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Perspective

# Impact of Mitochondrial Permeability Transition in Mitochondrial Disorders

**Mosomo Yeganeh***

*Department of Biology, Tohoku University, Sendai, Japan*

## DESCRIPTION

Mitochondria play a crucial role in cellular energy production and are involved in numerous cellular processes. Disruption of mitochondrial function has been associated with a wide range of human diseases, collectively known as mitochondrial disorders. These disorders can manifest in various organ systems and are characterized by defects in oxidative phosphorylation, mitochondrial DNA mutations, impaired mitochondrial dynamics, and altered calcium homeostasis.

One of the key events contributing to mitochondrial dysfunction in these disorders is the Mitochondrial Permeability Transition (MPT). The MPT refers to the opening of a non-selective pore in the inner mitochondrial membrane, leading to the dissipation of the electrochemical gradient, mitochondrial swelling, and the release of pro-apoptotic factors. This phenomenon has been extensively studied and linked to the pathogenesis of several mitochondrial disorders, including mitochondrial encephalomyopathies, neurodegenerative diseases, and metabolic disorders.

### Mechanism of the mitochondrial permeability transition

The precise molecular mechanisms underlying the MPT are not fully elucidated, but emerging evidence suggests the involvement of multiple factors. The most widely accepted hypothesis involves the formation of the Mitochondrial Permeability Transition Pore (mPTP), a complex composed of several proteins including Voltage-Dependent Anion Channels (VDACs) in the outer mitochondrial membrane, Adenine Nucleotide Translocase (ANT) in the inner mitochondrial membrane, and Cyclophilin D (CypD) in the mitochondrial matrix.

Under normal physiological conditions, the mPTP is in a closed state, maintaining mitochondrial integrity. However, in response to various pathological stimuli such as calcium overload, Reactive Oxygen Species (ROS), or elevated levels of inorganic phosphate, the mPTP can transition to an open state. This transition leads to the influx of solutes into the mitochondrial matrix, including calcium ions, which further exacerbate mitochondrial dysfunction and cell death.

### Consequences of mitochondrial permeability transition in mitochondrial disorders

The dysregulation of the MPT has profound consequences for mitochondrial function and contributes to the pathogenesis of mitochondrial disorders. The excessive opening of the mPTP results in mitochondrial swelling, disruption of the electrochemical gradient, and impairment of ATP production. The release of calcium from the mitochondria contributes to cytosolic calcium overload, leading to cellular toxicity and activation of apoptotic pathways. Furthermore, the release of pro-apoptotic factors, such as cytochrome c, from the mitochondria triggers caspase activation and apoptosis.

Several lines of evidence support the involvement of the MPT in specific mitochondrial disorders. For instance, in mitochondrial encephalomyopathies, a group of disorders characterized by central nervous system dysfunction and muscle weakness, studies have demonstrated aberrant calcium homeostasis and increased sensitivity to MPT induction. This suggests that the MPT may contribute to the neuronal cell death and muscle dysfunction observed in these disorders.

Neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, are also associated with mitochondrial dysfunction and MPT dysregulation. In these disorders, increased mitochondrial ROS production and impaired calcium handling contribute to neuronal cell death. The MPT is believed to play a pivotal role in amplifying the detrimental effects of these cellular abnormalities, leading to neurodegeneration.

In addition to neurologic disorders, mitochondrial permeability transition has been implicated in metabolic disorders, such as Non-Alcoholic Fatty Liver Disease (NAFLD) and type 2 diabetes. Mitochondrial dysfunction in hepatocytes and pancreatic beta cells contributes to insulin resistance and impaired glucose homeostasis. Dysregulated MPT has been linked to the loss of mitochondrial function and increased oxidative stress in these

**Correspondence to:** Mosomo Yeganeh, Department of Biology, Tohoku University, Sendai, Japan, E-mail: mosomoyeganeh@gmail.com

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disorders, further exacerbating metabolic abnormalities and promoting disease progression.

Moreover, the MPT has been implicated in ischemia-reperfusion injury, a phenomenon that occurs when blood flow is restored to a previously ischemic tissue. During ischemia, the lack of oxygen and nutrients leads to mitochondrial dysfunction. Upon reperfusion, the sudden influx of oxygen and restoration of blood flow result in an excessive production of ROS and calcium overload, triggering the opening of the mPTP. This leads to mitochondrial damage, cell death, and tissue injury. Strategies aimed at inhibiting or modulating the MPT have shown promise in reducing ischemia-reperfusion injury and improving outcomes in various organs, including the heart, brain, and kidneys.

Understanding the molecular mechanisms of the MPT and its involvement in mitochondrial disorders has paved the way for potential therapeutic interventions. One approach is the development of pharmacological agents that target the mPTP and modulate its opening. For instance, cyclosporine A, a known inhibitor of CypD, has been shown to prevent MPT induction and protect against mitochondrial dysfunction in preclinical studies. However, the clinical translation of these compounds has been challenging, and further research is needed to optimize their efficacy and safety.

Alternative strategies focus on targeting upstream signaling pathways that regulate the MPT. For example, interventions aimed at reducing oxidative stress, restoring calcium homeostasis, or modulating mitochondrial dynamics may indirectly impact MPT induction and mitochondrial dysfunction. These approaches hold promise for the development of more targeted and specific therapies for mitochondrial disorders.