

# Chapter 5

## Examining the Effect of Mitochondrial Fission and Fusion Events on the Heart: Role of the Mitochondria in Heart Disease

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### ABSTRACT

*Mitochondria constitute an integral structural and functional part of the cardiac muscle. The heart muscle relies on the mitochondrial production of fatty acids and ATP as sources of energy during different stages of human growth and development. New mitochondria are created from existing ones by a process called mitochondrial biogenesis which involves both fusion and fission events controlled by a bevy of proteins such as Drp1, OPA1, Mfn1, and Mfn2. In this chapter, we examine the role of these mitochondrial fission and fusion proteins in regulating various heart diseases, particularly, reperfusion injury, dilated cardiomyopathy, and heart failure. It is our intent to examine whether any of these proteins may serve as future candidates for cardiovascular therapy.*

### INTRODUCTION

#### Introduction to Heart Disease

Heart disease is a major contributor to morbidity and mortality in the developed world, and particularly in the United States. According to the Centers for Disease Control, 1 in 4 people, about 610,000 individuals, die annually due to heart disease. This loss of life is accompanied by a huge economic burden,

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especially due to hospitalization and loss of productivity for the even greater numbers of surviving individuals who live with heart disease and require lifelong care and services. Thus, understanding the molecular mechanisms of the normal physiology and pathology of the heart will foster the development of newer pharmacological interventions by identifying novel therapeutic targets for this devastating disease. Thus, exploring new ideas and therapeutic approaches to dealing with cardiovascular diseases constitute an urgent need.

Cardiovascular diseases may manifest in a variety of forms. The most common cardiovascular disease is Ischemic Heart Disease (IHD) that is also known by a variety of other names such as Coronary Artery Disease (CAD) or Acute Coronary Syndrome (ACS). This disease develops due to hypoxia of cardiac muscle when the blood flow to the heart is interrupted, most commonly due to atherosclerosis of the coronary blood vessels. IHD leads to the death of the myocardium and may lead to Sudden Cardiac Death of individuals. However, IHD may also induce arrhythmias. Contradictorily, surgical intervention such as angioplasty to remove the blood vessel clot has been shown to suddenly restore the myocardial oxygen supply and may lead to reperfusion injury.

Other examples of heart disease include those that develop as a consequence of structural damage to the heart or as a result of the compensatory adjustments that the heart undergoes to overcome heart failure. Heart failure is the inability of the heart to meet the oxygen demands of the body. To compensate for this deficiency, the heart undergoes structural modification over time such as the dilation of the ventricles, or an increase in the cell size or cell number of cardiomyocytes. These structural changes result in cardiomyopathy, which may be due to different causes ranging from alcohol abuse to genetic causes. These are only some examples of heart disease discussed in this chapter.

## **Need for Mitochondrial Research in Heart Disease**

Mitochondria are essential for cell function as they serve as sources of energy by allowing the production of ATP in the Electron Transport Chain; they are important for the production of fatty acids in the  $\beta$  oxidation process; regulate apoptosis; orchestrate phospholipid production, and modulate a variety of biochemical and cellular processes. In fact in the mammalian heart muscle, even the spatial arrangement of mitochondria is integral to the architecture of the muscle, since they are arranged in a “crystal-like” pattern, intertwined with myofilaments. These observations emphasize the central role played by the mitochondria in the development and function of the heart muscle.

Interestingly, mitochondria are not static organelles. In fact, they undergo cytoplasmic streaming in most cells, except cardiomyocytes, and also undergo fusion and fission. The latter two processes account for the creation of new mitochondria in cells. Thus, it is reasonable to assume that changes in mitochondrial ultrastructure or function or changes in mitochondrial number, or in the regulation of fission or fusion events may lead to overall changes in the heart muscle.

Thus, it is essential to explore the role of mitochondrial defects, deficiencies, and mutations in mitochondrial proteins in the development and exacerbation of heart disease. Not only will this provide a deeper understanding of the molecular processes involved in etiology and pathological progression of heart disease, this strategy may also identify novel therapeutic targets for heart disease.

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