Mitochondrial Regulation of Arterial Contractility (p 631)

Narayanan et al uncover the cause and effect of rising mitochondrial calcium levels in arterial muscle cells.

Muscle cell contractility is regulated by, among other things, changes in intracellular calcium. The sarcoplasmic reticulum (SR) is the major intracellular calcium store, but mitochondria can also take up and sequester calcium. What prompts the mitochondria to take up calcium and what effect the increase in mitochondrial calcium might have were two unknowns. Narayanan et al have now shown in rat arterial smooth muscle cells that mitochondrial calcium uptake is increased in response to SR calcium release (induced by endothelin treatment). Interestingly, mitochondrial calcium uptake did not occur in response to global intracellular calcium increase (induced by plasma membrane depolarization). Mitochondria can reside next to SR in cells, suggesting that a localized calcium boost might be needed to trigger mitochondrial uptake. The endothelin-induced increase in mitochondrial calcium resulted in the release of mitochondrial reactive oxygen species, which activated expression of a calcium channel protein, Ca_{1.2}. The activation of Ca_{1.2}, in turn, triggered vasoconstriction. Altered levels of reactive oxygen species, Ca_{1.2}, and vascular contractility have all been associated with hypertension. Thus, the new work suggests that mitochondrial calcium control may be a useful target for hypertension drug development.

IP₃R Signaling Regulates Cardiac Hypertrophy (p 659)

Blocking IP₃ receptor signaling could reduce hypertrophy, according to Nakayama et al.

An increase in the size of heart cells—hypertrophy—can occur for physiologic and pathologic reasons. Pathologic hypertrophy, if left unchecked, could lead to heart failure and death. A number of prohypertrophic stimuli have been shown to increase intracellular levels of inositol 1,4,5-trisphosphate (IP₃) but the importance of IP₃ in transducing the hypertrophic response has not been thoroughly established. Nakayama et al have made transgenic mice that overexpress an IP₃ receptor and also mice that express an IP₃ chelator, which mops up IP₃, thus inhibiting IP₃ signaling. Mice overexpressing the receptor developed mild hypertrophy by 3 months of age and were susceptible to more serious disease in response to hypertrophic stimuli. In line with these results, mice expressing the IP₃ chelator showed reduced symptoms in response to hypertrophic agents. The IP₃ receptor resides on the sarcoplasmic reticulum (SR), and when it binds IP₃, it activates the release of calcium from the SR. Mice that overexpressed IP₃ receptor were protected against induced hypertrophy if they lacked calcineurin—a calcium-dependent phosphatase. Thus, blocking the IP₃-to-calcineurin pathway could be one approach to reducing hypertrophy.

Circulating MicroRNAs in Coronary Artery Disease (p 677)

Preliminary studies by Fichtlscherer et al suggest potential new biomarkers for coronary artery disease—circulating miRNAs.

MicroRNAs (miRs) are short RNA molecules approximately 20–25 nucleotides in length that bind to and down-regulate target messenger RNAs. Although miRs generally act within the cell, recent reports have shown that miRs can be released into the blood stream. The circulating levels of certain miRs have been found to be altered in humans and animal models after a heart attack, and in patients with heart failure, a particular circulating miR has been identified as a potential prognostic biomarker. Fichtlscherer et al decided to look at the profile of circulating miRs in patients with coronary artery disease, the number one cause of death worldwide. They found that the endothelial cell miRs, miR-126, 17 and 92a, as well as the smooth muscle enriched miR-145, were reduced in patient plasma. Levels of the inflammation-associated miR-155 were also reduced. In contrast, two cardiac muscle miRs were increased. The finding that the endothelial cell miRs were reduced surprised the team, because vessel wall injury might be expected to increase release of these miRs; however, the mechanism for release or uptake of these miRs is, so far, entirely unknown.
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