‘Mighty-chondrial’ DNA Repair for Mitigation of Cardiac Injury – Focus on
“A Novel Mitochondrial DNA Repair Fusion Protein Attenuates Maladaptive
Remodeling and Preserves Cardiac Function in Heart Failure”

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A constant supply of high energy is required to maintain normal cardiac function. Since
the myocardium has a limited capacity of ATP storage, persistent energy generation is required
to meet the high demands (9). Mitochondrial electron transport chain (ETC) is a key component
for ATP generation through oxidative phosphorylation (OXPHOS) (9). Although most ETC
proteins are encoded by nuclear DNA, a small portion of ETC proteins are encoded by
mitochondrial DNA (mtDNA). The mtDNA is a double-stranded circular genome that encodes
13 proteins of the ETC including ND1-ND6 and ND4L subunits in complex I (15), cytochrome b
in complex III (10), and subunit I-III in cytochrome oxidase (14). An impairment of mtDNA has
been shown to contribute to a number of diseases due to compromised energy production (8). For
instance, in mitochondria of aged hearts, the cytochrome b defect leads to increased ROS
generation from complex III, which in turn augments cardiac injury during ischemia-reperfusion
(13). Due to its overall pathologic role favoring ROS generation, accumulation of mtDNA
damage contributes to cardiac injury during ischemia-reperfusion and heart failure development
(5).

Oxidative stress has been widely accepted to play a critical role in ischemia-reperfusion
injury and the progression of heart failure and ETC defects have been incriminated as key
sources of ROS generation in cardiac diseases. An uncontrolled ROS generation impairs cardiac
remodeling and increases apoptosis and fibrosis (4). Superoxide generated by the ETC from
complex I is released into the matrix and dismutated to H$_2$O$_2$ by manganese superoxide
dismutase (Mn-SOD) (3). It has been reported that generation of superoxide from complex I is
increased in mitochondria from failing dog heart (4). Interestingly, the activity of Mn-SOD is
also reduced in heart failure. Administration of antioxidants attenuates heart failure development
and therefore supports the detrimental role of ROS generated from mitochondria (4). Since
mtDNA is highly sensitive to oxidative stress and is in proximity with the ETC site of ROS generation, it is a likely target of oxidative damage (15). The damaging effects of ROS and other adverse signals leading to mutations in mtDNA are associated with cardiomyopathy and increased cell death. In fact, it has been shown that myocardial ischemia-reperfusion leads to cardiac mtDNA damage (1).

In this issue of the *American Journal of Physiology – Heart and Circulatory Physiology*, Bradley et al. (2) determined that significant mtDNA damage occurs in mice following transverse aortic constriction (TAC). Interestingly, administration of a novel targeted mtDNA repair fusion protein, Exscien 1-III, significantly attenuated TAC-induced left ventricular dilatation and cardiac dysfunction. Cardiac hypertrophy and maladaptive remodeling were also reduced following Exscien 1-III treatment. In addition to alleviation of pressure overload-induced heart failure with chronic treatment, a single dose of Exscien 1-III administered at the onset of reperfusion also attenuated acute cardiac injury following *in vivo* myocardial infarction (MI) in mice and the beneficial effects were persistent 4 weeks post-MI. Clearly, these results support the notion that mtDNA damage plays a key role in cardiac injury during ischemia-reperfusion and the development of heart failure following TAC. The observation that reperfusion therapy using a single application of Exscien 1-III exerted long-term benefit, up to 28 days, is especially striking. Such a remarkable finding warrants further investigation into the alterations in mtDNA following MI and the potential therapeutic window for intervention with novel mtDNA repair fusion proteins.

The study by Bradley et al. (2) also shows that administration of Exscien 1-III mitigates mtDNA damage and increases the content of Mn-SOD after TAC, coupled with a decrease in apoptotic markers. These results support the premise that ROS from the ETC leads to mtDNA
damage, which in turn promotes the development of heart failure. It has been previously reported that genetic knockdown of complex I subunits facilitates the development of heart failure following pressure overload (6). In this regard, it would be interesting to determine whether Exscien 1-III treatment attenuates complex I damage in the heart following TAC. Due to its short life span, ROS usually damages proteins and DNA in the vicinity of its generation sites. Interestingly, the study shows that cardiac fibrosis mainly occurred in interstitial and perivascular regions following TAC, which was attenuated with Exscien 1-III treatment. These findings, although intriguing, raise a few important questions regarding the mechanism through which ROS generated from mitochondria leads to fibrosis in the interstitial and perivascular regions of the heart. In addition to mitochondrial ROS, NADPH oxidase is a key source of ROS generation in the heart (11). There are two isoforms of NADPH oxidase in the heart including Nox2 and Nox4. Nox2 is located in the cell membrane, whereas Nox4 is localized to the perinuclear endoplasmic reticulum (ER), which is closely connected with mitochondria through an associated membrane. A decrease in complex III activity in mitochondria from aging heart increases the release of superoxide from complex III Qo center to cytosol (13). Cytochrome b, a subunit of complex III, is encoded by mtDNA. Since the study by Bradley et al. shows that TAC results in mtDNA damage, it is plausible that inhibition of cytochrome b during TAC may lead to decreased complex III activity that subsequently augments ROS release from mitochondria to the cytosol or ER (10). ROS generated from mitochondria may induce fibrosis through enhancing ROS generation from Nox2 and Nox4. Future studies are warranted to investigate the impact of Exscien 1-III treatment on the activity of Nox2 and Nox4.

In response to TAC, the heart undergoes hypertrophy as an adaptive mechanism to reduce increased wall stress. Ultimately, pathologic hypertrophy will lead to the development of heart
failure when pressure overload persists (12). Autophagy has been implicated to actively participate in this process as it is charged with removal of cytoplasmic components and damaged organelles through degradation in lysosomes (12). Damaged mitochondria are a major source of ROS generation and therefore their culling through mitochondrial autophagy (mitophagy) is critical for mitochondrial quality control (7). A decline in mitophagy contributes to the development of mitochondrial dysfunction. The study demonstrates that Exscien 1-III treatment protects the heart and mitochondria through reduction of ROS generation via enhanced expression of antioxidant Mn-SOD, however, this study did not evaluate the role of Exscien 1-III treatment in modulating mitophagy after TAC or MI. Based on the robust protective effects of a single treatment with Exscien 1-III in the setting of MI, it is reasonable to speculate that this novel targeted mtDNA repair fusion protein may also influence mitophagy and prevent persistent long-term damage caused by deranged mitochondria. Clearly, more studies are needed to address this important issue.

Taken together, the present pioneering study provides a promising strategy to attenuate the development of heart failure following pressure overload and decreases cardiac injury following ischemia-reperfusion. Future research should be directed at further testing the therapeutic efficacy of Exscien 1-III in large animal models of pressure overload and MI to facilitate the translation of this novel drug for treatment of heart failure in humans.

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