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SnapShot: Noncanonical Wnt Signaling Pathways

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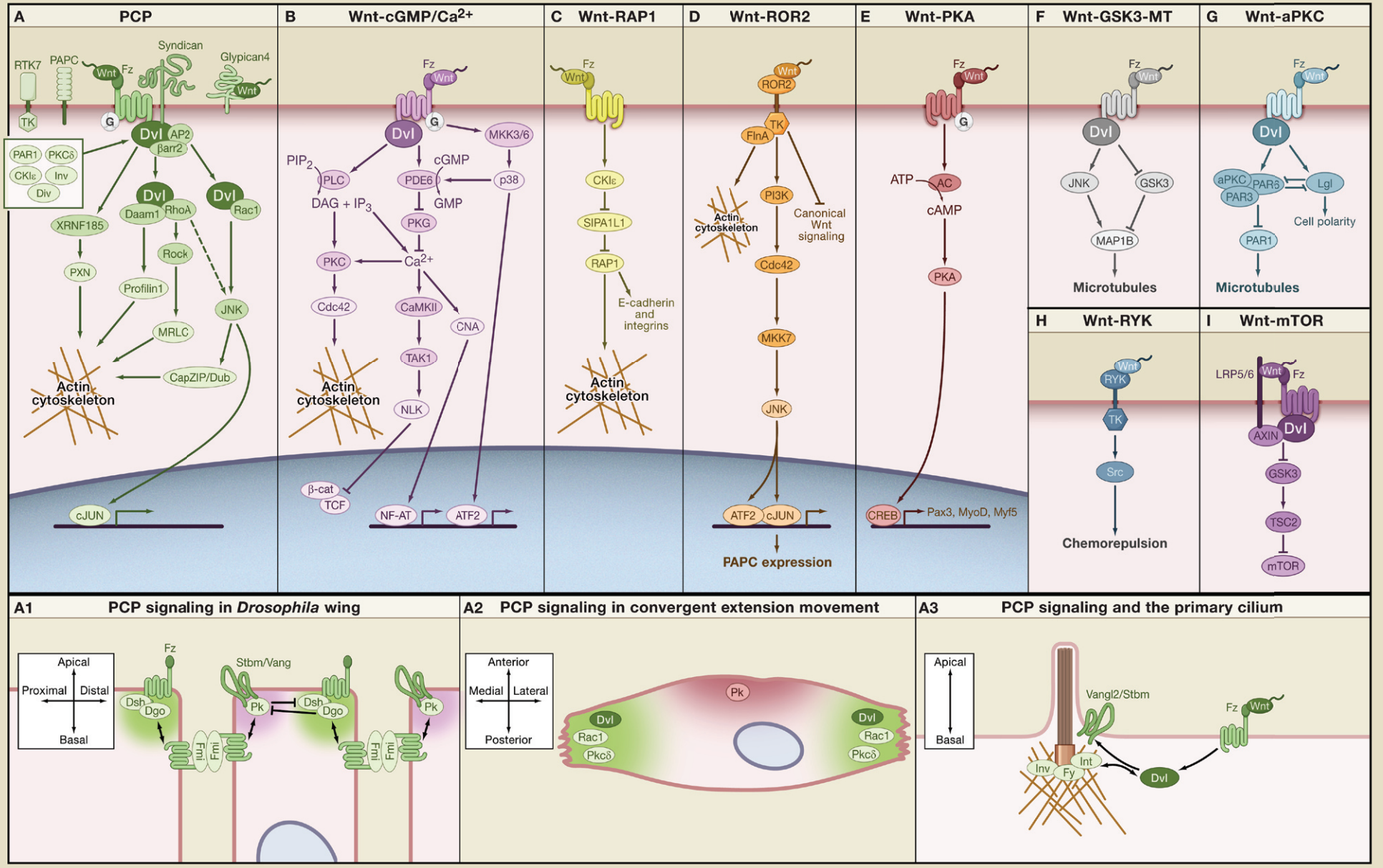
Cell



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Noncanonical Wnt signaling is defined here as Wnt- or Fz-initiated signaling that is independent of β-catenin transcriptional function. Noncanonical Wnt pathways are diverse and in many cases less characterized/defined. They are grouped into several categories for clarity and simplicity. Such classifications are not rigid as these pathways likely overlap with or intersect one another and are evolving.

(A) Wnt/PCP (planar cell polarity) signaling. Vertebrate Wnt5a and Wnt11 initiate signaling via Fz, which may activate trimeric G proteins and Dvl (likely via phosphorylation), and the assembly of Dvl/effector complexes. Multiple pathways downstream of Dvl regulate actin cytoskeleton/cell adhesion. The Dvl-Daam1-RhoA complex activates RhoA, which leads to Rock kinase activation and MRLC phosphorylation; Dvl-Rac1 complex activates JNK kinase, which may phosphorylate CapZIP/Dub; Dvl and XRNF185 (an E3 ligase) downregulate PXN protein level. Dvl recruitment to the membrane by Fz is regulated by kinases including Par1, CK1ε, and PKCδ. Dvl-binding proteins/complexes—including Div, Inv (related to *Drosophila* Dgo), endocytic β-arr2, and the AP2 complex—regulate Dvl PCP function. Proteoglycans like Glypican4/Knypek and Syndican and protocadherin PAPC also have roles in PCP signaling. RTK7 is involved in PCP signaling during neural tube closure. (A1) Polarized localization of PCP proteins is maintained by, and required for, PCP signaling in *Drosophila* wing epithelia. Antagonistic interaction between the Fz-Dsh-Dgo complex localized distally and the Stbm (Vang)-Pk complex localized proximally leads to planar polarization. Localization of both complexes is reinforced by interaction with Fmi. (A2) Polarized localization of PCP proteins in mesodermal cells during vertebrate gastrulation. Pk is localized anteriorly (in zebrafish) whereas Dvl, PKCδ, and Rac1 mediolaterally (in *Xenopus*). (A3) Fz, Dvl, Inv, and PCP effectors Fy, Int, Dub/CapZIP are involved in primary cilia formation in vertebrates because they govern apical actin assembly. Some of these proteins and Vangl2 may be localized to the centrosome and to the cilium.

(B) Wnt-cGMP/Ca^{2+} signaling. Wnt5a and Fz2 may regulate intracellular Ca^{2+} flux and levels. Wnt/Fz via the G protein activates PLC, leading to the generation of DAG and IP_3 that increases Ca^{2+} concentration in the cell. Wnt/Fz also activates cGMP-specific phosphodiesterase PDE6, thus depleting cellular cGMP and inactivating PKG, thereby leading to an increase in the cellular concentration of Ca^{2+}. Ca^{2+} activates PKCα, which may activate Cdc42 and regulate cell adhesion and tissue separation during vertebrate gastrulation. Ca^{2+} also activates CaMKII and phosphatase CNA, which activates transcription factor NF-AT that influences ventral patterning in *Xenopus*. Wnt5a-Ca^{2+}-CaMKII signaling can also activate TAK1-NLK kinases, which inhibit TCF/β-catenin signaling. Wnt5a stimulation of p38 kinase via MKK3/6 is required for PDE6 activation and in addition activates transcription factor ATF2. Conflicting data exist regarding Dvl involvement.

(C) Wnt-RAP1 signaling. Wnt8 activates CKIε, which phosphorylates and targets SIPA1L1, a Rap1-specific GAP (GTPase-activating protein), for degradation, thereby enhancing Rap1 activation. Rap1 regulates actin cytoskeleton and/or cell adhesion during vertebrate gastrulation.

(D) Wnt-ROR2 signaling. ROR2 is a RTK that binds Wnt5a. During gastrulation in *Xenopus*, Wnt5a/ROR2 activates a PI3K-Cdc42-MKK7-JNK pathway, resulting in activation of ATF2 and cJUN and the expression of PAPC. ROR2 also binds to FilaminA (an actin-binding protein) and promotes filopodia formation. Wnt5a/ROR2 signaling antagonizes β-catenin signaling.

(E) Wnt-PKA signaling. This pathway is implicated in myogenesis in mice. Wnt1/Wnt7a activates the G protein and AC to increase cAMP levels, which activates PKA and transcription factor CREB and myogenic gene expression.

(F) Wnt-GSK3-microtubule (MT) signaling. Wnt signaling via Dvl (possibly MT-associated) inhibits and activates GSK3 and JNK phosphorylation of MAP1B, respectively, resulting in increased MT stability during axonogenesis and synaptogenesis.

(G) Wnt-aPKC signaling. Wnt/Fz signaling via Dvl induces aPKC activation, possibly via Dvl association with the aPKC/Par3/Par6 complex. aPKC phosphorylates and inhibits Par1/MARK2 kinase, which regulates MT. Dvl also associates with Lgl, which is antagonistic to aPKC. This Wnt signaling regulates epithelial and neuronal polarity and cell migration. Axin and APC may be involved.

(H) Wnt-RYK signaling. RYK is a RTK-like receptor and binds to and mediates Wnt-induced repulsion of axons or cell migration in *Drosophila* and mice. Src kinase may act downstream of RYK/Derailed in flies.

(I) Wnt-mTOR signaling. Wnt inhibits GSK3 phosphorylation of TSC2, thereby activating mTOR-mediated translational regulation in tumorigenesis. This pathway may require both Fz and LRP5/6 and Dvl and Axin.

Abbreviations

AC, adenylyl cyclase; AP2, adaptor protein complex 2; aPKC, atypical protein kinase C; ATF2, activating transcription factor 2; β-cat, β-catenin; βarr2, β-arrestin 2; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase 2; Cdc42, cell division cycle 42 protein; CapZIP, CapZ-interacting protein; CKI, casein kinase 1; CNA, Calcineurin; CREB, cAMP response element-binding factor; Daam1, dishevelled associated activator of morphogenesis; Dgo, diego; Div, diversin; Dsh, *Drosophila* dishevelled; Dub, duboraya; Dvl, dishevelled; FlnA, filamin A; Fmi, flamingo; Fz, Frizzled; Fy, fuzzy; G, G protein αβγ subunits; GSK3, glycogen synthase kinase 3; Int, inturned; Inv, inversin; JNK, C-Jun N-terminal kinase; cJUN, jun oncogene; LGL, lethal giant larvae; LRP5/6, low-density lipoprotein receptor-related protein 5/6; MAP1B, microtubule-associated protein 1B; MKK, mitogen-activated protein kinase; MRLC, myosin regulatory light chain; mTOR, mammalian target of rapamycin; NF-AT, nuclear factor of activated T cells; NLK, nemo-like kinase; p38, mitogen-activated protein kinase 14; PAPC, paraxial protocadherin; PAR, partitioning-defective; PDE6, phosphodiesterase 6; PI3K, phosphoinositide 3-kinases; Pk, prickle; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; PLC, phospholipase C; PXN, paxillin; Rac1, Ras-related C3 botulinum toxin substrate 1; Rap1, small GTPase; RhoA, Ras-homologous A; Rock2, Rho-associated kinase 2; ROR2, receptor tyrosine kinase-like orphan receptor 2; RTK7, receptor tyrosine kinase 7; RYK, receptor related to tyrosine kinase; Src, avian sarcoma virus transforming gene; SIPA1L1, signal-induced proliferation-associated 1 like 1; Stbm, strabismus; TAK1, TGF-β activated kinase 1; TCF, T cell-specific transcription factor; TSC2, tuberous sclerosis complex 2; TK, tyrosine kinase; Vangl2, van gogh-like 2; XRNF185, *Xenopus* ring finger protein 185.

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