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CELL DIVISION

Hippo regulates cell division

A critical step during cell division is maintaining proper orientation of the cleavage plane with respect to cellular and tissue cues. Despite its major importance for development and tissue homeostasis, the details of this process remain incomplete. Hippo signalling regulates tissue growth, and its activation leads to the phosphorylation of the *Drosophila melanogaster* kinase Warts (LATS1 and LATS2 in vertebrates), which then prevents the transcription factor Yorkie (YAP and TAZ in vertebrates) from entering the nucleus and activating proliferation-promoting genes. Two papers in *Current Biology* now reveal that the Hippo pathway can influence cell proliferation, independently of Yorkie-mediated transcription, by controlling spindle positioning and asymmetric cell division.

Asymmetric cell division generates daughter cells that are unequal in size and function owing to the asymmetric partitioning of cell fate determinants and polarity proteins, mediated by precise positioning of the spindle in line with these cues. The study by Keder *et al.* found that when Hippo signalling was compromised in *D. melanogaster in vivo*, various defects were observed in asymmetrically dividing stem cell populations. The loss of Hippo signalling and, most notably, Warts activity, perturbed the localization of various polarity proteins and cell fate determinants, and also compromised spindle orientation. This was independent of Yorkie-mediated regulation of gene expression. One of the proteins identified as a Warts target was Canoe (afadin in vertebrates), which was previously shown to regulate spindle orientation and localization of cell-fate determinants. Warts-mediated phosphorylation of Canoe was responsible for the recruitment of a Dlg (Discs large) and Khc73 (kinesin heavy chain 73) complex to Pins (LGN in vertebrates). Pins serves as a scaffold for the spindle orientation machinery and closely links spindle orientation with polarity cues, whereas the Dlg–Khc73 complex, by interacting with the astral microtubules, can recruit and stabilize the position of the spindle pole. Thus, Warts appears to function as an important regulator of Dlg–Khc73-mediated spindle pole positioning and consequently spindle alignment and cell division.

Dewey *et al.* demonstrated that Warts can regulate (once again independently of Yorkie) Mud (NuMa in vertebrates), which is another spindle orientation-controlling protein. Similarly to Dlg–Khc73, Mud interacts with Pins to recruit the spindle pole and align the spindle with respect to polarity cues. The authors showed that in the cellular context, Warts co-localized with Mud, and that Warts activity was important for Mud to associate with Pins and consequently for Pins-mediated spindle orientation. Mud phosphorylation by Warts was further found to induce a conformational change that exposes its Pins-binding domain, thereby stimulating the Mud–Pins interaction. The authors also provided evidence that this pathway operates *in vivo*, as epithelial cells of the fly wing primordium displayed defects in spindle orientation following Warts inactivation.

Together, these results uncover a novel role for Hippo signalling in cell proliferation, by demonstrating its importance for spindle positioning and asymmetric cell division. These mechanisms appear to be independent of the canonical function of Hippo in regulating proliferation-promoting genes. Nevertheless, the different Hippo functions are likely to regulate cell proliferation cooperatively, and it will be interesting to investigate how they are coordinated to control tissue growth.

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ORIGINAL RESEARCH PAPERS Keder, A. *et al.* The Hippo pathway core cassette regulates asymmetric cell division. *Curr. Biol.* http://dx.doi.org/10.1016/j.cub.2015.08.064 (2015) | Dewey, E. *et al.* Warts phosphorylates Mud to promote Pins-mediated mitotic spindle orientation in *Drosophila*, independent of Yorkie. *Curr. Biol.* http://dx.doi.org/10.1016/j.cub.2015.09.025 (2015)

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