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RECENT ADVANCES IN MITOCHONDRIAL RESEARCH

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Mitochondria are fundamental regulators of life and death. Not surprisingly, their role in the cardiovascular system is an intense area of research, with many important advances in the field published recently. Such articles have continued to enhance our appreciation of the importance of mitochondria in cardiovascular health and have further contributed to the idea that mitochondrial dysfunction is a *sine qua non* of cardiovascular disease (CVD).

A primary question of old that has been addressed anew relates to mitochondrial form. How do the shapes of mitochondria regulate their function? Do conditions associated with CVD alter mitochondrial dynamics? And does mitochondrial structure impact CVD? If so, *how*? Over the past two years, there has been remarkable progress addressing these questions. Essential regulators of mitochondrial fission and fusion such as Mitofusins 1 and 2 (Mfn 1/2), Dynamin-related protein 1 (Drp1), and Optic atrophy 1 (Opa1) are proving to be important in cardiac development, vascular homeostasis, and cardiovascular disease. In the heart, Mfns have been shown to regulate permeability transition, cell death^{1, 2} and autophagy³, and Mfn2 was shown to be integral in the removal of damaged mitochondria⁴. Interestingly, loss of either Mfn1² or Mfn2¹ leads to increased tolerance to stress while loss of both is lethal after e9.5 of development⁵. It has also been reported that conditional ablation of both Mfn1 and Mfn2 in adult hearts causes mitochondrial fragmentation, respiratory dysfunction, and lethal dilated cardiomyopathy⁵. These effects of Mfn2 are likely related, in part, to its ability to tether mitochondria to sarco(endo)plasmic reticulum (SR), allowing for propagation of SR-mitochondrial Ca²⁺ signaling and regulation of bioenergetic responses to stress^{6, 7}. Not unexpectedly, Mfn 1 and 2 are essential for postnatal metabolic remodeling in the heart⁸ and cardiomyocyte differentiation⁹. Other regulators of mitochondrial fusion such as Opa1 have also been found to be critical for maintenance of cardiac function¹⁰. From a therapeutic angle, inhibition of mitochondrial fission has the potential to become a viable option to prevent cardiac dysfunction following myocardial infarction¹¹.

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Mitochondrial dynamics is proving to be a central regulator of vascular health as well. In smooth muscle, mitochondrial fission (via Drp1) was shown to be obligatory in the closure of the ductus arteriosus¹², which is required for the transition from the fetal to the neonatal pattern of circulation. Hence, the physiological changes in circulation occurring upon first breath hinge upon the structure of our mitochondria! Mitochondrial fission, however, may be a double-edged sword in smooth muscle. It promotes a hyperproliferative phenotype that could be deleterious in the context of diseases such as pulmonary artery hypertension^{13, 14}. Furthermore, diabetes and hyperglycemia elevate the expression of fission-1 protein (Fis1) and Drp1, resulting in mitochondrial fragmentation¹⁵. Similar to smooth muscle cells, mitochondrial fragmentation in endothelial cells is associated with a hyperproliferative phenotype, which generates higher levels of ROS and is prone to senescence. Silencing of pro-fission proteins restores mitochondrial networks and diminishes reactive oxygen species (ROS) production while increasing the activation state of nitric oxide (NO) synthase¹⁵, the latter of which could have a direct role in adaptive mitochondrial dynamics¹⁶. In healthy endothelium, regulatory proteins such as uncoupling protein 2 (UCP2) appear to be integrated with pro-fission responses to protect endothelial cells from the damaging ROS and p53 activation associated with the fragmented mitochondrial phenotype^{17, 18}.

Such changes in mitochondrial structure are known to be intricately linked with their removal via mitophagy¹⁹, which appears to be essential for eliminating damaged mitochondria and preserving bioenergetic function²⁰. Should damaged mitochondria fail to be removed, then cell death via necrosis or apoptosis is a likely fate²¹. Recent studies have shed further light into how the mitochondria regulate cell death and which specific pathways are activated by mitochondrial signaling. For example, loss of myeloid cell leukemia-1 (MCL-1), an anti-apoptotic BCL-2 protein, was found in two independent studies to impair mitochondrial respiration and lead to heart failure^{22, 23}. Results from the past two years have also imparted novel insights into the roles of Ca²⁺/calmodulin-dependent protein kinase II (CaMKII)²⁴⁻²⁶, G protein-coupled receptor kinase 2 (GRK2)²⁷, and mitochondrial signal transducer and activator of transcription 3 (Stat3)²⁸ in myocardial cell death and mitochondrial stress in the heart. New advances were also made with respect to the well-studied protein targets, p53 and cyclophilin D (CypD): p53 was shown to bind to CypD, resulting in mitochondrial permeability transition pore (mPTP)-dependent necrosis^{29, 30}. While CypD is best known as a regulator of the mPTP, studies also suggest it modulates branched chain amino acid, pyruvate, and fatty acid metabolism³¹, which could be related to its putative role in regulating the mitochondrial acetylome^{32, 33}. Interestingly, mitochondrial protein acetylation has also been suggested to play an important role in initiating mitophagy³⁴.

While there is still much to learn about cell death and the role of post-translational modifications such as protein acetylation, it is becoming increasingly clear that both cell death pathways as well as protein acetylation are regulated by pyridine nucleotides. Nicotine adenine dinucleotides (NAD⁺/NADH) and their phosphorylated forms (NADP⁺/NADPH) are known to play central roles in energy production, ion channel regulation, and antioxidant defense in cardiovascular tissues^{35, 36}. Recent studies have revealed that they regulate the Na⁺/Ca²⁺ exchanger to modulate Ca²⁺ homeostasis in cardiac myocytes³⁷, and a cytosolic form of the NAD⁺-utilizing enzyme ALDH2 (initially thought to be localized only in

mitochondria) was shown to be important in the bioactivation of nitroglycerin³⁸. The NAD⁺/NADH ratio also impacts the activity of the Sirtuin (Sirt) family of protein deacetylases, and this ratio is regulated by circadian rhythms³⁹. Interestingly, circadian control of NAD⁺-dependent Sirt3 was shown to generate cadence in the acetylation of oxidative enzymes in mitochondria, linking respiratory activity with daily cycles of fasting and feeding⁴⁰. Moreover, diminishing Complex I-supported mitochondrial respiration in the heart results in heightened NADH levels, elevated levels of protein acetylation, sensitization of mitochondria to PTP opening, and accelerated heart failure⁴¹. A deeper understanding of how pyridine nucleotides regulate energy metabolism could aid in the development of novel therapies for cardiovascular disease.

Recent work has also provided fresh insights into mechanisms underlying the salubrious effects of practical therapies such as caloric restriction and exercise. Caloric restriction is well-known to diminish symptoms of cardiovascular aging and increase longevity, in part due to its ability to not only regulate Sirt deacetylase activity, but mitophagy and PGC1-mediated processes as well⁴². During caloric restriction, deacetylation of specific subunits of the electron transport chain (reduced via caloric restriction) was shown to be protective against ischemic stress⁴³. Exercise functions as a calorie restriction mimetic of sorts and is one of the most robust activators of PGC1. Consistent with the idea that stimulation of PGC1 activity could prevent cardiovascular decline due to stress or aging, PGC1 β was demonstrated to maintain mitochondrial function following pressure overload and to prevent oxidative stress⁴⁴. Mitochondrial oxidative stress, in particular, could oxidize mtDNA, which is important in the fibrotic response that occurs following aortic constriction⁴⁵. Exercise may be important in preventing such mitochondrial changes: it was shown to prevent mtDNA depletion and mutations, increase oxidative capacity and promote healthy aging⁴⁶ as well as attenuate doxorubicin-mediated cardiac injury⁴⁷. A plausible idea concerning aging is that mitochondrial function and antioxidant capacity become mismatched over time, resulting in mitochondria-mediated oxidative stress, bioenergetic dysfunction, and cell death. This is supported by the fact that deletion of the regulator of mitochondrial biogenetic programming PGC1 α can increase mitochondrial ROS production leading to vascular dysfunction and inflammation⁴⁸ and that aortic stiffening and cardiac deterioration occur in mice expressing lower levels of the mitochondrial form of superoxide dismutase (SOD2)^{49, 50}. How exercise may balance mitochondrial activity levels with antioxidant capacity and delineating approaches to increase exercise capacity in obese and older individuals are areas of inquiry that, once addressed, could diminish the burden of disease associated with aging. With regards to exercise, it appears that we may be forced to abandon our 1980s approaches, as deficiency in creatine—long regarded by the exercising community to have remarkable health and performance benefits—was shown in rodents to neither affect exercise capacity nor change responses to chronic myocardial stress⁵¹.

In summary, recent studies have addressed not only important, long-standing problems in mitochondrial research, but they have also led to unprecedented discoveries and novel insights into how mitochondria impact our cardiovascular health. Building on these discoveries, our search to identify the composition of mitochondria^{52, 53} and the mPTP⁵⁴, to understand how metabolic enzymes regulate cardiovascular remodeling and function^{55–61}, and to solidify the identity of the mitoK_{ATP} channel^{62, 63} are likely to be active and

contentious areas of mitochondrial research. However, such controversy is important and useful, as it fosters thoughtful and thorough testing of mitochondrial therapies targeting critical determinants of cardiovascular cell function⁶⁴. We can rest assured that future findings regarding how mitochondria remodel, how miRNAs regulate mitochondria^{65, 66} and clarification of the actions and targets⁶⁷ of oxidants will further deepen our appreciation of the versatility of the mitochondrion and its critical roles in regulating cardiovascular physiology and disease.

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