<Barresi13e, Further Development_c04_10>

Hippo Signaling: An Integrator of Pathways

Most of the signal transduction pathways that we have discussed are named for the players involved in the initial signaling event at the cell membrane. The Hippo signal transduction pathway does not have a dedicated ligand or receptor, however. Hippo stands for one of several important kinases that are critical for organ size control. It was first identified in *Drosophila*, where its loss resulted in a "hippopotamus"-shaped phenotype due to excessive growth (Hansen et al. 2015). Loss of Hippo (or overexpression of its main transcriptional effector, Yorkie) causes cells to divide significantly faster while slowing apoptosis (Figure 1; Justice et al. 1995; Xu et al. 1995; Huang et al. 2005).

The essential players in the Hippo signaling cascade begin at the cell membrane with cell-to-cell interactions involving cell adhesion molecules such as E-cadherin or Crumbs. These cell adhesion molecules interact with the F-actin binding protein angiomotin, which initiates activation of the Hippo kinase cascade (Hansen et al. 2015). The main kinase in this cascade is the Large tumor suppressor 1/2 (Lats1/2; Warts is the *Drosophila* homologue), which functions to phosphorylate Yorkie or its mammalian homologue Yap/Taz. When phosphorylated, Yap/Taz will either be retained in the cytoplasm or degraded, whereas lack of Hippo signaling frees Yap/Taz to enter the nucleus and function as a transcriptional co-activator of Tead (Scalloped homologue). There are several ways in which Hippo signaling components can regulate the pathways of other paracrine factors such as Wnts, EGF, TGF-β, and BMP. Likewise, these pathways can modulate Hippo signaling, typically operating through Yap/Taz. Thus, the Hippo pathway is emerging as a major crossroad for the biochemical pathways of the cell, heightening our attention to the long-unsolved problem of understanding how all these conceptually linear pathways are truly integrated.

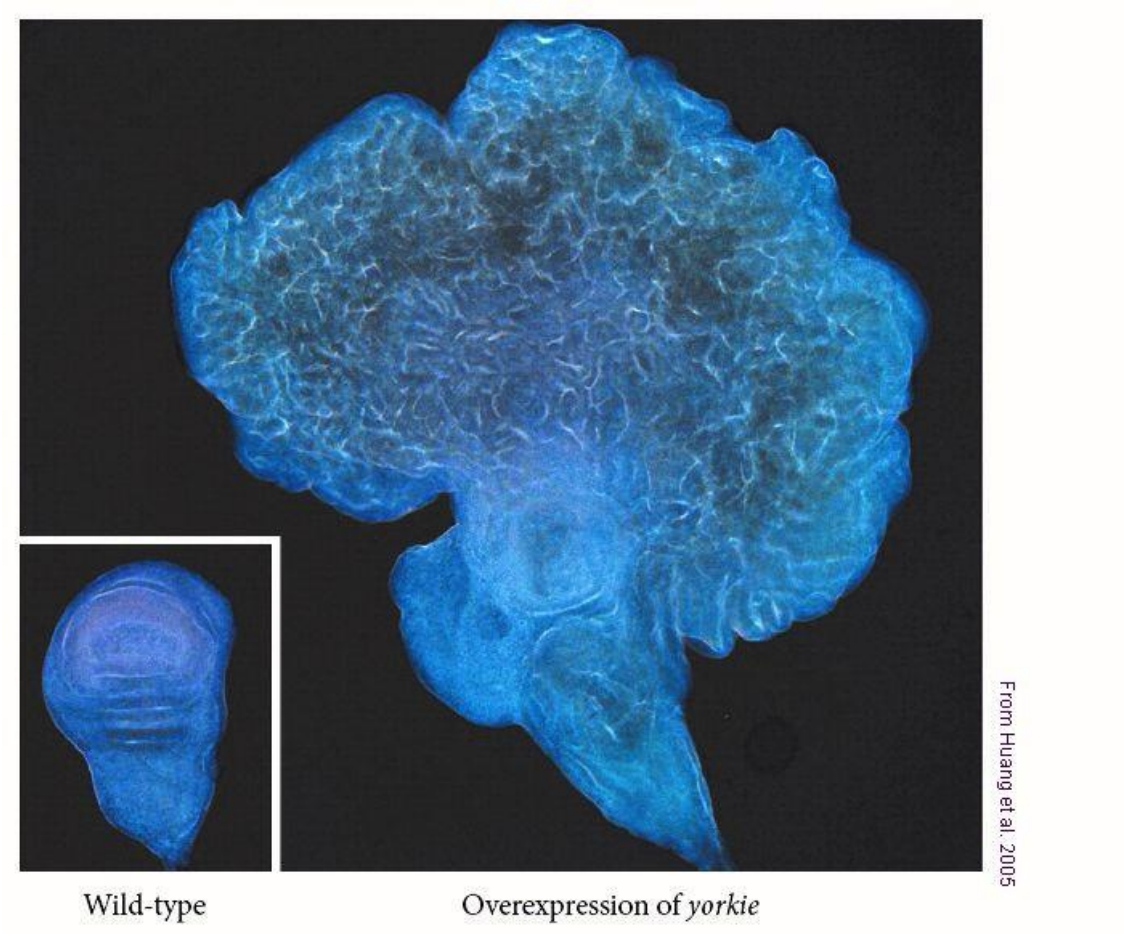

Figure 1 Hippo signaling is critical for controlling organ size. Overexpression of *yorkie* (the main transcriptional effector of the Hippo kinase) in *Drosophila* resulted in an extremely overgrown ("hippopotamus") wing imaginal disc compared with the same stage in a wild-type wing disc. (Photograph from Huang et al. 2005.)