

**Opinion**

## Significance of Respiratory Supercomplexes for Mitochondrial Function & Related Diseases

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### Respiratory Supercomplexes: Associated Partners in Oxidative Phosphorylation

Mitochondrion is a membrane-enclosed organelle which functions as the power house of the eukaryotic cells. The main pathway for energy production of eukaryotic cells, oxidative phosphorylation, takes place in the inner membrane of the mitochondria, especially in the cristae. Following the intake of food molecules, pyruvate and fatty acids are oxidized in the mitochondria; whereas, the electron carrier molecules, NAD and FAD are reduced into NADH and FADH<sub>2</sub> through the citric acid cycle, respectively. Then, these carrier molecules transfer electrons to the electron transport chain (ETC), which is located in the inner membrane of the mitochondria (IMM). In the meantime, an electrochemical gradient is formed across the IMM, which will then be employed for ATP production by ATP synthase [1]. The ETC proteins and ATP synthase exist as protein complexes in the IMM and are named as mitochondrial oxidative phosphorylation complexes. However, not all mitochondrial complexes exist as individual complexes. In fact, they form supercomplexes with each other or they exist as homodimers [2]. Various supercomplex combinations of complexes I, III, and IV have been detected so far in different organisms such as yeast, plants and humans [3]. Yet, any involvement of complex II in supercomplex formation has not been detected.

### Unveiling of Respiratory Supercomplexes

The experimental studies on investigation of supercomplex presence have been revolutionized by discovery of blue native gel electrophoresis [4]. Digitonin extraction followed by blue native polyacrylamide gel electrophoresis has been one of the most employed techniques for uncovering the structures of the intact supercomplexes with high resolution. The improvements in cryo-electron microscopy technique have made a major breakthrough in structural studies of bio molecules [5] and supercomplexes have got their piece of this pie. High-resolution 3D structures of supercomplexes in their native states have provided us the basis to perform further studies about their mechanism of association/dissociation and their interactions [6]. A recent approach to deduce the structures of supercomplexes has been cross-linking mass spectrometry

(XL-MS). Schweppes, D. *et.al* showed that the interactions between individual complexes were consistent with the cryo-EM structures of the supercomplexes [7].

### Respiratory Supercomplexes as Functional Units and Their Impacts on Health

In addition to the structural studies, functional studies on supercomplexes have also been conducted. The supercomplex assemblies of the complexes are found to improve the stabilization of the overall electron transfer process [8]. Also, they are found to enhance electron transportation by leading them from enzyme to enzyme in a direct manner so they prevent electrons to be released into the medium [9]. In addition, a decreased rate of reactive oxygen species production is revealed in the case of supercomplex formation [10]. All these functions and events are related with each other and supercomplex assembly has a key role in these relations. To be more precise, dissociation of supercomplexes would reduce the efficiency of electron transport since the electrons are being released to the medium during transport with separate complexes. This would also lead an increased rate of production of reactive oxygen species due to usage of the electrons floating in the medium. In brief, the lack of supercomplexes would lead to an impaired oxidative phosphorylation which is a definitive characteristic of mitochondrial dysfunction.

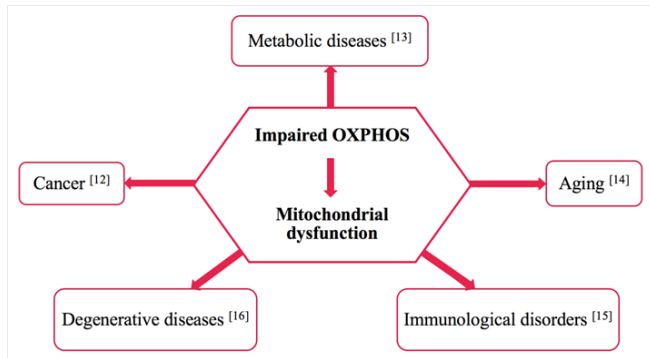
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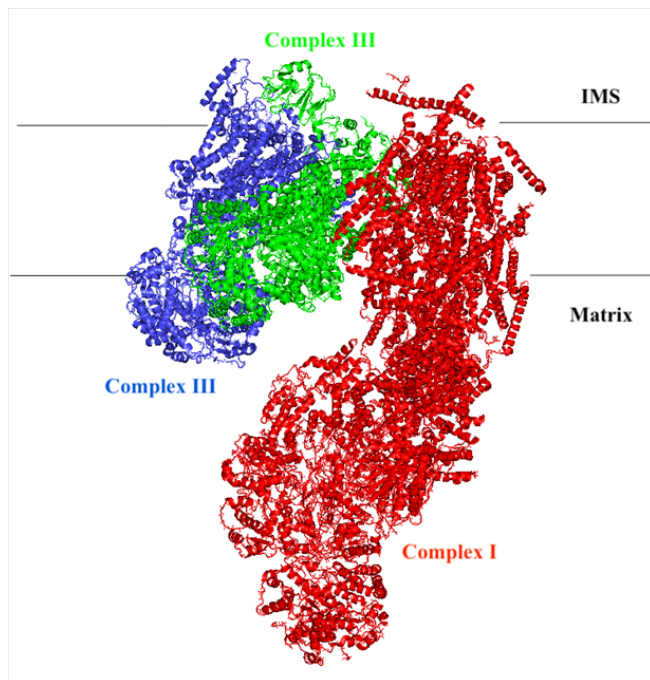
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Impaired OXPHOS and mitochondrial dysfunction go hand in hand and play significant roles in many diseases and conditions such as cancer, diabetes, neurodegenerative diseases, cardiac degenerative diseases, immunological disorders, and aging (Figure 1) [11].



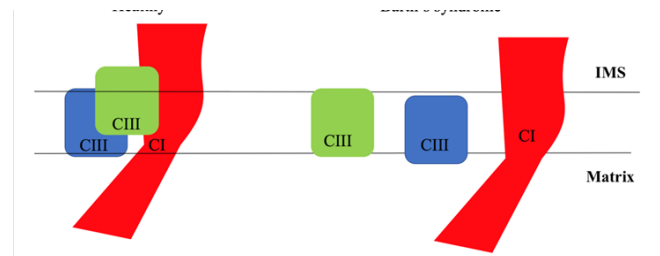
**Figure 1.** The effects of mitochondrial dysfunction on human health

Following this line of thought, several research studies have been performed in which supercomplex assembly has been investigated under different conditions. In Barth's syndrome patients, some supercomplexes were found to be dissociated. For example, supercomplex I-III<sub>2</sub> (Figure 2) were more labile in Barth's syndrome patients while supercomplex I-III<sub>2</sub> of healthy samples were intact (Figure 3) [17].



**Figure 2.** 3D structure of super complex I-III<sub>2</sub> (prepared by using PyMOL v1.7.4.5 Edu Enhanced for Mac OS X) (PDB ID: 5J8K) [18]

In another study, supercomplex dissociation coupled with a decreased rate of oxidative phosphorylation was linked to heart failure [19]. Also, it was shown that the assembly of respiratory supercomplexes in macrophages reduces in response to bacterial infection prior to further activation of immune system [20].



**Figure 3.** Model representations the intact super complex I-III<sub>2</sub> from healthy samples (on the left) and individual complexes from Barth's syndrome patients (on the right)

### Future Aspects

In conclusion, mitochondrial supercomplexes must be investigated for each of mitochondrial dysfunction-related disease and condition since their structural and functional properties are very prone to change and dependent on the unique situation of the cell. supercomplexes have not been investigated in cancer and it might be an interesting topic to explore since proliferating cancer cells exhibit decreased oxidative phosphorylation. This metabolic effect might be due to dissociation or lack of association of respiratory supercomplexes which are known to enhance electron transport. The mechanisms of supercomplex association and dissociation and their interacting partners need to be identified to gain an in-depth understanding of oxidative phosphorylation, thus, energy metabolism in different health conditions.

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