT signalling involves the degradation of WNT receptors.

But how are the membrane levels of ZNRF3 regulated to ensure tight control of WNT inhibition? Hao *et al.* show that the activator of both WNT pathways R-spondin, which has been shown to interact with the orphan transmembrane receptor LGR4, stabilizes WNT receptors by binding to the extracellular domain of ZNRF3. This binding enables the association of ZNRF3 with LGR4, which in turn downregulates ZNRF3 membrane levels by promoting ZNRF3 autoubiquitylation and degradation. Thus, the E3 ubiquitin ligase activity of ZNRF3 mediates ZNRF3 autoubiquitylation and turnover following R-spondin signalling.

> “this ZNRF3 function is evolutionarily conserved”

Finally, *in vivo* studies in zebrafish and *Xenopus laevis* embryos confirmed the central role of ZNRF3 in the regulation of canonical and non-canonical WNT signalling pathways during embryonic development. Moreover, analysis of *Znrf3*-knockout mice indicated that this ZNRF3 function is evolutionarily conserved.

Given the central role of WNT signalling in embryonic development and cancer, the authors predict that ZNRF3 and its functional homologue RNF43, which is often mutated in patients with pancreatic cancer, will be valuable therapeutic targets.

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