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In This Issue

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By John Ashkenas, Science Editor

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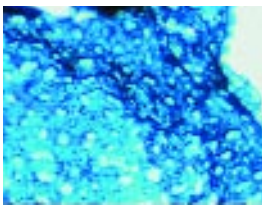
Recent work with mutant mice and zebrafish has begun to uncover the signaling pathways that drive the formation of blood vessels in the yolk sac, in the heart, and throughout the early embryo. Each of these vessels is induced by cooperation between endothelial cells and mesenchymal cells, which differentiate into vascular smooth muscle cells. Defects in specific growth factors, such as VEGF, or in many growth factor receptors cause cardiovascular defects and death by mid-gestation. For instance, neuropilin-1, which first came to light because of its role in axonal guidance, is now known to bind 1 isoform of VEGF and to promote its interactions with the VEGF receptor Flk1. Neuropilin-1 is expressed in both endothelial cells and vascular smooth muscle cells, and null mutations in this gene cause lethal cardiovascular defects. Yamagishi et al. now demonstrate expression in mesenchymal cells of dHAND, a transcription factor previously implicated in the growth and morphogenesis of portions of the embryonic heart. Without dHAND, the earliest stages of mesenchymal differentiation proceed normally, and these cells migrate to the usual sites of vasculogenesis, but they do not complete differentiation or make normal contacts with endothelial cells. Endothelial cells of the yolk sac consequently fail to undergo remodeling to form vessels, and the heart develops abnormally. Yamagishi and colleagues have also used subtractive cloning to identify mRNAs that are present in wild-type embryos but absent or reduced in dHAND$^{-/-}$ embryos of the same stage. They find that Neuropilin-1 is one such gene, indicating that dHAND directly or indirectly activates its expression. Hence, signaling through dHAND in the mesenchyme may be required for vessel cells of both types to respond to aspects of VEGF signaling.

Mac-1 in vascular injury

(See article on pages 293–300.)

Angioplasty is performed in order to clear the lumen of narrowed arteries, but the resulting improvement in circulation is often transient. Because it causes mechanical injury to endothelial cells, this procedure provokes local inflammation, which prompts smooth muscle cell proliferation in the vascular intima, thus narrowing the lumen of the vessel once again. Simon and coworkers have studied this complication, restenosis, in a new model of vascular injury, and they now identify a crucial step in the inflammation of the injured artery. In their system, endothelial cells are stripped completely from a region of the carotid artery. This injured region is soon covered with platelets, but the authors find that neutrophils in wild-type animals can cross the platelet layer into the arterial media, initiating inflammation and restenosis in the injured region. On the other hand, leukocytes from mice lacking Mac-1 — an adhesive receptor of the β2-integrin family — adhere to, but are unable to migrate across, a layer of platelets in an ex vivo translocation assay. In such mutant mice, neointimal thickening is blocked, and the artery remains unobstructed, indicating that neutrophil migration is a prerequisite for restenosis. Simon et al. note that the absence of Mac-1 might prevent neutrophil migration from outside the arterial media, in addition to blocking extravasation of these cells from inside the arterial lumen.



Inhibition of an ion channel by vesicular transport proteins

(See article on pages 377–386.)

Here, Naren et al. pursue an unusual molecular interaction between syntaxin 1A and the Cl^- channel CFTR. The former protein interacts with Munc-18, an orthologue of a yeast protein required for vesicle delivery to the plasma membrane. Both Munc-18 and syntaxin 1A also mediate vesicle docking and fusion. This same group showed earlier, using a heterologous system to express the proteins, that syntaxin 1A interferes specifically with CFTR-dependent Cl^- currents. However, because syntaxin 1A appeared to be restricted to neurons and to play a specialized role in the exocytosis of synaptic vesicles, it remained uncertain whether this interaction was physiologically relevant. Now the authors demonstrate that, although the amount of syntaxin 1A in the brain dwarfs the level seen in epithelial cells, primary human cells from the gut and lung still express this protein in a ~10-fold molar excess over CFTR. Cells engineered to express a soluble portion of syntaxin 1A show increased CFTR channel activity, as do cells overexpressing Munc-18. Presumably, these molecules block the interaction between syntaxin 1A and CFTR. Naren et al. cite earlier evidence that syntaxin 1A also inhibits the sodium channel ENaC, and they suggest that this protein prevents excessive loss of fluids across epithelia by inhibiting multiple classes of ion channels.