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The Oxidative Phosphorylation system of the mitochondria in plants

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ABSTRACT

Mitochondrial Oxidative Phosphorylation (OXPHOS) provides ATP for driving cellular functions. In plants, OXPHOS takes place in the context of photosynthesis. Indeed, metabolism of mitochondria and chloroplasts is tightly linked. OXPHOS has several extra functions in plants. This review takes a view on the OXPHOS system of plants, the electron transfer chain (ETC), the ATP synthase complex and the numerous supplementary enzymes involved. Electron transport pathways are especially branched in plants. Furthermore, the "classical" OXPHOS complexes include extra subunits, some of which introduce side activities into these complexes. Consequently, and to a remarkable degree, OXPHOS is a multi-functional system in plants that needs to be efficiently regulated with respect to all its physiological tasks in the mitochondria, the chloroplasts, and beyond. Regulatory mechanisms based on posttranslational protein modifications and formation of supramolecular protein assemblies are summarized and discussed.

1. Introduction

Adenosine triphosphate (ATP) formation by Oxidative Phosphorylation (OXPHOS) is of central importance for almost all eukaryotic cells. OXPHOS takes place in the mitochondria. Prerequisite for OXPHOS is the formation of 'reducing equivalents' (nicotinamide adenine dinucleotide [NADH] and flavin adenine dinucleotide [$FADH_2$]) by the oxidation of organic compounds, which is achieved by the tricarboxylic acid (TCA) cycle and its supplementary reactions. The first step during OXPHOS is the transfer of electrons from the reducing equivalents onto molecular oxygen. This process is based on the respiratory electron transfer chain (ETC) which is located in the inner mitochondrial membrane. Electron transfer is coupled to the formation of an electrochemical proton gradient across this membrane. In the second step, the proton gradient is used by the ATP synthase complex for phosphorylation of adenosine diphosphate (ADP). Resulting ATP can be exported from the mitochondria and provided to the entire eukaryotic cell.

In virtually all eukaryotic cells, the core of the ETC is composed of four protein complexes, the NADH dehydrogenase complex (complex I), the succinate dehydrogenase complex (complex II), the cytochrome *c* reductase complex (complex III) and the cytochrome *c* oxidase complex (complex IV). The complexes I and II transfer electrons onto ubiquinone, a mobile electron transporter within the inner mitochondrial membrane. Ubiquinol (the reduced form of ubiquinone) transfers electrons onto complex III. Electron transport from complex III to complex IV is mediated by cytochrome *c*, a small and hydrophilic protein localized in the mitochondrial intermembrane space. The ATP synthase complex, which, in a formal sense, is not part of the ETC, also is designated as complex V. All components together are referred to as the OXPHOS system.

OXPHOS is a highly conserved process that likewise occurs in mitochondria of animals, fungi, plants, and other groups of eukaryotes. However, in plants, OXPHOS takes place in the context of photosynthesis and various stress response reactions. Photosynthesis deeply affects OXPHOS for several reasons (see also van Dongen et al. 2011, Millar et al. 2011, Schertl and Braun 2014):

(i) At daytime, intermediates of the TCA cycle are partially needed for anabolic pathways in other cellular compartments, e.g. nitrogen assimilation in the chloroplasts. As a result, the TCA cycle largely switches into a non-cyclic mode, which limits formation of reducing equivalents (Nunes-Nesi et al. 2007, Sweetlove et al. 2010).
(ii) At the same time, mitochondria of photosynthetically active cells participate in another form of respiration, called photorespiration (Bauwe et al. 2010). Like 'normal' cellular respiration, which sometimes is termed 'dark respiration' in plants, photorespiration is based on O_2 consumption and CO_2 liberation. However, in contrast to dark respiration, photorespiratory O_2 consumption takes place in the chloroplasts (by the oxygenase activity of ribulose bisphosphate carboxylase/oxygenase, RubisCO), whereas CO_2 is liberated by the conversion of two molecules of glycine into one serine (by the glycine cleavage system in the mitochondria). The latter step is linked to the formation of NADH. It is assumed that, at

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daytime, NADH produced by the glycine cleavage system is the main substrate of the ETC, rather than NADH produced by the TCA cycle. Photorespiration may require substantial NADH re-oxidation capacities in mitochondria. In plants, this is partially achieved by the presence of type 2 ('alternative') NAD(P)H dehydrogenases (altNDs), some of which are synthesized in a light-dependent manner (Rasmusson et al. 2008, Rasmusson et al. 2020).

(iii) Large amounts of reducing equivalents are formed by the light reaction of photosynthesis in the chloroplasts and indirectly can be transferred to other cellular compartments. Consequently, plant cells are at risk to become 'over-reduced', especially in high light conditions. It is an additional task of the mitochondrial OXPHOS system to keep the redox state of the plant cell in balance. For this, excess of reducing equivalents need to be re-oxidized without formation of the electrochemical proton gradient across the inner mitochondrial membrane and subsequent formation of ATP. This molecular function is realized by extra enzymes, e.g. the alternative NAD(P)H dehydrogenases and by alternative oxidase (AOX), which directly transfers electrons from ubiquinol onto molecular oxygen. AOX is a very significant mitochondrial enzyme in plant cells, which is of great importance in the context of various responses of plants with respect to abiotic stress factors (Selinski et al., 2018; Vanlerberghe et al., 2016, 2020).

(iv) To further stabilize the redox balance, plant cells need additional reducing agents. One is ascorbate. The terminal step of the ascorbate biosynthesis pathway takes place in the mitochondrial intermembrane space in plants. The biosynthesis of ascorbate is linked to electron insertion into the ETC via cytochrome *c* (Bartoli et al., 2000, Millar et al., 2003).

(v) Chloroplast metabolism is regulated by light. Since OXPHOS in plants is much affected by photosynthesis, it also is light regulated. At night, plant mitochondria generate ATP for basic cellular functions. In contrast, at day time, plant mitochondria may produce less ATP (however, mitochondrially synthesized ATP still is considered to be very significant for central metabolic processes taking place in the cytoplasm at daytime, e.g. sucrose biosynthesis), but have to fulfill several other basic functions as mentioned above: they participate in photorespiration, stabilize the redox balance of the plant cell and contribute to the biosynthesis of reducing agents. All these extra functions need to be regulated with respect to availability of light. A mitochondrial form of thioredoxin has been identified as a key regulator of light responses in the mitochondria of plants (Daloso et al., 2015).

In conclusion, even though OXPHOS is a conserved process in animal, fungi and plants, the OXPHOS system of plants has extra functions. This review aims to summarize the current knowledge on the OXPHOS system in plants. Characterizing the protein complexes of the OXPHOS system of plants has revealed several surprises, which will be reported. Furthermore, insights into supramolecular assemblies of OXPHOS complexes in the mitochondria of plants will be summarized and discussed with respect to their possible functions in the context of photosynthesis.

2. Brief outline of research on the OXPHOS system of plants

The OXPHOS complexes were discovered and first biochemically purified from bovine heart mitochondria (Hatefi et al. 1961, reviewed in Hatefi 1985). In the field of plant biology, the purification of mitochondrial enzymes was hampered for a long time by the comparatively low abundance of mitochondria in plant cells, the robust cell wall surrounding plant cells, and the occurrence of various secondary compounds. First attempts to biochemically purify OXPHOS complexes from plants took place in the 1980s (e.g. Nakajima et al. 1984, Hawkesford et al. 1989). The development of Blue native polyacrylamide gel electrophoresis (BN PAGE) in the 1990s (Schägger and von Jagow 1991) greatly promoted research on the protein complexes of plant mitochondria (Jänsch et al. 1996). However, systematic identification and characterization of the subunits of the OXPHOS complexes had to wait until protein identifications by mass spectrometry routinely became possible around the year 2000 (Giegé et al., 2003; Eubel et al., 2003, Heazlewood et al., 2003a, Heazlewood et al., 2003b, Millar et al., 2004, Meyer et al., 2008). Meanwhile, in depth analyses have been carried out for all OXPHOS components of the mitochondria of plants based on biochemical preparations, BN PAGE, protein mass spectrometry, physiological analyses, and partially also on single particle electron microscopy. Several but not all of these investigations were performed on the model plant *Arabidopsis thaliana*.

3. The NADH dehydrogenase complex (complex I) of plants

Complex I is the largest enzyme complex of the ETC and at the same time the most prominent site for electron insertion into the ETC (Wirth et al. 2016). It is homologous to NADH dehydrogenase complexes occurring in several clades of bacteria. In eubacteria and mitochondria it consists of two elongated domains designated 'arms': the membrane arm, which is largely embedded into the bacterial or the inner mitochondrial membrane, and the peripheral arm, which protrudes into the bacterial lumen or the mitochondrial matrix. The two arms are connected end-by-end, forming an overall L-shaped particle. In eubacteria, the two arms of complex I consist of a minimal set of seven + seven subunits (called the core subunits). In contrast, mitochondrial complex I includes, besides the core subunits, around 30 so-called supplementary subunits. Its overall molecular mass is in the range of 1000 kDa. Structures with atomic resolution have been determined for complex I from bacteria (Baradaran et al. 2013), mammals (Fiedorczuk et al. 2016, Zhu et al. 2016) and fungi (Parey et al. 2018).

For plants, low-resolution structures of mitochondrial complex I obtained by single particle electron microscopy are available (Dudkina et al. 2005a, Peters et al. 2008, Bultema et al. 2009). Complex I from plants also has an L-like shape (Fig. 1). However, in contrast to NADH dehydrogenase complexes from all other groups of eukaryotes characterized so far, it has a second matrix-exposed domain, which has a spherical shape and is attached to the membrane arm at a central position (Fig. 1). In addition, the membrane arm of plant complex I is slightly longer in comparison to the mammalian enzyme complex. According to current knowledge, 49 subunits form part of complex I from Arabidopsis, 14 in the peripheral arm, 30 in the membrane arm and 5 in the spherical extra-domain (Senkler et al. 2017a; see Supp. Table 1 for a list of currently known components of the OXPHOS system in

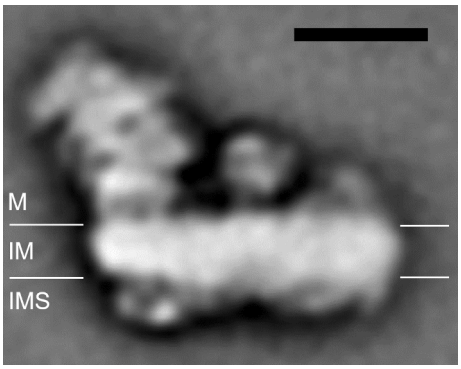

Fig. 1. Structure of complex I from *Solanum tuberosum* (potato) as revealed by single particle electron microscopy (Bultema et al. 2009). The complex was purified from isolated mitochondria by sucrose gradient ultracentrifugation. White lines indicate the boundaries of the inner mitochondrial membrane. The scale bar equals to 10 nm. M: matrix, IM: inner mitochondrial membrane, IMS: mitochondrial intermembrane space. Figure taken from Bultema et al. 2009, modified.

Arabidopsis thaliana).

The function of mitochondrial complex I has been investigated especially for mammals and fungi. NADH oxidation and ubiquinone reduction take place in two different functional domains, which both are part of the peripheral arm. The two reactions are linked by an electron transfer chain consisting of a flavin mononucleotide (FMN) and seven to eight iron-sulfur clusters. In contrast, proton translocation takes place by the membrane arm of complex I. Overall, four protons are transported from the mitochondrial matrix to the mitochondrial intermembrane space per oxidized NADH. The way of coupling of electron transfer and proton translocation within complex I is a matter of debate. It has been proposed that reduction of ubiquinone in the peripheral arm induces a conformational shift, which propagates through the entire center of the membrane arm (reviewed in Sazanov 2015). It is suggested to cause alternating opening and closing of proton half-channels at the matrix-exposed and the intermembrane space-exposed surfaces of the membrane arm. There are currently no indications that the functioning of plant complex I during NADH-ubiquinone oxidoreduction and proton translocation differs from the mechanism proposed for other groups of eukaryotes.

Comparison of the subunit compositions of complex I in mammals and the model plant *Arabidopsis thaliana* revealed that 40 subunits are conserved (Cardol, 2011, Senkler et al. 2017a). Four subunits are considered to be unique to mammalian complex I (one of which occurs in two copies per complex I particle) whereas nine subunits are unique to Arabidopsis: five proteins resembling gamma-type carbonic anhydrases, two small proteins of unknown function (termed P1 and P2), a protein resembling a subunit of the preprotein translocase of the inner mitochondrial membrane (accessions At1g18320 and At3g10110 in Arabidopsis) and L-galactono-1,4-lactone dehydrogenase (GLDH), the terminal enzyme of the ascorbic acid biosynthesis pathway. Interestingly, most (but not all) of the proteins unique in mammalian and plant complex I are located at the matrix-exposed surface of the membrane arm of complex I. Due to its large size and unique biochemical environment this site seems to be predestinated to bind enzymes not directly related to the function of complex I in OXPHOS.

3.1. The carbonic anhydrase domain of plant complex I

The carbonic anhydrase subunits were shown to be located within the spherical extra domain of plant complex I, which therefore is termed the ‘carbonic anhydrase domain’ (Sunderhaus et al. 2006, Klodmann et al. 2010). Three of the five proteins of this small Arabidopsis protein family have a conserved active site with respect to the bacterial prototypes of gamma-type carbonic anhydrases and are called CA1, CA2 and CA3. The two other members of the protein family are more derived and therefore were named carbonic-anhydrase-like (CAL) proteins, CAL1 and CAL2 (Parisi et al. 2004, Perales et al. 2004). Biochemical and genetic analyses revealed that the carbonic anhydrase domain most likely includes three copies of the CA/CAL proteins (reviewed in Fromm et al. 2016a). Experimental data indicate that the CA/CAL proteins have overlapping functions and partially can replace each other (Perales et al. 2005, Sunderhaus et al. 2006). At the same time, the CA/CAL proteins are essential for complex I assembly. If the gene encoding CA2 is deleted in Arabidopsis, the amount of complex I is drastically reduced (Perales et al. 2005). If the genes encoding CA1 and CA2 are simultaneously deleted, complex I is not detectable anymore (Fromm et al. 2016b). Indeed, evidence has been presented that the carbonic anhydrase subunits are involved in very early steps of the assembly of the membrane arm of complex I in plants (Meyer et al. 2011, Li et al. 2013, Ligas et al. 2019, Meyer et al. 2019).

The function of the carbonic anhydrase domain could not be elucidated so far. Direct evidence of carbonic anhydrase activity of the monomeric CA/CAL proteins has not been presented. However, *E. coli* cells overexpressing CA2 were shown to have increased CO_2/bicarbonate binding capacities (Martin et al. 2009). It has been proposed that the complex I-integrated carbonic anhydrases form part of an intracellular CO_2-transfer mechanism from the mitochondria to the chloroplasts to provide excess mitochondrial CO_2 for carbon assimilation by the Calvin cycle (Braun and Zabaleta 2007, Zabaleta et al. 2012). Indeed, the slow-growth phenotype of an Arabidopsis mutant deficient in CA2 and additionally either CAL2 or CAL1 could be partially rescued upon cultivation of the mutant in the presence of elevated CO_2 (Soto et al. 2015). In contrast, transformation of the heavily growth-retarded Arabidopsis complex I deficient CA1/CA2 knock out mutant with a gene encoding a truncated version of CA2 revealed a phenotype indistinguishable from wild-type Arabidopsis plants at the conditions tested (Fromm et al. 2016c). In conclusion, the physiological role of the complex I-integrated CA/CAL proteins should be further investigated. Very recently, coupling of redox driven proton pumping and CO_2-bicarbonate conversion has been reported for the photosynthetic complex I of cyanobacteria (Schuller et al. 2020). Furthermore, while this paper was under review, a manuscript reporting a first high-resolution structure of plant complex I (isolated from cabbage) has been made available at bioRxiv (Soufari et al. 2020). Results nicely confirm insights obtained by biochemical investigations but offer a much closer look at this OXPHOS complex.

3.2. The connection of GLDH and plant mitochondrial complex I

L-galactono-1,4-lactone (GL) dehydrogenase (DH) catalyzes the conversion of GL into ascorbate. The reaction takes place in the mitochondrial intermembrane space and involves electron insertion into the ETC via cytochrome *c* (Bartoli et al. 2000). Surprisingly, a minor version of complex I with a slightly reduced molecular mass (850 versus 1000 kDa) was discovered in Arabidopsis, which includes GLDH (Heazlewood et al. 2003a). It was postulated that the GLDH-containing complex I version might regulate ascorbate synthesis by monitoring the rate of NADH-driven electron flow through complex I (Millar et al. 2003). By characterizing an Arabidopsis mutant deficient in GLDH it later became clear that GLDH is required for complex I accumulation and possibly represents an assembly factor necessary for the formation of complex I (Pineau et al. 2008). Further biochemical experiments indeed indicated that GLDH is attached to at least three different complex I assembly intermediates in Arabidopsis (Schertl et al. 2012). The largest intermediate, the 850 kDa version of complex I, includes a complete peripheral arm, but lacks parts of the membrane arm. It later was confirmed that GLDH most likely represents an assembly factor for the membrane arm of complex I in Arabidopsis (Schimmeyer et al., 2016). However, association of GLDH with the fully assembled complex I currently cannot be excluded because it also has been detected in fractions including mature complex I (e.g. Peters et al. 2013). Furthermore, single particle electron microscopy revealed a class of complex I particles in potato with an added mass of 30–60 kDa attached to the membrane arm at its intermembrane space exposed surface, which may represent GLDH (Bultema et al. 2009). Therefore, a functional relationship of GLDH and complex I beyond the role of GLDH for complex I assembly can currently not be excluded and should be addressed by future investigations.

3.3. The assembly of plant complex I

The biosynthesis of all the subunits of complex I is of increased complexity in plants. Like in mammalian and fungal cells, most complex I subunits are encoded by the nuclear genome, synthesized on cytoplasmic ribosomes, and are posttranslationally transported into the mitochondria. Only seven very hydrophobic subunits of the membrane arm are encoded on the mitochondrial genome and synthesized at mitochondrial ribosomes. However, in plants, also two subunits of the peripheral arm, the so-called ND7 and ND9 subunits, are mitochondria encoded. This requires additional coordination between the two genetic compartments. Furthermore, biosynthesis of the mitochondrial encoded

subunits is incredibly complicated in plants due to the necessity of cis and *trans*-splicing events during maturation of the corresponding transcripts as well as extensive transcript editing before translation (reviewed in Braun et al. 2014). Nearly 200 nucleotide sites within the nine mitochondrial complex I transcripts have to be edited, which requires a very large number of additional protein factors, all of which are nuclear encoded. Finally, all complex I subunits have to be correctly assembled. Due to the presence of the carbonic anhydrase domain, the assembly process at least partially follows unique routes in plants (Meyer et al. 2011, Li et al. 2013, Ligas et al. 2019, Meyer et al. 2019) and also involves additional factors, like GLDH.

3.4. Regulation of complex I functions in plants

Plant complex I is essential for respiration, photorespiration and photosynthesis as revealed by numerous genetic and biochemical investigations. Furthermore, besides its function in OXPHOS, complex I of plants includes side activities, which possibly facilitate CO_2 transfer from the mitochondria to the chloroplasts (via its carbonic anhydrases) or the biosynthesis of ascorbate (via GLDH). At the same time, enzymes with overlapping activities are present in the mitochondria of plants, such as the alternative (type II) NADH dehydrogenases. Indeed, due to the extra NADH dehydrogenases, plant life can even take place in the absence of complex I, although mutants completely lacking complex I are drastically disturbed in physiology, development and fertility (Kühn et al. 2015, Fromm et al. 2016b). With regard to this intricate molecular background, how are the multiple functions of complex I regulated in plants? So far, this is only poorly understood. The half-life of complex I subunits is in the range of days (Nelson et al. 2014) and overall, their biosynthesis takes place rather constitutively. However, despite overall constant complex I abundance, complex I activity is certainly regulated at the posttranslational level. Numerous sites for thiol, phosphate and acetate-based posttranslational modifications have been identified (reviewed in Braun et al. 2014). Physiological implications of most of these modifications are awaiting further experimental investigations. Recently, thiol modifications of several defined amino acid positions at the peripheral arm of complex I were demonstrated to be relevant for activation of complex I during very early germination (Nietzel et al. 2020).

4. The succinate dehydrogenase complex (complex II) of plants

The succinate dehydrogenase complex is the only OXPHOS component that is involved in both, the TCA cycle and the mitochondrial ETC (Iverson 2013, Huang and Millar, 2013, Huang et al. 2019). It catalyzes the conversion of succinate to fumarate, a reaction of the TCA cycle. Electrons are taken up by an FAD group and transferred via a short electron transport chain, which consists of three iron-sulfur clusters, onto ubiquinone. Ubiquinol is finally released by complex II into the inner mitochondrial membrane and subsequently can be reoxidized by complex III or by the alternative oxidase. In contrast to complexes I, III and IV, complex II does not translocate protons across the inner mitochondrial membrane. However, it allows insertion of electrons into the ETC, which subsequently may contribute to proton translocation at the complexes III and IV.

The subunit composition of complex II is highly conserved in bacteria and the mitochondria of animals and fungi. It consists of four subunits designated SDH1-SDH4. SDH1 and SDH2 are hydrophilic and constitute the succinate dehydrogenase domain. In contrast, SDH3 and SDH4 are hydrophobic and are inserted into the inner mitochondrial membrane. They constitute the membrane anchor for SDH1 and SDH2. The overall mass of the complex is in the range of 120 kDa.

Characterization of complex II from flowering plants surprisingly revealed some striking peculiarities (Eubel et al. 2003, Millar et al. 2004). In plants, complex II is especially large (about 160 kDa) and comparatively fragile (it easily disintegrates upon detergent treatment).

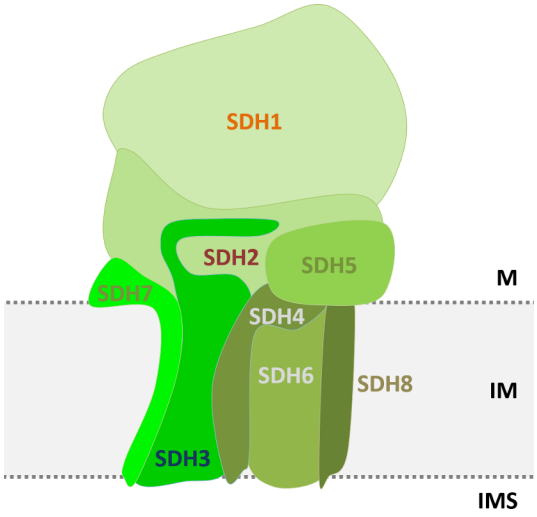

Fig. 2. Subunit arrangement of the Arabidopsis succinate dehydrogenase complex (complex II). SDH1-SDH8: subunits 1 to 8 of the succinate dehydrogenase (SDH) complex. M: matrix, IM: inner mitochondrial membrane, IMS: mitochondrial intermembrane space. Figure taken from Schikowsky et al. 2017, modified.

It consists of eight subunits: the SDH1-SDH4 proteins and four additional proteins termed SDH5-SDH8 (Fig. 2). Some of the subunits are present in isoforms (see Supp. Table 1 for details). Biochemical dissection of complex II of Arabidopsis and analyses of the dissection products revealed that SDH6 and SDH7 form part of the membrane anchor domain and possibly substitute membrane spanning helices, which are absent in SDH3 and SDH4 of plants (Schikowsky et al. 2017). SDH5 is probably located at the interface of the succinate dehydrogenase and the membrane anchor domains and the location of SDH8, which only is 4.9 kDa in mass, is currently not known. The additional subunits might insert an extra but so far unknown activity into plant complex II, like the carbonic anhydrase subunits attached to the mitochondrial complex I in plants. Due to the presence of extra subunits, it can be anticipated that assembly of complex II follows particular routes in plants (Huang et al. 2019).

5. The bifunctional cytochrome *c* reductase/mitochondrial processing peptidase complex (complex III) of plants

The cytochrome *c* reductase complex is the central segment of the mitochondrial respiratory chain. It couples electron transport from ubiquinol to cytochrome *c* with protein translocation across the inner mitochondrial membrane (Brandt and Trumpower 1994). The coupling of the two activities at complex III relies on the 'Q-cycle' and involves oxidation of ubiquinol and re-reduction of ubiquinone on opposite sides of the inner mitochondrial membrane. In animals and fungi, complex III is composed of 10 different subunits of 6 to 50 kDa which can be grouped into three functional categories: (i) three subunits directly participating in electron transport (the Rieske FeS protein and the heme-containing cytochrome c_1 and cytochrome *b* subunits), (ii) two large 'core subunits' on the matrix-exposed side of complex III (which are called core subunits because they were originally thought to be in the very center of complex III) and (iii) five small subunits < 15 kDa (termed the CQR6-QCR10 proteins), which surround the subunits directly involved in electron transfer. In bovine mitochondria, the presequence of the Rieske FeS subunit is retained within complex III upon removal from the precursor protein and considered to be an eleventh subunit (Brandt et al. 1993). In several bacteria, complex III consists only of the three electron-transporting subunits. Structures with atomic resolution have been determined for mitochondrial complex III of animals and fungi (Xia et al. 1997, Hunte et al. 2000). The complex always

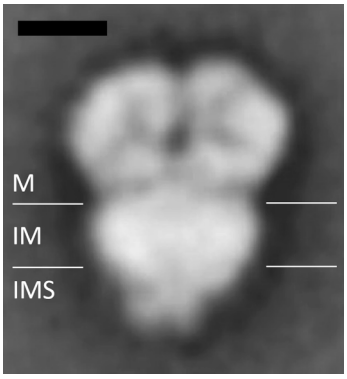

Fig. 3. Structure of dimeric cytochrome *c* reductase (complex III) of *Arabidopsis thaliana* as revealed by single particle electron microscopy (Dudkina et al. 2005a). The complex was purified from isolated mitochondria by sucrose gradient ultracentrifugation. White lines indicate the boundaries of the inner mitochondrial membrane. The scale bar equals to 5 nm. M: matrix, IM: inner mitochondrial membrane, IMS: mitochondrial intermembrane space. Figure taken from Dudkina et al. 2005a, modified.

is a dimer with 2 × 10 subunits and a molecular mass of around 500 kDa.

Complex III from plants initially has been studied in potato (Berry et al 1991, Braun and Schmitz 1992, Jänsch et al. 1995). A low-resolution structure has been obtained for *Arabidopsis thaliana* (Fig. 3; Dudkina et al. 2005a). Plant complex III also includes 2 × 10 subunits and resembles complex III from animals and fungi in several respects (reviewed in Braun and Schmitz 1995a). However, in plants, complex III includes the two subunits of the mitochondrial processing peptidase (MPP) (Braun et al. 1992, Eriksson et al. 1994). It was noted before that the two 'core subunits' of complex III from animals and fungi exhibit some sequence similarity to the two subunits of MPP (α-MPP and β-MPP) (Jensen and Yaffe 1988, Schulte et al. 1989). However, in animal mitochondria, the active site of the protease is not conserved within the 'core subunits'. Instead, two soluble subunits present in the mitochondrial matrix constitute an active MPP. All four proteins, α-MPP, β-MPP and the core 1 and core 2 proteins constitute a small protein family, with the core 2 protein most closely resembling α-MPP and the core 1 protein β-MPP. In *Neurospora crassa* mitochondria, it was found that the core 1 protein of complex III represents an active β-MPP subunit (Schulte et al. 1989). In plants, both core subunits represent the active protease subunits and a matrix-located MPP seems to be absent. Indeed, isolated complex III from plants efficiently removes presequences of nuclear encoded mitochondrial proteins as demonstrated by an *in vitro* protein processing assay (Braun et al. 1992, Eriksson et al. 1994, Braun et al. 1995; Fig. 4). Thus, complex III from plants is a bifunctional enzyme.

From an evolutionary perspective, it has been speculated that the integration of MPP into complex III represents a more original situation (Braun and Schmitz 1995b). MPP-like proteases also are present in alpha-proteobacteria (but are not involved in presequence removal). Such a bacterial protease probably became attached to the bacterial-type complex III in early mitochondrial evolution, perhaps for anchoring the protease at the matrix-exposed surface of the inner mitochondrial membrane, the site where nuclear encoded mitochondrial proteins enter the organelle. At a later evolutionary stage, gene duplications gave rise to the MPP/core protein family. From this perspective, the core subunits are relics of an ancient mitochondrial processing peptidase, which became inactivated during evolution in animals and fungi.

It recently has been discovered that assembly of complex III follows unique routes in plants (Schäfer et al. 2020). Plant mitochondria include a TatB protein which resembles a subunit of a bacterial-type protein translocase and which is not present in the mitochondria of animals and fungi. In the absence of TatB, late state complex III assembly intermediates accumulate because translocation of the Rieske FeS subunit is disturbed.

6. Cytochrome *c* of plants

Cytochrome *c* is a small heme-containing protein located in the mitochondrial intermembrane space. It transfers electrons from complex III onto complex IV. In plants, cytochrome *c* additionally accepts electrons from other metabolic pathways: (i) ascorbate biosynthesis and (ii) mitochondrial lactate-pyruvate conversion (Bartoli et al. 2000, Welchen et al. 2016, Welchen and Gonzalez 2016). Two isoforms of cytochrome *c* are present in Arabidopsis. Plants lacking the two genes encoding the two cytochrome *c* isoforms are not viable. Drastic reduction of cytochrome *c* by genetic manipulation causes a distinct decrease of the cytochrome *c* oxidase complex, without affecting the other complexes of the OXPHOS system in Arabidopsis (Welchen et al. 2012). It is concluded that cytochrome *c*, besides its function in electron transport, additionally has a role in the stabilization or assembly of complex IV in plants.

7. The cytochrome *c* oxidase complex (complex IV) of plants

Complex IV is the terminal enzyme of the ETC. It transfers electrons from cytochrome *c* onto molecular oxygen, which is reduced to water. Electron transfer is linked to proton translocation from the mitochondrial matrix to the intermembrane space (Wikström and Sharma 2018). The catalytic core of the enzyme is formed by the Cox I, Cox II and Cox III proteins. Cox I carries three of the four co-factors necessary for the electron transfer reaction, heme a, heme a_3 and the copper centre Cu_B. Cox II binds the copper centre Cu_A. The bacterial cytochrome *c* oxidase complex only consists of these three core subunits. In the mitochondria of mammals, the core subunits are surrounded by another nine subunits, which all are comparatively small (Kadenbach and Hüttemann 2015). Several of these subunits also are present in yeast mitochondria (Maréchal et al. 2012). The structure of complex IV from mammals has been resolved by x-ray crystallography (Tsukihara et al. 1996).

The subunit composition of plant complex IV has been analyzed by Blue native PAGE in combination with mass spectrometry (Millar et al. 2004, Klodmann et al. 2011, Senkler et al. 2017b). It consists of the three core subunits (Cox I, Cox II and Cox III) and several additional smaller subunits. Some of these small proteins resemble Cox subunits from animals and fungi (the Cox Vb, Cox Vc, Cox VIa, Cox VIb and Cox VIc subunits), while others seem to be specific for plants (termed Cox X1, Cox X2, Cox X3, Cox X4, Cox X5 and Cox X6; for details see Supp. Table 1). However, evidence that all these proteins are stoichiometric complex IV subunits in plants is limited so far (convincing data are available for Cox X1, Cox X2 and Cox X4, Senkler et al. 2017b). The plant specific subunits of complex IV might insert additional functions into this protein complex like reported for the ETC complexes I and III (and possibly also II) of plants.

8. The ATP synthase complex (complex V) of plants

Synthesis of ATP is the prime function of mitochondria. It is driven by the electrochemical proton gradient generated by the ETC and catalyzed by the ATP synthase complex. Considerable attention has been placed on the structure and function of this protein complex. It consists of two parts, the membrane inserted F_O part, and a spherical part, termed F_1, which protrudes into the mitochondrial matrix. F_1 and F_O are connected by a central and a peripheral stalk. A flow of protons through the inner mitochondrial membrane along its concentration gradient causes rotation of a protein ring formed by multiple copies of a small lipophilic protein within F_O (subunit c). The rotation is transmitted onto the central stalk, which thereby induces conformational changes within F_1, catalyzing the phosphorylation of ADP. The non-

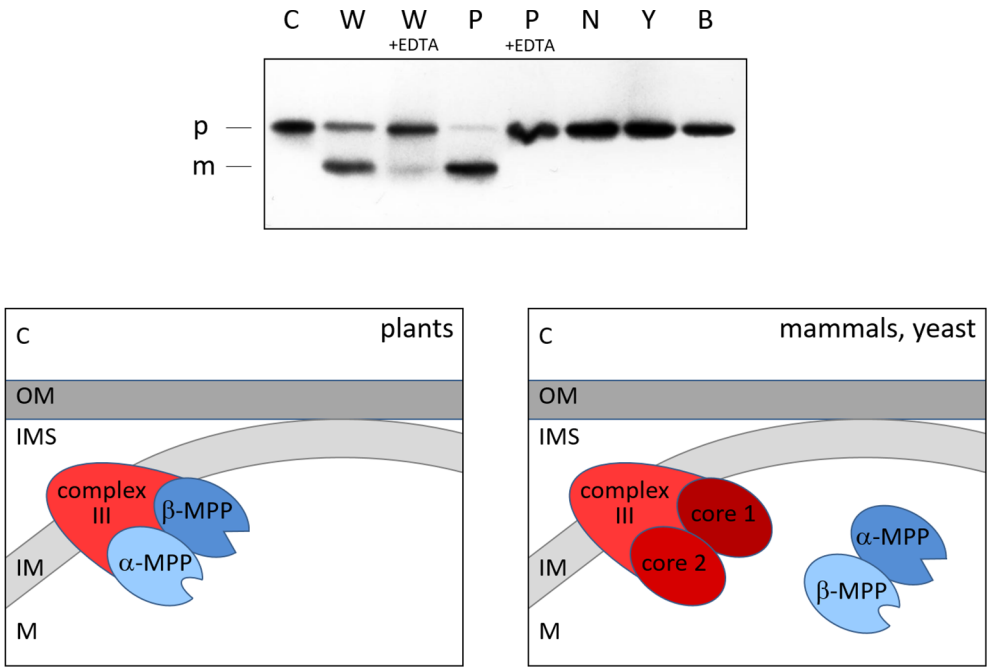

Fig. 4. Proteolytic activity of purified complex III from different organisms. Top: *In vitro* protein processing assay using isolated complex III. The precursor of the β subunit of the mitochondrial ATP synthase complex (synthesized *in vitro* in the presence of radiolabeled methionine) was incubated with purified complex III from wheat (W), potato (P), *Neurospora crassa* (N), yeast (Y) and bovine (B) mitochondria. SDS PAGE and autoradiography were employed to evaluate the result of the assay. Only complex III from wheat and potato can process the precursor (p) to its mature form (m). The processing activity is inhibited by addition of EDTA. C, control. Figure from Braun et al. 1995, modified. Bottom: Summary of the relationship between complex III and the subunits of the mitochondrial processing peptidase (MPP) in plants, mammals and yeast. M: matrix, IM: inner mitochondrial membrane, IMS: mitochondrial intermembrane space, OM: outer mitochondrial membrane, C: cytosol. Figure taken from Braun and Schmitz 1995b, modified.

rotating subunits of F_1 and F_O are connected and held in place by the peripheral stalk. Detailed structures of the mitochondrial ATP synthase complex have been presented (reviewed in Kühlbrandt 2019).

The F_1 part of mitochondrial ATP synthase (together with the central stalk) is composed of five types of subunits termed α, β, γ, δ and ε. The subunit composition of the F_O part (together with the peripheral stalk) slightly varies in different groups of organisms (reviewed in Artika 2019). It includes 13 and 14 types of subunits in bovine and yeast mitochondria.

A low-resolution structure of the mitochondrial ATP synthase from potato has been achieved by single particle electron microscopy (Bultema et al. 2009). It resembles the structures of mitochondrial ATP synthase from animals and fungi. The subunit composition of ATP synthase from plants has been systematically investigated by Blue native PAGE in combination with mass spectrometry (Heazlewood et al. 2003b, Meyer et al. 2008, Klodmann et al. 2011, reviewed in Zancani et al., 2020). All five subunits of the F_1 part have been described and additionally ten different subunits of the F_O part (termed a, b, c, d, g, FAD, OSCP, subunit 8, ATP17 and 6 kDa subunit in Arabidopsis, Supp. Table 1). Presence of additional F_O subunits in plants currently cannot be excluded. Several candidates have been identified by complexome profiling (Senkler et al. 2017b). In most plants, the α, a, b and c subunits as well as subunit 8 are mitochondria encoded (Unseld et al. 1997, Heazlewood et al. 2003b).

9. Alternative oxidoreductases of plants

Alternative oxidoreductases are a characteristic feature of the ETC in plants (and also several other groups of organism). Since they do not contribute to proton translocation, they are not directly involved in OXPHOS. However, alternative NAD(P)H dehydrogenases (altNDs) may insert electrons into the ETC, which contribute to proton translocation at complexes III and IV. Likewise, the alternative oxidoreductase (AOX) may transfer electrons originating from complex I onto molecular oxygen. Only if electrons inserted by the alternative NAD(P)H dehydrogenases are transferred by AOX onto molecular oxygen, translocation of protons is completely omitted. Indeed, the physiological roles of the alternative oxidoreductases are rather relevant in the context of the plant stress response than in the context of 'classical' OXPHOS. Numerous reviews have been published summarizing insights into the physiological roles of the alternative oxidoreductases in plants (Saha et al., 2016; Vanlerberghe et al., 2016; Selinski et al. 2018; Del-Saz et al. 2018; Møller et al., 2020; Vanlerberghe et al., 2020; Rasmusson et al., 2020).

In *Arabidopsis thaliana* and other flowering plants, small gene families encode altNDs and AOX. The designations of the proteins reflect similarities in amino acid sequence and functional properties (AOX1A, AOX1B, AOX1C, AOX1D, AOX2 and NDA1, NDA2, NDB1, NDB2, NDB3, NDB4 and NDC1 in Arabidopsis). AOX has a molecular mass of about 30 kDa and can form dimers of 60 kDa. A disulfide bond links the two subunits within the dimer. Under reducing conditions, the disulfide bond is cleaved. The non-covalently linked dimer is the active/activatable form of AOX. It can be fully activated in the presence of TCA-cycle intermediates, e.g. pyruvate. However, in Blue native PAGE and complexome profiling, AOX has an apparent molecular mass of about 140–150 kDa (Senkler et al. 2017b). This indicates that AOX dimers interact with other proteins at *in vivo* conditions. Interestingly, also the altNDs, which have molecular masses of about 50–60 kDa, are found in the 150 kDa range on native gels (Rasmusson and Agiusm, 2001, Klodmann et al. 2011, Senkler et al. 2017b). It has been suggested, but so far not experimentally proven, that AOX dimers and altNDs associate and form protein complexes. Some altNDs are part of structures in the 600–700 kDa range (Rasmusson and Agiusm, 2001, Senkler et al. 2017b). However, there are no indications that altNDs or AOX associate with the classical complexes of the ETC in plants.

10. Other enzymes contributing to OXPHOS in plants

The ETC is branched in plants due to the presence of numerous alternative oxidoreductases, but even further oxidoreductases contribute electrons to the ETC at other sites (reviewed in Rasmusson et al. 2008, Schertl and Braun 2014). It already has been mentioned that electrons from ascorbate biosynthesis and mitochondrial lactate-pyruvate conversion are inserted into the ETC via cytochrome *c* (Bartoli et al. 2000, Welchen et al. 2016). Furthermore, amino acid catabolism taking place in the mitochondrial matrix is linked to electron insertion into the ETC. Electrons from branched chain amino acid degradation are partially transferred via the electron-transfer-flavoprotein (ETF) / electron-transfer-flavoprotein:ubiquinone oxidoreductase (ETFQO) system into the ETC (Ishizaki et al. 2005, 2006) and electrons from

proline oxidation by proline dehydrogenase (Cabassa-Hourton et al., 2016). OXPHOS driven by amino acid catabolism is highly relevant for plants at defined stress conditions, e.g. severe light limitation or water shortage (Ishizaki et al. 2005, 2006, Hildebrandt et al. 2015, Pires et al. 2016). Other enzymes contribute electrons to the inner mitochondrial membrane on its intermembrane-space-exposed side, like glyceraldehyde 3-phosphate dehydrogenase and dihydroorotate dehydrogenase (reviewed in Rasmusson et al. 2008, Schertl and Braun 2014).

11. The supramolecular structure of the OXPHOS system of plants

The protein complexes of the mitochondrial OXPHOS system can associate in defined ways. This was first discovered for mammals and fungi by analyses based on Blue native PAGE (Arnold et al. 1998, Schägger and Pfeiffer 2000). The presence of respiratory supercomplexes meanwhile has been demonstrated for several groups of organism including plants. Recently, single particle cryo electron microscopy has allowed to elucidate the structures of some of these supercomplexes with atomic resolution (Gu et al. 2016, Letts et al. 2016, Sousa et al., 2016, Guo et al. 2017, reviewed in Wu et al. 2020). All respiratory supercomplexes include dimeric complex III. It is bound either laterally to the membrane arm of complex I, or to one or two copies of monomeric complex IV. Additionally, both types of interactions can take place simultaneously. Supercomplexes including the complexes I, III_2 and IV also are referred to as “respirasomes”, because they autonomously can catalyze respiratory electron transfer from NADH onto molecular oxygen (given that cytochrome *c* and ubiquinone are present). For mammals, two types of respirasomes have been described, which are of $I+III_2+IV_{(1-2)}$ or $I_2+III_2+IV_2$ composition. The physiological roles of the respiratory supercomplexes and respirasomes are still under debate (Acin-Perez and Enriquez, 2014, Milenkovic et al. 2017, Hirst 2018, Wu et al. 2020, Stuchebrukhov et al. 2020). Respirasomes are suggested to associate to even larger structures called respiratory megacomplexes, which, besides other functions, should be relevant for shaping the structure of the cristae membrane. Most notably, it has been demonstrated that dimerization of ATP synthase monomers causes bending of the inner mitochondrial membrane, which is of great significance for cristae formation (Paumard et al. 2002).

Respiratory supercomplexes of plants were first described by Blue native PAGE (Eubel et al., 2003, Eubel et al., 2004b, Krause et al., 2004, reviewed in Dudkina et al., 2006). The most stable interaction takes place between the complexes I and III_2 (Fig. 5). The Arabidopsis $I+III_2$ supercomplex was the very first respiratory supercomplex of any group of organisms, which has been structurally investigated (Dudkina et al. 2005a). Seen from the mitochondrial matrix, the membrane arm of complex I is bend. Dimeric complex III is attached to the concave side of the membrane arm of complex I. Associations of complex III_2 and IV are comparatively weak in plants. However, supercomplexes of $III_2+IV_{(1-2)}$ and $I_1+III_2+IV_{(1-4)}$ composition have been described by Blue native PAGE for potato and spinach (Eubel et al., 2004a; Krause et al., 2004b; Fig. 5) and meanwhile for several other plants. ATP synthase dimers are relatively fragile in flowering plants but have been reported for Arabidopsis and potato (Eubel et al., 2003a). In potato, dimerization of ATP synthase monomers takes place in a way that bends the inner mitochondrial membrane (Bultema et al. 2009). Extremely stable ATP synthase dimers were discovered in the green algae Polytomella sp. and used for first structural analyses (Dudkina et al. 2005b). It is anticipated that monomeric ETC complexes and supramolecular assemblies co-exist in the inner mitochondrial membrane at *in vivo* conditions (Fig. 5). Complete assembly of monomeric complexes into respiratory supercomplexes would require defined ratios of the involved protein complexes. These ratios are not observed (e.g. Fuchs et al. 2020).

In contrast to the situation found in most flowering plants, the association of complex III and IV is very stable in European mistletoe (*Viscum album*). *V. album* is an obligate hemiparasitic flowering plant that grows on branches of various trees. It has been proven to lack mitochondrial complex I (Maclean et al. 2018, Senkler et al. 2018, Petersen et al. 2020). The strong interaction of complexes III_2 and IV in *V. album* could be a consequence of absence of complex I. However, Arabidopsis mutants, which artificially lack complex I, do not exhibit increased interactions of complexes III_2 and IV. It therefore can be concluded that the intensity of the III_2-IV interaction varies in different plants. Likewise, stability of the $I+III_2$ supercomplex varies between different plants. Remarkably high stability of the $I+III_2$ supercomplex was described for *Arum maculatum* (Sunderhaus et al. 2010) and for the halophile plant *Cakile maritima* (Farhat et al., 2019).

An especially large respiratory supercomplex was described for several plants, which originally was suggested to be composed of two copies of monomeric complex I and two copies of dimeric complex III (I_2+III_4 supercomplex; Eubel et al. 2003). However, analyses of this

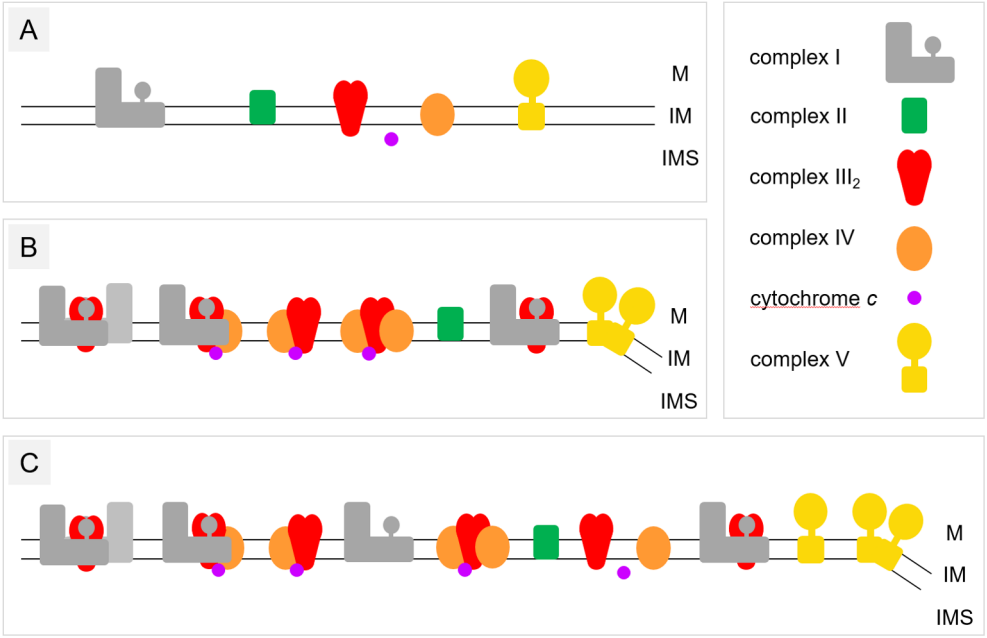

Fig. 5. Composition of the OXPHOS system in plants. Shapes and colors of the five OXPHOS complexes and of cytochrome *c* are given in the legend to the top right (ubiquinone/ubiquinol and alternative oxidoreductases omitted). A, monomeric OXPHOS components (except for complex III, which always occurs as a dimer). B, respiratory supercomplexes described for mitochondria of plants. C, co-existence of monomeric OXPHOS complexes and supercomplexes within the inner mitochondrial membrane, the supposed *in vivo* situation. M: matrix, IM: inner mitochondrial membrane, IMS: mitochondrial intermembrane space.

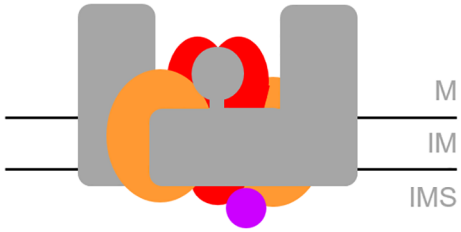

Fig. 6. Suggested arrangement of the plant $I_2+III_2+IV_2$ supercomplex (Bultema et al. 2009). Gray, complex I; orange, complex IV; red, complex III_2; purple, cytochrome *c*; M, matrix; IM, inner mitochondrial membrane; IMS, intermembrane space. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

supercomplex from potato by single particle electron microscopy (Bultema et al. 2009) revealed that it includes only one copy of dimeric complex III, which binds to two copies of monomeric complex I (this I_2+III_2 supercomplex has been erroneously mislabeled as I_2+III_4 supercomplex in several of our publications, which I regret). The I_2+III_2 supercomplex resembles the large-form respirasome of mammalian mitochondria ($I_2+III_2+IV_2$), except that it lacks the two complex IV monomers. However, since the association of complexes III_2 and IV is rather fragile in most flowering plants, the $I_2+III_2+IV_2$ respirasome has been suggested to be the physiologically most relevant assembly unit of the OXPHOS system in plants under *in vivo* conditions (Bultema et al. 2009; Fig. 6).

The alternative oxidoreductases characteristic for the OXPHOS system of plants also assemble into smaller and larger protein complexes (see above) of so far unknown composition. However, there are no hints that any of the alternative oxidoreductases associate with the respiratory supercomplexes formed by the classical ETC complexes. It has been suggested that alternative electron transport proteins might form 'alternative respirasomes' which exist separately from the classical electron transport complexes (Senkler et al. 2017b). Direct interactions of alternative NDs and AOX would allow efficient re-oxidation of mitochondrial reducing equivalents without contributing to the electrochemical proton gradient at the inner mitochondrial membrane.

The function of the OXPHOS supercomplexes, besides shaping the cristae membrane, is not precisely known in plants. It has been reported that changes in composition of plant mitochondrial supercomplexes are relevant for the plant response with respect to oxygen availability (Ramírez-Aguilar et al. 2011).

12. Outlook

Since the OXPHOS system is of central importance for ATP formation in most eukaryotic cells, it has been extensively investigated. However, many questions still have not been resolved and should be addressed by future studies. From the perspective of plant biology, the following directions of research are especially relevant: (i) The OXPHOS complexes of plants should be structurally investigated, e.g. by single particle cryo electron microscopy, which recently became the prime method for the characterization of large protein complexes. These analyses will give more insights into all the extra activities inserted into the ETC complexes in plants, e.g. the mitochondrial processing peptidase in complex III and the carbonic anhydrase subunits in the membrane arm of complex I. (ii) The supramolecular structure of the OXPHOS system in plants should be further investigated, especially with respect to its interplay with the alternative oxidoreductases characteristic for the mitochondria of plants. (iii) OXPHOS in plants takes place in the context of photosynthesis and therefore has to be regulated in response to light. The molecular basis for this regulation is not quite understood but might well occur on the level of posttranslational modifications, as recently demonstrated for the activation of mitochondria during very early germination in Arabidopsis (Nietzel et al. 2020). Additionally, various abiotic stress situations require special levels of OXPHOS regulation in plants. (iv) Plant life takes place in considerably differing habitats. Until now, mainly model plants have been investigating with respect to OXPHOS. The very unusual OXPHOS system discovered in European mistletoe might only be a first example of varying OXPHOS modes present in the kingdom of plants, which should be further explored (Petersen et al. 2020).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mito.2020.04.007.

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