Switching Metabolic Genes to Build a Better Heart

Heinrich Taegtmeyer, MD, DPhil

The heart makes its living by liberating energy from a variety of oxidizable substrates, either simultaneously or vicariously. Because of built-in mechanisms that choose the most efficient substrate for a given physiological environment, the heart is a true metabolic omnivore. The link between metabolism and function of the heart was discovered by Langendorff when he demonstrated that the mammalian heart receives oxygen and nutrients through the coronary circulation and not through the endocardium, as it had been assumed until then. Early investigators also knew already that the heart oxidizes fatty acids and glucose, and myocardial fuel economy became a focus of biochemical investigation in the 1960s. Biochemists “discovered” the heart as a convenient bag of enzymes to study muscle metabolism and found that fatty acids suppress glucose oxidation, chiefly at the level of the pyruvate dehydrogenase complex. Conversely, we later found that glucose suppresses fatty acid oxidation, chiefly at the level of fatty acid entry into the mitochondria. In short, fuel metabolism in the heart is highly regulated, allowing the heart to respond to substrate availability, circulating hormones (such as insulin or catecholamines), coronary flow, and workload by choosing the “right” substrate at the right moment. Unless blood supply is curtailed, as it is the case in ischemia, the heart is never short of fuel to burn.

Control and Regulation

What is, then, the principle that underlies substrate switching? As every nutritionist knows, fat has a higher caloric value than carbohydrates; at the same time, the oxidation of carbohydrates results in more efficient energy production than the oxidation of fat. The heart readily oxidizes both substances. Substrate switching in the heart is determined by an interaction of control and regulation of the metabolism of energy providing substrates. According to the metabolic control theory, metabolic control is the power to change the state of metabolism in response to an external signal, whereas metabolic regulation defines the way a metabolic system responds to environmental changes. For example, changes in workload control the rate of substrate oxidation, while coordinated changes in enzyme activities regulate substrate metabolism. The terms control and regulation are gaining new importance with the advent of metabolically relevant models of genetic manipulation.

Defective Energy Substrate Metabolism in Failing Heart

As the process of metabolic substrate remodeling progresses from adaptation to maladaptation, regulated pathways become misregulated pathways, and the failing heart loses its ability to switch to the most efficient fuel for energy production. Energy transfer is impaired at the level of intermediary metabolism. Most importantly, the failing heart develops an impaired capacity to oxidize fatty acids without a sufficiently high compensatory increase in glucose oxidation. At a molecular level, glucose transporter 1 (GLUT 1) expression...
is severely downregulated in failing human heart, as is PPARα. Thus, two key regulators of glucose and of fatty acid metabolism are downregulated in failing heart. While substrate supply remains unimpaired, the heart fails in the midst of plenty.

Compensating Defective Energy Substrate Metabolism

The study by Liao et al\textsuperscript{17} reported in this issue of Circulation demonstrates that the overexpression of one regulatory protein in glucose uptake and metabolism augments glucose uptake. The study sheds new light on the importance of substrate switching and the compensatory increase in glucose oxidation in the stressed heart. The investigators generated mice that overexpress the constitutively expressed glucose transporter GLUT1 in the heart and then induced hypertrophy by pressure-overload on the left ventricle. Pressure overload itself controls function and metabolism of the heart and induces the expression of fetal genes in rodent hearts, and the switching of metabolic genes is part of the heart’s adaptation to sustained increases in workload. Adaptive metabolic switching from fatty acids to glucose can precede the development of hypertrophy\textsuperscript{18} and may become maladaptive when glucose transporter expression and activity is down-regulated in failing heart.\textsuperscript{19} However, the present study by Liao et al\textsuperscript{17} shows that up-regulation of GLUT1 alone can prevent the decline in contractile function by preventing misregulation of glucose metabolism. Whether PPARα plays a role in this system remains to be seen.

Several lessons can be learned from the elegant experiments of Liao et al.\textsuperscript{17} First, the constitutively expressed glucose transporter GLUT1 is a regulator of glucose uptake and metabolism, as demonstrated by the phosphorylation of the glucose tracer analog 2-deoxyglucose. Secondly, the combined action of pressure overload-induced hypertrophy and overexpression of GLUT1 has far-reaching (beneficial) consequences for the performance of the heart. The process involves signaling pathways further downstream at the level of metabolism, growth, and gene expression. At this time, very little is known about the cross-talk between metabolism and the signaling pathways of cell growth and survival in the heart. However, we know already that the activation of fatty acid metabolism in the hypertrophied rat heart results in contractile failure, which suggests that metabolic switches are a prerequisite for the successful adaptation of the heart to an altered environment.

Glucose, Glycogen, and Other Potential Mechanisms

What are the potential mechanisms for the observed phenomena? The first and most direct explanation is increased glucose uptake and oxidation to make up for the energy deficit of the hypertrophied heart. The second, somewhat more complex explanation would link GLUT1 to the concomitant upregulation of the serine-threonine kinase Akt. This speculation is a testable hypothesis. Akt activation reduces myocardial cell death and induces cardiac hypertrophy\textsuperscript{20} while raising cardiac glycogen levels and protecting the heart from injury. All these features are also present when GLUT1 is overexpressed in the heart. It is reasonable to assume that overexpression of GLUT1 is accompanied by a host of transcriptional and phenotypic changes similar to the spectrum of changes caused by overexpression of activated Akt in the heart.\textsuperscript{20,21} A third explanation is linked to increased levels of myocardial glycogen in the present model, suggesting that rates of glucose uptake exceed rates of glycolysis and glucose oxidation. The protective effect of glycogen in the heart probably extends beyond the role of glycogen as an endogenous fuel. For example, in fatigued skeletal muscle, glycogen repletion restores Ca\textsuperscript{2+} sensitivity and maximum Ca\textsuperscript{2+}-activated force.\textsuperscript{22} Lastly, high intracellular glucose concentrations have been shown to cause a rise in intracellular [Ca\textsuperscript{2+}] of isolated cardiac myocytes.\textsuperscript{23} The plot begins to thicken, and it is very tempting to link glucose metabolism to the regulation of Ca\textsuperscript{2+} homeostasis in the cardiac myocyte.

Conclusion

Intermediary metabolism, with its complex maze of pathways, has long been regarded as “obsolete” and of little relevance for the understanding of cardiac physiology. The report by Liao et al\textsuperscript{17} in this issue of Circulation shows exactly the opposite. Increasing the amount and activity of one key regulator of myocardial glucose metabolism prevents the progression from adaptation to maladaptation, from compensatory hypertrophy to heart failure. Transcriptional responses in transgenic models are complex and by no means limited to the gene in question. Much more needs to be learned about these very complex mechanisms, but the basic concept is very simple: targeting metabolic interventions may indeed be the foundation for building a better heart. My teacher Hans Krebs wrote in his memoirs, “When studying a biological phenomenon, it is always important to examine the whole process and not merely a fragment in a damaged tissue.”\textsuperscript{24} The article by Liao et al\textsuperscript{17} is proof of this principle, as well as another important concept: metabolism is not an innocent bystander in the control of cardiac gene expression.

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References

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