Chapter 6

Mitochondria Dysfunction in Cardiomyopathy and Heart Failure

Overview

Cardiac failure is an endemic health problem of great magnitude in the Western world. In spite of considerable clinical and research efforts during the last decade and the development of new drugs and surgical modalities of therapy, mortality and morbidity remain high. Clinical cardiologists and basic researchers have shown great interest in mitochondria research, not only in their structure and function but also in the multiple roles that the organelle plays in cell homeostasis and in particular in programmed cell death and necrosis during cardiac failure, myocardial ischemia, and aging. The focus of an increasing number of publications, mitochondria are being intensively examined in the search for answers to outstanding questions in the pathogenesis and pathophysiology of a myriad of cardiovascular diseases and in particular in cardiac failure. This chapter focuses on the progress made in our understanding of the biochemistry and molecular analysis of mitochondria in cardiomyopathy and cardiac failure and on future directions in mitochondrial-directed therapies.

Introduction

Broadly used, the term heart failure (HF) refers to a pathophysiologic state where the heart is unable to meet the metabolic requirements of the body. A chronic disorder, HF is the principal cause of hospitalization in patients over 65 years of age. It has a progressive clinical course resulting in high morbidity and mortality and poses a tremendous burden for the health-care delivery system.

Taking advantage of the remarkable fusion recently achieved by genetics and biochemistry in molecular biology, mitochondrial
research is accelerating its application to cardiovascular pathologies. In this chapter, a discussion of how mitochondrial dysfunction may be related to other critical cellular and molecular changes found in cardiac hypertrophy and failure—including dysfunctional structural and cytoskeletal proteins, apoptosis, calcium flux and handling, and signaling pathways—is presented. Moreover, the biochemical and molecular changes occurring in severe HF secondary to primary cardiomyopathy (dilated/hypertrophic) in humans and in animal models of HF secondary to volume or pressure overload are examined. Finally, the available evidence that mitochondrial dysfunction plays a pivotal role in cardiac failure is presented.

**Mitochondria are the major source of bioenergy in the cardiac cell**

The heart is highly dependent for its function on oxidative energy generated in mitochondria, primarily by fatty acid β-oxidation, ETC, and OXPHOS (Figure 6.1). Mitochondria are abundant in energy-demanding cardiac tissue constituting over one-third of the cardiomyocyte cellular volume (i.e., a greater proportion than found in skeletal muscle). Energy production in mitochondria depends on genetic factors that modulate normal mitochondrial function, including enzyme activity and cofactor availability and on environmental factors such as the availability of fuels (e.g., sugars, fats, and proteins) and oxygen. In the postnatal and adult heart, fatty acids are the primary energy substrate for heart muscle ATP generation by OXPHOS and the mitochondrial respiratory chain, the most important supply of cardiac energy, whereas the fetal heart derives energy primarily from the oxidation of glucose and lactate supplied by the glycolytic pathway. The phosphotransferase enzymes, creatine kinase, and to a lesser extent adenylate kinase play a pivotal role in the distribution of ATP from its site of synthesis in the mitochondria to spatially distinct sites of ATP utilization within the cytosol [1].

During contraction and relaxation, over 75% of the cardiomyocyte ATP is utilized by actomyosin ATPase and various ion pumps. More-