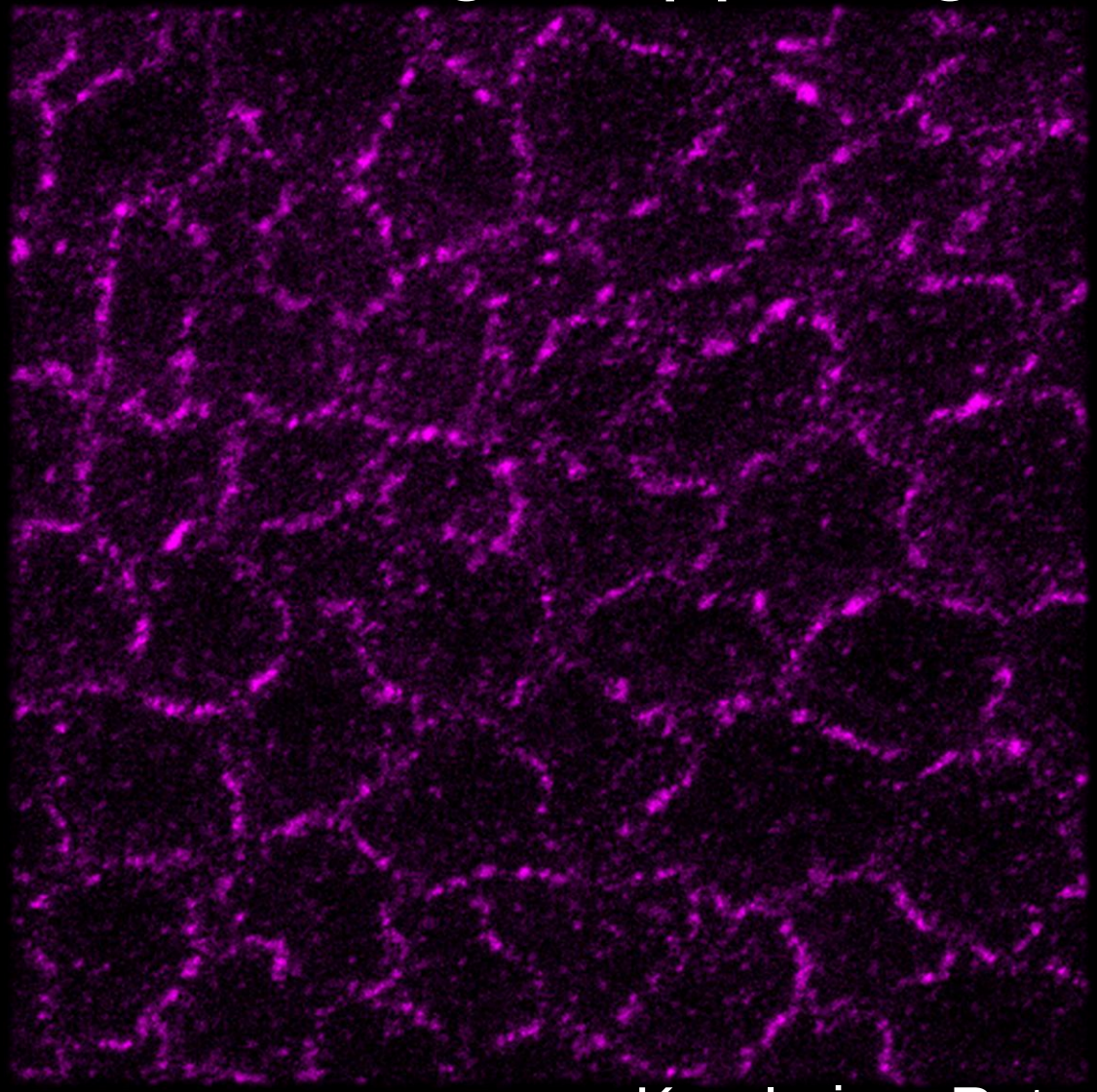
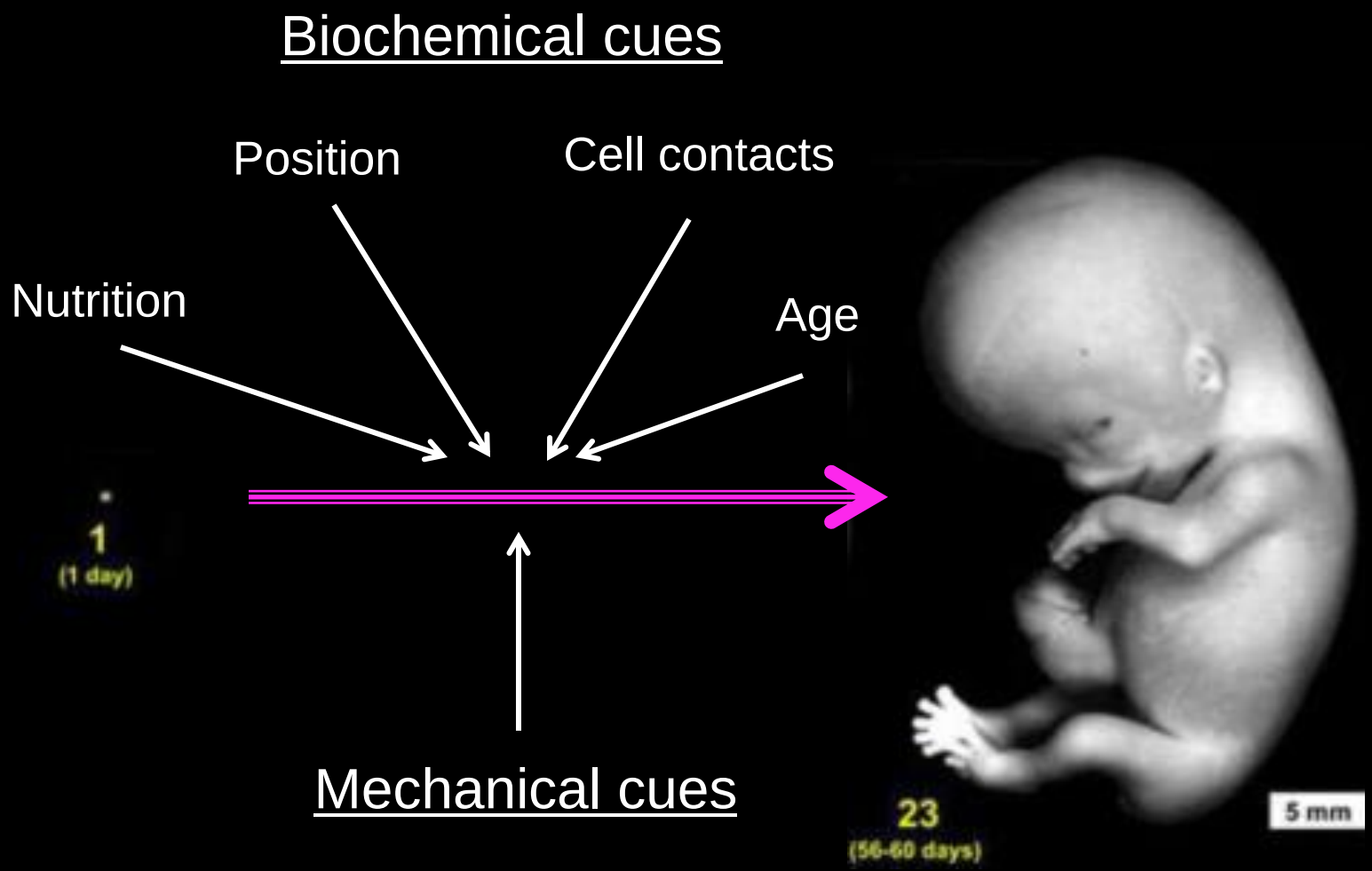
# Biomechanical Regulation of Organ Growth through Hippo Signaling



Ken Irvine, Rutgers University

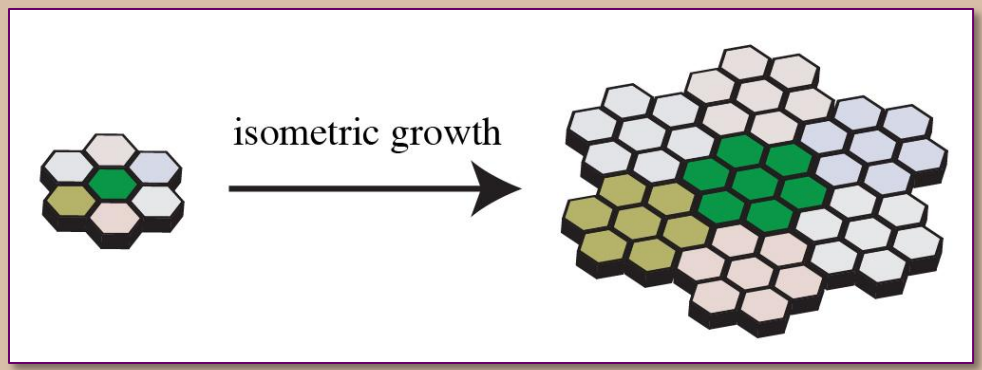
# Growth control requires integration of multiple signals

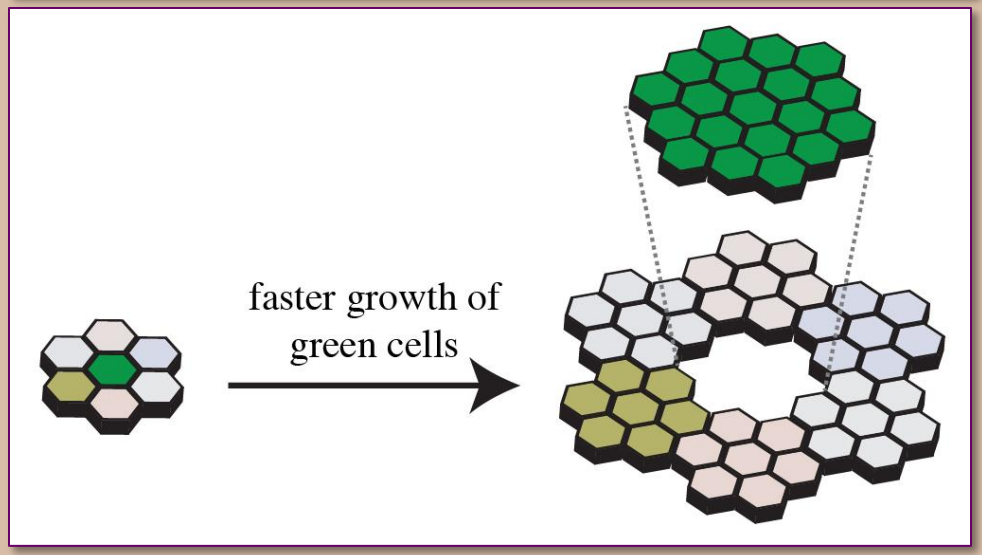


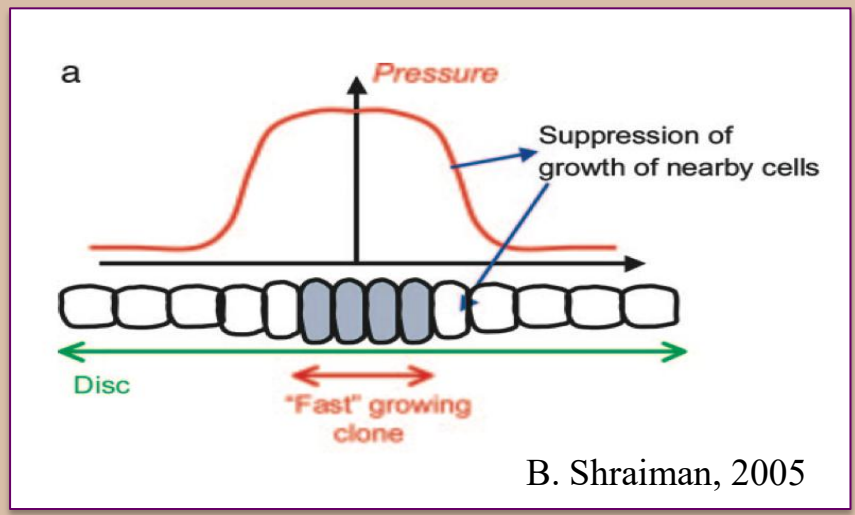
# Mechanical feedback as a possible regulator of tissue growth

Boris I. Shraiman†

3318–3323 | PNAS | March 1, 2005 | vol. 102 | no. 9



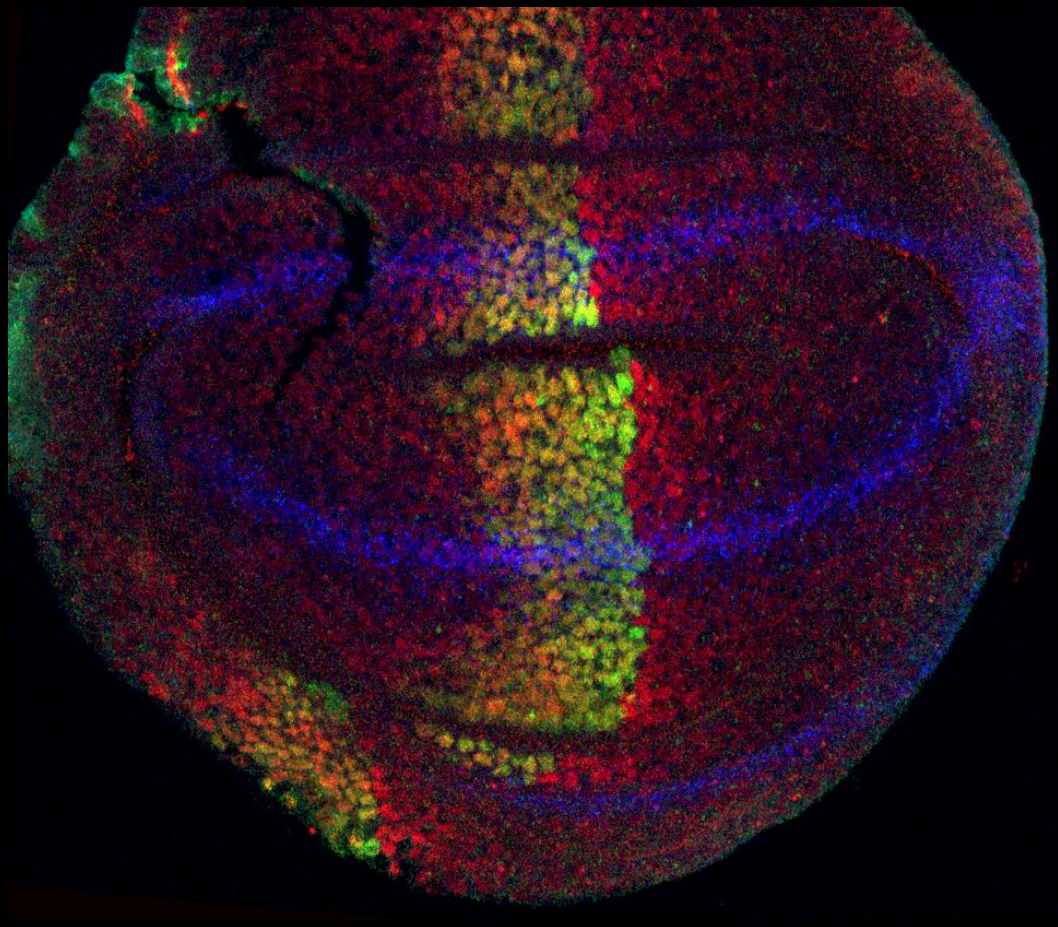



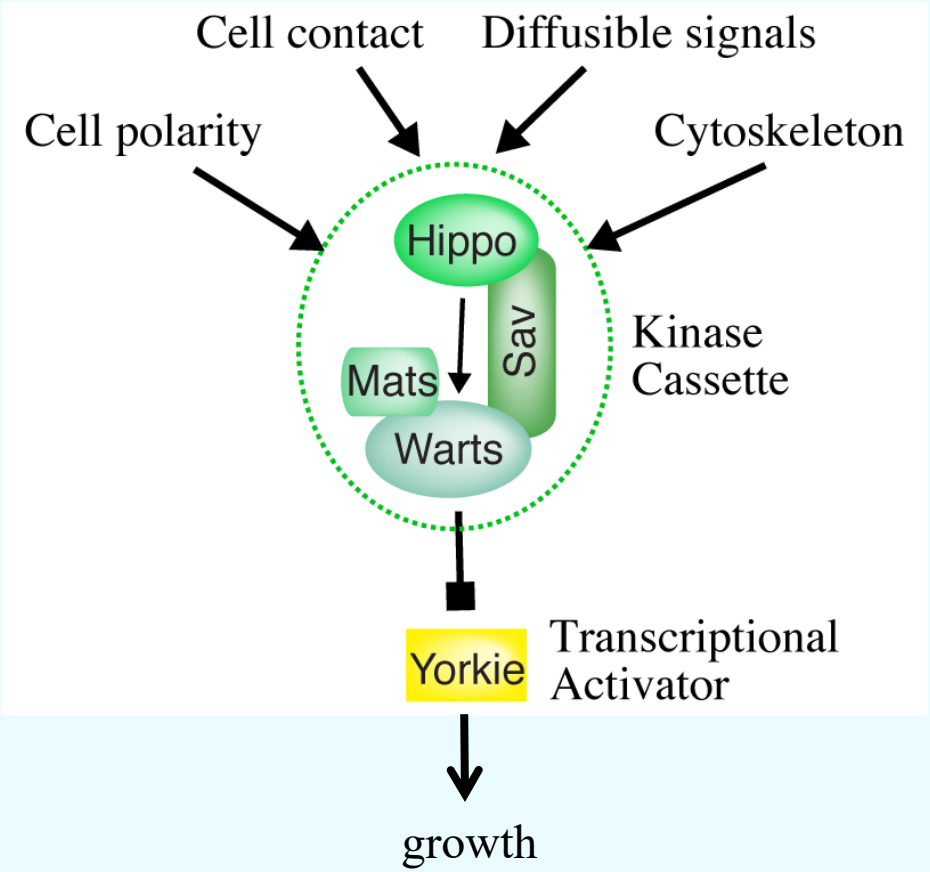

B. Shraiman, 2005

1. What contribution does tissue mechanics make to growth control?

2. What are the molecular mechanisms by which mechanical forces influence growth?

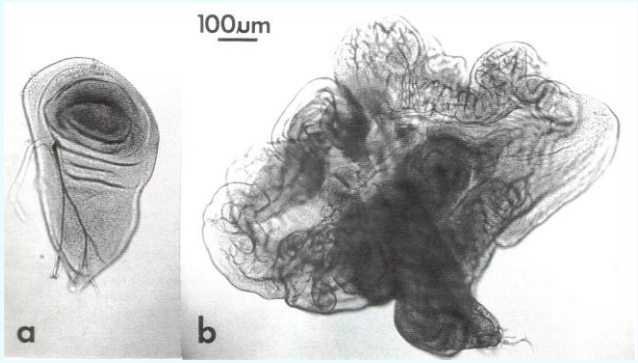


# Hippo Signaling




*Drosophila* tumor suppressor genes

*Wild type* *fat*



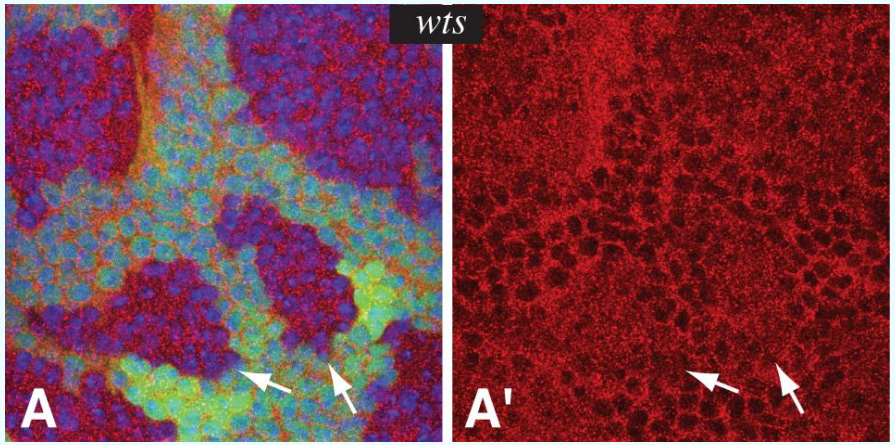

Mahoney *et al*, Cell 1991

*wart*

*s*

Xu et al., *Dev.*, 1995

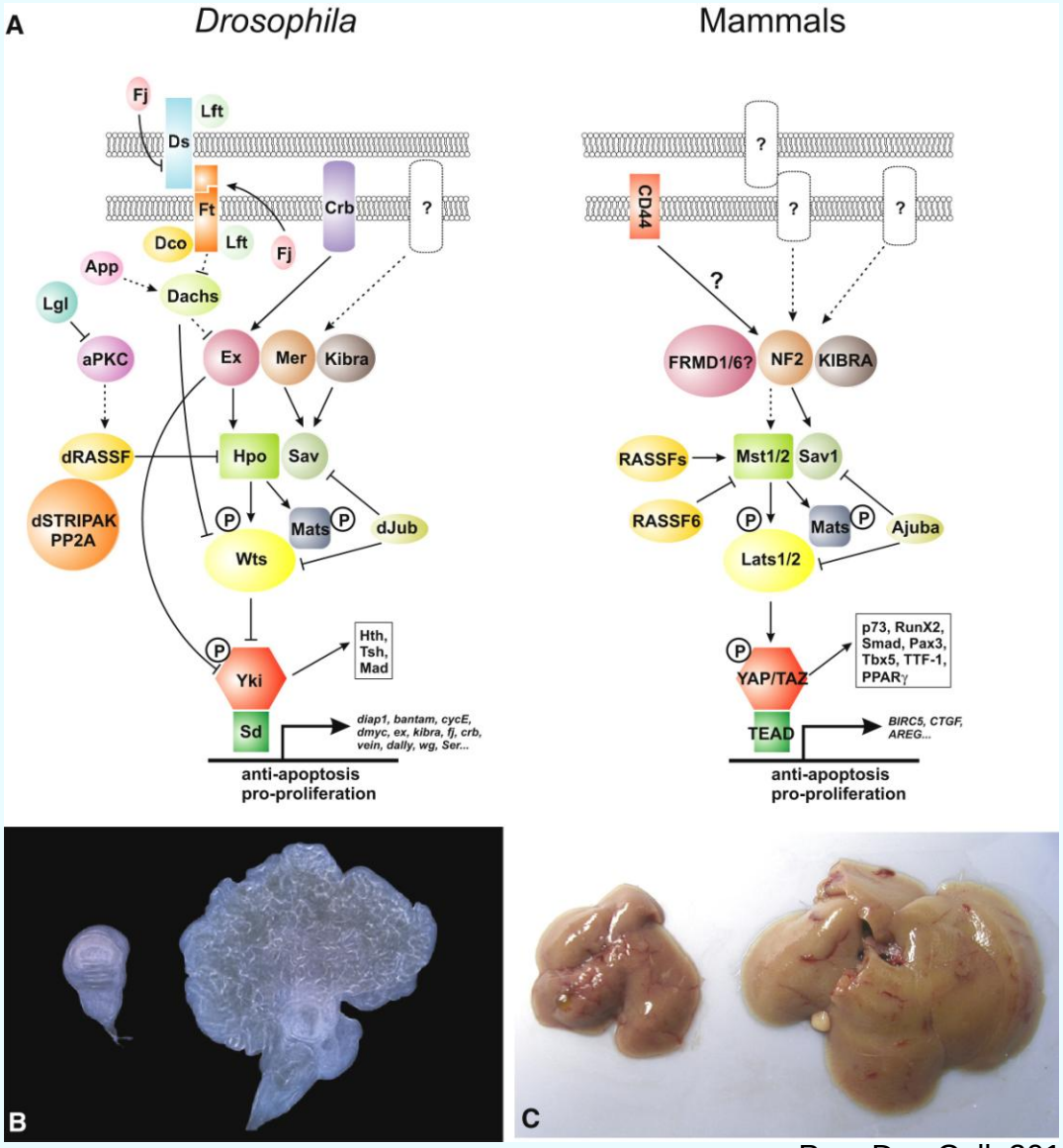
*warts* mutant clones




Oh & Irvine, 2008. **Dev**. *135*, 1081

Yki

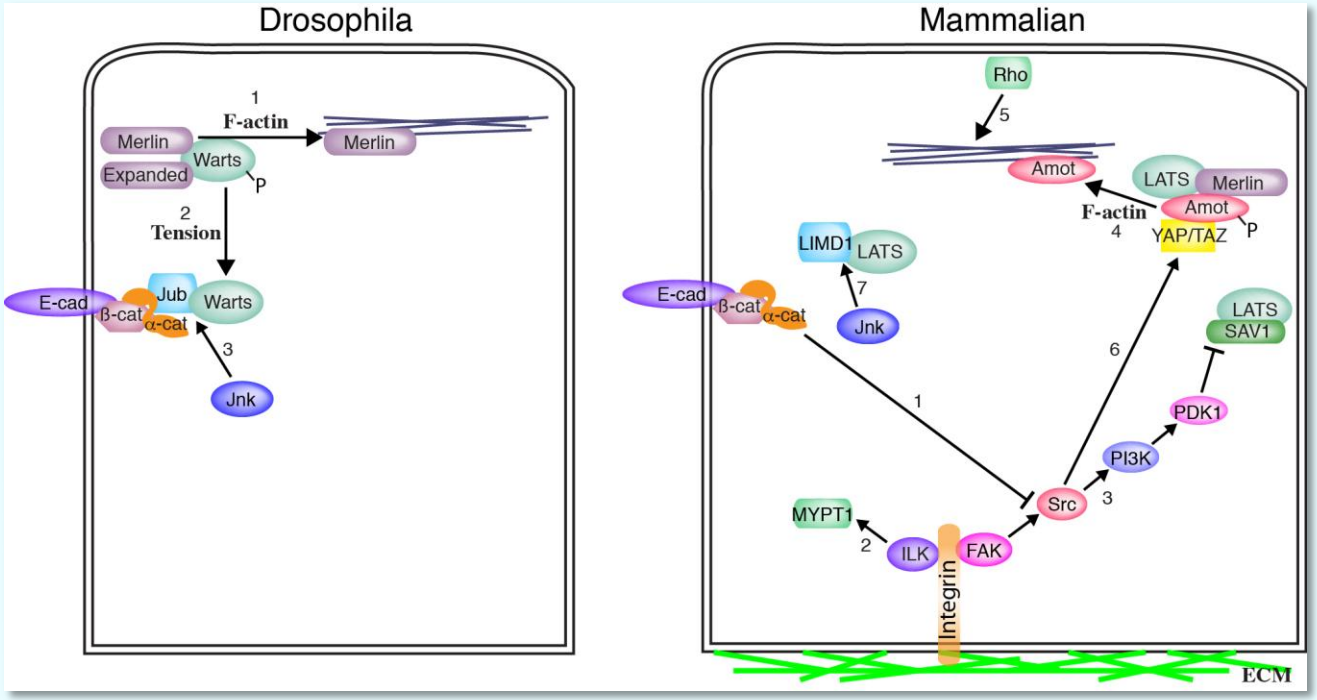
# Hippo Signaling is Conserved

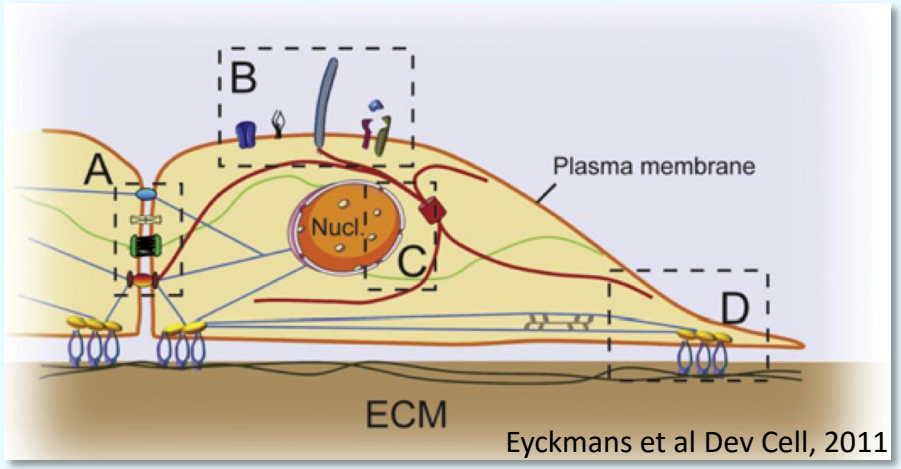



Pan, Dev Cell, 2010

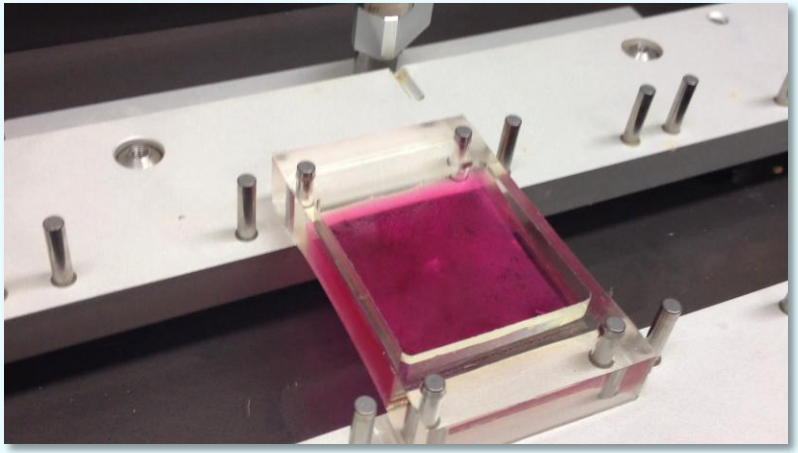
Activation of YAP is associated with many cancers

# YAP can be activated by cytoskeletal tension and F-actin accumulation



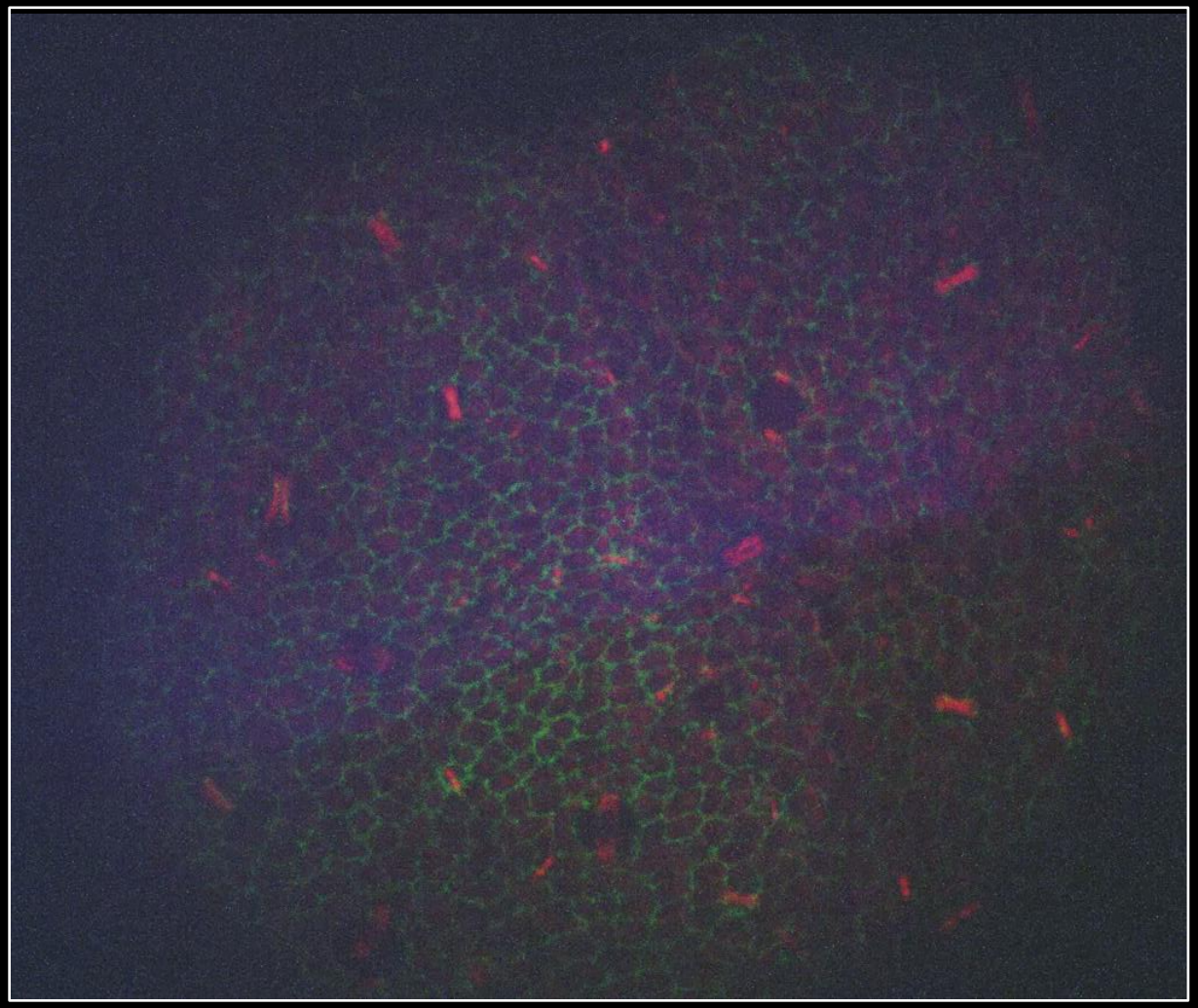



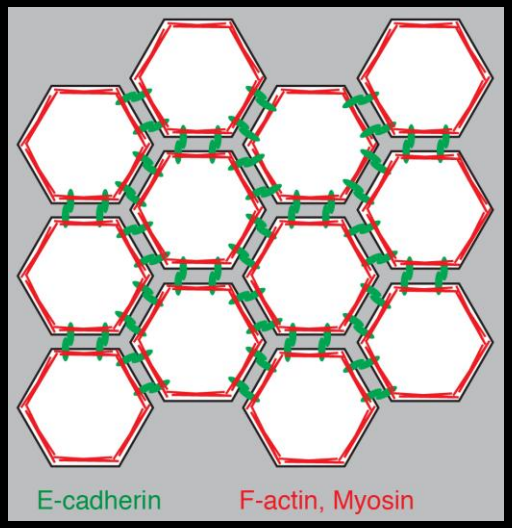

Eyckmans et al Dev Cell, 2011



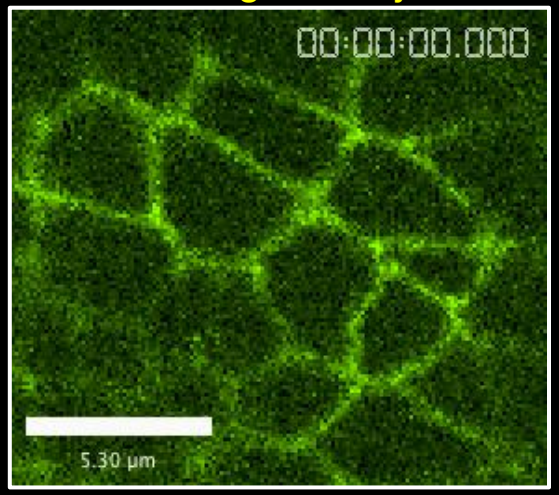
# Wing disc cells are under tension along cell junctions

*Drosophila* wing disc



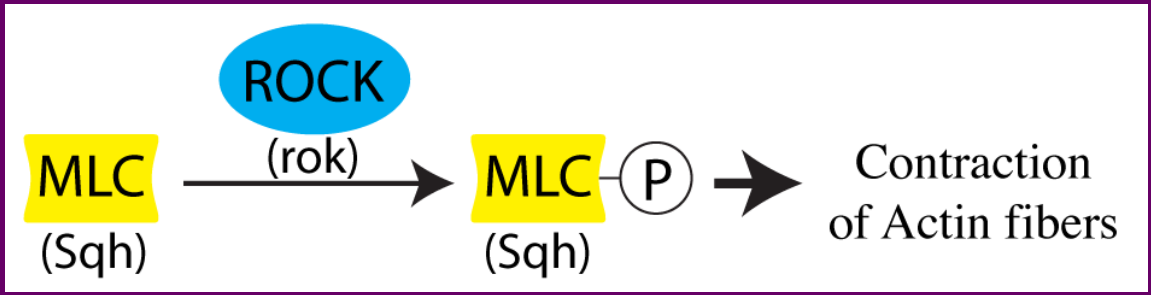


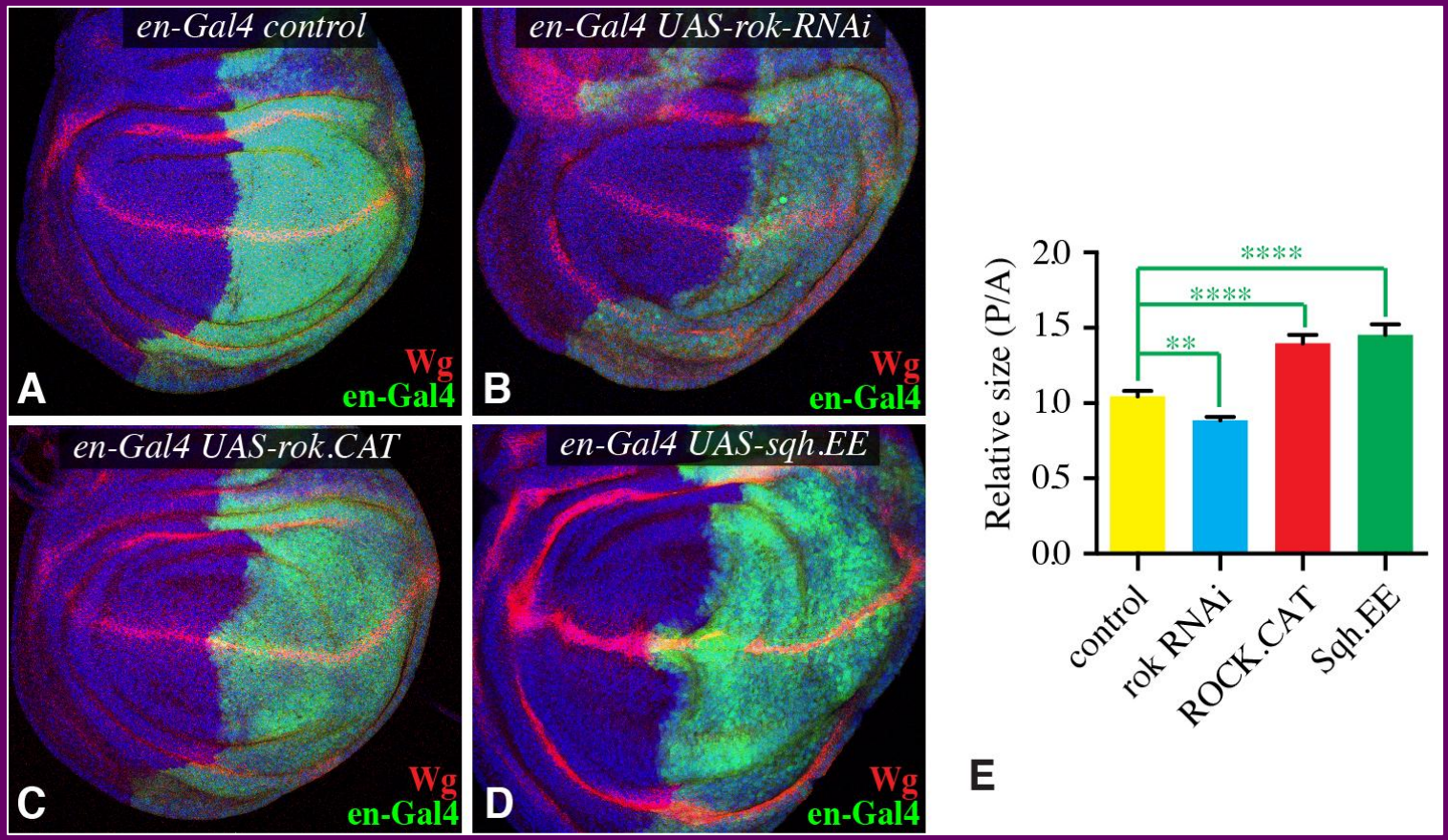

Laser cutting of cell junctions




E-cadherin:GFP

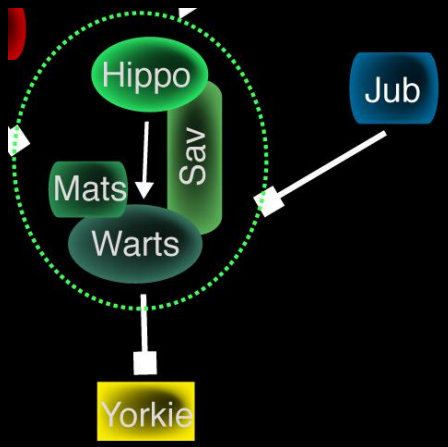
# Cytoskeletal tension can influence wing disc growth



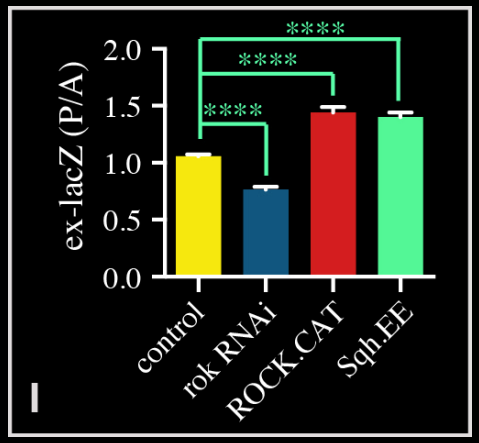



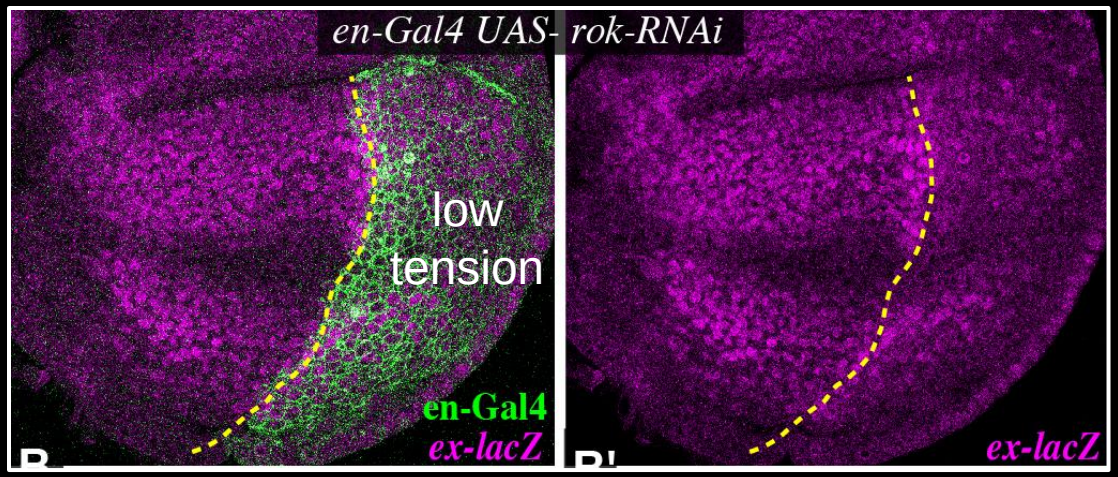

Rauskolb et al, *Cell* 2014

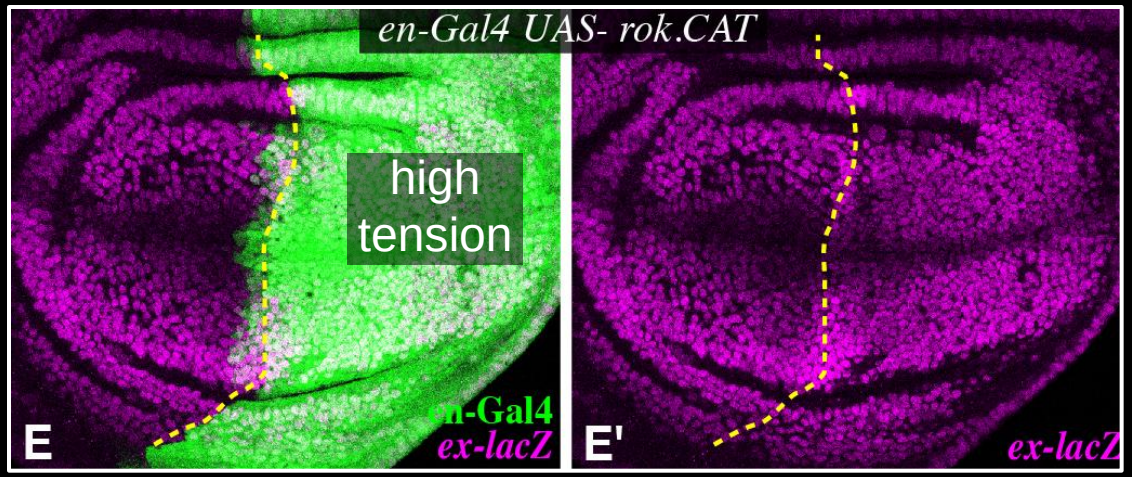
# Myosin promotes Yorkie activity in wing discs




ex-lacZ



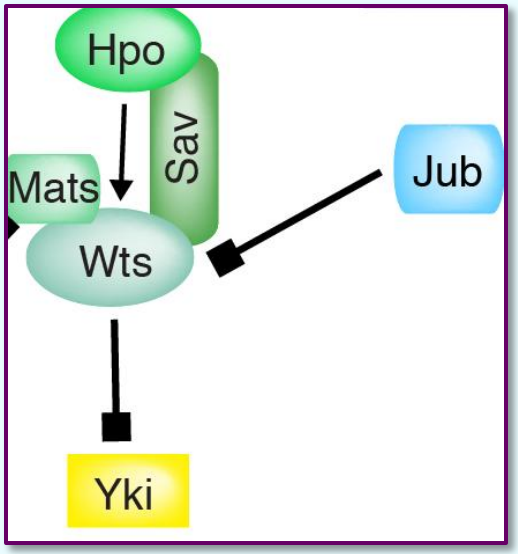



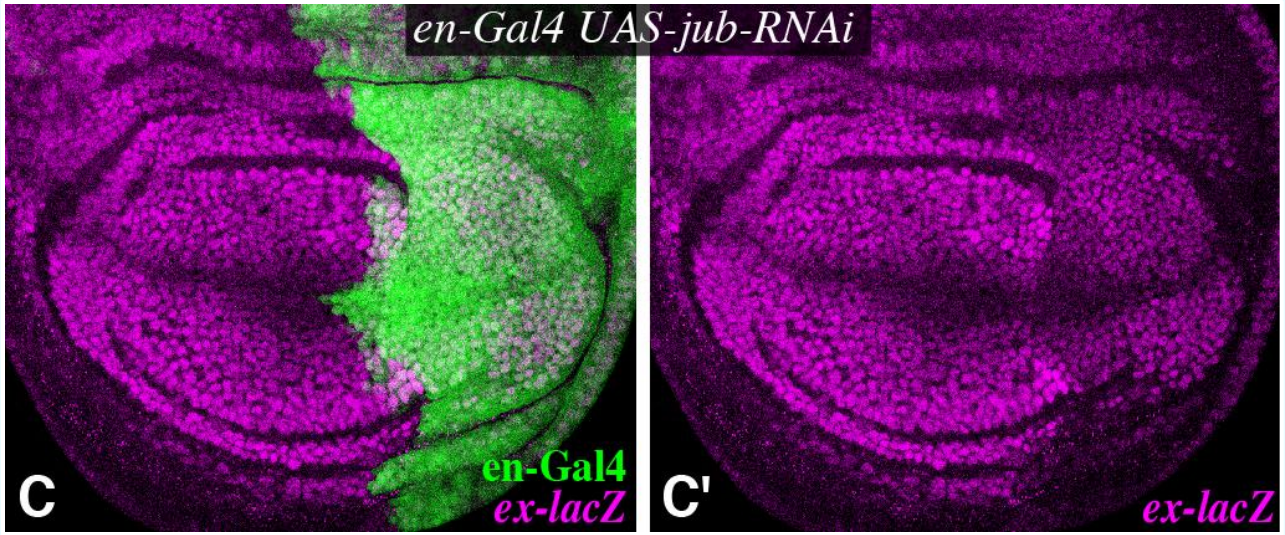

Myosin → Yorkie

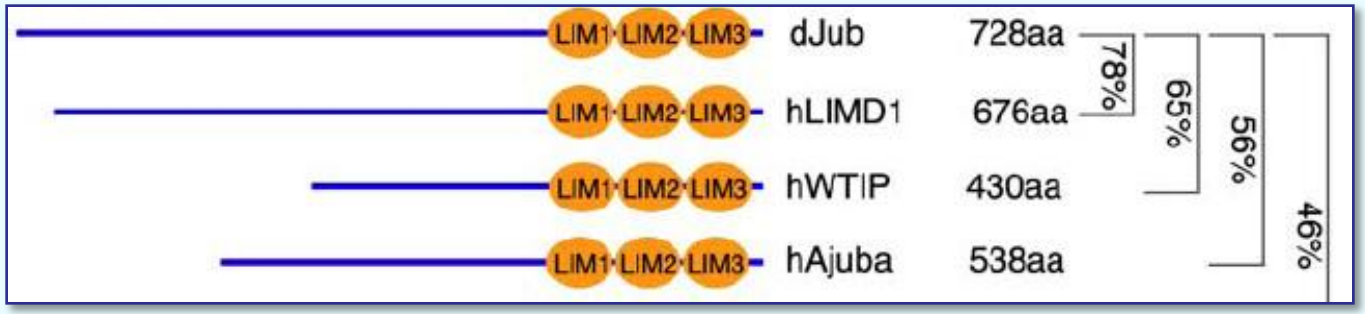
Rauskolb et al, *Cell* 2014

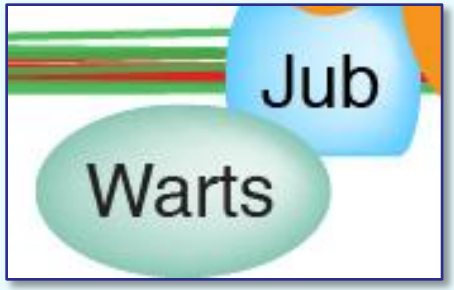
# Jub (Ajuba LIM protein), a negative regulator of Hippo Signaling

Das Thakur *et al*, Current Biol. 2010

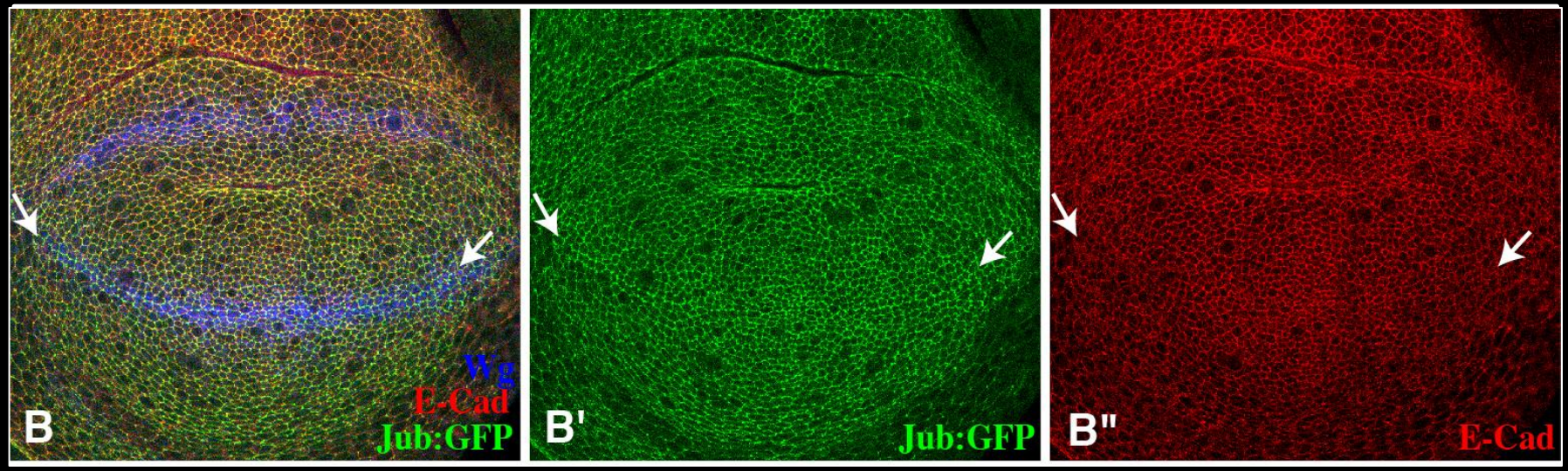


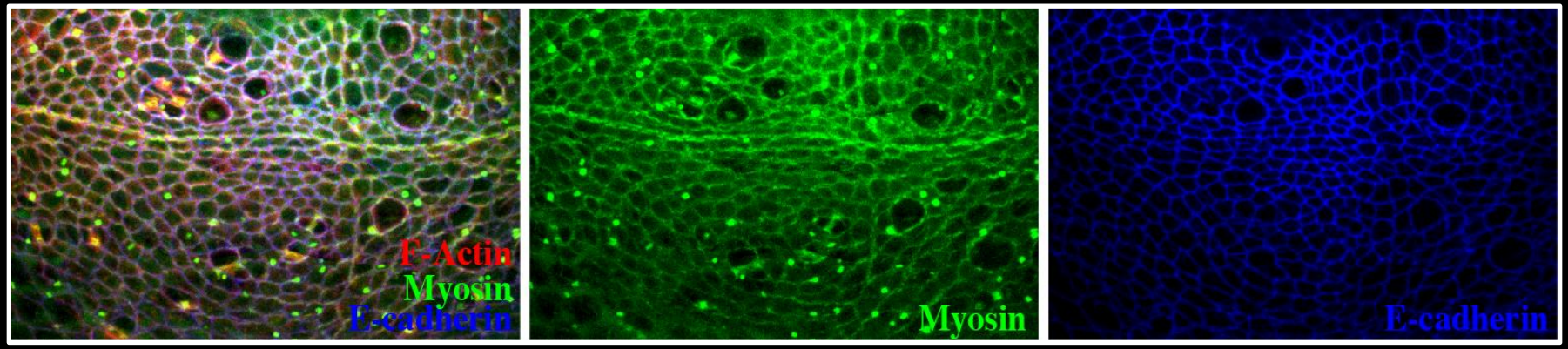



# Jub localization in wing discs

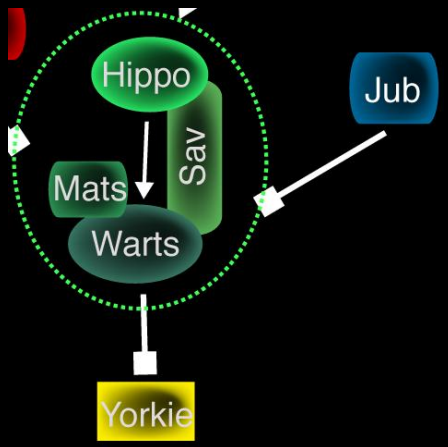


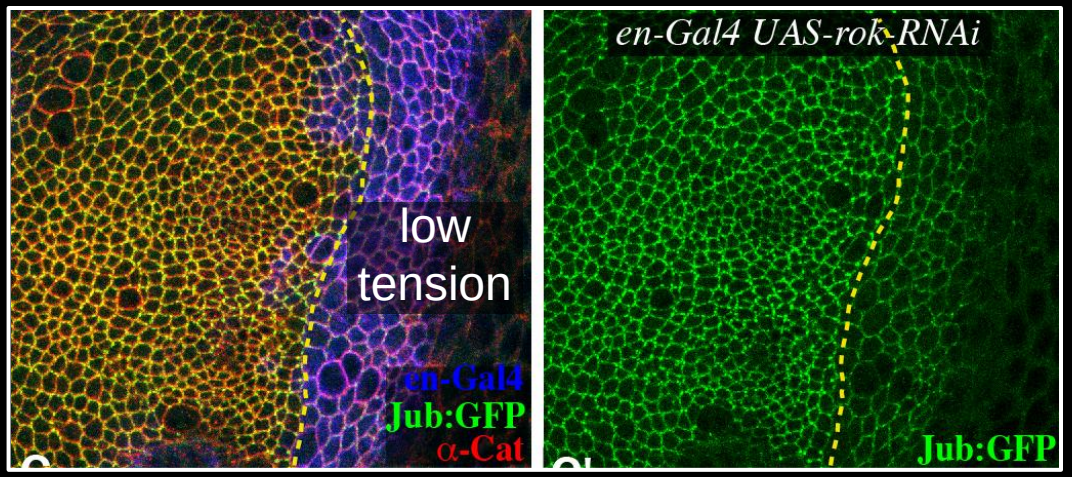



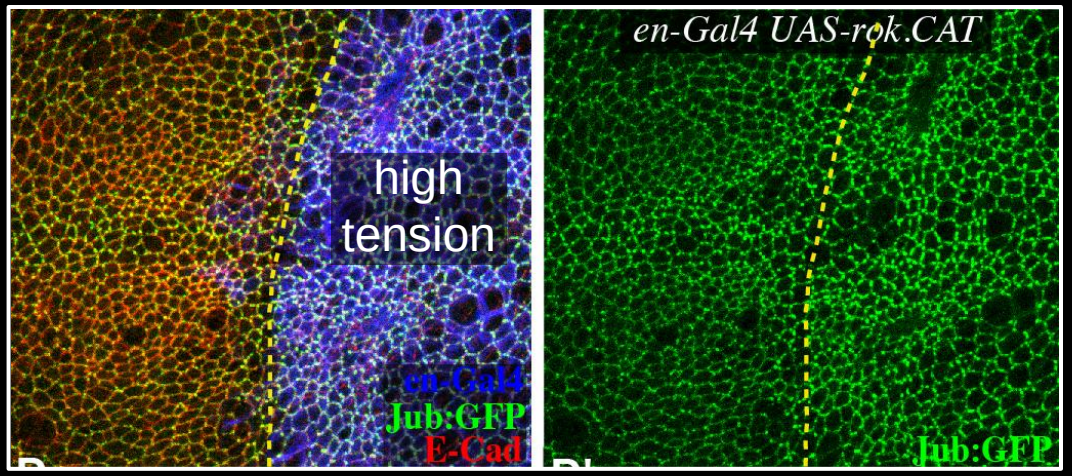

Major & Irvine, 2006. **Dev. Dyn 235, 3051**

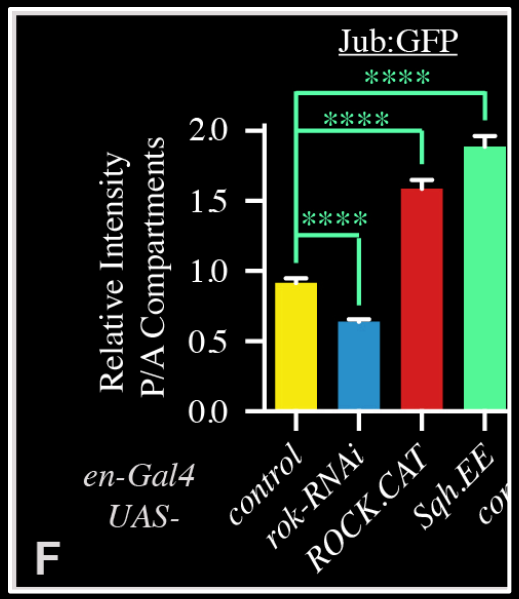
Jub accumulation is elevated where tension is higher

# Jub localization is regulated by myosin activity



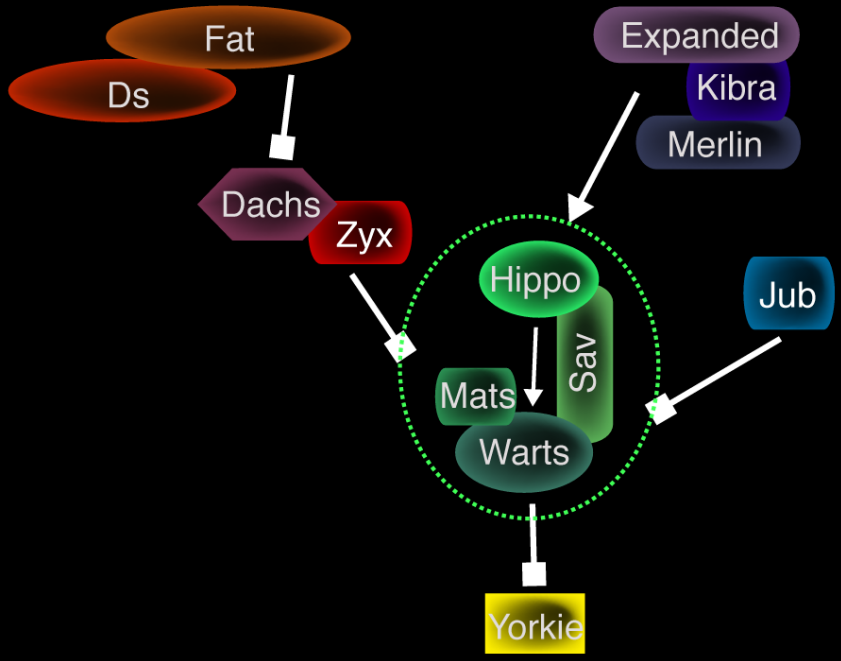



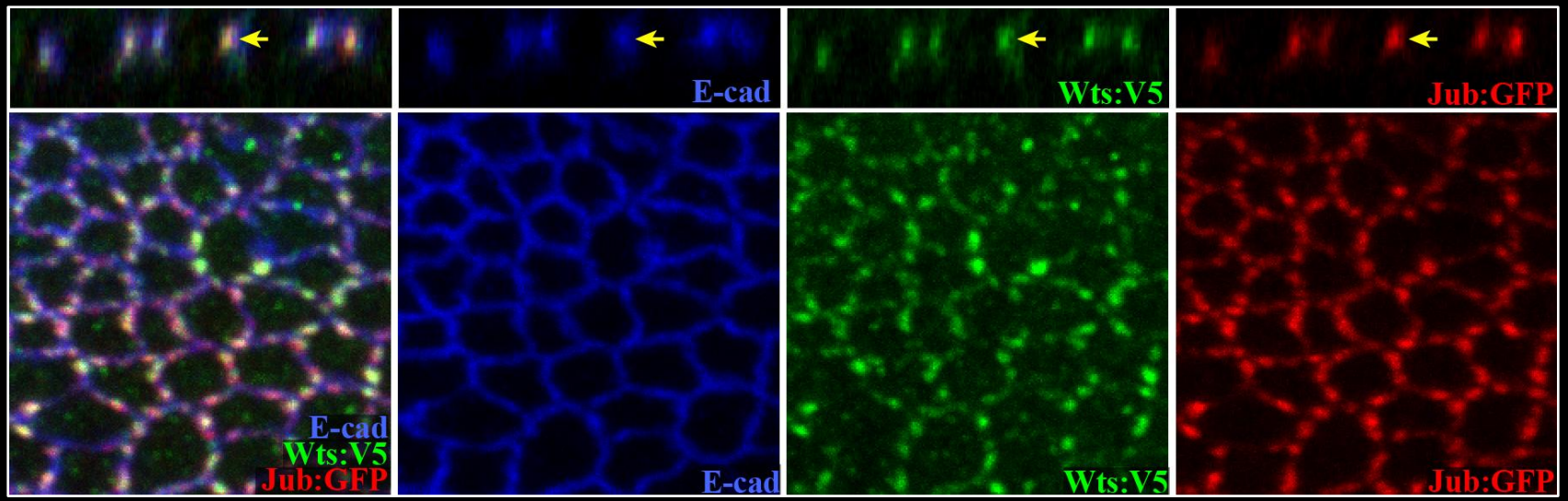




Myosin → Jub

Rauskolb et al, *Cell* 2014

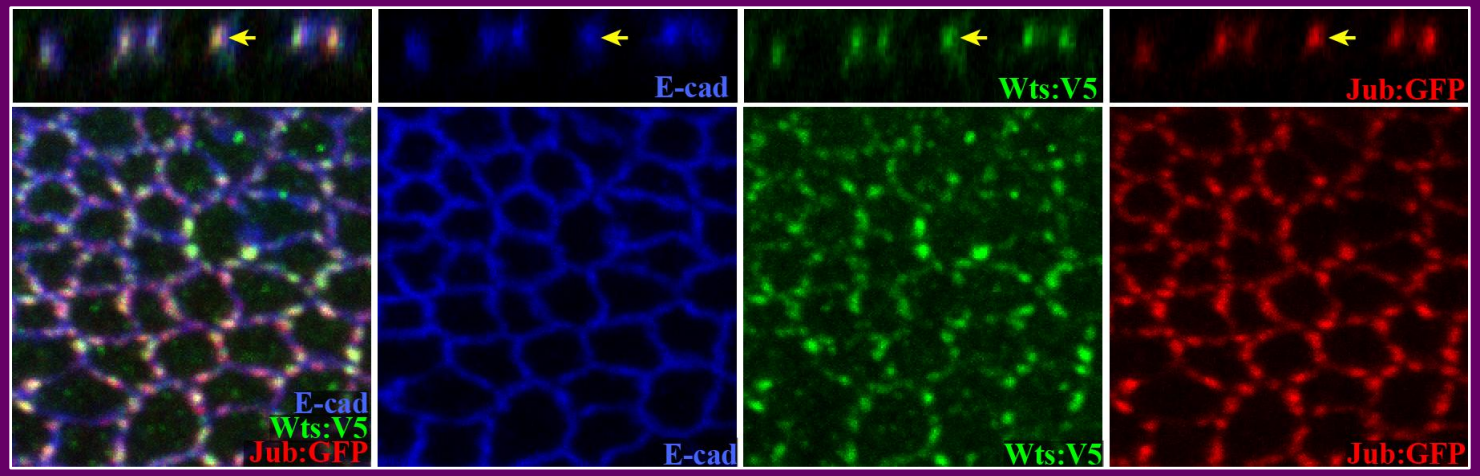
# Warts localization in vivo



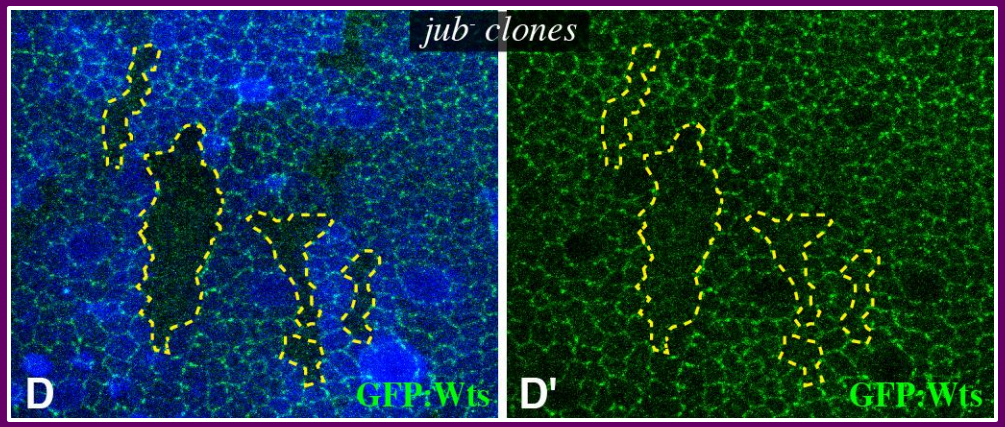




Shuguo Sun

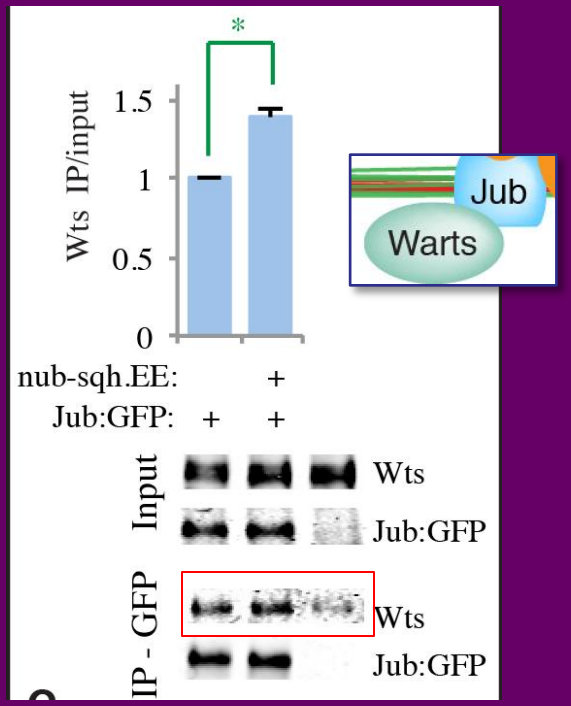
# Jub and Warts interact in vivo




## Jub is required for apical Warts localization



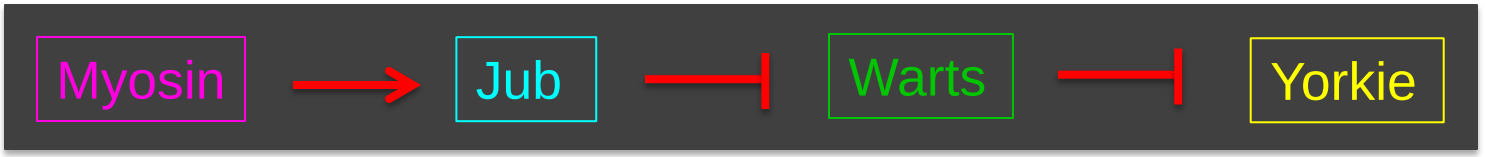

## Jub co-precipitates Warts




## Jub recruits Warts to apical junctions

# The Jub Biomechanical Pathway

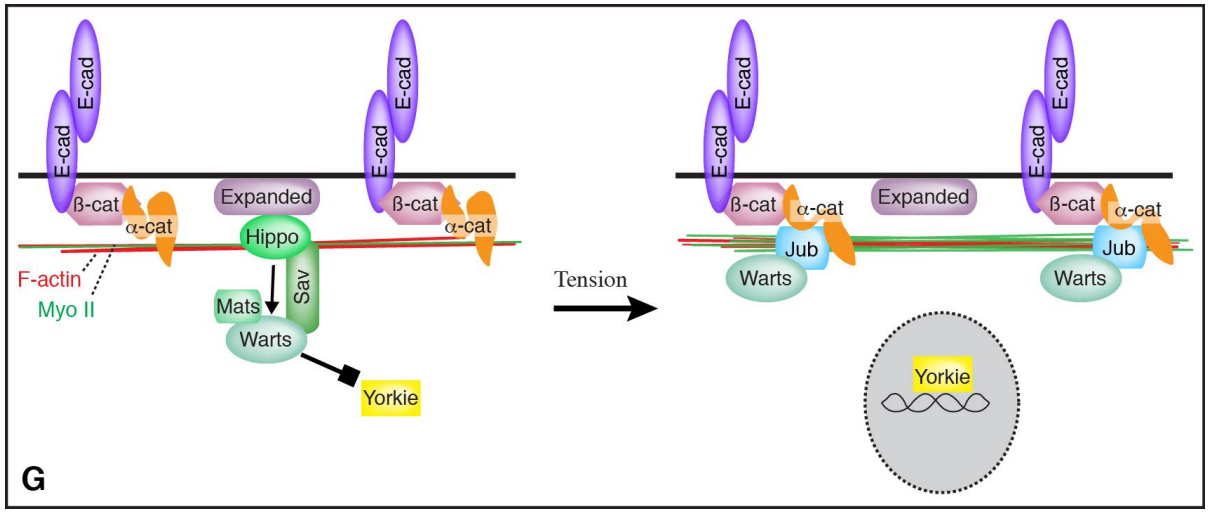
Regulation of Hippo signaling by tension-dependent recruitment of Warts into a complex with Jub.





Rauskolb et al, *Cell* 2014

# The Jub Biomechanical Pathway




1. Mechanism: How is Jub recruited to adherens junctions, and how does this influence Hippo signaling?

2. Function: What does this pathway contribute to growth regulation in vivo?

3. Conservation: Conservation of the Jub biomechanical pathway in mammalian cells?

THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 278, No. 2, Issue of January 10, pp. 1220–1228, 2003

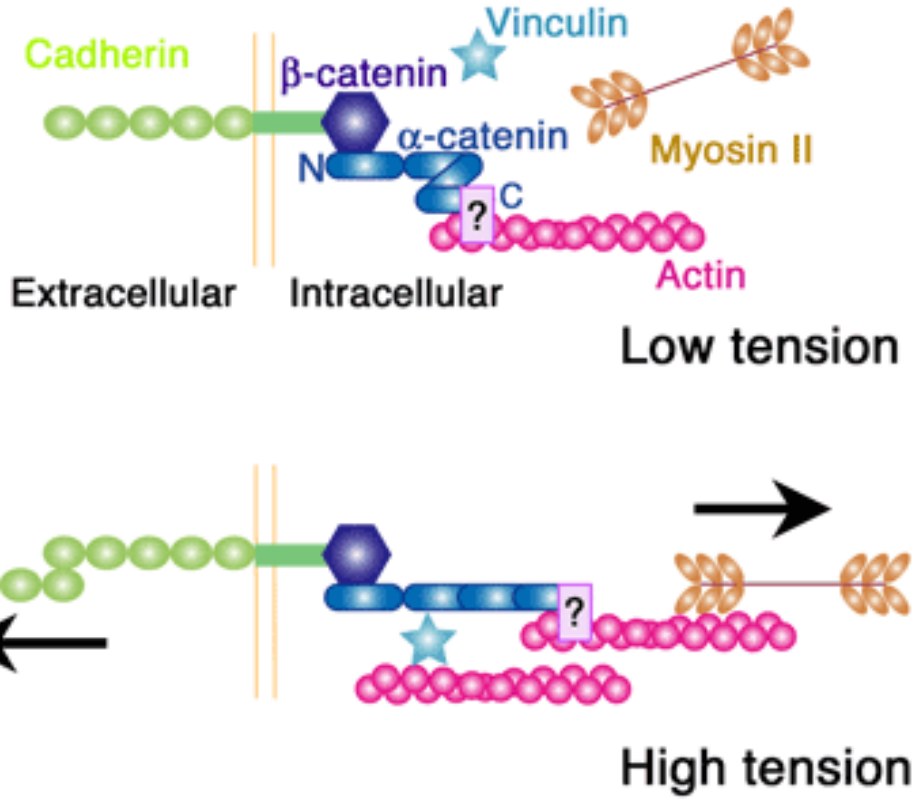
*Printed in U.S.A.*

# The LIM Protein Ajuba Is Recruited to Cadherin-dependent Cell Junctions through an Association with α-Catenin*

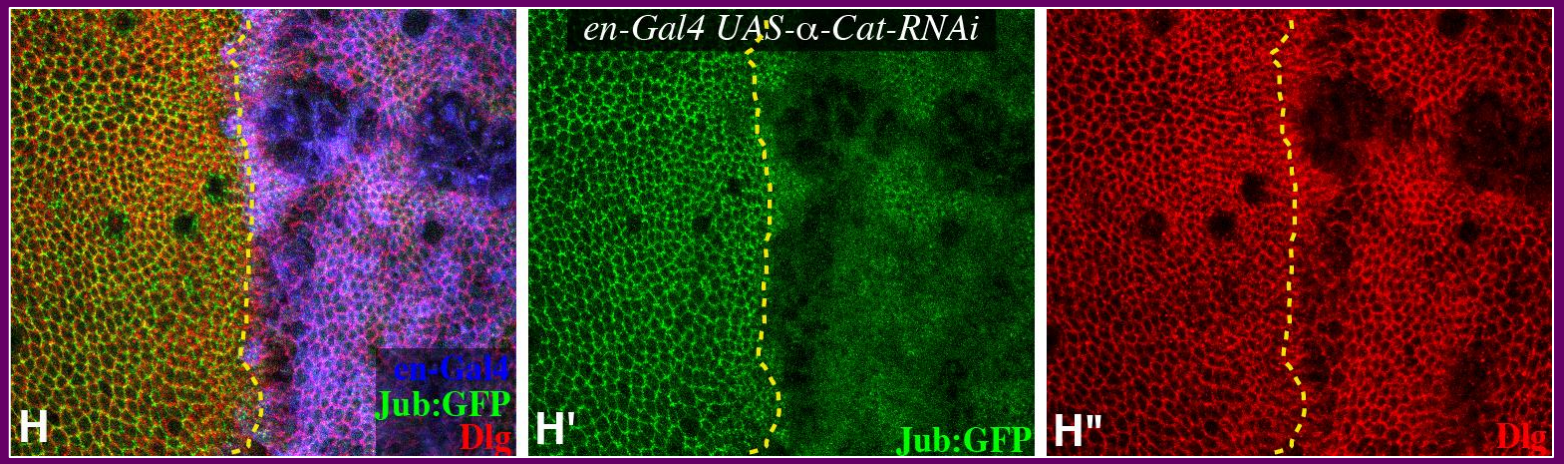
(Marie et al, JBC, 2003)

## α-Catenin as a tension transducer that induces adherens junction development

(Yonemura et al, Nat Cell Bio, 2010)

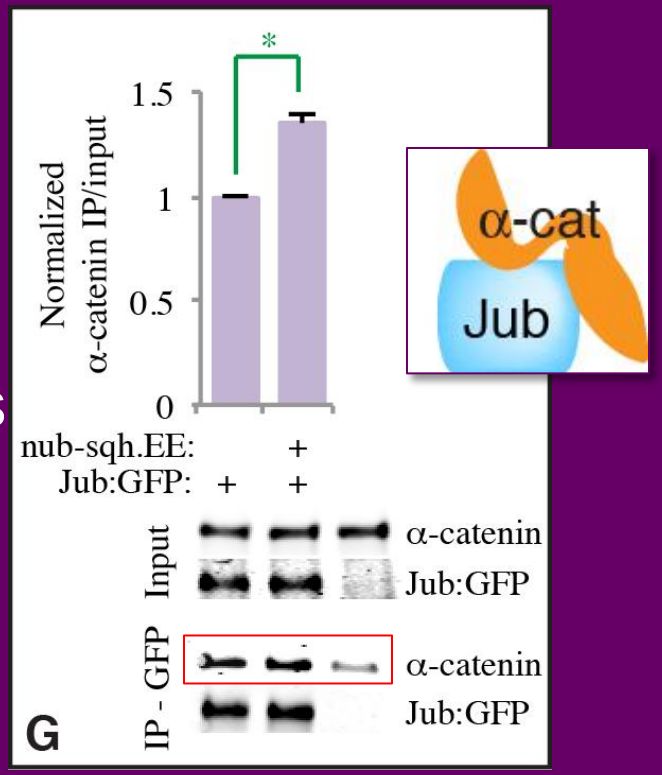


# Apical Jub localization requires α-catenin



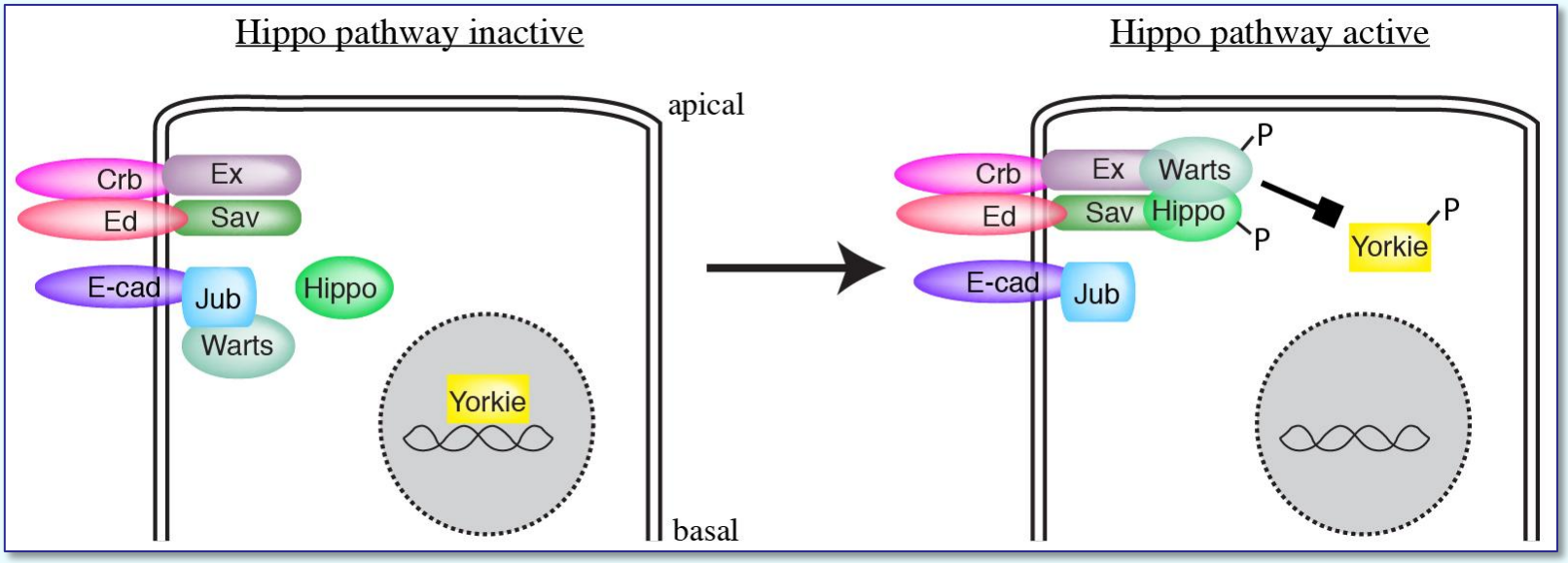

Jub associates with α-catenin

Jub-α-catenin co-precipitation is enhanced by myosin activity



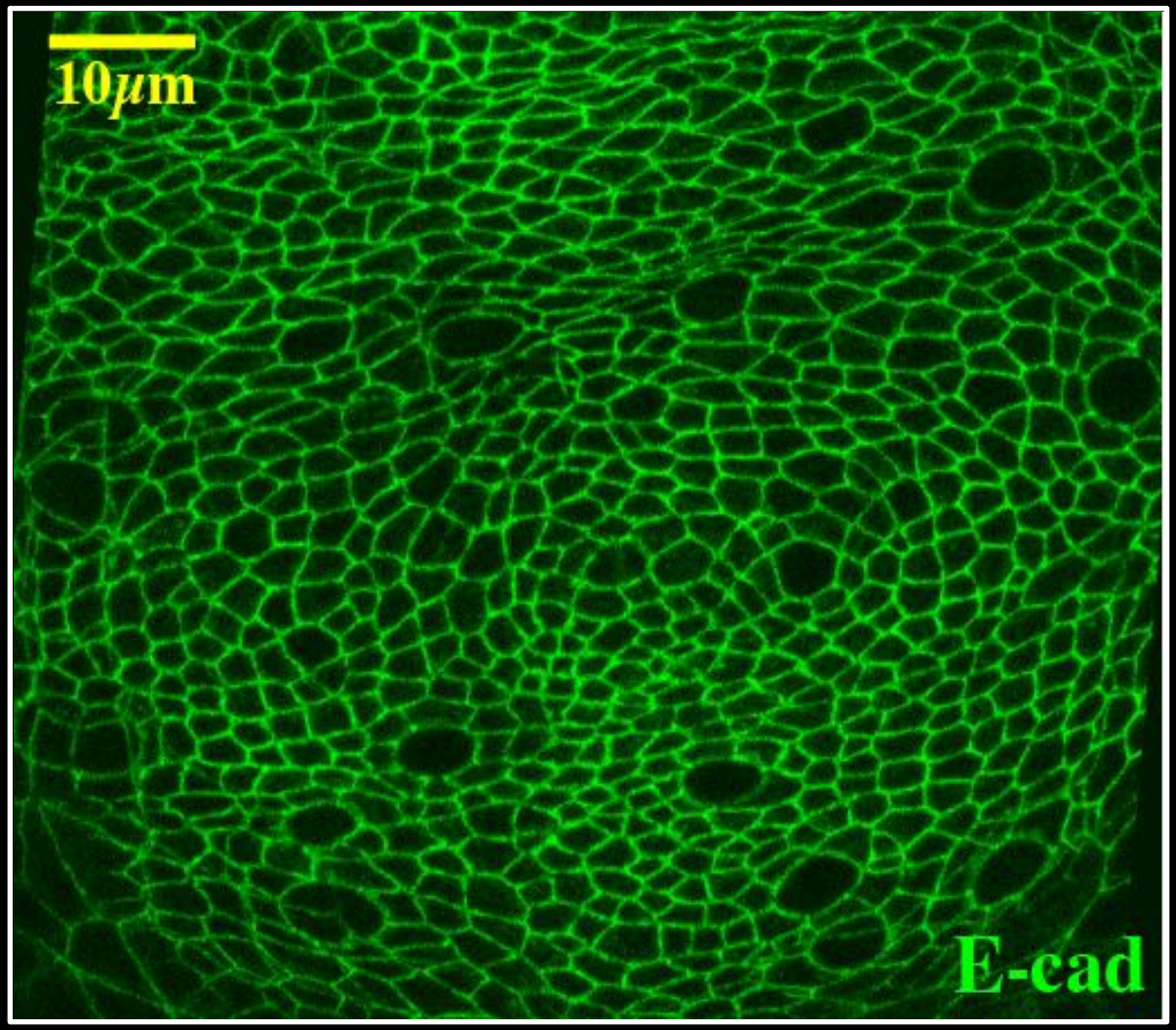

Rauskolb et al, *Cell* 2014

# Activation of Warts at Crumbs-Expanded junctions

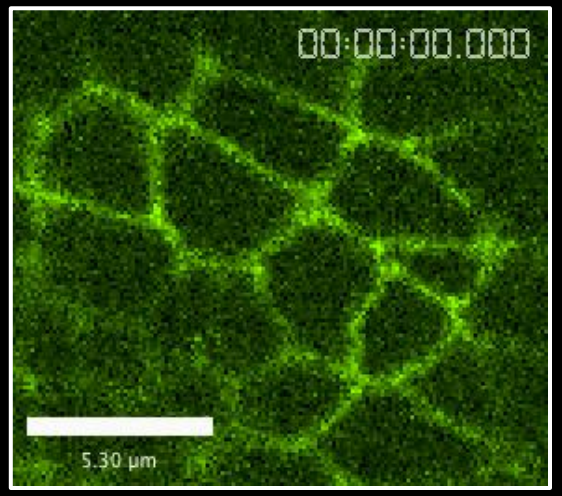



Sun et al 2015, Nature Communications

# How is Organ Growth is influenced by cells' mechanical environment in vivo?




Laser cutting of cell junctions




Yuanwang Pan

# Thanks to: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**Collaborators:** Boris Shraiman, Idse Heemskerk (UCSB), Yu-Chiun Wang (Riken)

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