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Supercomplex formation boosts respiration

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Mitochondrial respiratory chain complexes associate in supercomplexes, but the physiological role of these assemblies remains controversial. Recent studies in *EMBO Reports* reveal that supercomplexes promote metabolic fitness. Berndtsson *et al* (2020) demonstrate that supercomplex formation enhances electron transport by reducing the distance for diffusion of cytochrome *c* between cytochrome bc_1 complex and cytochrome *c* oxidase and thereby increases competitive fitness in yeast. Similarly, Garcia-Poyatos *et al* (2020) report that zebrafish lacking the supercomplex assembly factor SCAF1 display a reduced growth and decreased female fertility.

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See also: **C Garcia-Poyatos *et al*** (July 2020) and **J Berndtsson *et al*** (December 2020)

Mitochondria are known as the powerhouse of the cell since they produce the bulk of cellular ATP by oxidative phosphorylation. The respiratory chain complexes of the inner membrane transfer electrons from reducing equivalents to oxygen. The released energy is used to transport protons across the inner membrane to generate a proton gradient. The F_1F_O-ATP synthase uses the proton gradient to generate ATP from ADP and phosphate. The respiratory chain consists of four distinct protein complexes in mammalian cells: NADH dehydrogenase (complex I), succinate dehydrogenase (complex II), cytochrome bc_1 complex (complex III) and the cytochrome *c* oxidase (complex IV). Mitochondria from baker's yeast *Saccharomyces cerevisiae* lack complex I, but contain alternative NADH dehydrogenases that oxidizes NADH. Ubiquinone and cytochrome *c* shuttle electrons from complex I and complex II to the cytochrome bc_1 complex and between complex III and complex IV, respectively.

Mitochondrial respiratory chain complexes assemble into higher order structures termed supercomplexes (Schägger & Pfeifer, 2000; Böttinger *et al*, 2012). In mammalian mitochondria, several supercomplexes are formed, including the respirasome that consists of complex I, a complex III dimer and complex IV (Gu *et al*, 2016; Letts *et al*, 2016). In yeast, one or two copies of the cytochrome *c* oxidase bind to a dimer of the cytochrome bc_1 complex (Hartley *et al*, 2019; Rathore *et al*, 2019). Although the existence of such supercomplexes is now widely accepted, the physiological role of these structures remains controversial (Milenkovic *et al*, 2017). Different functions have been debated, including substrate channelling between individual complexes, reduction of reactive oxygen species as well as assembly and stability of individual complexes (Milenkovic *et al*, 2017). The main challenge to study the physiological role of supercomplexes is to selectively disrupt respiratory chain supercomplexes in the cell. Berndtsson et al showed in their high-resolution cryo-electron microscopic structure that Cor1 of the cytochrome bc_1 complex and Cox5a of the cytochrome *c* oxidase form a main interface between both protein complexes. The authors introduced point mutations in *COR1* that specifically disrupt its binding to Cox5a. Excitingly, the yeast mutant expressing the *COR1* variant displayed normal levels of respiratory chain complexes but selectively lost respiratory chain supercomplexes (Berndtsson *et al*, 2020).

The authors used the *cor1* mutant to study the physiological role of respiratory chain supercomplexes. Loss of supercomplexes did not affect growth rates, chronological ageing, oxidative stress and cell death. However, the competitive fitness of the *cor1* mutant was reduced when the cells were incubated together with wild-type cells in the same culture (Berndtsson *et al*, 2020). Similarly, Garcia-Poyatos *et al* (2020) reported that Zebrafish that lack the supercomplex assembly factor, SCAF1, were smaller in size compared to the wild-type and displayed a decreased female fertility. SCAF1 promotes the assembly of complex III and complex IV into respiratory chain supercomplexes (Cogliati *et al*, 2016). Consequently, loss of SCAF1 affects supercomplex formation. Remarkably, the defects in body size and fertility were rescued by increasing food intake, suggesting an inefficient metabolism in zebrafish lacking Scaf1. All these observations indicate that supercomplex formation is important to ensure full respiratory chain activity and fitness.

Why are supercomplexes required for full respiratory activity? Berndsson *et al* (2020) demonstrated that the maximal respiratory activity was reduced in the absence of supercomplexes. Detailed biochemical studies revealed that the electron transfer by cytochrome *c* between the cytochrome bc_1 complex and cytochrome *c* oxidase was reduced. Addition of exogenous cytochrome *c* *in vitro* and overexpression of cytochrome *c*

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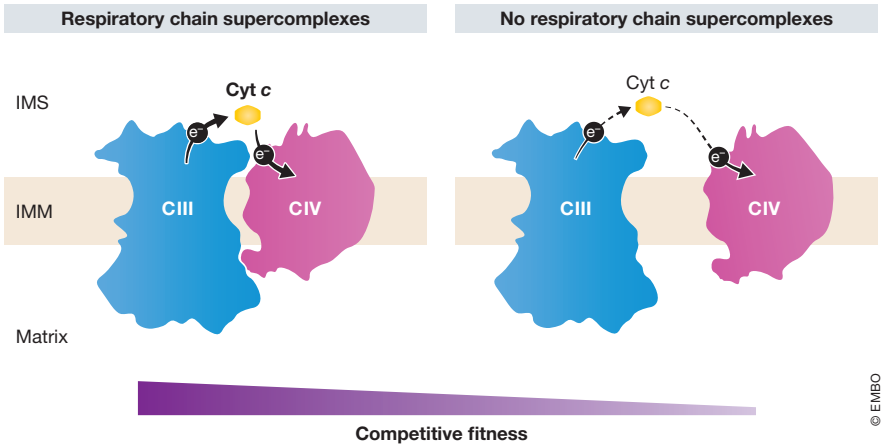

Figure 1. Supercomplex formation facilitates cytochrome *c* diffusion within the respiratory chain.
Supercomplex formation between complex III (CIII) and complex IV (CIV) of the respiratory chain increases the efficiency of electron transfer via shortening the diffusion distance of cytochrome *c* (Cyt. *c*). Disruption of the supercomplexes affects electron transfer by increasing the diffusion distance of cytochrome c, which in turn decreases cellular fitness. IMS: intermembrane space; IMM: inner mitochondrial membrane.

in the *cor1* mutant strain recovered the observed respiratory defects and restored competitive fitness. These findings indicate that the close vicinity of complex III and complex IV facilitates diffusion of cytochrome *c* between these complexes to optimize electron transfer within the respiratory chain (Fig 1). Thereby, supercomplex formation promotes competitive fitness of the organism.

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