The Wnt signalling pathway

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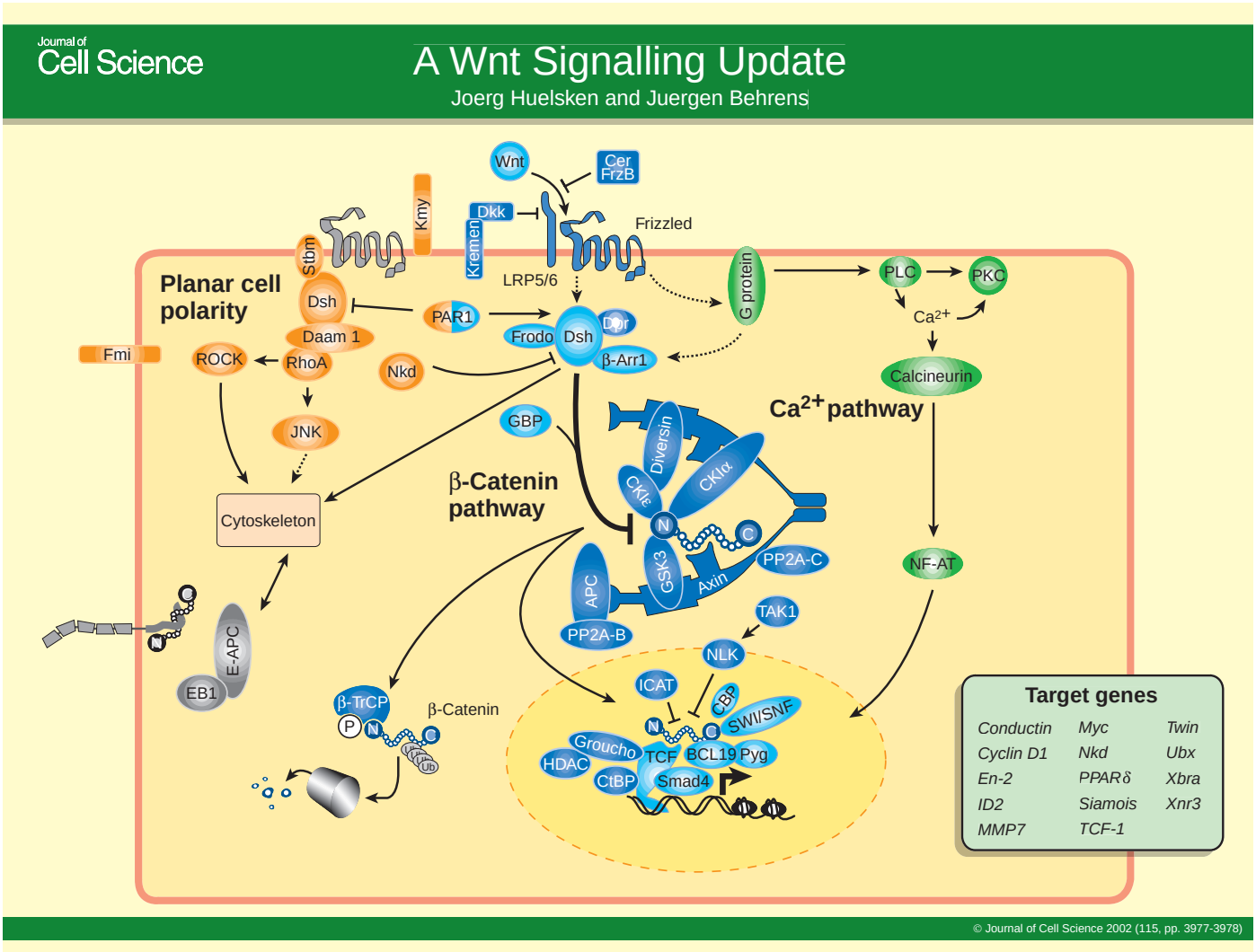
Recent advances in the field require an update of our Wnt pathway scheme (Hülsken and Behrens, 2000). Intracellular signaling of the Wnt pathway diversifies into at least three branches: (1) the β-catenin pathway (canonical Wnt pathway, blue), which activates target genes in the nucleus; (2) the planar cell polarity pathway, which involves jun N-terminal kinase (JNK) and cytoskeletal rearrangements (orange); and (3) the Wnt/Ca^{2+} pathway (green).

Wnts are secreted glycoproteins that bind to frizzled seven-transmembrane-span receptors, which may be coupled to heterotrimeric G proteins. LRP5/6 (*arrow* in Drosophila), which are members of the low-density lipoprotein receptor-related protein family, act as essential co-receptors of Wnt ligands for canonical β-catenin-dependent signal transduction. Various secreted factors, such as cerberus (Cer) and FrzB, bind to Wnts and block the interaction with frizzled proteins. Dickkopf (Dkk) antagonises Wnt action by blocking access to the LRP co-receptor and induction of LRP endocytosis in cooperation with kremen.

Intracellularly, Wnt signalling leads to stabilisation of cytosolic β-catenin. In the absence of Wnts, β-catenin is phosphorylated by casein kinase Iα (CKIα) and/or CKIε at Ser45; this in turn enables glycogen synthase kinase 3β (GSK3β) to phosphorylate serine/threonine residues 41, 37 and 33. Phosphorylation of these last two residues triggers ubiquitylation of β-catenin by βTrCP and degradation in proteasomes. Phosphorylation of β-catenin occurs in a multiprotein complex containing the scaffold protein axin, which can form a homodimer or a heterodimer with the related protein conductin/axin2, the tumor suppressor gene product APC and diversin, which links CK1ε to the complex. β-Catenin



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degradation is modulated by the multisubunit serine/threonine phosphatase PP2A. In the presence of Wnts, dishevelled (Dsh) blocks β-catenin degradation possibly by recruiting GBP/Frat-1, which displaces GSK3β from axin. Dsh activity is modulated by the kinase PAR1, which potentiates Wnt activation of the β-catenin pathway but blocks the JNK pathway. Other Dsh-interacting molecules include frodo and β-arrestin 1 (β-Arr1), which synergize with dsh, and the general Dsh antagonist Dapper (Dpr).

Stabilised β-catenin enters the cell nucleus and associates with LEF/TCF transcription factors, which leads to the transcription of Wnt-target genes (see box in right corner). Transcriptional activation is mediated by the interaction of β-catenin with the histone acetyl transferase CBP, the chromatin-remodeling SWI/SNF complex and Bcl9 bound to pygopus (Pyg). Interaction of TCF with Smad4 might connect the Wnt and BMP signalling pathways. When β-catenin is absent, certain TCFs repress transcription by interacting with the co-repressors CtBP and groucho bound to histone deacetylase (HDAC). Phosphorylation of TCFs by NEMO-like kinase (NLK), a target of TAK1 (a MAP kinase kinase kinase), as well as interaction of β-catenin with ICAT negatively regulates Wnt signalling. Further components reported to modulate canonical Wnt signalling but not depicted in the scheme are Idax, a Dsh-binding protein, duplin and pontin/reptin, which are β-catenin-interacting proteins, and HBP1, which binds to TCF.

In the planar cell polarity pathway, frizzled activates JNK and directs asymmetric cytoskeletal organization and coordinated polarization of cells within the plane of epithelial sheets. This pathway involves the cadherin-related transmembrane molecule flamingo (Fmi), the proteoglycan knypek (Kny), and the PDZ molecule strabismus (Stbm) and branches at the level of Dsh from the canonical pathway. Dsh is connected via Daam1 to downstream effectors such as the small GTPase Rho and Rho-associated kinase (ROCK). The product of the Wnt target gene *naked* (Nkd) was recently identified as an antagonist for Wnt signaling that binds to Dsh and blocks β-catenin but stimulates the JNK pathway.

The Wnt/Ca^{2+} pathway leads to release of intracellular calcium, possibly via G-proteins. This pathway involves activation of phospholipase C (PLC) and protein kinase C (PKC). Elevated Ca^{2+} can activate the phosphatase calcineurin, which leads to dephosphorylation of the transcription factor NF-AT and its accumulation in the nucleus. In *Xenopus* embryos, NF-AT activity suppresses canonical Wnt signals during axis formation.

A role for APC and the associated EB1 protein in the regulation of microtubule function has also been suggested. Furthermore, data in *Drosophila* indicate a function of E-APC, possibly together with cadherin-based cellular adhesion, in spindle orientation and asymmetric cell division (gray).

References

Hülsken, J. and Behrens, J. (2000). The Wnt signalling pathway. *J. Cell Sci.* **113**, 3545.

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