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FOCUS SEMINAR: GENETICS

STATE-OF-THE-ART REVIEW

The Emerging Role of Metabolomics in the Diagnosis and Prognosis of Cardiovascular Disease

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ABSTRACT

Perturbations in cardiac energy metabolism are major contributors to a number of cardiovascular pathologies. In addition, comorbidities associated with cardiovascular disease (CVD) can alter systemic and myocardial metabolism, often contributing to the worsening of cardiac function and health outcomes. State-of-the-art metabolomic technologies give us the ability to measure thousands of metabolites in biological fluids or biopsies, providing us with a metabolic fingerprint of individual patients. These metabolic profiles may serve as diagnostic and/or prognostic tools that have the potential to significantly alter the management of CVD. Herein, the authors review how metabolomics can assist in the interpretation of perturbed metabolic processes, and how this has improved our ability to understand the pathology of ischemic heart disease, atherosclerosis, and heart failure. Taken together, the integration of metabolomics with other "omics" platforms will allow us to gain insight into pathophysiological interactions of metabolites, proteins, genes, and disease states, while advancing personalized medicine.
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Over the last few decades, there has been a growing appreciation for the important contribution that myocardial energy metabolism plays in the regulation of cardiac function. As the heart is the most metabolically demanding organ in the body, it is not surprising that perturbations in cardiac energy metabolism are major contributors to a number of cardiovascular pathologies. In addition, comorbidities associated with cardiovascular disease (CVD) pathogenesis can alter systemic and myocardial metabolism, which often aids in the worsening of cardiac function and health outcomes. In no situation is this more relevant than in obesity and diabetes, where these conditions can cause major systemic metabolic disturbances that have a negative impact on organs such as the liver, skeletal muscle, adipose tissue, the vasculature, as well as the myocardium. However, even in the absence of obesity and diabetes, alterations in substrate metabolism of numerous organs resulting from the onset of CVD can contribute to changes in the metabolic profile of a patient. With numerous advancements in "omics" technology platforms, including genomics, transcriptomics, and proteomics, we now have a much broader understanding of the molecular/cellular/functional changes that take place in CVD,

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as well as predictions of how these changes may influence intermediary metabolism (**Central Illustration**). Furthermore, state-of-the-art metabolomic technologies that are now available give us the ability to measure thousands of metabolites in biological fluids or biopsies, providing us with a "snapshot" of the metabolic fingerprint of individual patients (**Table 1**). These snapshots can potentially serve as diagnostic and/or prognostic tools that can be used to identify impairments in systemic or myocardial metabolism occurring during the development and worsening of CVD, as well as help guide the types and timing of specific interventions/therapies. Thus, metabolomics is emerging as an important tool that can aid clinicians in better understanding the pathogenesis of CVD, and has the potential to significantly alter the management of CVD.

OVERVIEW OF CELLULAR METABOLISM

Substrate metabolism is an essential component of cellular heath and survival. Both anabolic and catabolic processes are necessary to support the numerous cellular events that contribute to cell, organ, and organism survival. From a simplistic perspective, when cells in the body generate energy in the form of adenosine triphosphate (ATP), they catabolize the various energy sources available, either from endogenous energy stores (primarily glycogen or triacylglycerols), or from exogenous substrates circulating in the blood (e.g., carbohydrates, fatty acids, amino acids, and ketone bodies, among others). By contrast, when cells need to build materials (e.g., phospholipids for membranes, proteins for growth, fatty acids for de novo lipogenesis, and so on) or perform many cellular processes (e.g., growth, ionic homeostasis, signal transduction, contraction, among others), they consume ATP, releasing the energy needed to support these functions. For the vast majority of cells in our body, carbohydrates (primarily in the form of glucose and lactate) and fatty acids represent the most common energy substrates metabolized by our cells to produce ATP.

Of the many substrates that can be used to generate energy, glucose and fatty acids are the major contributors to overall ATP production. For the former, following transport from the circulation into the cell, glucose can undergo anaerobic glycolysis to produce pyruvate and small amounts of ATP (2 ATP per glucose molecule) (**Figure 1**). In some cell types, if the energy need is low, the majority of this pyruvate is converted into lactate, which can exit the cell into the circulation (**Figure 1**). However, if the cellular energy demands are high and oxygen is present, pyruvate derived from glucose and/or lactate can enter the mitochondria, where it is converted to acetyl coenzyme A (acetyl-CoA) by pyruvate dehydrogenase (PDH). Acetyl-CoA is the common intermediate that links oxidative metabolism of all nutrient energy sources, and this acetyl-CoA is utilized by the tricarboxylic acid (TCA) cycle (also known as the Krebs cycle) to produce reducing equivalents (e.g., nicotinamide adenine dinucleotide and flavin adenine dinucleotide), which act as electron donors to drive the proton motive force that fuels ATP synthesis (**Figure 1**). This latter process of glucose breakdown from pyruvate to eventual ATP production is termed glucose oxidation, and ultimately generates a significantly greater amount of ATP than glycolysis (31 ATP from glucose oxidation vs. 2 ATP from glycolysis). During cellular fatty acid catabolism, fatty acids are either transported into and/or passively enter the cell, converted into fatty acyl-CoA esters, and then converted into a fatty acylcarnitine, which permits the fatty acid to traverse the mitochondrial membrane. There, it is reconverted back into a fatty acyl-CoA ester for subsequent mitochondrial β-oxidation (**Figures 1** and **2**) (1). The mitochondrial β-oxidation enzymatic machinery proceeds to repeatedly remove acetyl-CoA from the fatty acyl-CoA ester until it has been completely oxidized. Hence, complete oxidation of a fatty acid molecule, such as oleate or palmitate, produces more acetyl-CoA and reducing equivalents, and thereby a much larger amount of ATP than the complete oxidation of a glucose molecule (104 ATP from palmitate vs. 31 ATP from glucose oxidation).

Although glucose and fatty acids represent the most common fuels used by our cells to produce energy, the majority of cells in our bodies are also capable of metabolizing amino acids (e.g., hepatocytes, skeletal muscle myocytes) and ketone bodies (e.g., neurons) to produce acetyl-CoA for oxidative energy metabolism (**Figure 1**). In particular, cellular metabolism of the branched-chain amino acids (BCAAs) leucine, isoleucine, and valine, has been extensively studied, as BCAAs are potent regulators of systemic metabolism, energy expenditure, and muscle protein synthesis (2). In order for BCAAs to enter the mitochondria for oxidative metabolism,

ABBREVIATIONS AND ACRONYMS

ATP = adenosine triphosphate
BCAA = branched-chain amino acid
BCKA = branched-chain α-keto-acid
BNP = B-type natriuretic peptide
CAD = coronary artery disease
CoA = coenzyme A
CVD = cardiovascular disease
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
IHD = ischemic heart disease
L-C = long-chain
LC = liquid chromatography
LV = left ventricular
M-C = medium-chain
MI = myocardial infarction
MS = mass spectrometry
NMR = nuclear magnetic resonance
PDH = pyruvate dehydrogenase
PET = positron emission tomography
S-C = short-chain
T2D = type 2 diabetes
TCA = tricarboxylic acid
TMA = trimethylamine
TMAO = trimethylamine-*N*-oxide