Want to promote tissue growth? There’s an App for that!
Ben Short

Study describes how a palmitoyltransferase regulates the Hippo pathway in flies.

The Hippo signaling pathway controls the size of developing organs and tissues by regulating the activity of a transcription cofactor (called Yorkie in Drosophila and Yap in mammals) that promotes the expression of cell proliferation and anti-apoptotic genes (1). Matakatsu et al. describe how a palmitoyltransferase named Approximated (App) regulates the activity of two key inputs into the Hippo pathway, the protocadherin Fat and the atypical myosin Dachs (2).

Dachs appears to promote epithelial tissue growth by localizing to the apical junction region of epithelial cells, destabilizing a Hippo pathway kinase called Warts so that Yorkie is activated to induce cell proliferation (3). Fat, in contrast, restricts growth by inhibiting Dachs’ accumulation at apical junctions (4). In 2008, Hitoshi Matakatsu and Seth Blair discovered that the putative palmitoyltransferase App suppresses Fat signaling and promotes Dachs’ localization at apical junctions (5). Matakatsu then continued his work after joining Richard Fehon’s group at the University of Chicago as a postdoc. “We wanted to investigate whether App really did function as a palmitoyltransferase and, if so, how palmitoylation regulates this pathway,” Fehon says.

One possibility is that App palmitoylates Dachs, thereby promoting its association with the plasma membrane at the apical junction region of cells, but Matakatsu et al. saw no evidence of Dachs palmitoylation. Instead, the researchers found that App palmitoylates two cysteine residues in the intracellular domain of Fat (2). Mutating these cysteines reduced Fat palmitoylation and restricted Drosophila wing growth, indicating that Fat is more active and better able to inhibit Dachs when it is not palmitoylated by App.

Fat’s intracellular domain can also be phosphorylated by the kinase Discs-overgrown (Dco) (6, 7) and, in the absence of dco, Fat is less active, resulting in a greater accumulation of Dachs at apical junctions and tissue overgrowth. Deleting app, or mutating the palmitoyltransferase’s catalytic domain, suppressed the dco-null overgrowth phenotype, producing relatively normal-sized tissues with intermediate levels of junctional Dachs. This suggests that Dco and App antagonistically regulate Fat, with phosphorylation promoting and palmitoylation inhibiting the protocadherin’s growth-restricting activity.

Matakatsu and colleagues now want to investigate how App is regulated to ensure that tissues grow to the right size during development. To date, tension is the only physiological signal known to influence Hippo pathway activity, but whether mechanical signals regulate App and/or Fat is unknown. In addition, it remains unclear how Fat inhibits Dachs’ accumulation at apical junctions and how this activity can be inhibited by palmitoylation or promoted by phosphorylation. Answering these questions could be important because a human homologue of Fat, Fat4, has a conserved palmitoylation site and is a candidate tumor suppressor, suggesting that finding ways to inhibit palmitoylation and enhance Fat4 activity might be effective in reducing the progression of certain cancers.

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