PPAP2B protein regulates the response of vascular endothelium to shear stress, report Wu et al.

In a recent genome-wide study, the gene encoding the enzyme phosphatidic acid phosphatase type 2B (PPAP2B) was found to be associated with coronary artery disease. This gene encodes an integral membrane protein found on vascular endothelial cells that hydrolyses lysophosphatidic acid (LPA)—a lipid messenger known to circulate in the blood, accumulate at atherosclerotic plaques, and cause endothelial inflammation. Levels of LPA have been found to be elevated in patients with coronary artery disease. Now, Wu and colleagues have discovered that the expression of PPAP2B is reduced in human atherosclerotic plaques. Furthermore, in the healthy vessels of mice and pigs, the levels of PPAP2B were low in regions prone to atherosclerotic plaque formation—the curvature of the aortic arch, for example. Such regions experience oscillating blood flow and low shear stress, so the authors reasoned that the expression of PPAP2B, may be under hemodynamic control. In agreement with this hypothesis, they found that the microRNA miR92, which is induced by low shear stress, directly bound and suppressed PPAP2B mRNA. And that, conversely, the transcription factor KLF, which is activated by high shear stress, promoted PPAP2B expression. Finally, they show that PPAP2B inactivates LPA and, thereby diminishes endothelial inflammation; making PPAP2B a possible target for modulation in atherosclerosis.

Villa et al reveal how a longevity-associated protein exerts its rejuvenating benefits.

The secrets to a long and healthy life may be hidden in the genomes of long-lived people. In one attempt to uncover such secrets, researchers performed a genome-wide association study for longevity that flagged a handful of candidate genetic loci. Villa and colleagues have now tested these loci in two further populations of long-lived people and discovered that only one—a single nucleotide polymorphism in the protein BPIFB4—repeated the original association. The team discovered that BPIFB4, an innate immunity factor of unknown function, is expressed on stem and progenitor cells such as CD34+ pro-angiogenic progenitors that circulate in the blood. This suggested that BPIFB4 might be involved in vascular repair and regeneration, which tends to decline with age. Indeed, transfection of the longevity-associated variant of BPIFB4, but not the wild-type version of the protein, improved re-vascularization and reperfusion following hind-limb ischemia and decreased blood pressure in mice. The team went on to show that the longevity-associated variant of BPIFB4 when transduced into mice exerts these effects by enhancing production of the vasoprotective agent—nitric oxide. Together the results identify the variant of BPIFB4 as a therapeutic agent for protecting vascular function in aging.

Parkin-driven mitophagy is ramped-up and detrimental in cardiomyocytes that lack correct mitochondrial fission, report Song et al.

The heart is one of the most metabolically active organs in the body. Ensuring the high quality and efficiency of its mitochondria is thus of utmost importance and dysregulation of quality control processes could have disastrous effect. For example, interfering with correct mitochondrial fission, leads to cardiomyopathy and an associated loss of mitochondria. Song and colleagues now show that this loss of mitochondria is driven by the upregulation of the protein Parkin, which promotes the destruction of mitochondria by a process called mitophagy. The team showed that, in the hearts of healthy mice, increasing or decreasing levels of Parkin was well tolerated and did not lead to overt cardiac dysfunction. But, in heart with impaired mitochondrial fission (caused by deletion of the fission factor Drp1), the levels of Parkin increased disproportionately, provoking large-scale depletion of mitochondria. Indeed blocking Parkin activity in such animals reduced cardiomyopathy: contractile function was improved and ventricular remodeling reduced. The numbers of mitochondria also remained high and mitochondrial function was preserved. The authors argue that the results could be a cautionary flag for therapeutic inhibition of Drp1, which is currently under investigation for the treatment of cardiac disease.
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