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REVIEW ARTICLE

Mitochondrial oxidative stress and cardiac ageing☆

Beatriz Martín-Fernández*, **Ricardo Gredilla**

Departamento de Fisiología, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain

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KEYWORDS
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Abstract According with different international organisations, cardiovascular diseases are becoming the first cause of death in western countries. Although exposure to different risk factors, particularly those related to lifestyle, contribute to the etiopathogenesis of cardiac disorders, the increase in average lifespan and ageing are considered major determinants of cardiac diseases events. Mitochondria and oxidative stress have been pointed out as relevant factors both in heart ageing and in the development of cardiac diseases such as heart failure, cardiac hypertrophy and diabetic cardiomyopathy. During ageing, cellular processes related with mitochondrial function, such as bioenergetics, apoptosis and inflammation are altered leading to cardiac dysfunction. Increasing our knowledge about the mitochondrial mechanisms related with the ageing process, will provide new strategies in order to improve this process, particularly the cardiovascular ones.

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* Corresponding author.
E-mail address: bmartinfernandez@med.ucm.es (B. Martín-Fernández).

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Estrés oxidativo mitocondrial y envejecimiento cardíaco

Resumen De acuerdo con diferentes organizaciones como la Asociación Americana del Corazón o la Organización Mundial de la Salud, las enfermedades cardiovasculares se han convertido en la primera causa de muerte en países occidentales. Aunque la exposición a diferentes factores de riesgo, en particular los relacionados con el estilo de vida, contribuyen de manera significativa a la etiopatogénesis de enfermedades cardíacas, el incremento en la esperanza de vida y el envejecimiento de la población asociado a él se consideran los determinantes principales del inicio y desarrollo de las mismas. Las mitocondrias y el estrés oxidativo se han señalado como factores relevantes tanto en el envejecimiento del corazón como en el desarrollo de enfermedades cardíacas como la insuficiencia cardíaca, la hipertrofia cardíaca y la miocardiopatía diabética. Durante el envejecimiento, diferentes procesos celulares relacionados con la función mitocondrial, como la bioenergética, procesos de apoptosis o de inflamación, se ven alterados, lo que conlleva una reducción en la supervivencia celular, y como consecuencia, disfunción cardíaca. Aumentar nuestro conocimiento sobre los mecanismos mitocondriales relacionados con el proceso de envejecimiento proporcionará nuevas estrategias para mejorar de forma más eficiente este proceso y las diferentes enfermedades relacionadas con él, en particular las cardiovasculares.

Introduction

According to the World Health Organization, cardiovascular diseases are now the leading cause of death in western countries,[1] replacing neurodegenerative disorders. In Europe, despite the fact that the number of deaths related to cardiovascular diseases has decreased over recent years, these diseases are still responsible for the death of around 4 million people, almost 50% of all deaths in Europe. If we look at current statistics, Spain is high on the list of European countries with lower rates of mortality due to coronary heart disease, the number one cause of death among all cardiovascular diseases.[2]

Although certain environmental and lifestyle-related factors, such as diet and physical inactivity, play a major role in the aetiopathogenesis of heart disorders, ageing is considered the main determinant of heart disease. However, other age-related diseases, such as dyslipidaemia and diabetes mellitus, exacerbate the negative effects of ageing on the cardiovascular system. According to the *Instituto Nacional de Estadística* (Spanish National Institute of Statistics), life expectancy in Spain has increased an average of one year every five years since 1975. Also, over the last 20 years, life expectancy at birth has increased by approximately 5 years. This increase has a direct consequence: increase in incidence rates of age-related diseases, especially cardiovascular diseases. More importantly still, this increase in average life expectancy is expected to continue to rise over the next 20 years, when around 20% of the population will be aged 65 or older. The heart is primarily a post-mitotic tissue and exhibits a highly aerobic metabolism. These features implicate high dependence on mitochondrial function for proper functioning of the heart cells.[3] Mitochondria play a determining role in the function and survival of cardiomyocytes and are fundamental for meeting the high energy demands of the myocardium. Under physiological conditions, 20–30% of the total cardiomyocyte volume is occupied by mitochondria, but this value may increase when the energy requirements of the myocardium increase. The heart consumes the equivalent of 6 kg of ATP per day, the majority of which is generated through mitochondrial oxidative phosphorylation that is fuelled by catabolism of lipids and carbohydrates.[4] The heart's energy reserve includes ATP ($\approx$5 μmol/g wet weight) and phosphocreatine (PCr; $\approx$8 μmol/g wet weight), with the latter acting as a transport system and ATP buffer.[5] In mitochondria, the phosphate group of ATP can be transferred to creatine by mitochondrial creatine kinase to form PCr. PCr can easily diffuse through the mitochondrial membrane into the cytosol, where it can be used to generate ATP from ADP through reactions catalysed by the cytosolic creatine kinase.[6] There is a delicate balance between nuclear and mitochondrial gene expression, which regulates the assembly of mitochondrial