Hippo dances with hormones: Hints from fly research for study of cancer, stem cells

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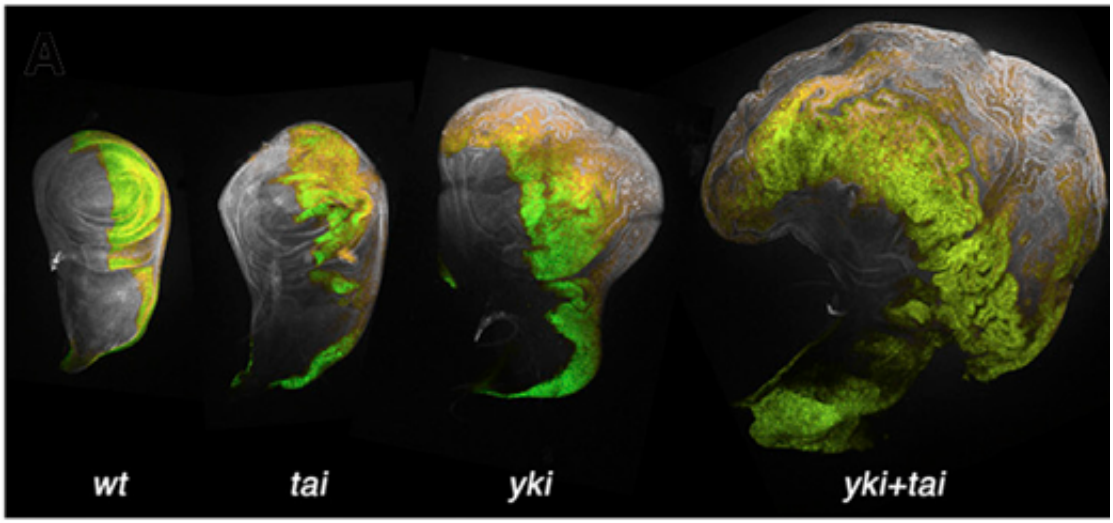

Taiman, needed for ecdysone response, and Hippo pathway member Yorkie drive growth in Drosophila wing imaginal discs. Note massive expansion in Tai + Yki. Green marks the posterior compartment (engrailed). Credit: Zhang et al. *Developmental Cell* 2015

Although fruit flies don't develop cancer, cancer and stem cell researchers have been learning a great deal from fruit flies - in particular, mutant flies with overgrown organs that resemble hippopotamuses.

A fly gene called Hippo and its relatives in mammals normally block cell proliferation and limit organ size. When flies have mutations in Hippo or

other genes (together dubbed the Hippo pathway), the resulting overgrowth distorts their tissues into hippopotamus-like bulges. In humans, the Hippo pathway is involved in forming embryonic stem cells, suppressing cancerous growth, and also in regenerative growth and wound healing.

Working with flies, researchers at Emory have found that the abnormal growth induced by Hippo pathway disruption depends on genes involved in responding to the steroid hormone ecdysone.

Their results are scheduled for publication in *Developmental Cell*.

"Ecdysone is, to some degree, the fly version of estrogen," says senior author Ken Moberg, PhD, associate professor of cell biology at Emory University School of Medicine.

In fly larvae, ecdysone triggers metamorphosis, in which adult structures such as wings and eyes emerge from small compartments called imaginal discs.. Ecdysone has a chemical structure like that of estrogen, testosterone and other steroid hormones found in humans. Ecdysone is not sex-specific, but it acts with the same mechanism as other steroid hormones, diffusing into cells and binding proteins that bind DNA and regulate gene activity.

Postdoctoral fellow Can Zhang, PhD and MD, PhD student Brian Robinson are co-first authors of the Developmental Cell paper. Collaborators at University of Massachusetts, Boston led by Alexey Veraksa, PhD contributed to the paper.

The research team discovered that when the Hippo pathway's control is broken, the resulting excess growth in fly imaginal discs,depends on proteins involved in the ecdysone response.

The genes that are activated by this combination of Hippo and ecdysone signals in imaginal disc 'tumors' include genes that are usually turned on only in germline stem cells, found in flies' reproductive organs. Activation of these germline stem cell factors by the Hippo pathway requires ecdysone response genes, the researchers found.

The researchers concentrated on a protein in flies called Yorkie, which is usually restrained by "upstream" parts of the Hippo pathway. When unleashed, Yorkie travels into the cell nucleus and turns on growth-related genes.

"We found that Yorkie does not just engage a developmental growth program in disc tumors," Moberg says. "It is capable of turning on an ectopic program only seen in germline stem cells."

The researchers were able to detect a physical interaction between Yorkie and Taiman, a protein important in ecdysone response. Taiman's closest human relative is named Amplified in Breast Cancer-1 or AIB1. These findings point to possible connections in human biology between AIB1 and the Yorkie homologs Yap1 and Taz, Moberg says.

"Since both groups of these proteins are often overexpressed in human cancers, we think our findings may have implications for the study of proliferative mechanisms in cancers and possibly cancer stem cells," he says.

More information: Recent summary of Hippo pathway in *Nature Reviews Drug Discovery*. www.nature.com/nrd/journal/v13 … n1/full/nrd4161.html

Provided by Emory University