Functional integration of body axes during regeneration is mediated by a PAK kinase and the Hippo/Yki pathway

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Successful regeneration of missing tissues requires seamless integration of positional information. Contrary to embryogenesis, during which the body axes are laid out sequentially, regeneration demands simultaneous rescaling and interpretation of positional information in the regenerating adult animal. Regenerating planarians robustly rescale the body axes to form appropriately proportioned complete animals. The planarian anterior-posterior (AP) axis is defined by the Wnt/β-catenin signaling, while the β-catenin-independent Wnt signaling shapes the medio-lateral (ML) axis. However, the molecular mechanisms, which facilitate crosstalk across multiple body axes remain poorly understood. We hypothesized that kinases and/or phosphatases may function at the intersection of multiple pathways to process the information from orthogonal axes. From a RNAi screen we identified a *p21-activated kinase, pak1* required for shaping both the AP and the ML axes during regeneration. *pak1* inhibits the Wnt/ β-catenin signaling along the AP axis and allows for head formation at the anterior. Along the ML axis of the animal, *pak1* synergizes with the β-catenin-independent Wnt signaling to restrict the width of the midline. Furthermore, reshaping of the orthogonal body axes by *pak1* is mediated by the components of the Hippo/Yki pathway, namely *warts* and *merlin*. Hippo/Yki pathway is a critical regulator of organ size in flies and mice, but our data suggest that it may function to regulate the shape rather than the size of planarians. Together, the data provides a signaling network functionally integrating positional information to mediate coordinated growth along multiple body axes during regeneration.