MicroRNA-181b Improves Insulin Sensitivity (p 810)

MicroRNA-181b improves insulin sensitivity in obese mice, report Sun et al.

Obesity is a risk factor for developing diabetes, and one of the root causes seems to be dysfunction of the adipose tissue—characterized by low-grade inflammation and aberrant adipocyte and endothelial cell (EC) function. Indeed, inflamed adipose tissue has been linked directly to insulin resistance. Among the many possible factors contributing to adipose tissue dysfunction, are several microRNAs (miRs) that have been found to be differentially expressed in the adipose tissues of obese and lean mice. Sun and colleagues now show that one such miR—miR181b (known for its anti-inflammatory activity)—is an important determinant of obesity-induced changes in adipose tissue. The team examined adipocytes and ECs of obese mice and found that levels of miR-181b were suppressed in ECs, but not adipocytes, after just one week of high fat feeding. Given the anti-inflammatory properties of miR-181b, the team hypothesized that reconstituting the miR in obese mice might ameliorate insulin resistance. Sure enough, they found that injections of a miR-181b mimic into obese mice improved insulin sensitivity and reduced inflammation. The team also found that protein phosphatase PHLPP2 mRNA is a direct target of miR-181b, and that suppression of PHLPP2 produced equivalent results to the miR treatment in obese mice. Lastly, the team noted that levels of PHLPP2 were higher in ECs of diabetic patients than controls, suggesting the new findings in mice are relevant to human disease.

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Transplant Mitochondrial PTP in Cardiac Myocytes (p 834)

Transient pores in mitochondria are physiologically normal, say Lu et al.

Mitochondria are ATP producing powerhouses of cells, and are abundant in highly aerobic tissues such as the heart. To enable ATP production, mitochondria maintain a voltage gradient across their inner membranes, which is highly impermeable. Indeed, cellular stress can prompt the formation of pores called permeability transition pores (PTPs) in mitochondrial membranes, causing voltage gradients and large molecules to be lost. ATP production to cease, leading eventually to cell death. Blocking PTP formation protects against cell death during ischemia-reperfusion, but paradoxically, chronic inhibition of PTP could also induce mitochondrial calcium overload and cardiac dysfunction. This suggests that some transient PTP (tPTP) events might be necessary for normal mitochondrial function. Lu and colleagues therefore investigated whether tPTPs occur in normal adult mouse cardiomyocytes. Using a confocal microscope to simultaneously observe hundreds of mitochondria, the team found that indeed tPTP events do take place, albeit with low frequency. Lasting less than a minute, tPTPs were characterized by reversible calcium release and voltage loss, and by the retention of large molecules. Determining the molecular differences between normal tPTP events and prolonged PTP opening will be a crucial question for future research.

Telomerase and Microvascular Function (p 856)

Telomerase reverse transcriptase may restore healthy vasodilation mechanisms in coronary artery disease, report Beyer et al.

In healthy blood vessels, flow-mediated vessel dilation is accomplished by the action of nitric oxide (NO), but in coronary artery disease (CAD), NO is replaced by H2O2 as the dilation mediator. Being both a proinflammatory and proatherogenic factor, H2O2 can thus further exacerbate CAD. Beyer and colleagues have now identified a somewhat unlikely enzyme as a potential candidate for restoring NO-mediated dilation in CAD patients. Telomerase reverse transcriptase (TERT) is an enzyme that maintains telomere length at the end of chromosomes in the nucleus. However, recent evidence suggests that TERT also moonlights outside the nucleus, and can be found in the mitochondria, for example, where it suppresses the production of reactive oxygen species including H2O2. Beyer and colleagues discovered that arterioles isolated from CAD patients, have unusually low levels of TERT. They also show that blocking TERT activity in healthy arterioles caused a switch from NO- to H2O2-mediated dilation. Lastly, the team discovered that boosting TERT with the synthetic compound AGS-499 (a known TERT activator) reduced H2O2 and restored NO in CAD patient arterioles. Collectively, the work highlights TERT as a putative target for improving vascular health in CAD.