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Nrg1 Sustains the Cardiac Gene Regulatory Network (p 715)

Lai et al report that Neuregulin 1, an essential heart development factor, regulates a network of genes in the developing ventricles.

Neuregulin (Nrg1)—ligand of a transmembrane receptor called ErbB—is expressed in the heart’s endocardium and is crucial for ventricular morphogenesis during development. Without Nrg1, trabeculation—the formation of structural ridges on the ventricle walls that set up correct electrical conduction—is impaired. Downstream signals of Nrg1 have been identified, but how Nrg1 ultimately affects the cardiac gene regulatory network was unknown. The team created mutant mice that lacked almost, but not all, Nrg1 and looked at the expression of 15 different cardiac genes during heart development. They found that a majority of these genes showed decreased expression and that, although Nrg1 is known for its involvement in trabecular formation, genes in both trabecular and nontrabecular tissue were affected. Also, across the ventricular walls of the mutant mouse hearts, the gene expression levels were graded, suggesting differential activity of Nrg1. Recent evidence suggests that ventricle growth and trabecular formation are influenced by hemodynamic forces. The authors suggest that such forces might stimulate Nrg1 expression—hence, the graded expression pattern—and that because Nrg1 promotes heart development, its stimulation by blood flow would set up a positive feedback loop of function and form. Aberrations to this loop, say the authors, might magnify congenital malformations in the developing heart.

AKAP5 Signaling Complexes in Heart (p 747)

The protein AKAP5 is crucial for controlling the heart’s fight-or-flight response, say Nichols et al. A-kinase anchoring proteins (AKAPs) help to spatially organize signaling events inside cells by targeting cAMP-dependent protein kinase A (PKA) to specific locations and complexes. More than 11 AKAPs have been identified in heart cells, and figuring out each of their individual roles remains a major long-term goal. For now, Nichols et al have focused their attention on AKAP5. The team made transgenic mice that lack AKAP5 and looked at the ability of the heart muscle cells to respond to sympathetic stimulation—a process that produces large amounts of cAMP and thus active PKA. Sympathetic stimulation in vivo increases heart rate as part of the animal’s fight-or-flight response and is controlled at the cellular level by increasing both the amplitude and decay rates of calcium transients. This response was missing in the AKAP5 mutant heart cells, showed the team. Without AKAP5, PKA and a complex of other proteins failed to associate with a particular subpopulation of L-type calcium channels. The authors conclude that this association is responsible for the full-and-fast calcium transients induced by sympathetic stimulation. Chronic stimulation of the sympathetic pathway can lead to hypertrophy and heart failure, raising the question of whether the AKAP5 complex and its associated channel are altered in the pathophysiology of the disease.

Plasma MicroRNAs in Diabetes (p 810)

Zampetaki et al reveal a profile of plasma microRNAs that predict the risk of type 2 diabetes.

MicroRNAs (miRs) are short chains of 20 to 25 nucleotides that regulate gene expression by binding to target messenger RNAs. It was recently discovered that miRs are not restricted to life inside the cell: they can travel outside, circulating in the bloodstream in small, protective vesicle packages. It has also been discovered that the circulating levels of specific miRs can be altered in certain disease states. A number of miRs have been implicated in the disease process of type 2 diabetes, but heretofore, no one had looked at circulating miRs. Now, Zampetaki et al have. They isolated RNA from blood samples of a random cohort of individuals who had been monitored during a 20-year period. Screening the samples revealed a consistent list of miRs that were differentially expressed between diabetic people and controls. One of the miRs on the list was the blood vessel-promoting miR-126, which was significantly reduced in diabetics. Interestingly, these miRs were predictive of disease, because their levels were altered in normal individuals who later went on to develop diabetes. Using the five most significant miRs, the team successfully identified 92% of controls and 70% of diabetics, highlighting the miRs’ potential usefulness as novel biomarkers.

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