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Asymmetric Cell Division

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Asymmetric cell divisions are characteristic of any occasion when the two daughters differ in fate, whether or not "stem cell" is one of the fates. In the case of the stem cell, the cell's first step must be to divide and to produce one daughter like itself, able to continue as a stem cell, and one daughter unlike itself, able to go down a path of differentiation.

Much insight has recently been gained regarding mechanisms underlying asymmetric cell division in several different systems. The following papers give a very brief overview about the latest developments in this broadening field.

For asymmetric cell division, both intrinsic cell fate programs and responses to extrinsic cues may be involved. In a thorough evolutionary survey of germline stem cells in metazoans, Extavour and Akam find that while in many model organisms preformation, a strategy using inherited determinants, seems to prevail, the strategy of inductive interaction is actually more often used, as for example in mammals.

Mechanisms of germ cell specification across the metazoans: epigenesis and preformation. Extavour CG and Akam M (2003). *Development* 130:5869.

Examples of Intrinsic Determination

Inherited determinants often direct fates of daughter cells, and for these daughters' fates to differ, their suite of inherited determinants must differ. A precursor to asymmetric cell division thus may be establishment of



polarity within one cell. Cellular polarity may be stable, as in early embryos and perhaps in stem cells, or it may be a transient feature of the cell, called on for specific purposes. Polarity affects processes as diverse as bacterial chemotaxis, absorption of nutrients at the intestinal epithelium, axon guidance and oogenesis, as well as the generation of dissimilar daughter cells.

A recent example is presented by Haecker et al. who describe the case in embryos of the small mustard-related plant *Arabidopsis*, where proteins of the WOX family (relatives of homeobox genes) are segregated at division of the zygote, with WOX2 going to the apical daughter cell that will generate shoot and leaf tissues, and WOX8 to the basal daughter that will generate roots.

Expression dynamics of WOX genes mark cell fate decisions during early embryonic patterning in *Arabidopsis thaliana*. Haecker A, Gross-Hardt R, Geiges B, Sarkar A, Breuninger H, Herrmann M, Laux T (2004). *Development* Jan 7 [Epub ahead of print].

In the sensory organ precursor cell of *Drosophila*, asymmetric localization of Frizzled, Strabismus and Prickle proteins define two opposite domains before mitosis of the precursor cell. During mitosis, Strabismus and Dishevelled proteins act in opposing fashions on Partner of Inscuteable to promote the protein's asymmetric localization at the anterior cortex of the precursor cell.

The planar cell polarity protein Strabismus promotes Pins anterior localization during asymmetric division of sensory organ precursor cells in *Drosophila*. Bellaiche Y, Beaudoin-Massiani O, Stuttem I, Schweisguth F (2004). *Development* 131:469.

However, proteins are not the only subcellular components that may be segregated asymmetrically. Lambert et al. show how mRNAs are segregated in the mollusk *Ilyanassa obsoleta* by tagging along with the centrosome.

Asymmetric inheritance of centrosomally localized mRNAs during embryonic cleavages. Lambert, J. D., and Nagy, L. M. (2002). *Nature* 420:682.

And even the oxidative damage accumulated during the life cycle of a cell can be distributed asymmetrically during cell division to spare the daughter cell, with carbonylated proteins remaining in the mother cell.

Asymmetric inheritance of oxidatively damaged proteins during cytokinesis. Aguilaniu, H., Gustafsson, L., Rigoulet, M., and Nystrom, T. (2003). *Science* 299:1751.

There may also be other sorts of cues that direct daughter cells to different fates. In the case of *Volvox*, an asymmetric cell division generates cells different only by size, and then by as yet unknown mechanisms the size of the daughter cell leads to activation of either a somatic or germline program.

Differentiation of germinal and somatic cells in *Volvox carteri*. Schmitt R. (2003). *Curr Opin Microbiol* 6:608.

The question now becomes how all these molecules are distributed in an unequal fashion within the cell. In recent years much progress has been made regarding the shuttling of molecules through the cytoplasm. The cytoplasm, once believed to be a "liquid soup" filling the cell, is now seen to include a sophisticated railway system of microtubules on which molecules are moved in different ways to their destination.

No surprise, then, that the microtubule system is critical for asymmetric cell division and distribution of molecules within the cell. Kusch et al. give an overview about how the spindle and microtubules, as well as certain highly conserved proteins, effect asymmetric division of cells.

Spindle asymmetry: a compass for the cell. Kusch, J., Liakopoulos, D., and Barral, Y. (2003). *Trends Cell Biol* 13:562.

Considerable research is now directed towards identifying the molecules that signal and enact asymmetry initiated by determinant factors. For example, progress into understanding how the eukaryotic cell spindle is positioned implicates the Dryk family kinases in *C. elegans* embryos.

The minibrain kinase homolog, mbk-2, is required for spindle positioning and asymmetric cell division in early *C. elegans* embryos. Ming Pang K, Ishidate T, Nakamura K, Shirayama M, Trzepacz C, Schubert CM, Priess JR, Mello CC (2004). *Dev Biol* 265:127.

Another example is shown by Barros et al., implicating the movement of nonmuscle myosin II during mitosis in the asymmetric partitioning of determinants in the *Drosophila* neuroblast.

***Drosophila* nonmuscle myosin II promotes the asymmetric segregation of cell fate determinants by cortical exclusion rather than active transport.** Barros, C. S., Phelps, C. B., and Brand, A. H. (2003). *Dev Cell* 5:829.

The bacterium *Caulobacter* presents yet a different strategy for differentiating the soon-to-be-daughter cytoplasmic compartments—fluorescence microscopy shows that shortly before actual cell division occurs, the *Caulobacter* cytoplasm is divided by cytoplasmic diffusion barriers into two compartments that only then begin to reorganize their contents, removing the CtrA master regulator protein from one of the compartments.

Fluorescence bleaching reveals asymmetric compartment formation prior to cell division in *Caulobacter*. Judd EM, Ryan KR, Moerner WE, Shapiro L, McAdams HH (2003). *Proc Natl Acad Sci U S A*. 100: 8235.

Another mechanism occurs in *Drosophila* follicle cells and oocytes, where phosphorylation status of a critical protein regulates whether it does or doesn't get localized to the cellular apex, thus organizing apical-basal polarity for the cell.

***Drosophila* PAR-1 and 14-3-3 inhibit Bazooka/PAR-3 to establish complementary cortical domains in polarized cells.** Benton R and Johnston DS (2003). *Cell* 115:691.

Although asymmetrical cytokinesis seems to require considerable attention from the cell, middle-of-the-road symmetrical cytokinesis is not necessarily a default. Howard et al., studying the rod-shaped bacterium *Bacillus subtilis*, propose that localization of certain proteins to each pole, in part because of the increased cell surface curvature at the poles, serves to exclude the cell division apparatus from the poles, thus leaving no choice but for cytokinesis to take the middle of the cell.

A mechanism for polar protein localization in bacteria. Howard M (2004). *J Mol Biol* 335:655.

Examples of Extrinsic Influences

As mentioned in the beginning, the strategy of inductive signaling from surrounding tissues is a mechanism frequently used to direct asymmetric division. A good example are the stem cell niches in the *Drosophila* testes and ovaries.

In the testes, cells that retain a physical attachment to the hub, a cluster of somatic cells, also retain identity as stem cells. Those cells that cytokinesis places away from the hub, without physical attachment, are launched off into the big wide world of spermatogenesis. Yukiko et al. add to this picture by showing that the stem cell uses the APC tumor suppressor protein to orient the

mitotic spindle perpendicular to the hub, thus ensuring a cell division that will place one daughter near, and one daughter away from, the hub.

Orientation of asymmetric stem cell division by the APC tumor suppressor and centrosome. Yamashita, Y. M., Jones, D. L., and Fuller, M. T. (2003). *Science* 301:1547.

In the *Drosophila* ovaries, the germline stem cell also maintains contact with the niche and maintains high levels of Dpp signaling. Chen and McKearin show that Dpp signaling directly results in repression of expression of the *bam* gene and maintenance of the stem cell, whereas the daughter cell dissociates from the niche, loses Dpp signaling and repression of the *bam* gene expression, and can thus start to differentiate.

Dpp signaling silences bam transcription directly to establish asymmetric divisions of germline stem cells. Chen D and McKearin D (2003). *Curr Biol* 13:1786.

Research into asymmetric cell division has recently exploded and the described mechanisms are more than abundant. And although we have only covered part of the topic, we hope to have provided sufficient food for thought for anybody inquiring into how stem cell self-renewal might be regulated.