How High-Density Lipoprotein Fuels the Failing Heart

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See related article, pp 1002–1007

Heart failure remains a major multifactorial health problem in the aging population. The causal cellular mechanisms are still incompletely understood, and further understanding of these mechanisms in heart failure is necessary to open up new perspectives for treatment and prevention. Distinct evidence suggests that cardiac energy metabolism in the failing heart is severely impaired. In fact, compromised cardiac energy metabolism might cause and worsen myocardial dysfunction. A growing body of evidence suggests that cellular energy expenditure in the diseased heart is crucial for understanding and treating cardiac dysfunction and thus needs to be investigated further. Nakajima et al now provide novel insights in the regulatory changes of cellular substrate use in the pathogenesis of heart failure.

Vast amounts of energy are required to fuel the perpetual pumping activity of the heart. Although the fetal heart predominantly generates ATP from carbohydrate oxidation, the adult human heart draws on free-fatty acids as the major substrate for energy supply. Approximately 60% to 90% of the ATP required is generated by β-oxidation of long chain fatty acids. The remaining 10% to 40% are obtained by oxidation of other substrates, such as glucose, lactate, and ketone bodies. So far, evidence has indicated that fatty acid demand in cardiac energy metabolism might cause and worsen myocardial dysfunction.

The present study by Nakajima et al introduces a novel player into the arena, namely endothelial lipase (EL). EL is a member of the triglyceride lipase family that is expressed in different tissues including the heart. Unlike other members of the triglyceride lipase family, EL primarily hydrolyzes fatty acids from high-density lipoprotein phospholipids, whereas triglyceride lipase activity is subordinate. Increased EL activity has been shown to be able to compensate for the absence of LPL in adipose tissue fatty acid uptake. Thus, Nakajima et al hypothesized that EL significantly contributes to cardiac fatty acid supply in conditions with increased energy demand or reduced LPL activity, such as in pressure overload-induced heart failure. A schematic overview is given in the Figure.

To evaluate the role of EL in the genesis of heart failure, Nakajima et al generated a murine model of pressure overload-induced cardiac hypertrophy and acute cardiac decompensation by means of ascending aortic banding in wild type (EL+/+) and EL-knock out (EL−/−) mice. In wild-type mice, acute pressure overload was followed by a significant increase in EL mRNA ≈ 1 day after aortic banding. At the same time there was a significant reduction of LPL mRNA. Both EL and LPL expression returned to a stable level ≈ 7 days after surgery, with a remaining slight increase in EL and decrease in LPL, respectively. Deletion of EL in EL−/− mice worsened pressure overload heart failure and congestion, suggesting that EL is essential in the regulation of cellular energy supply under failing conditions. The expression of genes facilitating cellular fatty acid uptake, fatty acid-binding protein CD36, and fatty acid transporter protein 6 remained unimpaired in both groups, after surgery. However, at the same time, EL−/− mice showed significantly lower expression of genes involved in mitochondrial fatty acid uptake and β-oxidation, carnitine-palmitoyltransferase 1, medium-chain acyl-dehydrogenase, citrate-synthase, and β-hydroxyacyl-CoA-dehydrogenase, after banding, compared with the wild type. Furthermore, EL−/− mice also showed substantially decreased myocardial ATP levels and increased cardiac triglyceride contents, after surgery, compared with EL-sufficient mice, suggesting that EL deficiency reduces cardiac lipid consumption by attenuating mitochondrial β-oxidation. In line with this notion, EL overexpression in cardiomyocytes significantly enhanced genes involved in mitochondrial fatty acid use and cellular ATP levels. Together, these results indicate that cardiac fatty acid supply through EL is essential in the setting of pressure overload heart failure to maintain mitochondrial β-oxidation and ATP generation, and that increased expression of EL in the early phase of pressure overload heart failure seems to be a compensatory response to maintain vital metabolic functions of the heart. Thereby, inhibition of the process by deletion of EL causes impaired fatty acid flux, resulting in attenuation of ATP generation, cardiac lipid accumulation, and aggravation of heart failure.
In conclusion, Nakajima et al3 present a novel concept for the generation of biochemical energy in the acutely failing heart. They found evidence that EL acquires a regulatory function, sustaining cardiac fatty acid availability and mitochondrial β-oxidation in pressure overload heart failure, thereby preserving cardiac function. The observation that EL expression is increased in the early stage of pressure overload heart failure while LPL expression is reduced suggests a reciprocal regulation of both lipases, which might be important for preserving cardiac function in cardiovascular disease. The novel insights gained by Nakajima et al3 will help to better understand the pathophysiological relevance of impaired energy metabolism in the diseased heart and the interplay between lipases involved in the process. It further supports the notion that refining lipid metabolism in heart failure is a promising objective for preserving cardiac function.

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