

In This Issue

Wnt separate ways, met later

Members of the Wnt family of secreted signaling proteins control a wide range of developmental and pathological processes, with each Wnt protein signaling through either the "canonical" or "noncanonical" pathway. Two papers in this issue (and a Comment on page 753) now bring these two pathways together, showing that the noncanonical can directly antagonize the canonical to regulate signals critical for vertebrate body axis determination, limb development, and possibly oncogenesis.

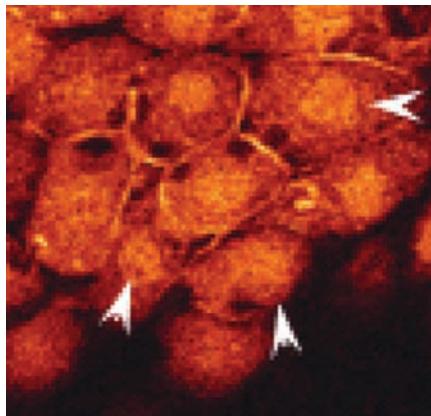
The canonical Wnt pathway stabilizes the signaling protein β -catenin against degradation, whereas the noncanonical pathway has been considered largely β -catenin independent, operating instead through a network of calcium-dependent intermediates.

Westfall et al. (page 889) identified the noncanonical Wnt family members in zebrafish and found that a loss of

function in one of them, Wnt-5, leads to an increase in β -catenin activity and activation of genes downstream of the canonical pathway. When Wnt-5 is absent from both the mother and the zygote, embryos become hyperdorsalized, showing that this noncanonical Wnt signal is required for proper embryonic axis formation.

Topol et al. (page 899) found that in mice the loss of a homologous gene, Wnt-5a, leads to an increase in canonical Wnt signaling in the distal limb bud. The unchecked canonical signal then inhibits chondrogenesis, causing defects in limb development. Analysis of cultured mammalian cells confirms that Wnt-5a signaling decreases β -catenin activity.

In both systems, the noncanonical signal increases β -catenin degradation, thereby inhibiting the canonical pathway and allowing development to proceed normally. Topol et al. also show that this



Loss of the noncanonical Wnt pathway boosts β -catenin levels.

activity of Wnt-5a requires APC, suggesting that Wnt-5a could also be an oncosuppressor. The authors are now trying to determine whether Wnt-5a is mutated in any human tumors. Meanwhile, Westfall et al. hope to use the zebrafish model to identify intermediates in the noncanonical Wnt pathway. ■

Linking formins to Arp2/3

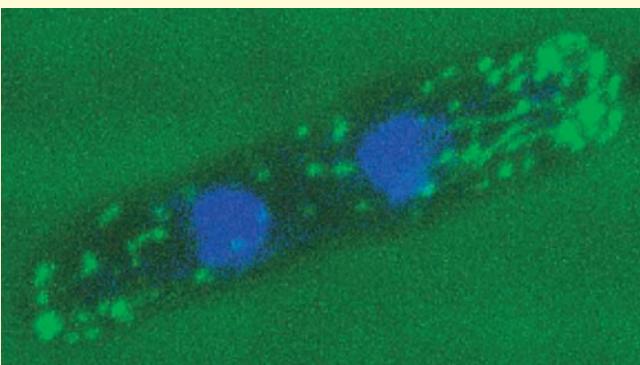
F-actin filaments can be induced to form by either of two pathways, but the elaborate cytoskeletal rearrangements seen in live cells imply that these mechanisms must somehow be coordinated. Now, Carnahan and Gould (page 851) provide the first evidence that a single, highly conserved protein links these two pathways during cytokinesis.

Previous work has shown that both the Arp2/3 complex and the formin family of proteins can induce F-actin nucleation, the rate-limiting step in filament formation. The authors show that

in the yeast *Schizosaccharomyces pombe*, the protein Cdc15p interacts directly with both the formin Cdc12p and an Arp2/3 complex regulator. Both Cdc12p and the Arp2/3 complex are essential for forming the cytokinetic actomyosin ring, a structure required for cell cleavage. The Cdc15p–Cdc12p complex appears in a medial structure in cells before ring formation, and Cdc15p is also required for the medial localization of Arp2/3 complex regulators. Cdc15p is highly phosphorylated in interphase, but becomes dephosphorylated early in mitosis.

The authors propose that dephosphorylation of Cdc15p allows it to associate with Cdc12p and initiate formation of a primary F-actin ring during metaphase. Arp2/3 could then join the complex, driving the maturation of the ring in late anaphase. In interphase, Cdc15p is distributed in a pattern very similar to that of actin patches, raising the possibility that it also coordinates cytoskeletal rearrangements at other times in the cell cycle.

As Cdc15p is the founding member of a highly conserved family of proteins, similar mechanisms are likely to be at work in many types of eukaryotic cells. Cdc15p may simply be a scaffold that brings Cdc12p and Arp2/3 together, or it could also have a catalytic function. ■



Cells lacking Cdc15p do not make a medial actin ring.