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CELL SIGNALLING

A Rac1–JNK2–β-catenin domino cascade

> “…Rac1 is a crucial component of the canonical Wnt signalling pathway.”

Researchers have found that the small GTPase Rac1 is a crucial component of the canonical Wnt signalling pathway. Reporting in *Cell*, Fanxin Long and colleagues now show that, in response to Wnt, Rac1 activates Jun N-terminal kinase-2 (JNK2), which phosphorylates β-catenin and promotes its nuclear translocation.

Working in a stromal cell line (ST2) that differentiates into osteoblasts in response to WNT3a, the authors observed that WNT3a activates Rac1. Expression of a dominant-negative form of Rac1 or RNA interference-mediated depletion of Rac1 inhibits the expression of a WNT3a reporter gene and prevents ST2 differentiation. In the absence of Rac1, endogenous β-catenin does not accumulate in the nucleus in response to Wnt signalling. So, Rac1 is required for the activity of canonical Wnt signalling during osteoblast differentiation, but how does Rac1 control the nuclear localization of β-catenin?

Dominant-negative Rac1 inhibits the activation of JNK2 and the chemical inhibition of JNK2 prevents the nuclear accumulation of β-catenin and reduces the expression of a reporter gene in response to WNT3a. Using biochemical assays, the authors showed that β-catenin, Rac1 and JNK2 interact in the cytosol of ST2 cells. Furthermore, in response to WNT3a, JNK2 phosphorylates Ser191 and Ser605 of β-catenin; phosphorylated β-catenin then migrates to the nucleus.

Canonical Wnt signalling is essential for limb outgrowth. To determine the physiological relevance of Rac1 in Wnt signalling, the authors genetically ablated Rac1 in the apical ectodermal ridge (AER) of the mouse embryonic limb bud. Embryos that lack Rac1 in the AER have limb truncation defects that are identical to those previously observed in β-catenin mutants. Furthermore, using a reporter mouse strain that had been engineered to reflect β-catenin signalling *in vivo*, the team showed that β-catenin signalling is not induced in the AER in the absence of Rac1.

Finally, embryos that lack one copy of *Rac1* and *β-catenin* had identical defects to *β-catenin* or *Rac1*-knockout embryos. Similar results were obtained by removing one copy of *Rac1* and overexpressing Dickkopf-1 (Dkk1), which is known to antagonise the canonical Wnt signalling pathway. These findings indicate that Rac1 genetically interacts with β-catenin and Dkk1 in the control of limb outgrowth.

Together, these data provide the first evidence that Rac1 controls the canonical Wnt signalling and elucidate the long-sought-after molecular mechanism that regulates nuclear translocation of β-catenin: in response to Wnt signalling Rac1 activates JNK2, which phosphorylates β-catenin. This modification causes it to move to the nucleus. Whether Rac1 has a similar role in other physiological events besides the development of the embryonic limb AER remains to be investigated.

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ORIGINAL RESEARCH PAPER Wu, X. *et al.* Rac1 activation controls nuclear localization of β-catenin during canonical Wnt signaling. *Cell* **133**, 340–353 (2008)