YAP and TAZ coordinate endochondral ossification

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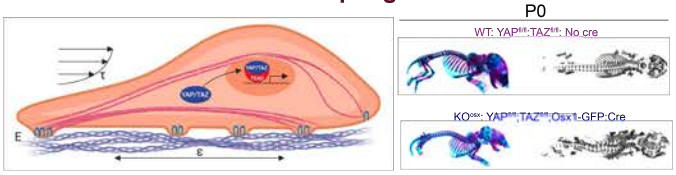
In development, bone formation occurs through two distinct modes: intramembranous and endochondral ossification. Intramembranous ossification involves the direct osteogenic differentiation of local progenitors. In contrast, endochondral ossification initiates from a cartilage anlage, which is replaced by bone through chondrocyte hypertrophy, co-mobilization of osteoprogenitors and blood vessels, and matrix remodeling, culminating in bone formation. However, ***a mechanistic understanding of progenitor behavior and crosstalk during embryonic endochondral bone morphogenesis remains poorly understood.*** Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) are transcriptional coactivators which have emerged as key mechanotransducers. We recently reported that YAP and TAZ combinatorially promote skeletal development in vivo1 with homozygous deletion of both genes causing perinatal lethality. In addition, we showed in endothelial cells that YAP and TAZ are cell-autonomously required for persistent cell motility in vitro by regulating cytoskeletal feedback3. **Here, we tested the hypothesis that YAP and TAZ are key molecular effectors that direct progenitor behavior/interaction during embryonic long bone morphogenesis.**

The molecular effectors of morphogenesis - YAP and TAZ?



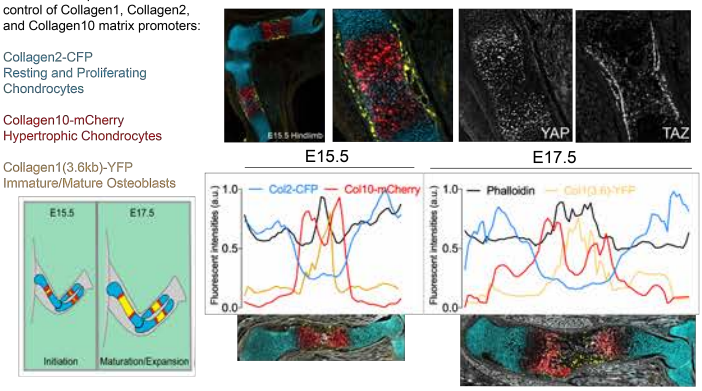
Fluorescent reporters characterize endochondral progression

Fluorescent reporters are under the control of Collagen1, Collagen2, and Collagen10 matrix promoters:

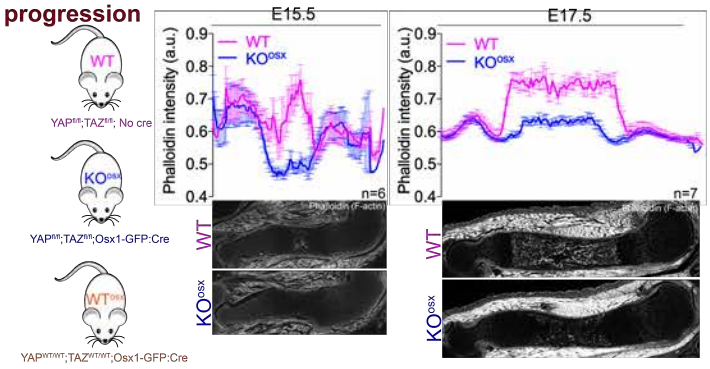
Collagen2-CFP
Resting and Proliferating Chondrocytes

Collagen10-mCherry
Hypertrophic Chondrocytes

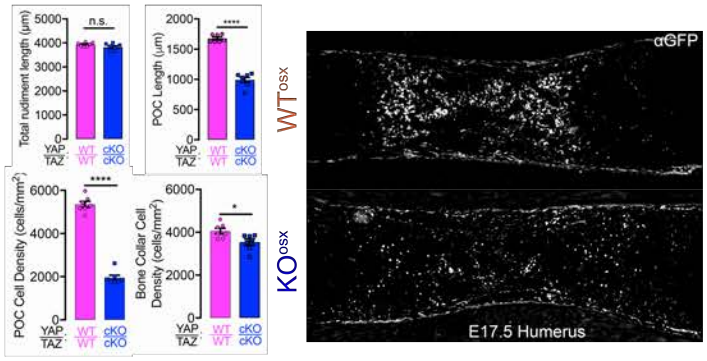
Collagen1(3.6kb)-YFP
Immature/Mature Osteoblasts



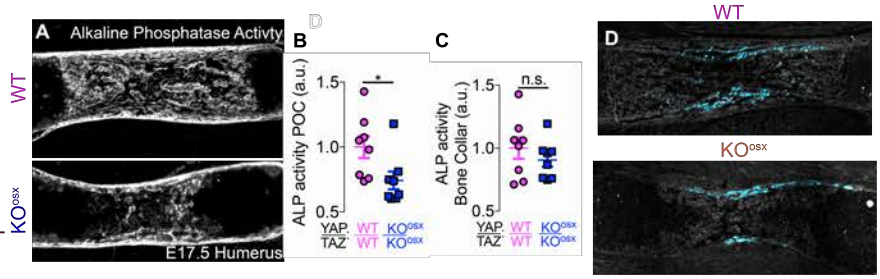
Deletion of YAP/TAZ limits primary ossification onset and progression



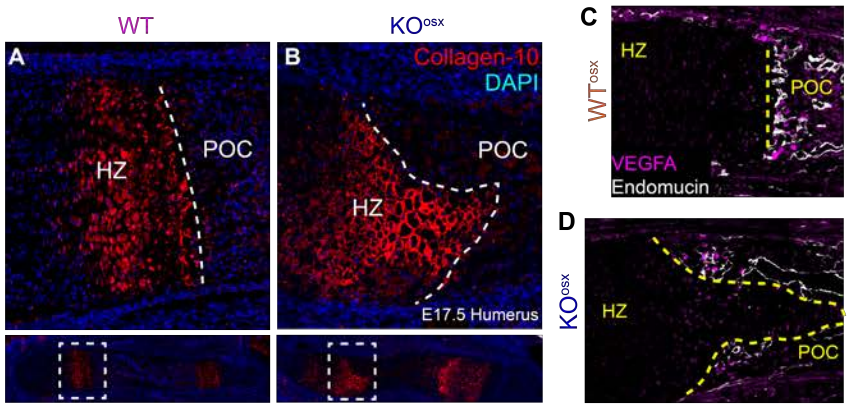
YAP/TAZ KO^osx impairs POC osteoprogenitor cell density



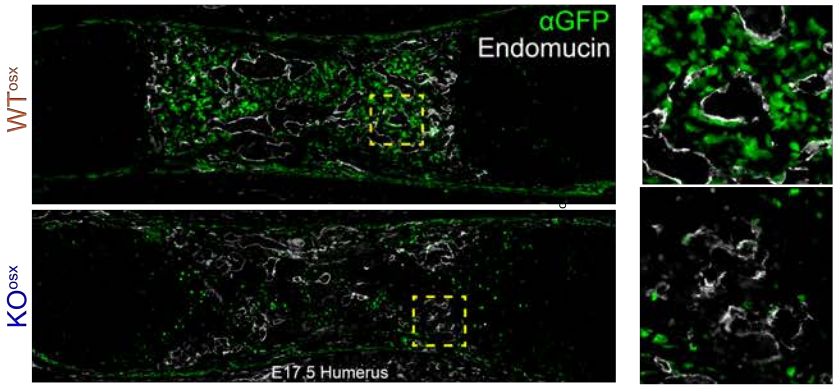
Osteogenesis is intact in the bone collar of KO^osx humeri



KO^osx Hypertrophic Cartilage maturation and matrix resorbtion are impaired



The neovasculature of KO^osx POC is reduced, disorganized, and leaky

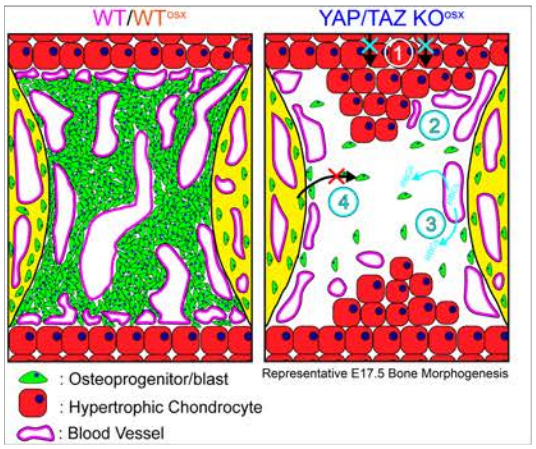


Conclusions

YAP and TAZ in Osterix1-expressing cells are critical for endochondral primary ossification initiation and expansion, but are dispensible for intramembranous ossification in the bone collar, per se. However, these data identify crucial roles for YAP and TAZ during endochondral development. Collectively, these data underscore the importance of endothelial-chondrocyte and endothelial-osteoprogenitor cell crosstalk during limb morphogenesis.

These data identify crucial roles for YAP and TAZ in:

1. Hypertrophic cartilage maturation
2. Hypertrophic matrix remodeling by cartilage-resorbing capillaries
3. Neovascular integrity
4. Osteoprogenitor mobilization
   a. Cell autonomous migration and/or
   b. Cell non-autonoumous recruitment and/or
   c. Proliferation



References: Kegelman+ FASEB J 2018, Mason+ JCB 2019, Rodda+ Development 2006, Romeo+ Nature Cell Biology 2019

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