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Editorial

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Mitochondrial Uncoupling: A Fine-Tuning Knob for Mitochondria-Targeting Therapeutics for Coronary Artery Disease

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Coronary artery disease is the leading cause of death worldwide. Regardless of aggressive lipid-lowering therapy with a combination of statins, ezetimibe, and PCSK9 inhibitors, substantial residual cardiovascular risks remain a major concern. Mitochondria are intracellular organelles that play a key role in intracellular energy metabolism. Recent advances in molecular biology have revealed that mitochondrial dysfunction is involved in the pathogenesis of not only rare mitochondrial disorders, caused by mitochondrial DNA (mtDNA) mutations, but also more common diseases, such as heart failure and diabetes mellitus. Furthermore, recent studies suggest the role of mitochondrial dysfunction and damage in the development of atherosclerosis[1]. Mitochondrial reactive oxygen species (ROS) is one of the potential therapeutic targets for coronary artery disease, but there are no large-scale randomized clinical trials of antioxidants that prevent coronary artery disease[2].

Mitochondrial uncoupling mitigates mitochondrial ROS generation through an increase in respiratory rate. Uncoupling proteins (UCPs) are endogenous physiological uncouplers that reduce ROS formation by allowing protons to leak back into the matrix and inducing partial dissipation of the proton gradient across the inner mitochondrial membrane. A series of evidence suggests the cell type-specific function of different UCPs in atherosclerosis. The transplantation of bone marrow from *Ucp2*$^{-/-}$ mice to *Ldlr*$^{-/-}$ mice promoted atherosclerosis associated with increased ROS generation as assessed by nitrotyrosine staining in plaques[3]. Conversely, mild respiratory uncoupling with inducible expression of UCP-1 in arterial smooth muscle cells increased oxidative stress, blood pressure, and dietary atherosclerosis in mice[4]. Contrarily, the effects of mitochondrial uncoupling by exogenous uncouplers on atherosclerosis are largely unknown.

In this issue of Journal of Atherosclerosis and Thrombosis, Dorighello *et al.* revealed the antioxidant role of mitochondrial uncoupling with very low doses of 2,3-dinitrophenol (DNP) in atherosclerosis[5]. The authors demonstrated that daily DNP treatment ameliorates the development of aortic atherosclerosis in hypercholesterolemic *Ldlr*$^{-/-}$ mice, which is associated with lower lesional accumulation of macrophages independently of classical atherosclerotic risk factors. In *in vitro* experiments, they showed that DNP decreases H_2O_2 production in peritoneal macrophages and skews them to anti-inflammatory phenotype with increased phagocytic activity and decreased foam cell formation. DNP was a commercially available diet drug with potentially lethal adverse effects. DNP works as a protonophore within oxidative phosphorylation. At the same time, this process breaks down carbohydrates and fats, allowing energy from cellular respiration to be released as heat. The excess heat production led to uncontrolled toxic hyperthermia associated with significant morbidity and mortality[6]. The history of DNP becomes an important lesson that clinical application of a mitochondrial uncoupler needs fine-tuned dosing regimens that spare adverse effects.

A similar problem occurs in the development of novel therapeutics targeting mitochondria-related phenomena because mitochondria play essential roles in physiological conditions in living cells. For example, abnormal mitochondrial dynamics and cell-free mtDNA are gathering attention as potential therapeutic targets for cardiovascular diseases, but targeting either of these mechanisms is also not straightforward.

In living organisms, mitochondria change their shape every moment, which was already reported

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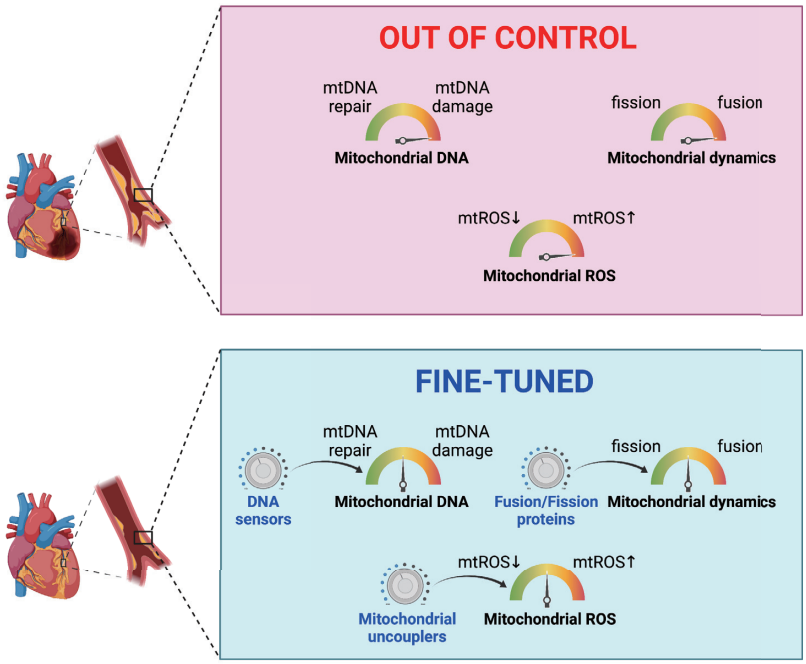

Fig. 1. Fine-tuning knobs of mitochondria-targeting strategies for the treatment of coronary artery disease

more than 100 years ago by Lewis MR *et al.*[7] In recent years, molecules that regulate mitochondrial dynamics, fission (Drp1) and fusion (Mfn1, Mfn2, Opa1), have been identified. We recently reported that the fission mediator Drp1-induced mitochondrial fission may induce macrophage activation and promote vascular remodeling after acute vascular injury[8]. In contrast, impaired efferocytosis of dead cells in atherosclerotic plaques and necrotic cores were observed in myeloid Drp1 deficiency in *Ldlr*$^{-/-}$ mice fed with a high-fat diet[9]. These conflicting results suggest that short-term inhibition of mitochondrial fission may be beneficial in the treatment of acute vascular injury, but long-term inhibition in atherosclerosis may exacerbate the condition.

During infection or stress, damaged mitochondria release mtDNA by degradation through the autophagy/lysosome system. mtDNA serves as a potent danger-associated molecular pattern, triggering an inflammatory response mediated by various pattern recognition receptors (PRRs)[10]. Recent studies suggest that mtDNA contributes to the pro-inflammatory activation of immune cells and pathogenesis of atherosclerosis through DNA sensors, such as TLR9[11] and STING[12]. Thus, although DNA sensors contribute to self-defense against pathogens and are indispensable in a steady-state condition, they also cause unfavorable inflammatory responses in pathological conditions, leading to the development of vascular and metabolic diseases.

In conclusion, emerging evidence including this work by Dorighello *et al.* suggests that mitochondrial dysfunction and damage could be a novel therapeutic target of coronary artery disease to solve residual cardiovascular risks. However, optimization of mitochondria-targeting therapeutic strategies for clinical application needs fine-tuned settings in dose regimens and duration of interventions **(Fig. 1)**.

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Conflict of Interest

None.

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