Dll1 Controls Vascular Branching (p 530)

Notch ligand Dll1 is an extravascular cue that tells vessels where to branch, report Napp et al.

During angiogenesis, the branching of new vessels begins when specific cells in the vessel wall become tip cells. The expression of the Notch ligand, Dll4, defines tip cells and prevents neighboring cells from adopting the same fate. Dll4 is induced by the external growth factor VEGF (vascular endothelial growth factor), which then prompts sprouting of the vessel led by the tip cell. But VEGF does not work alone. Napp et al now show that Notch ligand, Dll1, is also essential for tip cell selection. The team studied mice that had a heterozygous deletion of Dll1 and found that in the newborn retina, a site of abundant angiogenesis, there were fewer tip cells and fewer vessel branches. Expression analysis revealed that Dll1 was never found in the developing vessel’s endothelial cells themselves but rather was immediately adjacent to the vessels at the sites of tip cell formation. In vitro studies showed that recombinant Dll1 could induce human endothelial cells to upregulate tip cell–specific genes, including Dll4. Understanding the molecular mechanisms of angiogenesis has far-reaching implications in areas such as development, wound healing, and tumor formation.

Left-Right Asymmetry in Vascular Cells (p 551)

Given a choice of direction, vascular mesenchymal cells turn right and reveal an inherent asymmetry, say Chen et al.

Although animals might appear to be symmetrical on the outside, their innards reveal a striking left-right asymmetry in both the positioning of organs and the structure of the organs themselves. In the early embryo, the beating of cilia on the surface of certain cells sets up left-right asymmetry by washing molecules in one direction over neighboring cells. This model implies that cells themselves have an inherent left-right asymmetry, but the random orientation of cells in culture makes testing that theory rather difficult. Chen et al noticed that vascular mesenchymal cells (VMCs) form distinct patterns when grown on plates striped with adherent and nonadherent surfaces. Closer inspection revealed that as proliferating VMCs filled the adherent stripes and were forced to venture toward nonadherent stripes, they instinctively turned right, eventually leading to the observed patterns. This preference was dependent on intracellular stress fiber formation and was not unique to VMCs; 1 other cell type, ST2, showed a left turn preference, whereas 2 other cell types showed no preference. These findings could be important not only in studies of development but also in tissue engineering, say the team.

Bmp and Myocardial Differentiation (p 578)

de Pater et al have determined when and where BMP is needed during heart development.

Despite its name, bone morphogenetic protein (BMP) is required for differentiation of a variety of tissues, including the myocardium. In vitro studies of cardiomyocyte differentiation, however, have suggested seemingly contradictory roles for BMP. Pa ter et al have now set things straight, in the zebrafish at least. They showed that although BMP signaling is present in cardiac progenitor cells in the early fish embryo and is required for induction of cardiomyocytes, it is later detrimental to heart development and is downregulated. The team showed that inhibition of BMP signaling between 10 and 24 hours after fertilization reduced the numbers of atrial and ventricular cardiomyocytes, but inhibition of BMP after 24 hours had no effect. Once cardiomyocyte differentiation was under way, BMP activity in the embryo was normally inhibited by a signaling factor called Smad6. This reduction in BMP activity was essential for proper morphogenesis of the heart, because reactivation led to ectopic expression of BMP-target genes and impaired chamber formation. Understanding precisely when and where BMP is required should help researchers improve their in vitro methods for cardiomyocyte differentiation of embryonic or induced pluripotent stem cells.
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