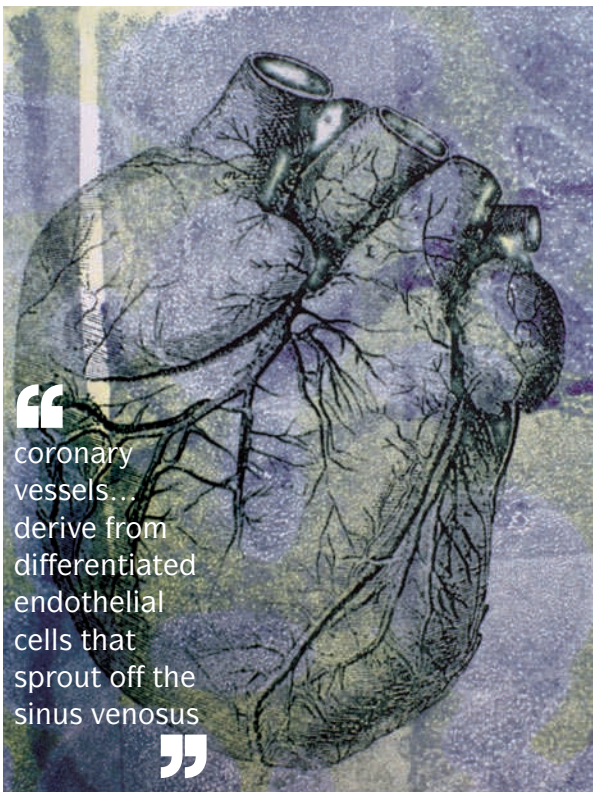
DEVELOPMENT

Getting to the heart of the matter

The origin and early development of coronary vessels is unclear, although the textbook view is that they arise from the proepicardium — a transitory structure in the embryo that contacts and spreads over the developing heart to form its epithelial covering (epicardium). Red-Horse *et al.* now show that coronary vessels, including coronary arteries, actually derive from differentiated endothelial cells that sprout off the sinus venosus — the vein that returns blood to the embryonic heart.



The authors analysed coronary vessel development during embryogenesis in mice expressing the *lacZ* reporter gene specifically in coronary endothelial cells and not endothelial cells of the endocardium (the innermost layer of tissue that lines the heart chambers). This allows these two cell types, which are both labelled by common endothelial markers, to be distinguished. They show that coronary vessel progenitors (endothelial cells) sprout from the sinus venosus, migrate over the entire heart and mature into coronary arteries, capillaries and veins.

To confirm their sinus venosus sprouting model, Red-Horse *et al.* analysed the origins of and requirements for coronary sprouting in a cardiac organ culture system. Developing hearts were isolated from *lacZ*-expressing mice at embryonic day 10.5, a stage after the proepicardium has formed the epicardium but before coronary vessels are present. Coronary vessels formed in 92% of intact hearts in culture. However, when ventricles with their epithelial covering were separated from the sinus venosus and atria, no coronary sprouts developed from cultures of either tissue. Combining a sinus venosus and atrium from *lacZ*-expressing mice with a wild-type epithelium-covered ventricle, but not a wild-type sinus venosus and atrium with an epithelium-covered ventricle from *lacZ*-expressing mice, results in the formation of *lacZ*-expressing coronary vessels on the epithelium-covered ventricle. These data suggest that coronary vessels arise from the sinus venosus and atria and require signals from the epithelium-covered ventricle for sprouting and outgrowth.

The authors next tested the sinus venosus sprouting model *in vivo*, using an inducible vascular endothelial cadherin (VE-cadherin) transgene to label individual endothelial cells and their descendents. They tracked clones labelled before coronary vessel formation back to cells expressing VE-cadherin. This, and experiments using a proepicardial-expressed transgene, rules out proepicardium cells, which do not express VE-cadherin, as the source of coronary vessels, and indicates that coronary progenitors arise from differentiated endothelial cells *in vivo*. In addition, most coronary artery cells are clonally related to sinus venosus cells, indicating that they originated in the sinus venosus.

Finally, assessing cells for arterial and venous markers revealed that coronary sprouts are initially differentiated venous cells, which dedifferentiate as they extend from the sinus venosus and subsequently redifferentiate and remodel into coronary arteries, capillaries and veins. Thus, differentiated endothelial cells, which sprout off the sinus venosus, are the long-debated origin of coronary vessels.

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ORIGINAL RESEARCH PAPER Red-Horse, K. *et al.* Coronary arteries form by developmental reprogramming of venous cells. *Nature* **464**, 549–553 (2010)