Histone demethylase Jmjd3 regulates endothelial, mesodermal, and cardiovascular differentiation of embryonic stem cells, report Ohtani et al.

The addition of three methyl groups to lysine 27 of histone H3—or H3K27me3—is a repressive epigenetic modification that leads to gene silencing. The protein Jmjd3 is a H3K27 demethylase and therefore activates genes that have been suppressed by the modification. Recent evidence has shown that endothelial genes in adult pro-angiogenic cells are suppressed by H3K27me3. This led Ohtani and colleagues to investigate whether Jmjd3 might promote the expression of such genes earlier in development and thus might contribute to cardiovascular lineage commitment. To test the role of Jmjd3, the team created mouse embryonic stem cells that lacked Jmjd3 and examined their differentiation in vitro. They found that mesodermal, endodermal, and cardiomyocyte differentiation were all perturbed, as evidenced by dramatically reduced expression of these lineage marker genes. The mesodermal marker genes, Brachyury and Mix1, also showed an expected increase in H3K27me3 at their promoter regions. Mice generated from these embryonic stem cells died at early stages of embryonic development, indicating an important role of this factor in the development of the cardiovascular system.

Jmjd3 and Differentiation (p 856)

Yang et al devise a clever transgenic approach for testing calcium channel regulation.

The calcium channel Ca\textsubscript{\textupsilon}1.2 plays an essential role in excitation-contraction coupling in cardiac muscle cells. Therefore, not surprisingly dysregulation of this channel has been implicated in electrical instabilities, arrhythmias, and even sudden cardiac death. The activity of Ca\textsubscript{\textupsilon}1.2 is controlled by \(\beta\)-adrenergic signaling, but the underlying mechanism remains incompletely understood. For example, it has been suggested that cleavage of Ca\textsubscript{\textupsilon}1.2 at alanine residue 1800 is required for \(\beta\)-adrenergic stimulation, and that this cleavage depends on a neighboring peptide motif. It has also been proposed that phosphorylation at serine residue 1700 is essential for \(\beta\)-adrenergic stimulation. But neither of these possibilities has been tested in native cardiomyocytes. Thus, Yang et al developed transgenic mice that expressed inducible, tissue-specific, and dihydropyridine-resistant versions of Ca\textsubscript{\textupsilon}1.2. Imparting dihydropyridine resistance enabled the investigators to separate transgenic Ca\textsubscript{\textupsilon}1.2 from the endogenous dihydropyridine-susceptible channel. The transgenic Ca\textsubscript{\textupsilon}1.2, however, carried mutations that disrupted either serine 1700 phosphorylation or the putative cleavage site residues. Yet surprisingly cleavage and \(\beta\)-adrenergic stimulation of Ca\textsubscript{\textupsilon}1.2 occurred as normal. These results highlight the importance of testing Ca\textsubscript{\textupsilon}1.2 in its native setting, and the new transgenic approach provides an ingenious and effective means to do so.

Adrenergic Modulation of Transgenic Ca\textsubscript{\textupsilon}1.2 Channels (p 871)

Madonna et al rejuvenate mesenchymal stem cells and improve their reparative potential.

Stem cell therapy is a promising approach for promoting the repair of ischemic tissue. However, it is believed that, the proliferative and the reparative capacity of stem cells diminishes with aging. Therefore, finding ways to rejuvenate the flagging potential of stem cells could improve their therapeutic efficacy. Madonna and colleagues now suggest that transducing mesenchymal stem cells (MSCs) with two factors—telomerase reverse transcriptase (TERT) and myocardin—could achieve such rejuvenation and improve the myogenic potential of these stem cells. TERT is an enzyme that maintains the telomeres of chromosomes, which normally shorten with age, while myocardin regulates cardiovascular myogenic development. When both factors were expressed in MSCs via lentiviral expression plasmids, the cells exhibited improved proliferation, survival and myogenesis in vitro. Importantly, when injected into ischemic hind limb muscles of mice, the transduced cells improved arteriogenesis and blood flow to a greater degree than that achieved with non-transduced MSCs. Taken together these results indicate that overexpression of TERT and myocardin could improve the therapeutic potential of MSCs and their efficacy in treating vascular disorders such as myocardial ischemia and peripheral artery disease.

TERT-MYOC Rejuvenation of AT-MSCs (p 902)
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