Links
β-catenin: http://us.expasy.org/uniprot/Q02248
axin: http://us.expasy.org/uniprot/O35625

GSK3: http://us.expasy.org/uniprot/Q9WV60

LRP6: http://us.expasy.org/uniprot/O88572

APC: http://us.expasy.org/uniprot/Q61315

CELL SIGNALLING

Fill in the Wnt gaps

> Further work is now required to refine the details of this process, and to investigate how these kinases become activated.

Wnt signalling is known to convey signals from the extracellular environment to the nucleus, through a cascade of signalling events that result in the activation of β-catenin. Reporting in *Nature*, Zeng *et al.* and Davidson *et al.* now tackle one of the fundamental questions in Wnt signalling: which kinases are involved in activating the Wnt receptor?

In the absence of Wnt, the formation of a complex between β-catenin and the β-catenin-binding proteins, axin, adenomatous polyposis coli (APC) and glycogen-synthase kinase-3 (GSK3), results in the phosphorylation of β-catenin by GSK3 and in β-catenin degradation. When cells are exposed to Wnt, the frizzled receptor and the low-density lipoprotein (LDL)-receptor-related protein-6 (LRP6) receptor become activated and form a complex. Axin is recruited to this receptor complex and β-catenin translocates to the nucleus where it regulates gene expression. The binding of axin to LRP6 has been associated with the phosphorylation of LRP6, which indicates that protein kinases must be recruited to the receptor after activation by Wnt. Zeng *et al.* and Davidson *et al.* sought to identify these kinases.

Wnt induces phosphorylation of LRP6 on several clusters of Ser and Thr residues that have a central proline-rich motif (PPPSP), so Zeng *et al.* first tested the PPPSP motif for phosphorylation activity. A combination of genetic and biochemical analysis revealed that GSK3 is a kinase that phosphorylates the Ser residue in this motif. These results indicated a dual role for GSK3 in Wnt signalling; GSK3 phosphorylates β-catenin, which mediates β-catenin degradation, but it also phosphorylates and activates LRP6.

In a complementary study, Davidson *et al.* found a second kinase that is involved in the phosphorylation of LRP6. Using a protein-modification screen for regulators of LRP6, the authors identified casein kinase-1γ (CK1γ), a membrane-bound member of the CK1 family. Genetic experiments showed that CK1γ is required for Wnt signalling in vertebrates, *Drosophila melanogaster* and *Xenopus laevis*. In addition, the authors showed that CK1γ is associated with LRP6, and that CK1γ-mediated LRP6 phosphorylation induces recruitment of axin to the receptor.

How Wnt induces LRP6 phosphorylation by GSK3 and CK1 remains unknown. Zeng *et al.* proposed that GSK3 phosphorylation is induced by Wnt, whereas CK1 activation might be constitutive. On the other hand, Davidson *et al.* suggested that the PPPSP motif is constitutively phosphorylated. Further work is now required to refine the details of this process, and to investigate how these kinases become activated.

Ekat Kritikou

ORIGINAL RESEARCH PAPERS
Davidson, G. *et al.* Casein kinase 1γ couples Wnt receptor activation to cytoplasmic signal transduction. *Nature* **438**, 867–872 (2005) | Zeng, X. *et al.* A dual-kinase mechanism for Wnt co-receptor phosphorylation and activation. *Nature* **438**, 873–877 (2005)
FURTHER READING
Nusse, R. Cell biology: relays at the membrane. *Nature* **438**, 747–749 (2005)