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Respiratory supercomplexes: plasticity and implications

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1. ABSTRACT

The plasticity model of the electron transport chain has slowly begun to replace both the liquid model of free complexes and the solid model of supercomplexes. The plasticity model predicts that respiratory complexes exist and function both as single complexes and as supercomplexes. The advantages of this system is an electron transport train which is able to adapt to changes in its environment. This review will investigate the current body of work on supercomplexes including their assembly, regulation, and plasticity, and particularly their role in the generation of reactive oxygen species and aging.

2. INTRODUCTION

Mitochondria play a role in several cellular processes. They are important for buffering calcium and controlling the production of ROS. They can initiate the intrinsic pathway of apoptosis by releasing cytochrome c, but arguably their most important function is in the generation of ATP through oxidative phosphorylation (1). To do this, mitochondria use four complexes, NADH-ubiquinone oxidoreductase (Complex I), succinate-ubiquinone oxidoreductase (Complex II), ubiquinone-cytochrome-c oxidoreductase (Complex III), and cytochrome-c-oxidase (Complex IV) to generate an electrochemical gradient across the inner mitochondrial membrane which is then used to power the conversion of ADP to ATP by ATP synthase (Complex V) (2). The textbook model of these complexes as separate, free floating entities which use cytochrome c and ubiquinone as electron carriers between them has slowly been rethought in recent years. The mitochondrial respiratory chain (MRC) is now thought to contain functional supercomplexes (SCs) which are formed by individual complexes coming together in various ratios to form stable, supra-molecular structures.

How these SCs are assembled and what their function is has been an intense debate. Though there is criticism that these SCs may just be an artifact that are only observed because of milder detergents like digitonin, this has largely been abated by evidence that these SCs are enzymatically active (3, 4). The plasticity model envisions the MRC as a combination of free complexes and SCs which are able to adapt to changing conditions. It accounts for lower SCs (I/III and III/IV) which may act as intermediates to the I/III/IV SC or may have functions of their own (5). What this means however in terms of how the assembly of SCs is regulated and what roles they may play under different conditions has yet to be explored.

3. SUPERCOMPLEX ASSEMBLY

Much of the work in recent years has focused on understanding the assembly of SCs and the discovery of SC assembly factors. It was determined that Complex I was dependent on both Complex III and Complex IV though neither complex was affected when Complex I was deficient (6-8). These evidences

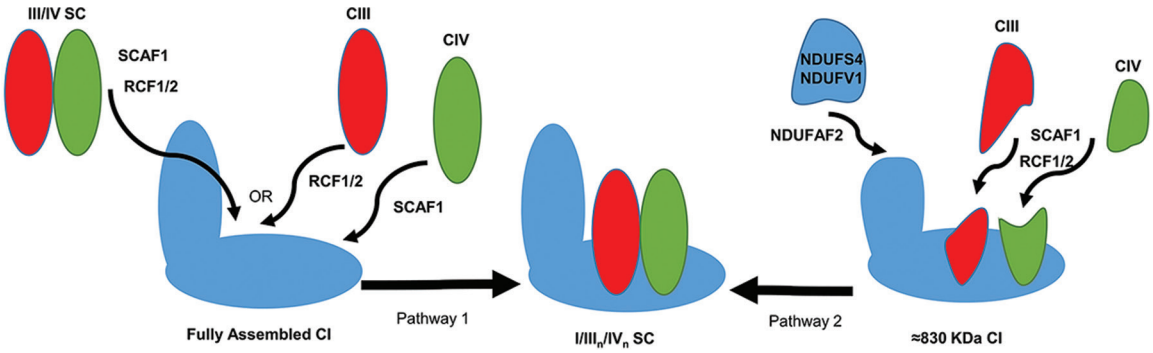

Figure 1. Possible pathways of SC assembly and the assembly factors involved are illustrated. The critical difference between the two major types of pathways is that one predicts that individual complexes assemble and then come together either individually or as the III/IV SC to form the I/III/IV SC while the other envisions the membrane arm of Complex I as a scaffold that subunits of Complexes III and IV can build on as Complex I assembly is completed.

led to the theory that Complex I assembly was dependent on SC assembly and that SC assembly should therefore follow the assembly of individual complexes. This process has major biomedical implications and helps explain threshold effects seen in mtDNA mutations (9-11). When wildtype mtDNA of either Complex III or Complex IV is depleted there is initially no effect on respiration due to excess amounts of Complex III and Complex IV. When the reserves of these complexes are depleted however the I/III$_2$/IV$_n$ SCs are unable to assemble. At this point respiration rapidly diminishes (9). The timing however of SC assembly has been a matter of contention however. In mouse fibroblast cells, (^{35}S) methionine-labeled mtDNA subunits were observed to assemble into individual complexes and then into various SCs (4). In contrast, a study in *Neurospora crassa* observed that the III/IV SC can assemble separately from Complex I, that Complex III and Complex IV interact with the membrane arm of Complex I, and that this interaction is important for the full assembly of Complex I (12). Later work supported these observations by depleting the OXPHOS complexes with doxycycline treatment and then monitoring the assembly of complexes by blue-native gel electrophoresis. They observed that Complex I assembly occurred as previously reported up to an 830 KDa intermediate which they deemed the first SC intermediate. At this point Complex III and then Complex IV subunits begin to attach to the membrane arm of Complex I. The final step in this process involves the attachment of the catalytic subunits NDUFS4 and NDUFV1 of Complex I before activation of the I/III$_2$/IVn SC (Figure 1) (13).

SC assembly factors have recently been the focus of most studies on SCs. Originally the existence of SC assembly factors was only theoretical. It was proposed that either SCs share assembly factors with the individual complexes particularly in the case of Complex I whose late stage assembly factor NDUFAF2 interacts with the 830 KDa subcomplex in the insertion of the N module or SCs may have their own exclusive set of assembly factors which when lost affect only the levels of SCs but not the levels of individual complexes (13). These two ideas may not be mutually exclusive in the sense that there may be a set of factors common to individual complexes and SCs as well as a set that is exclusive to SCs. In terms of classification though, it is simpler to keep the two separate and only label the second class as *bona fide* SC assembly factors. For the purpose of expanding current knowledge of SC dynamics the identification of true SC assembly factors is of paramount importance to allow researchers the ability to modulate SC assembly under various conditions.

The biomedical significance of SC assembly factors is best exemplified by cardiolipin and its role in Barth Syndrome. Cardiolipin is a phospholipid which is primarily found in mitochondrial membranes (14). It is necessary for the maintenance of membrane potential, ATP synthesis, and mitochondrial function (15-17). Barth syndrome is an X-linked disorder which presents with cardiomyopathy, skeletal myopathy, and neutropenia and is caused by a mutation in the taffazin (TAZ) gene which is responsible for the remodeling of cardiolipin (18-20). It was known that cardiolipin is essential for electron transfer between Complex I and Complex III and that cardiolipin was necessary for the formation of the

III/IV SC, but the link between cardiolipin, SCs, and Barth Syndrome was not established until a landmark study by McKenzie *et al* in 2006 which demonstrated that SCs particularly the $I/III_2/IV$ SC were destabilized in Barth Syndrome (21-24). Additionally it was biochemically determined that cardiolipin has binding sites for Complexes I, III, IV, and V (21, 25, 26). To compensate for the changes in the MRC, it was shown by electron microscopy that there is an increase in mitochondrial mass in Barth Syndrome which prevents a dramatic decrease in respiration, but there is also loss of intrinsic apoptosis signaling (27). Taken collectively these studies establish a precedent for understanding SCs in terms of their possible biomedical significance.

In 2012, two proteins renamed rcf-1 and rcf-2 were shown in yeast to interact with Complex IV and indirectly with Complex III. Additionally this interaction is necessary for the formation of the III/IV SC (Figure 1) (28-30). The function of these proteins was previously unknown except that they are important for maintaining mitochondrial function (31, 32). This would suggest that rcf-1 and rcf-2 are SC assembly factors, but because rcf-1 is required for the assembly of Cox13 into Complex IV and for rcf-2 assembly into SCs, it may be more appropriate at least for rcf-1 to categorize them as general Complex IV assembly factors (5, 30). The mammalian orthologs of these proteins are the hypoxia-induced genes HIG1A and HIG2A. Knockdown of HIG1A has no effect on the level of SCs, but loss of HIG2A reduced the levels of all SCs containing Complex IV without a reduction in the amount of free Complex IV (28). Therefore regardless of classification, rcf-1 and rcf-2 are important players in SC assembly.

In contrast, the cochaperone MCJ/DnaJC15 was discovered to act as a negative regulator of mitochondrial respiration. MCJ localizes at the inner mitochondrial membrane where it interacts with free Complex I and inhibits the formation of SCs. When MCJ is lost there is an increase in ATP production, membrane potential, and Complex I activity possibly due to its incorporation into SCs. There is not however an increase in ROS which would normally accompany these increases which may be explained by the increase in SC formation. Interestingly under altered metabolic conditions such as fasting or high-cholesterol diets, the loss of MCJ prevents lipid accumulation and steatosis by favoring lipid metabolism and glycogenesis in the liver (33). This example provides evidence of the importance of SC assembly in response to altered metabolic conditions.

The first true SC assembly factor identified in mammalian cells was identified by proteomic analysis of MRC bands on a blue-native gel. The protein Cox7a2l was present in I/III/IV SCs and III/IV SCs, but not free complexes. This protein was also found to be mutated in several common mouse lines. The mutation caused a short, unstable version of Cox7a2l which ablated the interaction between Complexes III and IV. The protein was renamed SC assembly factor 1 (SCAF1). Without SCAF1, Complex IV will not assemble into SCs; with SCAF1, Complex IV can assemble into the III/IV SC and the I/III/IV SC (Figure 1). This effectively creates three pools of Complex IV: one receiving electrons exclusively from NADH in the I/III/IV SC, one exclusively from $FADH_2$ in the III/IV SC, and fee Complex IV which can receive electrons from either carrier. This segmentation may prevent competitive inhibition and allow the cell to maximize oxidation of multiple substrates by adjusting the SC composition of its MRC (34). To demonstrate this, mice with and without the SCAF1 mutation were subjected to 18 hours of starvation to activate fatty acid oxidation. In fatty acid oxidation the ratio between NADH and $FADH_2$ decreases, creating a situation where the mitochondria would need to maximize their ability to utilize $FADH_2$. Accordingly after starvation it was observed that the $SCAF1^+$ mice had a reduction in the amount of Complex III associating with Complex I. Additionally pyruvate and malate driven respiration decreased while succinate driven respiration increased. These results indicate that when FA oxidation is activated, the NADH only I/III/IV SC is decreased allowing for maximized oxidation of $FADH_2$ through the III/IV SC and free Complexes III and IV pathways (5, 34). This study demonstrates that metabolic changes can affect the composition of SCs. It is worth noting however that in this model it is necessary for cytochrome c to demonstrate pool behavior acting both as a channeled substrate in SCs and as a free-diffusing substrate to interact with free Complex IV. This pool behavior is still under debate. Electron microscopy has revealed binding sites for cytochrome c with a diffusion distance less than 10 nm supporting the ability of cytochrome c as a channeled substrate (35, 36). Evidence in yeast however demonstrated that the observed pool behavior of cytochrome c is artificially introduced by the use of

chaotropic agents that disassociate the individual complexes from a single unit respiratory complex and thus does not exist under physiological conditions (37).

4. SUPERCOMPLEX PLASTICITY AND METABOLISM

One important question that is only just starting to be answered is whether or not a cell's SC composition is fixed or if it can change over time or in response to different stimuli. The "plasticity" of SCs may have biomedical implications in that the loss of SC plasticity may either be an indicator of or directly cause pathologies. Therefore study of the mechanisms and regulation of SC plasticity may lead to the discovery of novel therapeutic targets for treating mitochondrial dysfunction.

The lipid content of the inner mitochondrial membrane (IMM) is especially important for maintenance of SCs. The OXPHOS proteins in the IMM are densely packed so that the average distance between complexes is only a few nanometers (38). At low integral protein concentrations, the proteins are randomly dispersed in the IMM (39). Counterintuitively as the protein concentration increases it becomes more entropically favorable for the integral proteins to aggregate into SCs because lipids bound to the proteins are able to return to the disorganized lipid pool (40). Outer membrane-inner membrane contacts and the tubular connections of cristae also favor immobilization of integral proteins (41, 42). Additionally matrix enzymes are able to bind to respiratory chain complexes particularly Complex I which is known to interact with the NAD-linked dehydrogenases: pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, malate dehydrogenase, and beta-hydroxyacyle-CoA dehydrogenase forming a "metabolome" where electrons can pass straight from the dehydrogenases through the ETC (43, 44). Furthermore lipid peroxidation causes many changes in the lipid bilayer including the breakdown of lipid-protein interactions possibly decreasing the stability of SCs (45, 46). As described previously, cardiolipin is important for the stabilization of SCs (47). It was biochemically determined that the formation of the I/III complex is determined by the concentration of phospholipids in that an increase in phospholipids beyond a certain threshold leads to more free complexes (48, 49). In contrast, cardiolipin concentration is important to keep SCs stable. In a yeast mutant lacking cardiolipin the III_2/IV_2 SC was present but less stable than in the parent strain, and this instability couldn't be rescued by an increase in other phospholipids including phosphatidylthanolamine (PE) and phosphatidylglycerol indicating that they could not substitute for cardiolipin (47, 50). It was later determined that lack of PE actually stabilizes SCs. In yeast mutants lacking PE there was a loss of membrane potential, defects in protein import, a decrease in respiration and Complex IV activity, but lack of PE also increased the assembly of III/IV SCs (51). These studies indicate that lipid composition of the IMM is important for the formation and stability of SCs. Therefore it appears that there is a very delicate balance between the protein/lipid ratio and SCs in the IMM in that the overall concentration of lipids must be low enough to favor protein aggregation and thus SC formation but the concentration of cardiolipin specifically must be high enough (and therefore the concentration of other phospholipids low enough) to sufficiently stabilize SCs after their assembly.

Membrane potential may also be responsible for regulating SC assembly. Studies on membrane potential control on respiration observed that in the uncoupled condition Complex IV has a low reserve capacity and a large control coefficient which is lost once the mitochondrial electrochemical potential is established (52, 53). It was suggested that a high membrane potential would indicate a low energy demand for the cell. The respirasome would then break apart into individual complexes causing a decrease in oxygen consumption. As ATP is used, the membrane potential would decrease and the respirasome would reform to satisfy the requirement for a higher rate of respiration (52). Similarly low mitochondrial pH and hypoxia were shown in plants to induce Complex I to disassociate from the I/III/IV SC causing an increase in the III/IV SC (54). The changes observed under hypoxia are especially interesting in regards to cancer and the Warburg effect (55). It may be that during early stages of cancer, hypoxia causes a loss of SCs as the cell switches from OXPHOS to glycolysis based metabolism.

On the macro level a few processes have been identified as necessary for SC stability. The fission/fusion cycle as well as mitophagy are important quality control mechanisms for the cell. Defects in these processes have been linked with pathologies such as Parkinson's disease (56, 57). During fusion, cristae reorganization requires that the SCs are disassembled and then reassembled. Two factors,

OPA1 and mitofilin are required for maintaining tight cristae junctions (58-61). By modulating the expression of OPA1, it was discovered that SC assembly requires intact cristae junctions (62). Interestingly mutations in OPA1 can cause dominant optic atrophy, an optic nerve degeneration disease characterized by loss of retinal ganglion cells. In a study of a mouse model of this disease, premature age-related axonal and myelin degenerations, increased mitophagy, and SC instability followed by degeneration and cell death were observed (63). Further research into the relationship between these quality control mechanisms and SC stability may therefore elucidate possible therapeutic targets for disease.

Post-translational modification of proteins is an important process for quickly and transiently modifying the structure of a protein causing changes in enzyme activity as well as interfering or aiding protein-protein interactions. To date no work has specifically analyzed the role of post-translational modifications in SC assembly or function, but there is a large body of information on post-translational modifications of individual respiratory complexes and other mitochondrial proteins. Three NAD-dependent deacetylases; SIRT3, SIRT4, and SIRT5; are localized to the mitochondria. SIRT3 in particular has been implicated in regulating metabolism by deacetylating the Complex I subunit NDUFA9 to maintain ATP levels as well as matrix proteins like the mitochondrial ribosomal protein MRPL10 to regulate protein synthesis and the SdhA subunit of succinate dehydrogenase (Complex II) demonstrating the role of acetylation/deacetylation in regulating oxidative phosphorylation (64).

Phosphorylation modification of respiratory complexes provides an exciting link through kinase cascades between changes in a cell's environment such as endocrine signaling molecules like insulin and glucagon and changes in the MRC. Kinases and phosphatases for both serine/threonine and tyrosine residues are present in mitochondria (65-67). The activity of Complex I as well as its ROS generating capacity have been linked to phosphorylation (68-70). Protein kinase A, a cAMP-dependent kinase, is known to phosphorylate the Complex I subunits NDUSF7, NDUFA1, and NDUFS4 (71). Phosphorylation of NDUFS4 is required for import of this subunit into mitochondria (72). These phosphorylation events lead to stabilization of Complex I and a decrease in ROS generation. Phosphorylation of NDUSF7 by pyruvate dehydrogenase kinase however has the opposite effect (71). Complex IV phosphorylation however has had conflicting results. The Complex IV subunit COX-I is phosphorylated at Tyrosine-304 after an increase in cAMP which causes a loss of COX activity. This residue is near the interaction of this subunit with COX-II and may enhance monomer-monomer interaction (73). This is the site of interaction between Complex IV and its partners in the $I/III_2/IV$ SC (74) and may explain the prevalence of cAMP/PKA dependent phosphorylation in free Complex IV (75). Other PKA phosphorylation sites in Complex IV which may affect its ability to bind with other proteins were found in subunits II, III, IV, Va, Vb, VIa, VIb, VIc, and VIII (76). Contrastingly phosphorylation of COXI and COX IVb was shown to increase respiration and reduce ROS. The study also identified a soluable-adenylate cyclase specific to mitochondria that is activated by bicarbonate produced by CO_2 generated in the TCA cycle which when inhibited reversed the phosphorylation at these sites as well as the changes in mitochondrial function (77). Regardless of the conflicting results, it is clear that phosphorylation particularly by PKA is important for regulation of oxidative phosphorylation. Whether or not this regulation also acts on the level of SCs has yet to be explored.

5. SUPERCOMPLEXES, ROS AND AGING

The mitochondrial theory of aging predicts that over time oxidative stress causes mtDNA mutations leading to a loss in the integrity of respiratory machinery (78). This loss of integrity inevitably causes an increase in reactive oxygen species (ROS) which in turn cause mtDNA mutations in a vicious cycle leading to an overall decline in mitochondrial function (Figure 2) (79). This loss of bioenergetic function is predicted to be the cause of aging and age-associated degenerative diseases (80). The majority of ROS produced by the mitochondria comes from Complexes I and III with Complex I being the major contributor (81, 82). ROS can have multiple damaging effects besides causing mtDNA mutations. They can oxidize the complexes themselves or cause peroxidation of phospholipids which leads to a dramatic loss of cardiolipin content (83). Additionally ROS has been shown to increase with age (82).

It has been proposed that SCs help decrease the production of ROS by substrate channeling, which limits the amount of electron leakage, as well as the sequestering of vulnerable sites which protects the complexes from oxidative

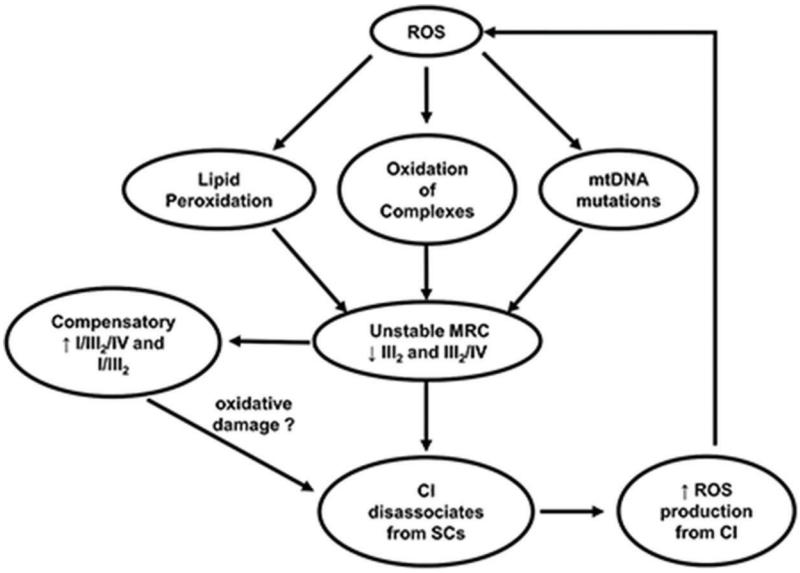

Figure 2. Reactive oxygen species can cause three main types of damage in the mitochondria. ROS can peroxidize lipids which in the case of cardiolipin may be especially damaging to SC stability. ROS can also directly oxidize the complexes possibly affecting their ability to interact with each other, and finally ROS can cause mtDNA mutations which can affect the integrity of the MRC complexes. These three types of events over time may cause SCs to become unstable though evidence suggests that the higher order SCs may increase as a compensatory mechanism. Eventually however enough oxidative damage may make all SCs unstable. Complex I will then disassociate from SCs, and the amount of ROS produced by Complex I will increase causing a vicious cycle of oxidative damage.

damage (38, 84). A recent study discovered that mtSODs interact directly with the I/III/IV SC and may protect it from oxidative damage (85). SCs have been observed to decline with age in the rat heart (86). In rat skeletal muscle, the levels of CI, CIII, and CV in old rats was significantly less than in young rats, but though there was a decrease in lower molecular weight SCs, there was an increase in higher molecular weight SCs. This may be a compensatory mechanism to prevent further ROS generation and oxidative damage (87). Similarly a cytochrome b p.278Y to C mutation causes an increase in superoxide production and a decrease in the III_2 and III_2/IV SCs but an increase in the $I/III_2/IV_n$ SCs (88). This switch to higher order SCs (SCs of higher molecular weights with greater stoichiometric ratios of complexes e.g. the $I/III_2/IV_n$ is a higher order SC compared to the III_2IV) may act as a way to contain Complex I which most likely produces more ROS in its free state (38). It is tempting to predict that over time with enough oxidative damage, it's possible that these higher order SCs will become unstable and release Complex I thereby increasing ROS production (Figure 2), but further study is needed to determine if this process occurs and if the switch to higher molecular weight SCs is in fact a compensatory mechanism to reduce ROS or just a result of certain SCs being more susceptible to aging.

In particular the main function of the I/III_2 SC may be to limit the production of ROS from Complex I. A study in rat cortex observed an age-associated 40% decline in SCs containing Complex I which was predominately caused by the 58% decline in I/III_2 SCs (89). Recently Maranzana *et al* investigated this relationship. The site of electron escape from Complex I is controversial, but two main sites have been proposed: FMN or the iron sulfur cluster N2. The N2 site may be predominant when CI is present in SCs while FMN may only become available after CI isolation when its loss of stability may cause the FMN site to become free to interact with oxygen. Maranzana *et al* investigated the I/III_2 SC in two different systems, bovine heart mitochondria and reconstituted proteoliposomes composed of CI and CIII at different lipid: protein ratios. When the bovine heart mitochondria were treated with DDM, a detergent which causes the complexes in SCs to disassociate, there was a decrease in efficient energy transfer and an increase in ROS. Similarly proteoliposomes in a high lipid: protein ratio (30:1) which prevented I/III_2 assembly had enhanced ROS generation compared to proteoliposomes in a 1:1

ratio. Treatment of the 1:1 ratio proteoliposomes with DDM caused an increase in ROS due to the disassociation of CI from the I/III_2 SC. This study is the first of its kind to directly demonstrate the relationship between the loss of SCs and an increase in ROS production from CI (90). How this increase in ROS relates to aging and the possibility of modulating this process is an exciting area of research in the SC field.

6. FUTURE DIRECTIONS

The debate over whether or not SCs are functional seems to be slowly ending. Mounting evidence that they are not only functional but essential members of the MRC has accumulated in the last couple of years, and their involvement in various disease pathologies is just beginning to be understood. To date, only one protein has been identified as a true SC assembly factor in a mammalian system, SCAF1 (34). It is unlikely that this is the only assembly factor necessary for SC formation. This area of research needs to be explored because identifying assembly factors that are specific to SCs is necessary for researchers to modulate the levels of SC assembly in order to better understand the physiological consequences of SC depletion. Without these tools, it will be harder to establish causal links between SCs and mitochondrial function. Additionally the pathway of SC assembly is unclear and requires further investigation. Identification of SC intermediates is difficult since they are most likely not present at steady-state levels, but there are two possibilities that need to be explored. One is that the complexes are fully assembled and then come together to form SCs, or as was previously proposed, SC assembly starts when subunits from different complexes come together before the whole individual complexes are formed (13).

The plasticity model predicts that a cell's SC composition can change in response to stimuli. Of particular interest is how the MRC responds to metabolic changes or signals. This is likely to depend heavily on cell type. It has been proposed that SCs may be especially important for cells like neuron and muscle cells that require large amounts of ATP and rely predominantly on OXPHOS instead of glycolysis to acquire this level of energy (91). Therefore studies on SCs should primarily be done in these tissues as they are most likely to heavily depend on their SCs. Moreover how this process is regulated may have profound biomedical implications. Of particular interest may be the effects of various post-translational modifications of complexes on SC assembly and function. Phosphorylation in particular provides a link between changes in the metabolic state of an organism and possible changes in SCs through endocrine signaling and kinase cascades.

Finally, SC deficiencies have been linked to various disorders. Barth syndrome is the most characterized of these disorders, but SCs have to a lesser extent been implicated in cancer progression, neurodegeneration, CI deficiency disorders, as well as aging. In studying the mechanism for SC involvement in these diseases one idea has become very clear. Often the disease or the effect loss of SCs has on the disease is the result of an increase in ROS. Substrate channeling and sequestering of vulnerable sites have been proposed to be the main reason SCs are able to reduce ROS generation. This may turn out to be their main purpose. Though there also tends to be an increase in respiration with SCs, this reserve energy capacity is not generally necessary for cell survival. Only when cells are stressed and need this reserve capacity does the loss of SCs become a problem (5, 38, 77). During normal conditions, a shift towards higher order SCs in response to outside metabolic stimuli may allow the cell to maximize OXPHOS while limiting an increase in ROS. It is possible that SC disorders characterized by ROS may be the result of a defect in SC plasticity which would prevent the cells from limiting their ROS production. Overtime the accumulation of oxidative damage may lead to neurodegeneration and may play an important step in the aging process. In conclusion, the study of SCs is ready to move beyond the debate of whether or not they are simply artifacts and on to gaining a better understanding of their role in disease.

7. ACKNOWLEDGEMENTS

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