Lack of functional assembly in mitochondrial supercomplexes: a new insight into impaired mitochondrial function?

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This editorial refers to ‘Cardiac mitochondria in heart failure: decrease in respirasomes and oxidative phosphorylation’ by Rosca et al., 1 pp. 30–39, this issue.

A new mitochondrial disorder in heart failure that fits in the category of mitochondrial cytopathies is the exciting finding in the paper by Rosca et al. 1 presented in this issue of Cardiovascular Research, which also explores a new insight into the functionality of mitochondria in the heart.

The function of heart muscle is highly dependent on the energy generated by mitochondria by oxidation of fatty acids and carbohydrates through the tricarboxylic acid cycle, which is the direct source of electrons for the respiratory electron chain where oxidative phosphorylation and associated ATP synthesis takes place. Defects in mitochondrial structure and function have been found in association with cardiovascular diseases such as dilated and hypertrophic cardiomyopathy, cardiac conduction defects and sudden death, ischaemic and alcoholic cardiomyopathy, as well as myocarditis. While a subset of these mitochondrial abnormalities has a defined genetic basis, other abnormalities appear to be due to a more sporadic or environmental cardiotoxic insult or have not yet been characterized. 2,3

A major function of mitochondria is the conversion of energy released by mitochondrial processes in the mitochondrial matrix into the energy currency of the cell—ATP—a process mediated by the oxidative phosphorylation system (OXPHOS), a group of transmembrane protein complexes which constitute the electron transport chain (which generates an electrochemical gradient across the mitochondrial inner membrane), and ATP synthase (which synthesizes ATP using the energy stored in the electrochemical gradient). The electron transport chain is made up of four major multi-subunit complexes called NADH:CoQ reductase (Complex I), succinate:CoQ reductase (Complex II), ubiquinol:cytochrome c reductase (Complex III), and cytochrome c oxidase (Complex IV), with electron transfer between them ensured by collisional interactions of low molecular weight connecting molecules (co-enzyme Q and cytochrome c). This is the so-called random diffusion model or liquid-state model, which implies a random distribution of electrons through freely diffusible mitochondrial complexes. 4,5

This model is supported by the fact that all the complexes can be purified in a physiologically active form, and also by lipid dilution experiments using isolated mitochondrial membranes (reviewed in Hackenbrock et al.). 6

In contrast, several other lines of evidence support an alternate possibility, the solid-state model, which was revised when Schägger 6 found structural evidence by blue-native electrophoresis of specific associations in yeast and mammalian mitochondrial respiratory complexes. This group introduced the model ‘supercomplexes’, confirming earlier observations in favour of specific intercomplex interactions (cf. 7, 8 for an extended list of references). However, interactions of OXPHOS complexes are not simply ‘solid’ but rather should be considered to be of a dynamic nature. In recent years, there have been an increasing number of reports about these supercomplexes in very different kinds of electronic transport chains from numerous cell types. 5, 8, 9 It is interesting to point out that these supercomplexes are always formed by the same complexes, i.e. C-I, C-III, and/or C-IV, the same three involved in electrochemical gradient generation. Complex II, which is not involved in this process, has never been found associated with supercomplex structures. 10 There are also studies about Complex V, ATP synthase, and the possibility that it could also form supercomplexes by oligomerization, which has been proposed to play an important role for mitochondrial cristae formation and to be involved in regulating ATP synthase activity. 11

These supercomplexes could still be interpreted as aggregates that are caused by the isolation procedure with detergent treatment. However, there have been the first structural insights by electron microscopy of these multi-complex assemblies, and a distinctive structure has been observed for all supercomplexes investigated, giving clear
proof for a specific interaction of the respiratory chain complexes (partially reviewed by Boekema and Braun). Among others, the first 3D map of a supercomplex has been determined recently, the one made up of bovine complexes C-I, C-III, and C-IV (1:2:1) denoted I,III,IV, which has been named as ‘respirasome’ because it is able to do all the electronic transport by itself.

What is the advantage of these superstructures? Probably, the answer can be found in a better electronic transfer in the solid state, since the two low molecular weight electron carriers (co-enzyme Q and cytochrome c) have short diffusion distances in these assemblies, supporting the notion of a more efficient electron transfer through supercomplexes as opposed to the fluid-state model, where electron transfer depends on the random encounter of the respiratory chain components. Moreover, there is evidence that the higher order organization of the respiratory chain complexes could be an essential feature of mitochondrial architecture.

Roscas et al. have described in their paper an interesting new possibility concerning supercomplexes. They have studied the effect of heart failure on the cardiac mitochondria OXPHOS system, including the levels of respirasome I,III,IV. This study has been carried out in both heart tissue mitochondrial fractions, which exist as functionally and biochemically distinct populations: subsarcolemmal (SSM) mitochondria, which are situated beneath the plasma membrane, and interfibrillar (IFM) mitochondria, which are located among the myofibrils. The results obtained are quite interesting because they found the same behaviour in both heart failure mitochondrial populations: about a 50% decrease in ADP-stimulated oxygen consumption without any change in the amounts of the individual OXPHOS complexes. Moreover, this effect was accompanied by a decrease in the amount of respirasome I,III,IV in both SSM and IFM, so this decrease in oxygen consumption could probably be assigned to a lack of assembly of the complexes constituting this respirasome. This becomes a very intriguing observation.

In the end, the paper indicates that heart failure has produced a lack of assembly of the functional respirasome. This is a newly identified mechanism associated with decreased mitochondrial functionality after heart failure and, as such, opens a whole new field of research into mitochondrial functional alterations. Thus, the further study of mitochondrial supercomplexes, their presence, and their assembling mechanisms is very important, not only for their structural and mechanistic implications, but also because of the possibility of their relevance in mitochondria-related diseases.

References