Metabolic Modulation of Hippo–Yorkie Signaling Drives Tumor-Like Eye Overgrowth in *Drosophila melanogaster*

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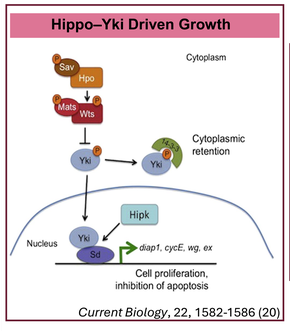
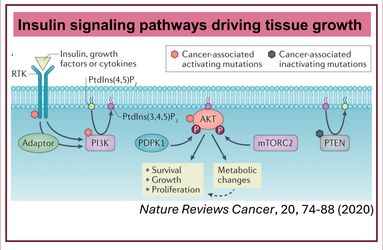
Abstract

- Hippo–Yorkie (Yki) controls tissue growth, while insulin receptor (InR) signaling regulates metabolism and cell growth. Thus, we hypothesized their genetic interaction may influence abnormal tissue expansion.
- Using drosophila eye as a model system, our preliminary data showed that reducing InR or Akt activity suppresses Yki^{CA}-induced overgrowth in the eye, suggesting insulin signaling is required for full tumor-like proliferation.
- Increasing insulin signaling enhances Yki-mediated hyperplasia, demonstrating that InR signaling can amplify Yorkie-driven tissue expansion.

Insulin signaling acts as a key modulator of Yki-driven growth, providing strong evidence of crosstalk between metabolic and growth-control pathways in the Drosophila eye.

Background





- Hippo signaling normally inhibits Yorkie (Yki); loss of Hippo activity or hyperactive *Yki^{CA}* causes excessive proliferation and tumor-like eye overgrowth in *Drosophila*.
- Insulin signaling also regulates cellular growth, raising the question of whether crosstalk between Hippo–Yki and insulin pathways contributes to abnormal tissue expansion in vivo.

Research Question

Does insulin signaling interact with the Hippo–Yorkie pathway to modulate *Yki^{CA}*-driven tumor-like overgrowth in the *Drosophila* eye in vivo?

Methods

- The Drosophila melanogaster eye was used as an in vivo tumor model, where GMR-Gal4–driven expression of constitutively active Yki^{CA} induces strong eye overgrowth.
- To test insulin pathway involvement, InR and Akt activity were genetically reduced or enhanced in the Yki^{CA} background through targeted crosses with RNAi, constitutively active, and mutant lines.
- F1 adult progeny were sorted, and eye morphology was analyzed microscopically, comparing control and experimental groups to assess the extent of Yki-mediated tumor-like overgrowth.

Results

Figure 1. Increasing the level of hyperactive *Yki^{CA}* and *InR^{CA}* specifically in the Drosophila melanogaster eye caused massive eye growth abnormal eye morphology

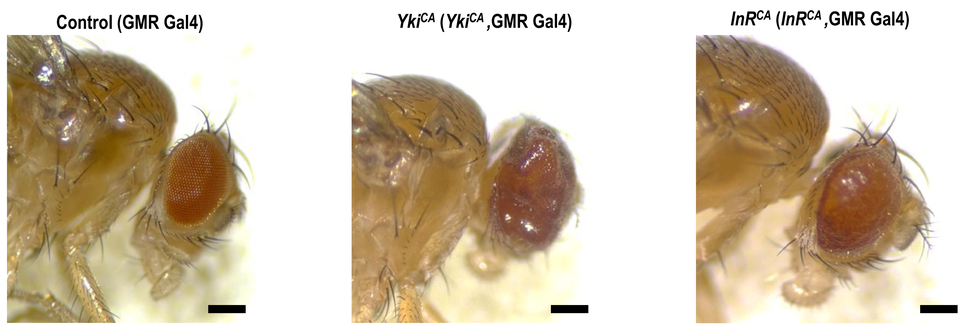


Figure 2. InR receptor is required for *Yki^{CA}*-mediated abnormal tissue growth

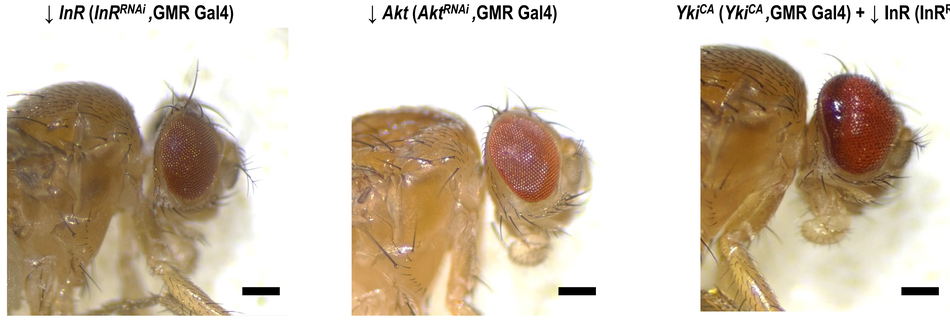
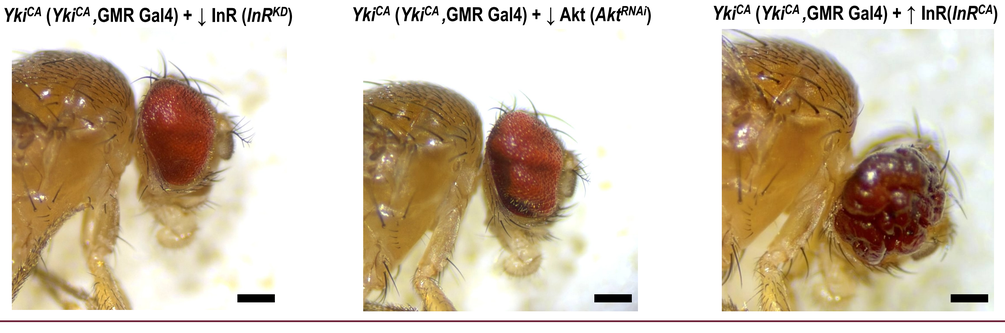


Figure 3. Insulin signaling is both required and sufficient for *Yki^{CA}*-mediated abnormal tissue growth



Discussion

- Our preliminary data showed that reducing InR or Akt activity markedly suppresses Yki^{CA}(YkiS168A)-mediated eye overgrowth, demonstrating that insulin signaling can negatively regulate Yorkie-driven tissue expansion.
- Constitutive activation of InR greatly enhances the hyperplastic phenotype, showing that insulin signaling can potentiate Yki-induced overproliferation.

The dependence of Yki-mediated tumor-like growth on insulin pathway activity reveals strong crosstalk between metabolic signaling and the Hippo–Yorkie system, indicating that metabolic state can significantly modulate tumor severity.

Future Research

- **Define Hippo–insulin crosstalk mechanisms** by determining how InR/Akt signaling regulates Yki activity (phosphorylation, localization, or kinase interactions).
- **Identify metabolic targets** of Yki–insulin interaction, including changes in glycolysis, lipid synthesis, and mitochondrial activity driving tumor-like growth.
- **Assess tissue and disease relevance** by testing crosstalk in other tissues and its conservation in mammalian Hippo–YAP systems.

Acknowledgments

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