Metabolic Biomarkers in Heart Failure

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KEYWORDS

• Heart failure metabolomics • Arginine • Nitric oxide • Myocardial energy utilization • Acylcarnitine • TMAO

KEY POINTS

- Metabolomics is the study of small, organic, molecules of biochemical pathways, some of which are strongly implicated in heart failure pathogenesis and progression.
- Modern developments in mass spectrometry and nuclear magnetic resonance (NMR) have enabled identification of approximately 40,000 human metabolites.
- The failing heart exhibits metabolic derangements, particularly in energy utilization and oxidation.
- Creation of metabolomic profiles may aid in the diagnosis, management, and prognosis of heart failure.
- Metabolomics extends to human and microbial products, further adding to the complex gene, protein, and environmental interactions in heart failure.

INTRODUCTION

Heart failure is a complex disease process that affects an increasing number of patients due to advancements in cardiac care and increased longevity of the aging population. From an epidemiologic and macroscopic perspective, timely diagnosis and early interventions in heart failure are likely to have far-reaching impact on health care economics and public health. Many discoveries in pathophysiology and pharmacotherapy have already improved mortality and morbidity in this population of patients in the past few decades. However, for all the progress in the diagnosis and management of this complex disease, there remain many unresolved mysteries, the unlocking of which could lead to profound understanding of heart failure pathogenesis, treatment, and prognosis. From a microscopic perspective, heart failure is a manifestation of metabolic derangements on the cellular, genetic, proteomic, and metabolic levels.[1]

Traditionally, genetic information is translated from DNA into RNA and transcribed into protein. The proteome is made of a variety of proteins that can then undergo posttranscription modification, and through interactions with environmental factors, produce metabolites used for energy production. A metabolite is thus defined as any small organic molecule detectable in the human body with a molecular weight of 50 to 1500 Da. The source of metabolite generation can include any biofluid, such as blood, urine, saliva, and respiratory gases. Thus, a rich collection of metabolites, including peptides, oligonucleotides, sugars, nucleosides, organic acids, ketones, aldehydes, amines, amino acids, lipids, steroids, alkaloids, and small molecule drugs, are included in the study of metabolomics. The metabolite may arise from external sources, such as exposure to medications, toxins, or microbes, or it may be generated by the human host in the homeostatic process of energy utilization (Fig. 1). With growing interest in this field and improved

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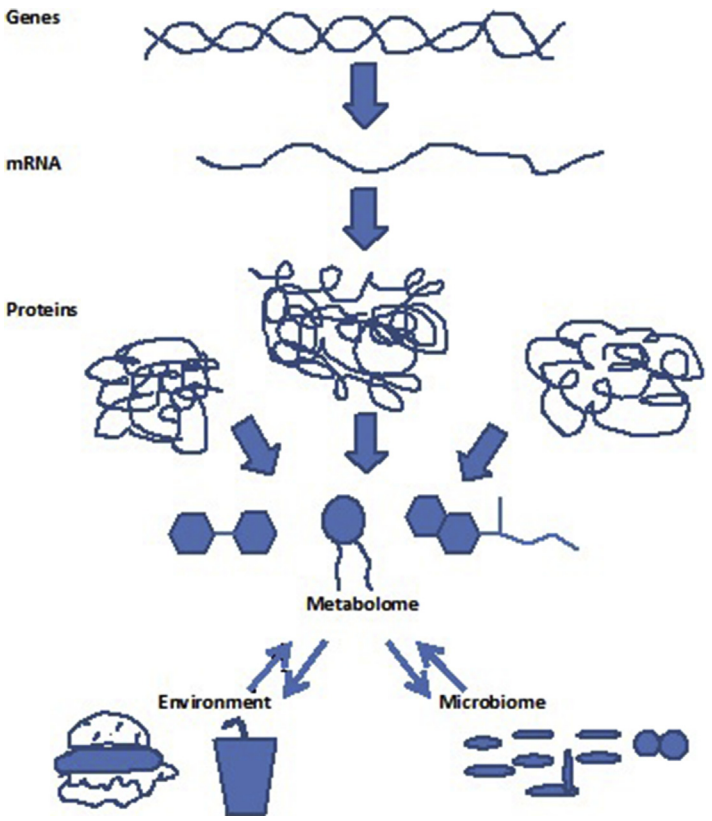

Fig. 1. Scheme of interactions of the metabolome with the genome, proteome, environment, and microbiome.

methods of identification, more than 40,000 unique metabolites have been identified in the Human Metabolome Database.[2] With this expansive list of metabolites, we are now poised with the opportunity to discover metabolomic biomarkers of the failing myocardium to facilitate in the early detection of heart failure,[3] appropriate targeted medical therapy of heart failure,[4] and offer prognostic insights into the progression of this disease. The study of metabolomics, then, represents another example of the spirit of translational research, bridging the gap from bench to bedside. This article will first examine the definition of a clinically useful biomarker, with respect to the biochemical utility of metabolomics, then delve into the methods of metabolomic profiling, examine several metabolomic pathways being pursued in heart failure (**Table 1**), present possible avenues of clinical application, and discuss challenges in the utilization of metabolomics.

METABOLITES AS BIOMARKERS: A PROLIFIC PROFILE

With advancements in technology, it is now feasible to generate large databanks of metabolites, and these extensive repositories of metabolites have become hypothesis generating in the pathogenesis

Table 1
Summary of metabolites in heart failure

Metabolite	Findings in heart failure
Nitric oxide	Improves left ventricular dilation, vasodilation[14–16]
Arginine	Bioavailability and methylation affects nitric oxide synthesis[17–20]
Ketones	Myocardial metabolism switch from lipids to ketogenic state in heart failure[23,26]
Long-chain acylcarnitines	Myocardial metabolism switch in heart failure states[24,25]
Breath analysis of pentane, acetone, nitric oxide	Heart failure patients may expel a unique "breathprint"[28–31]
Trimethylamine *N*-oxide (host-gut microbiome interactions)	Elevated levels implicated in poor prognosis in myocardial infarction and chronic and acute heart failure[38,39,41–44,48]