

# Small non-coding RNA's journey to the mitochondria $\alpha \pi \omega$

## Parkinson's disease

METGen-01-

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$\Delta\psi$

The heart consumes large amounts of energy through the processes of excitation-contraction (EC) coupling in cardiac myocytes. To match energy supply to demand, mitochondria take up  $\text{Ca}^{2+}$  via the  $\text{Ca}^{2+}$  uniporter (MCU), where  $\text{Ca}^{2+}$  stimulates rate-limiting enzymes of the Krebs cycle. The main products of the Krebs cycle, NADH and  $\text{FADH}_2$ , donate electrons to the electron transport chain (ETC) to build up the mitochondrial membrane potential ( $\Delta\psi$ ) that is the driving force for ATP production. Furthermore,  $\text{Ca}^{2+}$ -induced Krebs cycle stimulation also regenerates NADPH for the antioxidative capacity of the mitochondrial matrix. In heart failure, the balance between ADP-induced oxidation and  $\text{Ca}^{2+}$ -induced reduction of NADH and NADPH is disturbed through changes in cytosolic  $\text{Ca}^{2+}$  and  $\text{Na}^+$  handling, sarcomeric alterations and increased hemodynamic workload. The resulting energetic deficit and oxidative stress result in arrhythmias, maladaptive cardiac remodeling and contractile dysfunction. Pharmacological interventions targeting mitochondria can ameliorate these processes and therefore, may become therapeutic tools to treat patients with heart failure.

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