Log of Research Documents

Hailee Peck

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1. Tumaneng, et al.: YAP mediates crosstalk between the Hippo and PI3K-TOR pathways by suppressing PTEN via miR-29.
    - YAP is main downstream target of mammalian Hippo pathway, promotes organ growth
    - YAP activates mTOR (major regulator of cell growth)
    - YAP is phosphorylated and inhibited by LATS
    - Cell density is known to regulate YAP phosphorylation and activity
    - Yorkie (Drosophila) induces expression of bantam microRNA that serves as a critical mediator of Yorkie's biological functions
    - Establishes a functional link between Hippo and TOR in mammals
2. Kockel, et al.: Dynamic Switch of Negative Feedback Regulation in *Drosophila* Akt-TOR Signaling
    - Three basic concepts of downregulating signaling pathways: control via specific inhibitory ligands/receptors, negative cross-regulation by distinct signaling pathways, auto-regulation by negative feedback mechanisms
    - TORC1 and TORC2 both participate in Akt-TOR signaling but act at different levels in the pathway and integrate distinct stimuli: TORC2 responds to growth factors and might determine substrate specificity of Akt, TORC1 mediates signaling by amino acids and cellular energy stress.
    - dAkt-TOR pathway in Drosophila regulates cell proliferation, developmental timing and sizing of cells, organs, and whole fly
    - Drosophila has only one dAkt gene (mammals have 3)
    - Phosphorylation of dAkt is regulated by negative feedback from Tsc1/Tsc2-TOR-S6K but independent of FoxO
    - Negative feedback regulating dAkt activity is independent of S6K under normal TORC1 activity or dependent on S6K when TORC1 activity is high. Thus, S6K is a sensor of TORC1 that provides additional suppression of the signal when TORC1 is highly active.
3. Zhao, et al.: The Hippo pathway in organ size control, tissue regeneration, and stem cell self-renewal

- Hippo pathway limits organ size by phosphorylating and inhibiting Yki, a key regulator of proliferation and apoptosis
- Hippo pathway is regulated by cell polarity, cell adhesion and cell junction proteins
- Core components of Hippo pathway: warts (wts), hippo (hpo), salvador (sav), all tumor-suppressor genes
- Wts directly phosphorylates and inhibits Yki
- Merlin (Mer) and Expanded (Ex) were found to activate the Hippo pathway
- Fat protocadherin, a cell surface molecule, is an upstream regulator of Hippo pathway. Its activity is regulated by binding to Dachsous (Ds) and is modulated by Dco, Fj, and Lft. Dpp and Wg affect expression of Fj and Ds.
- Yki induces cycE and E2F1 (regulation of cell proliferation), EGFR ligands and Jak-Stat ligands
- An imbalance of Hippo pathway activity in neighboring cells may induce cell competition through differential expression of dMyc in Drosophila
- Mechanism by which upstream regulators of the Hippo pathway are integrated to initiate or terminate signaling is not yet fully understood

4. Sun, Irvine: Cellular Organization and Cytoskeletal Regulation of the Hippo Signaling Network

    - Cell-cell junctions serve as platforms for Hippo signaling by localizing scaffolding proteins that interact with core components of the pathway
    - Hippo was first discovered in Drosophila through the identification and characterization of genes that when mutated cause severe overgrowth phenotypes
    - Hippo signaling is influenced by or crosstalks with multiple pathways that respond to growth factors, that promote growth linked to positional information, or that influence growth in response to nutritional and metabolic status.
    - Hippo signaling is also affected by contacts with neighboring cells and the ECm, and by mechanical forces.
    - Yki is downregulated by phosphorylation by the kinase Wts which promotes cytoplasmic localization of Yki (doesn't allow it into the nucleus)
    - Core of the Hippo network: four proteins that regulate Yki, Hpo, Wts, Sav, and Mats
    - Dachs influences Wts prtein levels and inhibits Wts association with Mats
    - Mer promotes Wts activation by bringing Wts and Hpo together at cell membranes.
    - cell-cell junctions are under tension in Drosophila epithelia, promoting Yki activity
    - Outstanding questions: Are different core components of the Hippo signaling network regulated by different upstream inputs?; How are different cytoskeleton dependent form sof regulation integrated and coordinated?; What additional cellular sites of Hippo and Warts activation remain to be discovered?

5. Vidal, Cagan: Drosophila models for cancer research

    - The excess proliferation observed in cancer can be attributed to both a deregulation of the mechanisms underlying cell growth and a loss of inducers of apoptosis
    - Yorkie is normally inactivated by Warts and mediates the transcription of cyclin E and DIAP1 (Drosophila inhibitor of apoptosis 1)
    - Border cells migrate as an epithelial patch without undergoing an EMT.
    - In a homotypic environment where all cells in the tissue are scrib negative, cells display neoplastic growth and produce tumors
    - In discrete clonal patches where scrib negative cells are mixed with wild type ones, the scrib negative cells undergo apoptotic death

6. Hemalatha, Prabhakara, Mayor: Endocytosis of Wingless via a dynamin-independent pathway is necessary for signaling in Drosophila wing discs

    - Wingless forms a spatial gradient across the boundary and activates distint concentration-dependent transcriptional programs ensuig coordinated tissue growth
    - Study provides evidence for a mechanism wherein cells leverage multiple endocytic pathways to coordinate signaling during patterning
    - Honestly not sure what the importance of this paper is in the scheme of looking at the Drosophila Hippo pathway

7. Shimobayashi, Hall: Making new contacts: the mTOR network in metabolism and signalling crosstalk

    - TOR pathway integrates stimuli from growth factors, nutrients, and cellular energy status to activate the metabolic pathways that ultimately drive cell growth
    - Gives an overview of downstream effectors and upstream regulators of mTOR signaling, but (obviously) focused on mammalian

8. Harvey, Zhang, Thomas: The Hippo pathway and human cancer

    - Nice figure detailing the components of the Hippo pathway in Drosophila
    - Else, mainly focuses on mammalian Hippo pathway

9. Lin, Othmer: A model for autonomous and non-autonomous effects of the Hippo pathway in Drosophila

    - Hippo pathway controls cell proliferation and apoptosis in Drosophila and mammalian cells
    - Growth control in wing disc involves both local signals within the disc and system-wide signals such as insulin that coordinate growth across the organism
    - pathways are tightly linked so strengths of interactions determine outcome – Boolean model insufficient, need quantitative model

- Hippo pathway is a highly-conserved kinase cascade made of Hippo (Hpo), Warts (Wts), and adaptor proteins Salvador (Sav) and Mob as tumor suppressor (Mats)
- Key effector is Yorkie (Yki) and Wts is its master regulator
- Yki controlled by Wts through phosphorylation–once Yki is phosphorylated, it cannot enter the nucleus, so it cannot control cell proliferation or expression of genes upstream of Hippo module
- Hippo has two upstream modules: one based on Crumbs, Expanded, Merlin, and Kibra which affect Hippo kinase, and one based on Fat (Ft) and Dachsous (Ds) that regulate Wts. Input to Hippo assumed to be constant, so more important is second upstream module
- Ft and Ds are cadherins (calcium-dependent adhesion, bind cells together) which have intracellular, transmembrane, and extracellular domains. The ICDs mediate signaling within a cell while the ECD on adjacent cell membranes can associate to strengthen signaling and mediate cell-cell interaction
- Binding between Ft and Ds is regulated by Fj (Fj phosphorylates ECD of Ft, increasing its affinity to Ds, and phosphorylates ECD of Ds, decreasing its affinity to Ft)
- Signaling from ICD of Ft suppresses growth via Dachs (Dh): overexpression of Dh increases wing size, while Dh loss of function mutant decreases wing size
- Amount of Dh localized on membrane controls cell growth
- Effect of Ft on growth is not a strictly decreasing function of Ft level: overexpression of Ft above wild type levels decreases wing size and complete knockout of Ft increases wing size, but partial knockout of Ft decreases instead of increases wing size
- Effect of Ds is non-monotonic: loss of Ds enlarges wing discs but overexpression can either reduce or enhance growth
- When Fj and Ds are co-overexpressed, the reduction in wing size is greater than for either separately
- **Central components for model: Ft, Ds, Dh, Riq, Wts, Yki**
- Phosphorylation: phosphate group (provided by ATP) added to a protein by kinases. THis alters the activity of a protein after the protein has already been formed.
- Dh degraded more rapidly when bound to Ds so in the absence of Ds, Wts inhibition by Dh is increased since there is more of it around, leading to higher Yki bc less Wts to phosphorylate it (?)
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10. NIH proposal

- Primary morphogens in the wing disc are wingless (Wg, a segment polarity gene), and decapentaplegic (Dpp, a bone morphogenic protein)
- **Goal: develop a multi-scale, 3D computational model of signaling in the wing disc**

- Essential to incorporate detailed structure in a horizontal slice of the disc, and transport and signaling in the vertical direction
- The morphogens Hh, Dpp, and Wg control the downstream network (they are each at the top of a signaling pathway)
- Local inputs to Hippo pathway are from links to adjacent cells via Ft and Ds, and the key effector is Yki, a cotranscription factor whose nuclear localization is controlled by the kinase Wts (when Yki phosphorylated by Wts, cannot enter nucleus)
- WAMND–what are my neighbors doing model
- Binding of Ds to Ft activates Wts by relieving the inhibition of Wts by Dachs. Activated Wts phosphorylated Yki to prevent entry into nucleus, controlling cell growth
- Incorporated in Hippo pathway: Ft, Ds, Fj, Dachs, Wts, Riq, Ex, and Yki
- Test whether feedback loops created by Yki control of Fj and Ds expression leads to the observed spatial profiles of Ft and Ds (how do these loops affect Yki activity within a cell)

11. Zhang, Lai: Mob as tumor suppressor is regulated by bandtam microRNA through a feedback loop for tissue growth control

    - Yki upregulates transcription of Expanded and Merlin in Drosophila
    - bantam microRNA is a downstream target of Hippo pathway; promotes tissue growth by stimulating cell proliferation and inhibiting cell apoptosis.
    - Show: ban indirectly regulates mats expression in developing tissues