Pressured into making a kidney

Developmental biologists spend a great deal of time studying molecular signals that determine the when and where of organogenesis. But recent results indicate they may be overlooking something. Mechanical forces provided by the vasculature are also at work, according to a new study by Fabrizio Serluca, Ian Drummond, and Mark Fishman (Harvard Medical School, Boston, MA), who examine the development of the zebrafish kidney glomerulus.

The glomerulus is made up of unique layers of vessel endothelium that filter fluid from the blood without removing proteins or cells. Fluid flows between the endothelial cells, before moving sequentially through the basement membrane of the kidney and epithelial cells known as podocytes, and finally into the tubules of the kidney. During zebrafish embryogenesis, the podocytes form the glomerulus by migrating and coalescing to an area surrounding a vessel outgrowth of the aorta.

Now, it seems that mechanical forces from these vessel endothelium cells initiate podocyte migration. Fishman’s group identified multiple mutants with disrupted glomerular assembly, each of which shares the common feature of impaired circulation. The group showed that hemodynamic forces from the aorta are essential for glomerular development by stimulating podocyte migration. “Cell fate in the mutants is normal; only organogenesis is affected,” says Fishman. “The cells just don’t get together as they should.”

This force-initiated podocyte migration requires the collagen-degrading enzyme matrix metalloproteinase-2 (MMP-2). MMP-2 may be turned on by stretch-sensitive ion channels or by some other stretch-sensitive signal transduction pathway. In turn, MMP-2 may allow the vessels to migrate more easily into the epithelium by disrupting extracellular collagen. Alternatively, MMP-2 may activate matrix stores of inactive vessel-promoting signals. Homologues of the zebrafish signals may be involved in human disorders caused by hemodynamic forces, including atherosclerosis resulting from high blood pressure.

Reference: Serluca, F., et al. 2002. *Curr. Biol.* 12:492–497.

A pathway required for blood vessel development in vertebrates also functions in flies, according to new results from Nam Cho, Mark Krasnow (Stanford University, Stanford, CA), and colleagues. The results imply that cell migration, not angiogenesis, may have been the original function of the vascular endothelial growth factor receptor (VEGFR) tyrosine kinase family and its ligands.

The active migration of blood cells, or hemocytes, occurs during fly embryogenesis when the heart has not yet begun pumping. Fly blood does not travel through a closed circulatory system, but Cho found that flies have homologues of the VEGF pathway, which is required for vertebrate blood vessel development. This suggests that the proteins have a more ancient function.

That function appears to be the migration of blood cells during embryogenesis, according to the new study. Cho and colleagues found that, in flies lacking VEGFR, blood cells differentiate, but do not migrate normally and aggregate in the anterior of the embryo. Inactivation of all three homologues of the VEGF ligand resulted in the same cell migration defect. Ectopic expression of a VEGF ligand caused misrouting of blood cells, suggesting that it may act as a chemoattractant to assure that the hemocytes travel along pathways where phagocytosis of apoptotic cells is required.

Blood cell chemoattractant activity has also been demonstrated in vitro for a vertebrate VEGF, but has largely been ignored. “While most of the press for VEGF involves its role in angiogenesis… it may have originally evolved for blood cell functions,” says Cho. However, it is not known whether the vertebrate homologues still serve similar functions in blood cells. The simple genetics of the fly system should facilitate the identification of signaling molecules downstream of VEGF, which may aid in the discovery of therapeutic agents for blocking angiogenesis during tumor growth or increasing vascular growth after injuries such as heart attack.

Reference: Cho, N., et al. 2002. *Cell.* 108:865–876.

From migration to circulation

Blood cells (red) do not migrate when VEGFR is missing (bottom).