iCM Reprogramming Factor Stoichiometry (p 237)

Wang et al shuffle the gene order in reprogramming vectors and improve fibroblast-to-cardiomyocyte conversion.

Scar tissue that forms after myocardial infarction reduces heart function and can ultimately lead to heart failure and death. Fibroblasts of the scar tissue, however, can be directly reprogrammed into cardiomyocytes—by transfecting the cells with the transcription factors Gata4 (G), Mef2 (M), and Tbx5 (T). While the approach holds great promise for regenerating functional heart muscle its clinical utility is limited by its inefficiency. Getting a precise balance of the three factors might be important for reprogramming efficiency. Thus, Wang et al made six polycistronic vectors—each with the factors in a different possible order (GMT, GTM, MGT and so on)—and compared their reprogramming capacities. They also compared these polycistronic vectors with combined yet separate vectors encoding G, M, and T. Transfection experiments with different vectors showed that each of the constructs produced different ratios of factor expression, and importantly different reprogramming efficiencies. The two constructs in which Mef2 was most 5’—and which happened to have the highest Mef2 expression—reprogrammed fibroblasts more efficiently than other vectors. Indeed, the MGT vector improved reprogramming 10-fold over that seen with individual factor vectors. This improved vector could serve as a platform for further mechanistic studies and optimization, say the authors.

Cardiac Exosome Modeling and Therapy (p 255)

Gray et al discover that exosomes from hypoxia-treated cardiac progenitor cells promote heart regeneration.

To regenerate heart tissue after a myocardial infarction, researchers have investigated cell therapies involving cardiac progenitor cells. These cells can differentiate into heart cells such as cardiac myocytes, endothelial cells and fibroblasts, but it is not clear whether this differentiation is the sole or even main reason for the improvement of cardiac function after transplantation with progenitor cells. Indeed, there is evidence to support the notion that the paracrine effects of factors secreted by these cells contribute to their beneficial effects. In support of this idea, it has been shown that many cell types, including cardiac progenitors, secrete membrane-bound vesicles called exosomes that can exert certain paracrine effects. Gray and colleagues therefore studied the effects of cardiac progenitor-derived exomes on cardiac cells in vitro and in vivo. To mimic infarction they exposed the progenitors to hypoxia before collecting the exosomes. They showed that compared with exosomes derived under normoxic conditions these hypoxic exosomes induced capillary-like tube growth in cardiac endothelial cells and reduced expression of fibrosis-associated genes in fibroblasts. Moreover these exosomes improved the function of injured rat hearts. The team went on to identify specific microRNAs contained in the exosomes that were associated with hypoxia, which could have positive effects on cardiac function and therefore warrant further analysis.

CD34+ Cells and Mortality (p 289)

Low numbers of circulating progenitor cells indicate high risk of death in coronary artery disease patients, report Patel et al.

Progenitor cells, originating primarily from the bone marrow, are important for the regeneration and repair of injured blood vessels. Patel and colleagues therefore hypothesized that a lack of progenitor cells in a person’s blood might indicate an impaired ability for vessel regeneration. To test their hypothesis, the team recruited two cohorts of 502 and 403 patients with coronary artery disease. They counted the progenitor cell numbers in the patients’ blood, and followed their progress for 2.7 years and 1.2 years respectively. The team defined progenitor cells as mononuclear cells expressing the marker CD34. They also examined subsets of these cells that expressed CD133 (a marker of more primitive stem cells), VEGFR2, or CXCR4 (both associated with stem cell recruitment and homing). The team found in both cohorts that the number of CD34− or CD34+/CD133− cells in a person’s blood was inversely correlated with risk of all-cause death, as well as cardiovascular mortality. Indeed patients with the lowest number of these progenitor cells were almost three times more likely to die. These results suggest not only that progenitor cells may be a useful biomarker for coronary artery disease prognosis, but also that these cells may be useful targets for regenerative therapies.