**CHRF Regulates Hypertrophy (p 1377)**

Wang et al identify two noncoding RNAs that regulate cardiac hypertrophy.

After a myocardial infarction, heart cells enlarge in order to compensate for damaged cells. But if this hypertrophic growth becomes permanent it can actually weaken the heart, leading to heart failure and eventually death. Therefore, a better understanding of the factors that control cardiac hypertrophy is needed to develop more effective strategies for prevention and treatment. Noncoding RNAs are known to be important regulators of cellular processes, so Wang and colleagues decided to search for noncoding RNAs involved specifically in hypertrophy. They discovered a noncoding, 23-nucleotide microRNA (miR) called miR-489 that was downregulated in cardiomyocytes treated with Ang-II—a potent inducer of hypertrophy. The team went on to show that knocking down miR-489 in cardiomyocytes caused the cells to become larger, while overexpression of the miR prevented the cells from growing and expressing hypertrophy markers. Transgenic mice that overexpressed miR-489 also displayed a reduced response to hypertrophy induction. Upon further investigation, the team discovered that miR-489 was itself regulated by another noncoding RNA—a 1843-nucleotide RNA they call cardiac hypertrophy related factor (CHRF). Unlike miR-489, CHRF was upregulated during hypertrophy. CHRF, it turned out, directly bound and inhibited miR-489, thus promoting hypertrophy. The team suggests that both CHRF and miR-489 might be suitable targets for developing new therapies for heart failure.

**MALAT1 and Endothelial Cell Function (p 1389)**

A long noncoding RNA called MALAT1 promotes endothelial cell proliferation, report Michalik et al.

The growth of new blood vessels, or angiogenesis, is required for the regeneration of tissues damaged by ischemic injury. On the other hand, preventing angiogenesis can inhibit the growth of life-threatening tumors. There is thus a continuing quest to find factors that promote or reduce angiogenesis. In their own search for such factors, Michalik and colleagues decided to investigate regulatory noncoding RNAs. They found that MALAT1 (metastasis-associated lung adenocarcinoma transcript 1), a long noncoding RNA, was highly expressed in endothelial cells in culture and that its expression was profoundly increased by hypoxia. In vitro, the silencing of MALAT1 increased endothelial cell migration but impaired proliferation. Indeed, the team showed that MALAT1 downregulated the expression of several genes that control the cell cycle. They also found that mice lacking MALAT1 exhibit impaired blood vessel extension and reduced vessel density in their retinas. Taken together, these results suggest that increasing the expression of MALAT1 might be a potentially useful strategy for preventing tissue ischemic injury, while inhibiting MALAT1 might prevent tumor growth.

**SR Ca²⁺ and Cardiac Alternans (p 1410)**

Wang et al observe calcium release dynamics in the whole heart.

In heart cells, tight control of calcium release and re-uptake from the sarcoplasmic reticulum (SR) is critical for establishing sturdy excitation-contraction coupling. Indeed, beat-to-beat variations in SR calcium release can lead to beat-to-beat variations in heart cell repolarization—known as alternans. Studies of SR calcium release dynamics and alternans have largely relied on single cell measurements. Wang et al now report simultaneous measurements of intracellular calcium release and transmembrane potential in the intact heart. Using a fluorescent calcium sensor, together with a voltage-sensitive fluorescent dye, they showed that as arrhythmia was experimentally induced, SR calcium release alternans preceded action potential alternans. Furthermore, the onset of alternans varied across the heart. The team also showed that ryanodine receptors (RyR)—calcium release channels of the SR—were to blame for the alternans. RyRs naturally remain closed, or refractory, after calcium release, allowing the SR stores to replenish. But if this refractoriness was pharmacologically reduced—by caffeine treatment—the hearts became less susceptible to alternans. These findings suggest that targeting the refractoriness of RyR could be used for the treatment of some arrhythmias, and that whole heart analysis could be a useful tool for assessing those treatments.

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