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CELL DIVISION

Different daughters

The asymmetric division of stem cells is necessary to produce distinct daughter cells with either self-renewal or differentiation capacity. Nusse and colleagues set out to investigate how such division might be regulated at the single cell level by growth factors such as WNT ligands, which are often presented to cells in a localized manner during development. They show that WNT3A signalling can mediate asymmetry of daughter cells by orienting cell division.

To test how a localized growth factor cue can influence cell behaviour, the authors used beads that were chemically coated with mouse WNT3A protein to present a spatially localized signal to mouse embryonic stem (ES) cells *in vitro*. WNT3A is known to maintain the self-renewal of ES cells and prevent differentiation to epiblast stem cells. As WNT5A does not maintain ES cell pluripotency, it was used as a control. Individual cells with a bead attached were followed by live-cell microscopy as they divided, and the location of various signalling molecules and cell division components in the daughter cells was tracked by antibody staining and fluorescence.

In the presence of WNT3A–beads, the WNT receptor Frizzled 1 and the co-receptor LRP6 (low-density lipoprotein receptor-related protein 6) were asymmetrically localized to the side of the ES cell contacting the bead prior to division. In addition, the signalling molecules APC (adenomatosis polyposis coli) and β-catenin accumulated on this side of the cell. This asymmetry was maintained during division such that the daughter cell proximal to the WNT3A–bead had higher levels of LRP6, APC and β-catenin than the distal daughter cell.

To investigate the mechanism of asymmetry, the authors looked at how the plane of cell division was affected by the WNT3A–bead. They showed that in 75% of dividing cells, the axis of mitotic division was in line with the WNT3A–bead (compared with 12% for a WNT5A–bead). This correlated with the asymmetric inheritance of centrosomes, with the 'older' centriole being inherited by the WNT3A-proximal daughter cell.

How does this asymmetric division affect the fate of the daughter cells? Transcriptional activity and protein levels of the pluripotency-associated factors Nanog, REX1 (also known as ZFP42), SOX2 and Stella were markedly higher in the WNT3A-proximal daughter cell than in the distal daughter cell, and these differences could be detected before cytokinesis was completed. By contrast, the expression of epiblast stem cell markers such as Claudin 6 was higher in most WNT3A-distal cells.

The authors propose that WNT3A signalling can regulate the plane of cell division such that the distal daughter cell ends up in a position that is out of range of the pluripotency-inducing effects of WNT3A and instead enters a differentiation programme. In support of this model, they showed that beads coated with a WNT inhibitor induced asymmetric cell division resulting in distal (rather than proximal) daughter cells with higher levels of pluripotency markers. The effects of bead-localized WNT3A or a WNT inhibitor could be rescued by cell culture medium that activates the WNT–β-catenin pathway. Moreover, cells exposed to two WNT3A–beads at either end divided symmetrically, which shows that a uniform WNT signal is required to produce identical daughter cells. Although little is know about the spatial distribution of WNT ligands in tissues *in vivo*, studies in *Caenorhabditis elegans* and *Drosophila melanogaster* indicate that they do have a physiological role in establishing cell polarity.

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ORIGINAL RESEARCH PAPER Habib, S. J. *et al.* A localized Wnt signal orients asymmetric stem cell division *in vitro*. *Science* **339**, 1445–1448 (2013)