Fueling the heart: Shifting the myocardial metabolome by targeting endothelial autophagy

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The heart is a contractile mass in perpetual motion, and the metabolic demands of the heart exceed those of any organ in the body. Fuel for the heart is generated primarily through oxidative phosphorylation, where mitochondria, oxygen, and intracellular enzymes are used to generate adenosine triphosphate from fatty acids and carbohydrates. Of the 2, fatty acids are used in greater quantity (~70% of cardiac energy requirements), but carbohydrates are a more efficient energy substrate. For this reason, investigators have recently hypothesized that increasing glucose oxidation (at the expense of fatty acid oxidation) may improve cardiac efficiency and function in disease states with deranged myocardial bioenergetics, such as ischemia–reperfusion injury and heart failure.1

In the current issue of the Journal, Altamimi and colleagues2 explore the role of endothelial cell autophagy in regulating metabolic substrate use by the myocardium. Autophagy is the process of recycling cellular components to maintain cellular homeostasis, and prior studies from this group and others have suggested that endothelial autophagy may be important for a host of physiologic processes including metabolism. Experiments using isolated working mouse hearts demonstrated that tissue-specific inhibition of autophagy within the endothelium led to a diminished reliance on fatty acids as a fuel source in response to insulin, as well as after ischemia–reperfusion injury. In vitro studies further demonstrated that inhibiting endothelial autophagy reduced the expression of lipid chaperone fatty acid binding proteins, hinting that decreased fatty acid translocation may represent the mechanism of action. However, despite achieving a more “efficient” metabolic profile with reduced fatty acid use, there were no improvements in cardiac function with inhibition of endothelial autophagy. The authors speculate that although inhibition of endothelial cell autophagy led to what should be a more favorable metabolic profile, autophagy may play an important role in other cellular processes important for recovery from ischemia–reperfusion injury. Thus, the metabolic benefits of inhibiting endothelial autophagy may have been offset by detriments in other areas.

The study by Altamimi and colleagues2 is notable for several reasons. Autophagy has been identified as a cellular process with a novel role in regulating metabolic substrate use by the myocardium. The process of recycling cellular components to maintain cellular homeostasis, and prior studies from this group and others have suggested that endothelial autophagy may be important for a host of physiologic processes including metabolism. Experiments using isolated working mouse hearts demonstrated that tissue-specific inhibition of autophagy within the endothelium led to a diminished reliance on fatty acids as a fuel source in response to insulin, as well as after ischemia–reperfusion injury. In vitro studies further demonstrated that inhibiting endothelial autophagy reduced the expression of lipid chaperone fatty acid binding proteins, hinting that decreased fatty acid translocation may represent the mechanism of action. However, despite achieving a more “efficient” metabolic profile with reduced fatty acid use, there were no improvements in cardiac function with inhibition of endothelial autophagy. The authors speculate that although inhibition of endothelial cell autophagy led to what should be a more favorable metabolic profile, autophagy may play an important role in other cellular processes important for recovery from ischemia–reperfusion injury. Thus, the metabolic benefits of inhibiting endothelial autophagy may have been offset by detriments in other areas.

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References
