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HEART FAILURE IN HUMANS: MITOCHONDRIAL STRUCTURE AND FUNCTION

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Abstract: Despite clinical and scientific advancements, heart failure is the major cause of morbidity and mortality worldwide. Both mitochondrial dysfunction and inflammation contribute to the development and progression of heart failure. Although inflammation is crucial to reparative healing following acute cardiomyocyte injury, chronic inflammation damages the heart, impairs function, and decreases cardiac output. Mitochondria, which comprise one third of cardiomyocyte volume, may prove a potential therapeutic target for heart failure. Known primarily for energy production, mitochondria are also involved in other processes including calcium homeostasis and the regulation of cellular apoptosis. Mitochondrial function is closely related to morphology, which alters through mitochondrial dynamics, thus ensuring that the energy needs of the cell are met. However, in heart failure, changes in substrate use lead to mitochondrial dysfunction and impaired myocyte function. This review discusses mitochondrial and cristae dynamics, including the role of the mitochondria contact site and cristae organizing system complex in mitochondrial ultrastructure changes. Additionally, this review covers the role of mitochondria-endoplasmic reticulum contact sites, mitochondrial communication via nanotunnels, and altered metabolite production during heart failure. We highlight these often-neglected factors and promising clinical mitochondrial targets for heart failure.

Keywords: cardiovascular diseases, heart failure, hypertension, mitochondria, myocardium

Cardiovascular diseases (CVDs), which affect blood vessels or the heart, are the leading cause of death globally, accounting for % of US deaths. Although CVD generally affects the left ventricle, the right ventricle plays a crucial role in cardiovascular diseases, including pulmonary hypertension. Other forms of heart disease include valvular heart disease, cardiomyopathy, and arrhythmias. The most common form of heart disease is coronary artery disease, which results from the buildup of plaque in the arteries that supply blood to the heart. Coronary artery disease leads to chest pain, heart attacks, and heart failure (HF),– which is defined by the American Heart Association as a condition in which the heart pumps insufficient blood to meet the body's needs. HF, which presents clinically with or without preserved ejection fraction and is the result of cardiomyocyte injury, is characterized by the inability of the heart to fill and expel blood from the left ventricle effectively., Injury to the myocardium can result from hypertension, diabetes, and coronary artery disease. Various types of HF present with different symptoms that can include shortness of breath, fatigue, congestion, and peripheral edema

It is important to understand the molecular bases of the various types of HF. CVD increases with age, as does mitochondrial dysfunction. Many lines of evidence from animal models and human studies implicate mitochondrial DNA (mtDNA) heteroplasmy and mitochondrial biogenesis impairment occurring before and during early HF, suggesting mitochondrial dysfunction is an early hallmark of HF and a potential therapeutic target in CVD., Reviews

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that consider mitochondria for the treatment of HF– have focused on mitochondrial dynamics or function. The multifaceted regulation of mitochondrial structure and function is poorly understood, especially in the context of age-dependent HF. Tools that allow for this understanding have only been developed and become more widely available within the last years. For example, focus ion-beam scanning electron microscopy (SEM), serial block face SEM, and correlative light electron microscopy, have all undergone significant improvements, which have allowed for -dimensional (D) structures of organelles including mitochondria to be better interrogated in heart development and failure. D tomography has also been used to perform morphological analysis of cardiac mitochondria to provide greater insights into ultrastructural changes. Concurrent advances in cryo-electron microscopy have enabled the resolution of the mitochondrial oxidative phosphorylation machinery, such as the mitochondrial supercomplex IIIIIV. Outside of microscopy, proteome, and acetylome analyses have accelerated, which have allowed researchers to glean the functional role of specific acetylation sites. The study of in vivo freshly excised hearts has used high-resolution respirometry to study respiratory function,while mechanistic studies have continued to be guided by broader advancements such as those in CRISPR/Cas. Together, these technologies have continued to bolster our understanding of mitochondria.

Mitochondria are central to many of the signaling cascades involved in HF (reviewed by He et al). Here, we highlight recent developments and important future directions in the field, including the potential role of mitochondrial dynamics and interactions in HF. We discuss the dynamic nature of mitochondria and cristae and the role of the mitochondria contact site and cristae organizing system (MICOS) complex in these dynamics. We also discuss mitochondrial communication via both mitochondria-endoplasmic reticulum contacts (MERCs) and nanotunnels, as well as HF-associated changes in metabolite production. By taking an interconnected view of mitochondria, we consider areas of further study that may offer greater insights into mitochondrial-mediated roles in HF.

RISK FACTORS OF HF

It is pertinent to study mitochondria in the context of HF as the burden of HF continues to grow and new therapies are necessary. Within the United States, the burden of HF continues to grow, with roughly . million American adults (ie, + years old) having HF in the span of time from to , representing approximately a % increase over the preceding -year period. In , this cumulative prevalence represents an estimated cost of over $ billion. Current projections expect this prevalence to only continue growing, nearly by %, to reach over million American adults with HF by . The probability of developing HF during one's lifetime varies significantly by race and gender, with estimates ranging from % to % in men and % to % in women, highlighting higher risks in Black women, but overall exuberated risk in men.

HF disproportionately affects racial minorities within the United States: Black people, who are affected by socioeconomic and social factors, such as John Henryism,, have higher rates of hypertension compared with other racial and ethnic groups. Moreover, as a result of disparities in health care access and socioeconomic factors, Black and Hispanic individuals are more likely to have both poor prognoses and outcomes in the context HF. Race is a social construct; however, the cumulative effects of intergenerational stressors, hereditary factors, and exposome (ie, the totality of external environmental exposures one experiences throughout their life) factors may change mitochondrial function, leading to an increased

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risk of HF. Other risk factors for CVD include obesity, diabetes, smoking, a sedentary lifestyle, and poor diet, all of which can be correlated with lower socioeconomic status. As a result, while non-Hispanic White women have an ≈.% prevalence of HF, this is more than double, at .%, in Black women. Although exposome factors have been implicated in affecting mitochondria, it remains unclear the full extent which these factors are involved in mitochondrial regulation.

Generally, men develop heart disease at younger ages than women. Risk for the development of CVD in women increases significantly after menopause when they experience a decline in estrogen, a hormone with beneficial effects on blood vessels and lipid metabolism.– In addition to the protective effect of estrogens on blood pressure,estrogens may also alter mitochondrial membrane permeability and microviscosity,,concurrently improving mitochondrial D shape. In general, women with diabetes are at a higher risk for heart disease than men,– suggesting that the protective effects of estrogens premenopause are unable to overcome this risk factor. Yet, while the loss of estrogen in postmenopausal women blunts the sex-dependent difference, unlike many other CVDs, men typically are still at a higher risk of HF in old age. This suggests that even in the absence of active estrogen, women have long-lasting cardioprotective effects against HF. However, other factors could conceivably be at play beyond estrogen, and it is still too early to clearly explicate the impact of gender-affirming hormonal treatments on the risks associated with HF.

Age is the greatest risk factor for HF. According to the to National Health and Nutrition Examination Survey, a small percent of the population from to years old have HF (ie, .% for men and .% for women). However, this progressively increases with a more pronounced sex-dependent difference, especially at to years of age (ie, HF prevalence is .% for men and .% for women) and over years old (ie, HF prevalence is .% for men and .% for women). Aging may have a further confluence with race, as HF before years of age is more common among Blacks, with Black men of to years old having an incidence of HF of . per person-years, which is much higher than White men of the same age (. per person-years) and even among White men of to years old (. per person-years). Generally, however, with age these differences begin to narrow, while sex-dependent differences remain more pronounced. Hypertension, another risk factor for the development of HF, increases with age. Thus, mechanisms associated with aging may provide a key to understanding and treating CVD, particularly the progressive loss of mitochondrial function., Although there is some dispute concerning the mechanisms associated with aging and mitochondrial dysfunction, the escalating decline of mitochondria with age and its potential role in HF has led to greater interest in mitochondria as a therapeutic target for HF.

MITOCHONDRIAL FUNCTION IN THE HEART

In the s, Mitchell introduced the chemiosmotic hypothesis, proposing a mechanism for ATP synthesis in biological systems, with energy transfer and ATP synthesis in mitochondria, coupled by a transmembrane electrochemical potential gradient. We have now come to understand this mechanism as oxidative phosphorylation (OxPhos), the process through which mitochondria respond to the energetic needs of the body, with reactive oxygen species (ROS) as a deleterious byproduct. The heart needs large amounts of energy in the form of ATP to produce contractions strong enough to fulfill systemic demands, but ATP storage is

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low. To overcome storage limitations, mitochondria, the primary producers of ATP,comprise ≈% to % of the cardiomyocyte volume. Every day, this large volume of mitochondria produces ≈% of the ATP that the heart uses, generating kg a day and nearly kg across one's lifespan. The other % volume of cardiomyocytes is typically occupied by myofibrils, which can undergo changes in orientation and size in HF.

ATP is generated by OxPhos machinery, which primarily consists of complexes. Deficiency of Complex I—a subunit complex that serves as an entry point for electrons through oxidization of NADH, —through inhibition of Ndufs decreases respiration and accelerates HF. Right-ventricular failure, conversely, is associated with increased levels of Complex II—a direct link between the TCA cycle and the electron transport chain that couples the oxidation of succinate to the reduction of coenzyme Q without pumping protons—which in turn increases oxidative stress, a byproduct of the electron transport chain. In interfibrillar mitochondrial, aging decreases complex III activity—transfers electrons from reduced coenzyme Q to cytochrome c via a mechanism that is coupled to proton pumping—leading to ischemia-reperfusion injury due to tandem defects in electron flow and increased oxidant production. In HF, unchanged cardiolipin levels in cardiac mitochondria concomitant with increased phosphorylation of complex IV—the terminal electron acceptor that moves electrons from cytochrome c to molecular oxygen while vectorially transporting protons into the intermembrane space—alters oxidative phosphorylation by either hindering the incorporation of complex IV into supercomplexes or reducing their stability. Although the extent of OxPhos changes in HF goes beyond these specific examples, a key regulator of mitochondrial cardiomyopathies are mitochondrial mutations which can cause deficiencies through both mutations in the nuclear and mitochondrial genome (reviewed by El-Hattab and Scaglia).

Mitochondrial DNA (mtDNA) plays a central role in the pathogenesis of human HF. A study from left ventricular tissue from end-stage HF has shown that in a failing heart, mtDNA content is decreased by >%, with significantly reduced replication, which in turn impairs mitochondrial biogenesis. Additionally, mitochondrial DNA depletion is an early sign in right-ventricular hypertrophy during the transition from hypertrophy to failure in patients with congenital heart disease. The Atherosclerosis Risk in Communities, a broad study conducted over ≈ years, showed an inverse relationship between the mtDNA copy number and the risk of incident HF. This loss in mtDNA content is preceded by oxidative stress and results in decreased expression of mtDNA-encoded genes and respiratory chain complex enzymes. Notably, this oxidative stress only affects mtDNA, not the nuclear genome,potentially due to the lack of protective histones in mtDNA, which generally has less clearly defined epigenetic modification. Still, this oxidative stress affecting mtDNA has been targeted through MitoQ antioxidants, which can in turn reduce oxidative stress.

Mutations in mtDNA similarly may contribute to the pathogenesis of HF through the release of cytochrome c. However, the cardiac involvement of mutations varies across cohorts and specific mutations (eg, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, myoclonus epilepsy with ragged-red fibers, and Kearns-Sayre syndrome), so it remains unclear if certain polymorphisms across certain genetic backgrounds may be responsible for the increased risk of HF in certain populations. Notably, Cao et al showed that Acsl is a genetic determinant of diastolic function, which may confer sex-dependent differences in HF. This involvement of mtDNA mutations in HF has raised mtDNA repair

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mechanisms as potential therapeutic targets (reviewed by Marín-García). Nuclear genomics are equally important, as recent results have demonstrated that IFIT, XAF, RSAD, and MX are all mitochondrial-related genes that serve as biomarkers for HF.

HETEROGENEITY IN HF

In addition to ATP production, mitochondria play a vital role in cellular metabolism, calcium (Ca+) homeostasis, lipid synthesis, and redox regulation in the myocardium. Altered metabolism, a principal pathomechanism of human HF, and its relevance to the treatment of HF have been reviewed extensively. This altered metabolism can confer heterogeneity in HF across regions and types of HF.

There are several types of HF (Figure), including HF with preserved ejection fraction (ie, diastolic HF) and HF with reduced ejection fraction (ie, systolic HF). Although over % of patients have diastolic HF, in both of these types of HF, mitochondrial function is central to the pathogenesis, with abnormal myocardial stiffness in diastolic HF and impaired energy production in systolic HF., In HF with preserved ejection fraction, oxidative stress is a key regulator with increased proinflammatory and pro-fibrotic signaling, myocardial fibrosis, and altered Ca+ handling. Furthermore, in diastolic HF, impaired mitochondrial function and altered TCA cycle metabolites are significantly associated with a protein hyperacetylation pattern, which was effectively ameliorated by nicotinamide riboside supplementation. In a mouse model of cardiac hypertrophy, reduced mitochondrial oxidative metabolism led to an energy deficit, potentially driving the progression from hypertrophy to systolic HF. Yet, it remains unclear if mitochondrial function is directly correlated to ejection fraction. Knez et al found a correlation between mtDNA content and ejection fraction in ion-ischemic HF. Another study found that cardiac phosphocreatine/β-ATP ratios, while inversely related to age, was not significantly linked to ejection fraction. Thus, it remains an open area of research to understand whether distinct hallmarks of mitochondrial dysfunction are associated with specific types of HF and can serve as a biomarker of relative ejection fraction.

Cardiomyocytes have heterogeneous populations of mitochondria with discrete roles.,The organization of mitochondria within the heart include intermyofibrillar, subsarcolemmal, or perinuclear locations (Figure). Generally, HF may cause mitochondrial structure to change on the basis of these mitochondrial subpopulations. Heterogeneity also arises on the basis of cardiac region. Interestingly, differences in the rates of aging of various tissues affect the function of the heart and other organs; thus, mitochondria may exhibit different characteristics in HF tissues compared with other organs. Based on D analysis, murine cardiac tissue mitochondria display different phenotypes than their murine skeletal muscle counterparts during aging. An earlier review focused on the role of mitochondria in regulating neonatal cardiomyocyte maturation, which may be due to the unique mitochondrial network that forms in cardiac tissue. Because energy changes may differ by heart tissue subtype and by region-specific mitochondria, mitochondrial fusion, and fission proteins could be expressed differently in each region. For example, the endocardium (ie, the inner lining of the heart chambers), the myocardium (ie, the thick, muscular middle layer responsible for the heart's contraction), and the pericardium (ie, protective double-layered sac encasing the heart) may functionally express different dynamics components that impact mitochondrial function and distribution. In particular, the elastic pericardium plays

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important roles in systolic function, hemodynamics, and ventricular function. Conversely, endocardial smooth muscle cells may play a role in reducing left ventricular wall stress and systolic dysfunction. Because we do not know mitochondrial structures across the entire geography of the heart and whether there exist correlations between a given structure and how that area pumps blood, we do not understand how the structural and functional relationships depend on unique signatures of aging in the various cardiac regions. Understanding these differences is crucial to developing targeted therapies for HF.

DYNAMIC NATURE OF MITOCHONDRIA

Mitochondrial dynamics refers to the coordinated, continuous cycles of fusion and fission– as mitochondria respond to the changing energy demands of the cell. Mitochondrial morphology is intricately linked to function; thus, mitochondrial dynamics affect HF. Mitochondrial fusion pools mtDNA, preserving the mitochondrial genome, and contributes to the maintenance of mitochondrial OxPhos machinery., Conversely, mitochondrial fission facilitates the elimination of damaged mitochondrial components through autophagy, also called mitophagy, regulates mitochondrial size and energy distribution, and modulates mitochondrial quality control., A healthy mitochondrial network balances fusion and fission cycles, and identifying the regulators of these cycles may provide therapeutic targets for HF.

A key hallmark of the failing heart is the dysregulation of mitochondrial dynamics. There is generally an increase in levels of fission-associated proteins (eg, DRP [dynamin-related protein]) and a decrease in levels of fusion-associated proteins (eg, MFN (mitofusin) and OPA [optic atrophy]). The fusion of outer versus inner membranes of mitochondria is mediated by different proteins. Fusion of the outer mitochondrial membrane (OMM) depends on conformational changes and GTP-dependent dimerization of dynamin-like proteins, mitofusin (MFN) and MFN, which are reduced across aging.,, This is counterbalanced by fission, which is typically mediated by DRP . The absence of MFN or MFN leads to distinct types of fragmented mitochondria. Cells lacking both MFN and MFN have severe cellular defects, including impaired growth, mitochondrial membrane potential heterogeneity, and reduced cellular respiration. In HF, there is decreased expression of the mitochondrial dynamics regulator MFN (eg, in diabetic mice), leading to excessive mitochondrial fission that is linked to the development of HF in rats and humans with pulmonary arterial hypertension. As previously reviewed, this results in a shift in the MFN:DRP ratio toward pro-fission states in HF. As discussed, beyond shaping mitochondria, these dynamics-related dysfunctions also alter the structure of cristae, in turn disrupting ATP production. Although excessive fission drives decreased respiration, inhibition of this fission may in turn restore ATP production, improve cardiac fractional output, and reduce mitochondrial dysfunction, cumulatively protecting against HF. Yet, the complete ablation of DRP causes dilated cardiomyopathy, since fission is necessary for the distribution of mtDNA nucleoids, protein-bound structures that contain active mtDNA.Thus, there must be a careful balance of fusion and fission in the heart.

Fusion of the inner mitochondrial membrane (IMM) is facilitated by OPA, a membrane-bound GTPase. OPA is highly vulnerable to mutations, which can in turn increase ROS, reduce mtDNA content, and increase the risk of cardiomyopathy. OPA is decreased in HF likely by a posttranscriptional mechanism. Fusion requires partial proteolytic cleavage of OPA, yielding a soluble short form and a long transmembrane form., Both forms of OPA

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also contribute to the formation of the MICOS complex that regulates the width of cristae. An imbalance of mitochondrial fusion versus fission can lead to devastating alterations in mtDNA and trigger cellular apoptosis. Proteolytic processing of OPA by ATP-dependent metalloproteases, YMEL (YME Like ATPase) and OMA (OMA zinc metallopeptidase), results in the inhibition of IMM fusion.,, OPA also regulates cristae morphology and mitochondrial fragmentation.,,– Overexpression of OPA decreases mitochondrial fission, inhibiting autophagy. Conversely, low OPA caused by its excessive processing by the overlapping stress-activated proteolytic activity of OMA, inhibits fusion, resulting in mitochondrial fragmentation, that leads to cell death and eventually heart disease. Similarly, samples from human patients with HF show reduced OPA expression, which correlates with mitochondrial fragmentation,, and a reduction of OPA increases the risk for cardiomyopathy due to decreased

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