Heartburn medication promotes aging of vascular cells, report Yepuri et al.

Proton pump inhibitors (PPIs) are used to treat gastroesophageal reflux disease (chronic heartburn). These drugs are approved for short-term treatment, but their over-the-counter availability has led to both inappropriate and long-term use. Worryingly, recent findings suggest PPI use may increase the risk of myocardial infarction, renal failure, and dementia. Similar to their counterparts lining the stomach, proton pumps also exist within cellular lysosomes, which are acid-containing organelles involved in waste disposal and therefore could be secondary PPI targets. Hence, Yepuri and colleagues examined lysosomes in PPI-treated vascular endothelial cells—which, if dysfunctional, can contribute to heart, kidney, and dementia problems—and found that lysosomal pH was increased (less acidic) upon PPI treatment. Lysosomal enzyme activity was also impaired, and the cells showed signs of protein aggregation suggesting that waste disposal was defective. Accumulation of waste proteins in these lysosomes was associated with signs of cellular aging, including decreased angiogenic potential, decreased proliferation, and increased oxidative stress. Although the researchers did not ascertain whether the proton pumps themselves were affected, the results revealed adverse effects of PPIs and suggest the drugs should be evaluated for their long-term safety.

Zhang et al examine the much-disputed developmental origin of coronary arteries.

During embryonic development, coronary veins are thought to originate from endothelial cells of the sinus venosus (SV), whereas coronary arteries have been suggested to arise from the SV, the ventricular endocardium (VE), or both. A recent study utilizing a putative VE-specific marker, Nfatc1, reported that the majority of coronary arteries are of VE origin, but other studies suggest a greater role for the SV. Zhang et al examined Nfatc1 marking of embryonic cells more closely and found that Nfatc1 is actually expressed in the SV at early stages of development and therefore cannot be considered a VE-specific factor. By examining single-cell expression profiles of SV and VE cells, the team went on to identify a novel robust marker of VE cells: the protein Npr3. Contrary to earlier reports, they showed that cells labeled with Npr3 contribute minimally to coronary vessel development in the embryonic ventricle walls. From these observations, the authors conclude that SV is likely to be the major source of coronary vessels—both veins and arteries alike. This new insight into the origins of coronary vessels could enlighten studies into not only the development of the heart vasculature, but also, potentially, into the process of post-injury regeneration.

Boosting autophagy improves heart function in mice with proteotoxic cardiomyopathy, report Gupta et al.

Autophagy is a key pathway regulating the clearance of waste proteins and in the maintenance of protein quality control, essential for the health of cells. It is a complex, multistep process in which sumoylation, the post-translational addition of a small sumo peptide moiety to target proteins—is thought to drive certain protein aggregates to an autophagic fate and to regulate some key autophagy components. Therefore, to understand protein quality control in cardiomyocytes in the heart, Gupta and colleagues examined sumoylation and autophagy in rat ventricular cardiomyocytes. They found that increasing sumoylation via the overexpression of UBC9—an enzyme that catalyses the addition of sumo to target proteins—directly increased autophagy in the rat cells. They also found increased autophagy in genetically engineered mice in which UBC9 was specifically overexpressed in cardiomyocytes. Then to test the role of UBC9 in clearance of misfolded proteins in the heart, the team overexpressed UBC9 in a mouse model of desmin-related cardiomyopathy (DRM), in which misfolded proteins accumulate in cardiomyocytes disturbing heart function. In this model, the UBC9-induced increase in sumoylation and autophagy promoted clearance of the toxic protein aggregates, improved heart function, and extended animal survival. Taken together, these results suggest that promoting sumoylation could be a means to increase autophagy and reduce tissue injury in proteotoxic cardiac diseases.
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