Cytochrome c oxidase Assembly Factors

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An overview of cytochrome c oxidase assembly factors in baker's yeast and humans with hypotheses regarding the assembly process in low oxygen conditions and during initial entry into the inner mitochondrial membrane.

Keywords: mitochondria ; cytochrome c oxidase ; oxidative phosphorylation ; electron transport chain

1. Introduction

Energy generation is a fundamental process that supports all forms of life on earth. The universal energy currency in life is adenosine triphosphate (ATP) which captures energy from bioenergetic and metabolic processes powered by substrate-level and oxidative phosphorylation. In eukaryotes a major portion of ATP is generated through mitochondria, a double-membrane organelle derived from a symbiotic relationship at the origin of multicellular life [1]. Mitochondria harbour a series of multi-subunit complexes that perform electron transfer and proton translocation from the internal mitochondrial matrix space to the inter-membrane space (IMS) through the inner mitochondrial (IMM). This generates an electrochemical gradient across the IMM where proton concentration is higher in the IMS than the matrix. The accumulated protons can re-enter the matrix through ATP synthase - a proton transporter that couples the proton gradient to the synthesis of ATP. The electron transport complexes are an ordered series of multi-subunit complexes that accept electrons from carriers such as nicotinamide adenine dinucleotide (NAD^+/NADH) and flavin adenine dinucleotide ($FAD/FADH_2$) produced through metabolic pathways such as glycolysis, citric acid cycle and β-oxidation. NADH is oxidised by NADH dehydrogenase enzymes, such as multi-subunit Complex I in many eukaryotes or single subunit Ndi1p in *Saccharomyces cerevisiae.* The first step in Complex I sees the electrons passing through a series of co-factors and prosthetic groups such as iron-sulphur (Fe-S) clusters and flavin mononucleotide (FMN). The electrons are passed to the membrane soluble lipid based redox carrier co-enzyme Q (ubiquinone/ubiquinol). In addition, $FAD/FADH_2$ is reduced by succinate dehydrogenase of the citric acid cycle which also acts as complex II of the electron transport chain (ETC). Complex II contains Fe-S clusters and haem prosthetic groups to again pass electrons to Co-enzyme Q. Reduced Co-enzyme Q (ubiquinol) is oxidised by complex III (co-enzyme Q:cytochrome *c* oxidoreductase) using Fe-S and haem groups to reduce cytochrome *c*, the next mobile electron carrier in the ETC. Cytochrome *c* localises to the IMS face of the IMM to shuttle electrons from complex III to complex IV using a haem prosthetic group. Complex IV (cytochrome *c* oxidase) is the final complex of the ETC catalysing the reduction of molecular oxygen, the terminal electron acceptor to form water via copper and haem groups. The process of electron transfer is coupled to proton translocation from the matrix to the IMS and is mediated by complexes I, III and IV to generate the electrochemical gradient.

The ETC complexes are multi-subunit assemblies with protein subunits derived from both nuclear and mitochondrial gene products. To ensure efficient assembly of complexes co-ordinated post-translational processing and protein-protein interactions are required. This is accomplished by a stepwise biogenesis pathway that requires the function of specific chaperones. As oxidative phosphorylation (OXPHOS) is an evolutionarily conserved process in all eukaryotes much understanding of the assembly process can be gleaned from the study from all eukaryotic organisms where mitochondria exist. This is true for single cell eukaryotes such as the budding yeast *Saccharomyces cerevisiae* and photosynthetic alga *Chlamydomoas reinhardtii* to multicellular higher eukaryotes such as human and mouse. The combination of genetic manipulation of eukaryotic model organisms and naturally occurring mutations in human disease has provided much information we have at the moment about how assembly of the ETC occurs. The molecular details of the most studied mammalian organisms and yeast OXPHOS complex structure and assembly have very many similarities but also some differences. These differences are in the number of structural subunits forming complexes as well as the post-translational processing required for correct assembly. Furthermore, multicellular eukaryotes express tissue-specific subunits that provide unique functions to the complexes. Budding yeast has been a powerful model system to understand assembly of OXPHOS complexes as they are facultative anaerobes, meaning they can sustain energy requirements in the absence of functional OXPHOS if grown on a carbon source, such as glucose, that does not require the functions of OXPHOS. When grown on carbon sources such as ethanol, glycerol and lactate, that require functional OXPHOS, any defects in assembly

or function of the ETC or OXPHOS results in a lack of growth. This has enabled a large number of genes to be identified that are responsible for ETC and OXPHOS assembly and function through powerful genetic and phenotypic analysis [2]. Recently, more homologues have been identified in higher eukaryotes demonstrating the conservation of the assembly of the complex as well as the enzymatic function [3].

2. Cytochrome *c* oxidase Structure and Function

In order to understand the assembly pathway of multi-subunit complexes it is important to put this in the context of the fully assembled and functional complex. Each subunit has a defined three-dimensional organisation and interacts with certain subunits, both required for full function. Mammalian and yeast cytochrome *c* oxidase (COX) are composed of 3 subunits derived from mitochondrial DNA and between 8 and 11 subunits derived from nuclear genes. The mitochondrial encoded subunits Cox1p and Cox2p contain prosthetic groups and co-factors required for electron transfer including haem groups in Cox1p and copper ions in Cox1p and Cox2p. These two subunits are also responsible for the translocation of protons from the matrix to the IMS through hydrophilic channels. The post-translational associations of prosthetic groups and co-factors as well as proteolytic processing and membrane insertion are accomplished by a number of chaperones, some specific to COX and others shared with other OXPHOS complexes. All of these chaperones are encoded by the nuclear genome and for the most part functional homologs are conserved from budding yeast to higher mammals with some exceptions. The functions of many of these chaperones have been determined and are conserved; however, there are still some genes without assigned functions or functional homologs [4]. Determination of gene function and functional homologs will allow for a more complete understanding of the process of COX biogenesis.

Defects in OXPHOS are responsible for an array of genetic disorders that impact on tissues and organs with high metabolic demands or dependency on mitochondrial metabolic pathways. Specifically for COX there are a number of mutations in assembly factor and structural genes that cause forms of Leigh Syndrome, mitochondrial Complex IV deficiency and rare syndromes that result in neurological disorders along with impacts on the heart [5], liver [6], kidney [7] and digestive system [8]. The neurological disorders differ in their onset severity depending on the nature of the mutation. For example, encephalopathies display clinical features due to specific mutations in all OXPHOS complexes as well as other mitochondrial genes involved in mitochondrial DNA maintenance, e.g., DNA polymerase γ [9]. Variation in severity is also observed by certain combinations of clinical features, for example, encephalopathies presenting with tubulopathy and hepatopathy, caused by mutations in the Complex III gene BCS1L [10]. Specific mutations associated with these diseases are individually rare, but when combined with other diseases that cause defects in OXPHOS occur at approximately 1 in 5000 births, representing one of the highest incidences of inherited metabolic diseases affecting humans. Through recent advances in diagnosis of mitochondrial disease and investigation of the molecular basis of the disease insights into the functions of assembly factors is improving [11].

In humans and other higher mammals, most assembly factors and structural subunits have an orthologue in budding yeast. The human COX enzyme is composed of 14 subunits, which is 3 more than budding yeast. As with most of the nuclear encoded structural subunits these are single trans-membrane spanning polypeptides that surround the core catalytic subunits and do not interfere with conserved interfaces and interactions [12]. Recently, other subunits have been identified as associated with purified COX including the hypoxia inducible gene Rcf1p/HIGD2A which acts as a link between Complex III to support supercomplex formation especially under anaerobic conditions when Cox5bp is expressed [13][14]. The structure of mammalian COX has been known since the 1980s and recently the 14th subunit was identified. NDUFA4 was originally attributed to Complex I, but biochemical and genetic studies revealed deficiencies in COX activity and an equal stoichiometry with other COX structural subunits without impact on Complex I activity [15][16][17]. NDUFA4 has been identified in purified COX containing supercomplex structures determined by X-ray crystallography at the interface of COX dimers [18]. This is further supported by the presence of a homologue in budding yeast, MIN8/YPR010C-A, identified through proteomics [19]. *S. cerevisiae* do not express a multi-subunit Complex I NADH dehydrogenase, fully supporting another role for this gene. It is annotated as a mitochondrial gene of unknown function. Further work is required to understand the function of this gene as this has not been identified as a gene required for respiratory deficiency in previous studies. The function of these extra subunits is subject to speculation. *S. cerevisiae* COX can retain function in the absence of the Cox8p and Cox13p subunits indicating that not all structural subunits are required for activity [20]. COX8A is the human homologue of yeast Cox8p, and it is the smallest subunit of human COX. In contrast to *S.cerevisiae,* a mutation in this subunit is responsible for neurological disorder due to loss of COX function [21]. *S. cerevisiae* COX13 has two homologues in humans-COX6A1 and COX6A2-tissue specific isoforms in the liver and striated muscle, respectively. Mutations in the isoform COX6A1 have been shown to be the cause of Charcot-Marie tooth disease, a neuropathological disorder [22][23]. Mutations in the second isoform COX6A2 can lead to muscle specific Complex IV deficiency [24]. These discrepancies indicate differences in the essential nature of these peripheral subunits. The 3 human specific subunits in human COX are COX6C, COX7C and NDUFA4. Mutations in NDUFA4 are associated

with Leigh Disease [25], while mutations in the two other subunits COX6C and COX7C have not been associated with disease. Even though there are differences between the phenotypes of yeast and humans, this should be taken with some caution as some homologous subunits do not have the same common origin [26].

3. Cytochrome c oxidase Assembly Factors

Biogenesis of multi-subunit complexes requires specific maturation steps for subunits to ensure correct localisation and topology, post-translational modifications and interactions with other subunits. These biogenesis pathways also require quality control points to verify each step has been correctly performed but also to determine whether downstream steps can occur. Assembly factors for COX can be broadly grouped by function including transcription and translational regulation, membrane insertion, proteolysis, co-factor and prosthetic association or an as yet undefined function. The process of COX assembly ensures appropriate association of correctly matured subunits with incorporated co-factors and prosthetic groups when in adequate abundance. This prevents accumulation of mid-assembly intermediates that can cause potentially detrimental effects due to excess reactive oxygen species (ROS) or overloading of protein quality control systems. Due to the number of subunits that need to associate in the IMM, and the number of maturation steps required, there are many assembly factors to ensure each of these steps are performed correctly. The assembly pathway still needs further elucidation to assign functions to specific assembly factors and how certain assembly intermediates interact, but general functions are beginning to be understood.

4. Mutations in Cytochrome *c* oxidase Assembly Factors as Cause of Human Disease

Understanding of COX assembly has also been captured from the study of patients suffering from disease caused by mutations in these genes. Mutations in genes could result in the absence of assembled COX but also in mutation in critical residues for the activity of the enzyme. The inheritance pattern of these diseases also contributes to the severity of the disease. This is why mitochondrial diseases present as a heterogeneous spectrum of disorders that are difficult to diagnose and treat. A number of mutations in assembly factors are the cause of these diseases [11]. The most common cause of complex IV deficiency is through mutation of SURF1. There are at least 36 different mutations in this gene that result in disease, these are located throughout the length of the gene and result in missense and nonsense mutations. Some of these have been introduced into budding yeast SHY1 at conserved sites and result in the accumulation of intermediates at different stages of Cox1p module assembly. This indicates that Shy1p function can be sensed by the Mss51p checkpoint, but has functions later in the assembly process [27]. The wide variety of disease causing SURF1 mutations, along with the evidence of a weak and spontaneously suppressible respiratory defect in budding yeast, indicate that defects in SURF1 can be overcome by changes in a variety of other genes in the Cox1 assembly pathway. A similar explanation may be behind the number of mutations identified in the copper chaperones, COX10 and COX15 [28][29][30]. There are a number of homologues in this pathway that if altered in expression could explain the disease. Furthermore, as elevated copper can suppress yeast mutations, alterations in cellular copper handling could explain how a mutation is overcome to enable viability. Mutations in other genes are much less frequent and this is most likely explained by a defect that cannot be overcome by changes in gene expression. This also indicates that during embryonic development there is an essential function lacking when a mutation in other genes are present that cannot be overcome and the embryo is not viable. There are several examples where genes harbouring mutations lead to COX deficiency, but the role has not been fully characterised. CEP89 was identified as the mutated gene in a patient with COX deficiency. This mutation caused loss of COX activity and function [31]. The exact role of CEP89 in this process still has to be determined. In contrast to *S. cerevisiae*, a point mutation in COX14 results in decreased synthesis of COX1 with an expected loss of COX expression and activity potentially highlighting a divergence in the assembly process [32]. Mutations in COA3, which functions at a similar point to COX14, also result in a mitochondrial disease due to specific loss of COX expression [33]. Mutations in COA5, the human homologue of Pet191p, results in infantile cardioencephalomyopathy, caused by COX deficiency. Analysis of native complexes demonstrated a Cox1 containing assembly intermediate that may represent MITRAC [34]. COA7 mutants result in COX deficiency causing leukoencephalopathies and peripheral neuropathies [35][36] and this deficiency can be restored by inhibiting cytosolic degradation of COA7 indicating these mutations delay COA7 import into mitochondria which are still capable of contributing to COX assembly [37]. Mutations in PET100 also cause COX deficiency through a truncation and an import defect [38][39][40]. PET117 mutations cause COX deficiency, most likely through its role in assisting haem synthesis coupling to association into Cox1 [41]. In patients with COX10 mutations COX expression is decreased and Cox1 exists in a sub-assembly that migrates similar to MITRAC [42][43]. COX15 mutations also show similar deficiencies of COX; however, the assembly intermediates in these patients have not been investigated

[44][30][45][46][47]. Mutations in the copper handling proteins, SCO1 and SCO2, have also been identified resulting in COX deficiency [48][49][50][51][52][53]. COA8, a less characterised protein identified as having a role in programmed cell death, when mutated can also cause COX deficiency [54].

5. Summary

In summary, the assembly of COX is a conserved process that requires the essential function of many assembly factors, somewhat unexpectedly more than the number of structural genes. This indicates the complexity and importance of the process. Without a functional COX enzyme, mitochondria are not able to produce ATP which has devastating consequences in the context of severely debilitating diseases that often lead to early death. Through further understanding of how COX assembly occurs better points of diagnostic and therapeutic intervention will be developed to improve the quality of life of patients suffering from these diseases, and families facing choices that cause anxiety and distress.

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