DEVELOPMENTAL GENETICS

Transitions with the benefit of Hindsight

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URLs

Entrez Gene

cubitus interruptus
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=43767

cut
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=44540

Hedgehog
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=42737

String
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=43466

Expasy

Hindsight
http://www.expasy.org/uniprot/O46205

Notch
http://www.expasy.org/uniprot/P07207

Despite being a fundamental step in development, little is known about the mechanisms that regulate the switch from proliferation to differentiation. Work in the fruitfly now provides details of one such transition, which involves interactions of the Notch pathway with both cell-cycle regulators and Hedgehog (HH) signalling components.

The follicular epithelial cells that cover the *Drosophila melanogaster* germ line undergo mitosis until stage 6 of oogenesis, after which they stop proliferating, enter an endoreplication phase and begin differentiating. Notch signalling is needed for the switch from mitosis to endoreplication (the M–E switch), and the effects of Notch in this context are partly mediated by downregulation of the homeodomain gene *cut*, which itself controls a subset of cell-cycle regulatory proteins.

To identify other mediators of Notch function in the M–E switch, Sun and Deng did an antibody-based screen for proteins that show expression changes during the transition period and identified Hindsight (HNT), a zinc-finger transcription factor. Mutants that are defective for Notch signalling showed a loss of HNT expression in follicle cells, which also showed a reduction in the size of their nuclei, indicating an impaired M–E switch. So, Notch seems to upregulate HNT expression, which is needed for the transition out of proliferation. Consistent with this, the authors provided direct evidence that the M–E switch is impaired in *hnt* mutants. Furthermore, misexpression of *hnt* in follicle cells before stage 6 led to their premature entry into endoreplication.

How does *hnt* regulate the cell cycle to drive the M–E switch? Sun and Deng made flies with egg chambers that were mosaic for a *hnt* mutation, and found that the cell-cycle regulator CUT is continuously expressed in mutant cells, rather than being downregulated after stage 6. The authors also showed that *hnt* is required for the regulation of a second cell-cycle regulator, String, which provides a missing link between Notch signalling and the G2–M transition.

HH signalling is known to be involved in follicle-cell proliferation and, as the authors confirmed, components of this pathway are downregulated around the time of the M–E switch. Importantly, the authors showed that Notch signalling is required for this downregulation: in cells that expressed a defective form of Notch, HH effector proteins were aberrantly expressed beyond stage 6. By examining levels of these effector proteins in mosaic *hnt*-mutant egg chambers, Sun and Deng showed that HNT is required for the negative regulation of HH signalling by Notch. Furthermore, examination of the expression of *cubitus interruptus*, a key mediator of the HH signalling output, showed that HNT regulates the transcription of this gene.

This work in the fruitfly has clearly shown how interactions between major developmental signalling pathways, and their influence on the cell cycle, can trigger the switch between proliferation and differentiation. Future studies should clarify whether similar interactions have a role in other developmental contexts.

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ORIGINAL RESEARCH PAPER Sun, J. & Deng, W.-M. Hindsight mediates the role of Notch in suppressing Hedgehog signaling and cell proliferation. *Dev. Cell* **12**, 431–442 (2007)