Regulation of VSMC Function by miR-663 (p 1117)

Li et al identify a new microRNA that regulates phenotype switching in human vascular smooth muscle cells.

Fully differentiated vascular smooth muscle cells (VSMCs) in situ are generally non-proliferative, but after a vessel injury these cells dedifferentiate, proliferate and migrate. It is believed that such phenotype switching is an essential part of the healing process, but it can also lead to vessel narrowing, restenosis and other associated problems. Among the factors controlling this phenotype switch are microRNAs (miRs)—that suppress the expression of target mRNAs. While a number of such miRs have been identified in animal VSMCs, little is known about miRs in human VSMCs. Li and colleagues thus analyzed changes in miR expression in human VSMCs following induction of the phenotype switch. They found that miR-663 in particular, was dramatically downregulated. They also found that overexpression of miR-663 in VSMCs induced the expression of differentiation markers, whereas blocking miR-663 expression increased both proliferation and migration. MiR-663 targeted the mRNA of transcription factor JunB, suppressing its expression in human VSMCs. Li and colleagues thus analyzed changes in miR expression in human VSMCs following induction of the phenotype switch. They found that miR-663 in particular, was dramatically downregulated. They also found that overexpression of miR-663 in VSMCs induced the expression of differentiation markers, whereas blocking miR-663 expression increased both proliferation and migration. MiR-663 targeted the mRNA of transcription factor JunB, suppressing its expression in human VSMCs. Although miR-663 is not conserved between humans and mice, its target sequence in the JunB mRNA is, and the team found that transfection of miR-663 into mice could suppress JunB expression and could block vessel narrowing. Boosting miR-663 activity or suppressing JunB might thus be strategies for preventing restenosis.

Somatic Mesoderm and the Proepicardium (p 1128)

Schlueter and Brand investigate the origins of the heart’s proepicardium and discover that some of the cells derive from somatic mesoderm.

During embryogenesis, the proepicardium gives rise to epicardial cells as well as cells of the coronary vasculature and cardiac fibroblasts. But the origin of the proepicardium itself is unclear. In addition, it is also unclear how the proepicardium develops its characteristic left-right asymmetry—though the growth factor FGF8 and transcription factor SNAI1 are both known to be involved. Schlueter and Brand now show that a known target gene of SNAI1, a transcription factor called TWIST1, is asymmetrically expressed in lateral plate mesoderm of the early chick embryo, being highly expressed on the right-hand side. Furthermore, the team showed that these cells give rise to a population of proepicardial cells. They found that loss of TWIST1 expression in the right-hand mesoderm led to malformation of the proepicardium, while overexpression of TWIST in the left-hand mesoderm caused these cells to adopt characteristics of the right-hand proepicardium. The findings could have implications not only for understanding cardiac development, but also for understanding disease processes like myocardial fibrosis and for developing approaches for regenerative therapies.

MicroRNAs in Cardiac Fibroblasts (p 1138)

Abonnenc et al confirm the role of microRNAs in extracellular matrix secretion by cardiac fibroblasts.

Changes to the composition of the extracellular matrix (ECM) contribute to the development of fibrosis, a characteristic feature of myocardial remodeling in a number of cardiac diseases. Previous studies have identified several microRNAs (miRs) that regulate cardiac fibrosis, including miR-30c and miR-29b. But a systematic analysis of the targets of these miRs is lacking. Rather than searching for messenger RNA targets of miR-30c and 29b—via computer prediction software or microarray analyses—Abonnenc and colleagues opted to search for proteins secreted by cardiac fibroblasts in response to the two miRs, thus allowing for the identification of both direct and indirect targets. The team used mass spectrometry to study the secretomes of primary mouse cardiac fibroblasts in which the two miRs were either over-expressed or inhibited. While miR-29b suppressed the expression of ECM and fibrosis proteins, including collagens, matrix metalloproteases, leukemia inhibitory factor (LIF) and insulin-like growth factor-1 (IGF-1), miR-30c had little effect on these proteins. The proteomic approach identified previously predicted and novel targets for the two miRs and, say the authors, offers a valuable resource for future studies into cardiac fibrosis.