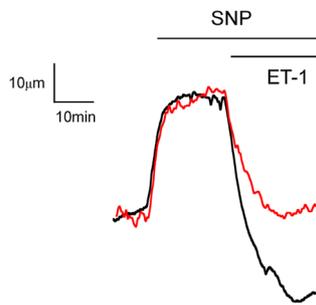


High Throughput Screen in Cardiomyocytes (p 604)

McLendon et al identify factors influencing protein aggregation within cardiomyocytes.

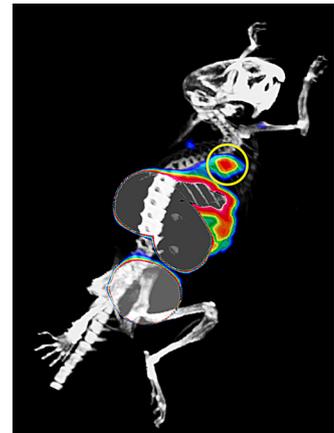
Accumulations of misfolded proteins within cells can impair cellular functions. Cellular aggregates of misfolded proteins are cleared mainly by the autophagic and proteasomal pathways, and this clearance is particularly important in postmitotic cells, such as those in the brain and heart. Indeed, protein aggregates are a hallmark of certain neurodegenerative disorders as well as heart conditions including desmin-related myopathy (DRM)—a disease characterized by heart and skeletal muscle degeneration. Using a mouse cardiomyocyte model of DRM and a library of silencing RNAs, McLendon and colleagues have now carried out an unbiased genome-wide screen for novel genes that either prevent protein aggregates or promote their clearance. The team identified a number of novel candidates, including the tyrosine kinase, Jak1, whose inhibition reduced protein aggregation by at least 50%. Further analysis of Jak1 in the mouse cells revealed that knock down of the kinase increased proteasomal, but not autophagic, activity. This work not only indicates that Jak1 could be a target for promoting protein clearance in DRM and other protein aggregation diseases, but also provides a list of other protein clearance candidates worthy of consideration.



ET-1 Stimulates Vasoconstriction Through Rab11A (p 650)

Zhai et al determine the intracellular mechanics of endothelin-1 induced vasoconstriction.

Controlling contraction and relaxation of arteries involves the careful balancing of opposing vasoconstrictive and dilatory signals, which act upon the smooth muscle cells (SMCs) of the vessel walls. Ion channels that regulate both the influx and intracellular levels of calcium within SMCs control contractility, but how the vasoconstrictive and dilatory signals regulate these channels is largely unknown. To learn more, Zhai and colleagues focused on the BK channels of SMCs. They found that the vasoconstrictor endothelin-1 prevents the trafficking of an essential BK subunit ($\beta 1$) to the plasma membrane of arterial SMCs, and thus diminishes BK activity. Reduced trafficking of $\beta 1$ to the cell surface involved endothelin-1 activation of protein kinase C followed by phosphorylation (and inhibition) of the intracellular trafficking factor Rab11a. In contrast, nitric oxide, a potent vasodilator, activated Rab11a and promoted trafficking of $\beta 1$ to the plasma membrane. The study provides insight into the mechanisms controlling arterial constriction and dilation and reveals potential targets, such as Rab11a, that might be manipulated pharmaceutically to regulate vascular contractility.



Ambient Temperature Controls Monocyte Egress From Marrow (p 662)

Warm ambient temperatures reduce atherosclerosis in mice, report Williams et al.

Epidemiological data shows an association between cold temperatures and adverse cardiovascular events. Yet, cold temperatures also stimulate thermogenesis within brown and beige fat, which is thought to improve weight loss and insulin sensitivity. To gain a better understanding of the effects of ambient temperature on cardiovascular disease, Williams and colleagues housed mice that are prone to atherosclerosis in rooms where the ambient temperatures were 4°C, 22°C, or 30°C. Although total plasma cholesterol levels did not differ between the 3 groups, animals housed at 4°C had the greatest plaque burden, while those housed at 30°C had the lowest. The ambient temperature also inversely correlated with the abundance of monocytes emerging from bone marrow and infiltrating plaques, with animals housed at 30°C exhibiting the lowest levels of both and the lowest numbers of circulating monocytes overall. The team went on to show that monocyte counts in humans were also inversely correlated with seasonal temperature changes. Williams and colleagues argue that while activation of brown and beige fat may instigate beneficial metabolic changes for combating obesity, promoting exposure to cold as a means to achieve this end, could have adverse effects.

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