Seemingly confounding and contradictory, the ability of bone morphogenetic proteins (BMPs) to promote both proliferation and terminal differentiation (and even apoptosis!) of neuronal stem cells—to both expand and limit precursor cell numbers—now makes perfectly good sense. At least it does in light of the conclusions drawn by Ronald McKay, David Panchision, and colleagues (National Institutes of Health, Bethesda, MD), who postulate a mechanism by which BMP ligands control both the production and fate of neural precursor cells.

Panchision attributes this “dynamic process” to the sequential and linked expression and function of two BMP receptors, BMPR-IA and BMPR-IB. In this model, “the BMP-mediated induction of receptor IB accounts for features of stem cell proliferation, identity, differentiation, and death,” says McKay.

Expression of mutant BMP receptors in CNS stem cells in vitro and in transgenic mice led to the startling discovery of a “feed-forward” mechanism. Activation of the BMPR-IA receptor early in development promotes proliferation of neural precursor cells and determines their dorsal identity. But BMPR-IA also induces the expression of Bmpr-1b. BMPR-IB activation then mediates mitotic arrest, resulting in either apoptosis (early in development, perhaps to control cell numbers) or terminal differentiation (later in development, for those cells that are left). Additional competence signals must be required to interpret the BMPR-IB signal into an apoptotic or differentiation response.

An induction–termination sequence could, suggests Panchision, be a general property of signaling in stem cells. It is unclear whether this self-limiting sequential mechanism, which dead-ends at terminal differentiation or cell death, could be reactivated on demand to regenerate tissues, say during wound healing or limb amputation. McKay envisions using knowledge of the linked receptor model to control stem cell proliferation and differentiation, with an eye toward potential applications in cell therapy and cancer therapeutics.


A new and clever strategy for studying stem cell dynamics, devised by Darryl Shibata and colleagues (University of Southern California, Los Angeles, CA), uses DNA methylation tags as markers of stem cell fate. The authors applied this technique to track changes in methylation patterns among stem cells in human colonic crypts and to test the two competing models of stem cell dynamics. Their conclusion: the data support the stochastic model, as demonstrated by the similarity of methylation patterns within individual crypts and the large variability in the numbers of unique tags per crypt.

These findings lend credence to the theory that crypt niches contain multiple long-lived stem cells that self-renew most of the time through asymmetric division. Loss of methylation tags occurs as random stem cells fail to generate replacements and bottlenecks develop. One implication of these bottlenecks for stem cell dynamics is that the periodic death of stem cells might eliminate potentially cancerous cells.

Perhaps the most surprising outcome, in Shibata’s view, is that “a population genetics type of approach worked for human crypts,” and that epigenetic patterns, in this case methylation, can serve as a marker of cell fate. The ability to map stem cell fate in human tissues and cancer cells could offer a glimpse into the process of cell aging, by allowing the construction of cell fate maps that detail which cells survive longest.

Desmosomes sort it out

Long known for providing strong adhesion, and thus maintenance of tissue architecture, desmosomes are turning up as important regulators of epithelial morphogenesis and cell positioning. Evidence from David Garrod’s laboratory (University of Manchester, Manchester, UK) suggests that desmosomal adhesion may be as important as E-cadherin-mediated adhesion in determining epithelial morphogenesis, at least in the mammary gland, the model system used in these studies. Sarah Runswick, a coauthor of the report, anticipates that these findings may stimulate renewed interest in cross-talk between desmosomes and adherens junctions and how they regulate key cellular events.

Garrod’s group showed that blocking the desmosomal cadherins, desmocollins (Dsc) and desmogleins (Dsg), disrupts normal cellular aggregation and cell positioning of mammary luminal and myoepithelial cells maintained in a rotary culture system.

The newly discovered importance of desmosomal adhesion molecules in morphoregulation and positioning of epithelial cells probably applies well beyond the realm of the mammary gland to a variety of other tissues. The authors speculate that disruption of desmosomal adhesion might contribute globally to tissue disorganization, such as occurs in cancer and other diseases.


Tagged From birth

Click! Even as a snapshot records a moment in time, so too do the progeny of neuronal stem cells record and remember the transcriptional regulatory factors present at the time of their birth. For it is these factors that determine the cells’ fate—their temporal identity and spatial destiny.

In the fly, the genes hunchback (hb), pdm1/pdm2 (pdm), and castor (cas) are expressed at different times in the embryonic central nervous system and have been suggested to specify temporal identity of neuroblast daughter cells. Now, Chris Doe and colleagues (University of Oregon, Eugene, OR) propose that sequential expression of these factors defines identity in neuroblast lineages.

Doe and colleagues first add the gene krüppel (Kr) to the proposed temporal cassette, and find that individual lineages sequentially make Hb, then Kr, then Pdm, and finally Cas. Hb and Kr are necessary and sufficient to specify the fate of first- and second-born progeny, respectively.

Birth order, not cell type, correlates with the layered expression of these gene. Thus, the same sequence of gene expression is followed regardless of whether the original progeny cell is a motorneuron, interneuron, or glial cell. First-born progeny express Hb and occupy the deepest cortical layers, whereas second-born progeny express Kr and reside in the next deepest layer.

A cell-cycle dependent clock, rather than a global timing mechanism, appears to regulate the sequential expression of these genes. If the cell cycle is stopped, the sequence of changes in gene expression also stops.


Arp bent out of shape

Biochemical and kinetic studies have failed to provide a unified view on how the Arp2/3 complex nucleates actin filaments. Does the complex, which mediates actin filament nucleation and branch formation at the leading edge of motile cells, bind to the side of an older actin filament, or does it become incorporated into that filament?

Structural studies now add a new dimension to the discourse, supporting the side-binding, dendritic nucleation model. These studies provide visual evidence that the seven subunit actin-related protein (Arp) complex is not inserted into the mother filament during actin filament nucleation in Acanthamoeba castellanii and Saccharomyces cerevisiae.

Additionally, and rather unexpectedly, imaging by electron cryo-microscopy provides evidence that the Arp2/3 complex undergoes a major conformational change during branch formation.

This rearrangement of the complex was “rather surprising to see,” says Dorit Hanein (The Burnham Institute, La Jolla, CA). Hanein describes her work with Niels Volkmann and colleagues as the “first serious attempt to look at the structural changes associated with the mechanism of actin nucleation by Arp2/3 complex.” The group’s approach incorporates various electron microscopy imaging techniques combined with single particle analysis of activated Arp2/3 complexes and image analysis of Arp2/3 in actin filament branch junctions. The structural findings provide direct evidence that Arp2 and Arp3 form the first two subunits of the developing daughter filament.