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Link of impaired metal ion homeostasis to mitochondrial dysfunction in neurons

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Manganese, iron, copper, and zinc are observed to play essential roles in mitochondria. The overload and depletion of metal ions in mitochondria under pathological conditions, however, could disturb mitochondrial compartments and functions leading to cell death. In this review, we mainly summarize how impaired metal ion homeostasis affects mitochondrial systems, such as membrane potentials, the tricarboxylic acid cycle, oxidative phosphorylation, and glutathione metabolism. In addition, based on current findings, we briefly describe a recent understanding of the relationship among metal ion dysregulation, mitochondrial dysfunction, and the pathogeneses of neurodegenerative diseases.

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Introduction

Mitochondria are the principle organelles responsible for the production of adenosine triphosphate (ATP) *via* their own systems [*e.g.*, tricarboxylic acid (TCA) cycle, oxidative phosphorylation (OxPhos) (Figure 1)] [1]. In addition to ATP generation, mitochondria have crucial roles in metal ion homeostasis, modulation of Ca(II)-mediated signaling, regulation of reactive oxygen species (ROS), and programmed cell death [1,2,3•]. Structurally, mitochondria are surrounded by a double-membrane system, composed of the outer membrane and inner membrane (OM and IM, respectively), separated by an intermembrane space (IMS) (Figure 1). The IM forms invaginations known as cristae which extend into matrix (Figure 1). Recently, the detailed structures and functions of mitochondrial protein complexes, essential for understanding the dynamic activities of the organelles, have been identified following the development of biochemical and biophysical methods, including immunopurification, mass spectrometry, cryo-electron microscopy, and X-ray crystallography [1,4,5].

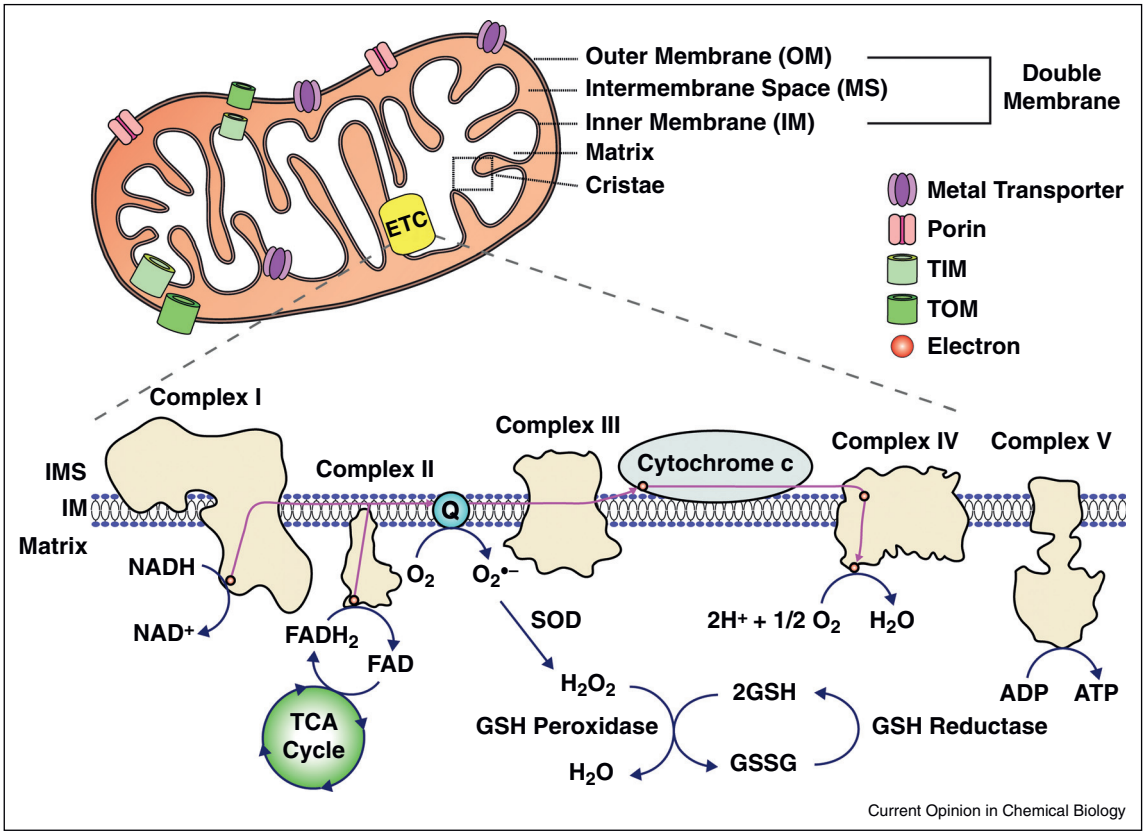
Most mitochondrial proteins are synthesized in cytosol and enter mitochondria as unfolded forms *via* the translocase of the outer membrane (TOM) and the inner membrane (TIM) (Figure 1) [3•,6]. Metal ions in mitochondria contribute to the metalation of the intrinsic mitochondrial proteins indispensable for proteins' folding and stability [3•,6]. Moreover, metal ions help mitochondrial proteins' functions, such as electron transfer and enzymatic catalysis, as cofactors (*e.g.*, Fe–S clusters, heme centers) [3•,6]. The overall concentrations of metal ions in mitochondria are elaborately regulated by metallochaperones and metal transporters (*e.g.*, mitoferrin-1 and mitoferrin-2 for iron; ZIP8 and ZnT-2 for zinc; ATP7A and ATP7B for copper) [3•,6,7]. Breakdown of metal homeostasis upon misregulation of metal trafficking, observed under pathological conditions in neurons, however, could affect mitochondrial compartments and functions [8,9•,10••,11•]. For example, the deficient iron level was observed to be associated with the fusion and aggregation of mitochondria in dopaminergic neurons [9•]. Moreover, altered metal ion homeostasis in mitochondria could be linked to pathological features observed in neurodegenerative diseases [*e.g.*, Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS)] [9•,11•,12]. To elucidate how the imbalance between the uptake and efflux of metal ions could induce the impairment of mitochondrial systems, various studies have been carried out [3•,6,7,9•,10••,11•,12–14,15•]. Herein, we review the current knowledge on the impacts of disrupted metal ion homeostasis on mitochondrial compartments (*e.g.*, membrane) and functions [*e.g.*, TCA cycle, OxPhos, glutathione (GSH) metabolism]. We also briefly discuss a relationship among metal ion dysregulation in mitochondria, mitochondrial dysfunctions, and neurodegenerative diseases.

Impairment of mitochondrial compartments and functions induced by dysregulation of mitochondrial metal ions

Membranes of mitochondria

The transport of biomolecules into mitochondria is strictly controlled by the mitochondrial double-membrane system [1,6]. In particular, the IM does not allow

Figure 1



Structure and functions of mitochondrion. Mitochondrion consists of the outer membrane (OM), intermembrane space (IMS), inner membrane (IM), and matrix. The electron transfer chain (ETC) protein complexes [complex I (NADH dehydrogenase); complex II (succinate dehydrogenase); complex III (cytochrome bc_1 complex); complex IV (cytochrome c oxidase)] and complex V (ATP synthase) are located in cristae. The ETC protein complexes and the chemiosmosis between IMS and matrix are involved in OxPhos. In addition to OxPhos, the tricarboxylic acid (TCA) cycle is another cellular respiration process which occurs in matrix. To prevent cellular damage mediated by reactive oxygen species (ROS), the redox systems of glutathione (GSH) are responsible for intrinsic antioxidative defense in mitochondria.

the movement of metal ions without transporters and channels (*e.g.*, mitoferrin-1, ZIP8, ATP7B), different from the OM, which has been indicated to possess pore-forming membrane proteins (*e.g.*, porins) and permit free diffusion of metal ions [1,3•,6]. This impermeable barrier helps mitochondria remain with negative membrane potentials ($\Delta\Psi_m$) and trans-membrane electrochemical proton gradients required for ATP synthesis [1,3•,6]. Impaired regulation of metal ions in mitochondria, however, could contribute to alteration of mitochondrial $\Delta\Psi_m$ and integrity (Figure 2) [3•,16–18,19•]. Weiss and coworkers reported that the submicromolar levels of Zn (II) decreased $\Delta\Psi_m$, monitored based on the uptake of triphenylphosphonium cations into matrix [16]. They also suggested the involvement of Zn(II) accumulation in the opening of mitochondrial permeability transition pore (mPTP), whereas it has still been controversial [16,17]. Reynolds and coworkers presented that inhibition of the transmembrane gradient could be induced by Zn(II) uptake *via* the mitochondrial Ca(II) uniporter (MCU) rather than the opening of mPTP [17]. Under Fe(II)-rich conditions, the uptake of Fe(II) *via* the MCU could also cause the depolarization of mitochondrial membrane and generate ROS through the Fenton reaction [18]. In addition to metal-rich conditions, the deficiency of metal ions could also be detrimental to mitochondrial membranes [19•]. In Zn(II)-deficient neuronal precursor cells, Levenson and coworkers indicated the translocation of phosphorylated p53 to mitochondria with its phosphorylation followed by the increased level of BAX protein [19•]. In the OM, the BAX pores formed by the interaction with p53 were observed to allow the release of apoptosis-inducing factors (AIFs) to cytosol, disrupting mitochondrial membrane integrity (Figure 2) [19•].

Furthermore, metal-mediated ROS overproduction is known to affect mitochondrial lipid environments [20]. In the mitochondria isolated from ATP7B-knockout transgenic mice, the animal model for Wilson's disease, the overload of Cu(I/II) triggered the fragmentation of