Abstract. The mammalian mitochondrial electron transport chain (ETC) includes complexes I-IV, as well as the electron transporters ubiquinone and cytochrome c. There are two electron transport pathways in the ETC: Complex I/III/IV, with NADH as the substrate and complex II/III/IV, with succinic acid as the substrate. The electron flow is coupled with the generation of a proton gradient across the inner membrane and the energy accumulated in the proton gradient is used by complex V (ATP synthase) to produce ATP. The first part of this review briefly introduces the structure and function of complexes I-IV and ATP synthase, including the specific electron transfer process in each complex. Some electrons are directly transferred to O₂ to generate reactive oxygen species (ROS) in the ETC. The second part of this review discusses the sites of ROS generation in each ETC complex, including sites IF and IQ in complex I, site I(II) in complex II and site IIIQ₀ in complex III, and the physiological and pathological regulation of ROS. As signaling molecules, ROS play an important role in cell proliferation, hypoxia adaptation and cell fate determination, but excessive ROS can cause irreversible cell damage and even cell death. The occurrence and development of a number of diseases are closely related to ROS overproduction. Finally, proton leak and uncoupling proteins (UCPs) are discussed. Proton leak consists of basal proton leak and induced proton leak. Induced proton leak is precisely regulated and induced by UCPs. A total of five UCPs (UCP1-5) have been identified in mammalian cells. UCP1 mainly plays a role in the maintenance of body temperature in a cold environment through non-shivering thermogenesis. The core role of UCP2-5 is to reduce oxidative stress under certain conditions, therefore exerting cytoprotective effects. All diseases involving oxidative stress are associated with UCPs.

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1. Introduction

The chemiosmotic theory proposed by Peter Mitchell (1) in 1961 states that the transfer of electrons derived from substrate oxidation and ATP synthesis are coupled in the mitochondrial ETC, but that does not mean that the transfer of electrons is 100% efficient. Due to the existence of electron leak and proton leak, not all electrons in the ETC can be transferred to the final electron acceptor O₂ and the energy released by the transferred electrons cannot be completely coupled with ATP generation. However, both the ROS generated by electron leak and the UCPs implicated in proton leak play an important role in the physiology and pathology of cells. Therefore, it is extremely important to understand the process of electron transfer in the ETC and the mechanism of electron leak and proton leak.

In this review, the basic components of the ETC are discussed and the process of electron transfer in each complex, including the structure, composition and function of each complex is reviewed. In addition, the ROS generation sites in the ETC are summarized and the ROS regulation is mentioned. Moreover, proton leak is emphatically introduced, including the structure, tissue distribution, functions and regulatory factors of UCPs. The diseases implicated in ROS or UCPs are simply summarized.

2. Mitochondrial ETC and ATP synthase

The ETC, which is composed of transmembrane protein complexes (I-IV) and the freely mobile electron transfer carriers ubiquinone and cytochrome c, exists in the folded inner membranes called cristae (Fig. 1). The complexes must
be assembled into a specifically configured supercomplex to function properly (2,3). These assembled components together with F,F₂ATP synthase (namely, complex V) become the basis of ATP production during oxidative phosphorylation (OXPHOS). To better understand the whole process of how electron transportation produces ATP via the ETC, it is necessary to know the ultrastructure and function of the individual complexes.

**Complex I (CI).** CI, also called NADH-ubiquinone oxidoreductase, is the largest multisubunit enzyme complex in the ETC. The key role of CI is to transfer electrons from matrix NADH to ubiquinone, as the name implies. A number of studies have reported the structure of the bacterial mitochondrial CI using X-ray crystallography at a nearly atomic resolution (4,5). Mitochondria from the *Bos taurus* heart have been regarded as the best model for human CI (6-9). These studies demonstrate that the L-shaped eukaryotic CI contains two domains: The membrane arm embedded in the inner membranes and the matrix arm protruding into the matrix. The two domains are mainly composed of 14 core subunits that are conserved from bacterial CI and are the core of the enzymatic reaction. There are 45 clearly identified proteins that participate in the formation of the core subunits. The matrix arm contains seven core subunits (NDUFS1, NDUFS2, NDUFS3, NDUFS7, NDUFS8, NDUVF1 and NDUVF 2) that contain the following cofactors: A flavin mononucleotide (FMN) molecule; 7-9 FeS accessory subunits are arranged around the core subunits. The form FMNH₂ by accepting a pair of electrons derived from NADH to coQ in cI from the matrix into the intermembrane space (14-17). Several probably (not definitively) induce the pumping of four protons a hypothesis that two protons are indirectly pumped out in a membrane arm protruding into the matrix. The two domains are directly pumped out by the induction of ubiquinone redox.

**Complex II (CII).** CII, namely, succinate dehydrogenase, is a component of the Krebs cycle as well as the ETC, serving as a link between metabolism and OXPHOS (19,20). As a part of the Krebs cycle, CII catalyzes the oxidation of succinate to fumarate. CII is another entry point for electrons and donates them from succinate to CoQ via FeS clusters, similar to CI. CII consists of four subunits (20). A total of two of the subunits, the membrane-anchor proteins CybL and CybS, are hydrophobic, anchor the complex to the inner membrane, and contain the CoQ binding site. The other two subunits are located on the matrix side of the inner membrane and contain the binding site of the substrate succinate, three FeS clusters [(2Fe-2S), (4Fe-4S) and (3Fe-4S)], and a flavoprotein covalently bound to a FAD cofactor. The assembly steps of the four subunits are detailed elsewhere (21). FAD is reduced to FADH₂ after receiving electrons from succinate and then transfers the electrons to FeS clusters. Then, CoQ is reduced to QH₂ after obtaining the electrons from the FeS cluster (3Fe-4S) (22). Electron transport in CII is not accompanied by the translocation of protons.

**Complex III (CIII).** CIII is commonly referred to as a cytochrome bc₁ complex, or CoQ-cytochrome c reductase and transfers the electrons carried by QH₂ to cytochrome c. CIII is a symmetrical dimer with 11 subunits per monomer (23). The catalytically active subunits are cytochrome b (b₆ and b₇), cytochrome c₁ and a high-potential (2Fe-2S) cluster wrapped by an iron-sulphur protein (24). There are two CoQ binding sites on both ends of cytochrome b encoded in the inner membrane of the mitochondria, one of which is the Q₂ oxidation site (Q₆) located at the cytoplasmic side, which is related to the low potential cytochrome b₇. The other is the Q₆ reduction site (Q₇) on the side of the matrix, which is related to the high potential cytochrome b₆(25). The electron transfer process of CIII is accomplished by the Q₆-cycle (24-27). Q₆ is oxidized to ubisemiquinone (QH) after transferring an electron to the (2Fe-2S) cluster and two protons are concurrently released into the mitochondrial intermembrane space (IMS) from the matrix (28). The (2Fe-2S) cluster transfers this electron to cytochrome c₁, from which it is transferred to cytochrome c, a mobile electron carrier. Then, the highly reductive QH⁺ formed at the Q₆ site rapidly transfers the second electron to cytochrome b₆, which in turn transfers it to cytochrome b₆ at the Q₆ site. Reduced cytochrome b₆ transfers this electron to the CoQ of the Q₆ site, forming a QH. To complete the Q₆-cycle, the second QH₂ molecule is oxidized at the Q₆ site while displacing the other two protons. Similarly, one electron is transferred to the (2Fe-2S) cluster and the other electron to cytochrome b₆ and finally to QH of the Qi site to produce QH₂.

**Complex IV (CIV).** CIV, also known as cytochrome c oxidase, transfers electrons from cytochrome c to the terminal electron acceptor O₂ to generate H₂O. Mammalian CIV consists of 13
different subunits containing four redox-active metal centers, namely, Cuα, heme a (Feα) and a binuclear center composed of heme a3 (Fea3) and Cuβ (29,30). Subunits I, II, III are encoded by mitochondrial DNA and are the core subunits, while the 10 nuclear-coded subunits are the accessory subunits (31,32). Subunit I contains three of the four cofactors, heme a to O2 (29). Subunits II and III are located on both sides of subunit I and there are two Cuα cofactors on the side of the intermembrane space of subunit II. Subunit III stabilizes the other two core proteins and is mainly involved in proton pumping (33,34). The nuclear-coded subunits participate in the modulation of physiological activity via the allosteric ATP-mediated inhibition of CIV, which depends on the ATP/ADP-ratio (35-39).

Cytochrome c, similar to CoQ, is a mobile electron carrier that is loosely connected to the outer surface of the inner mitochondrial membrane by electrostatic interactions, allowing it to interact with the cytochrome c1 of CIII and to accept electrons (39). The reduced cytochrome c moves along the surface of the membrane and interacts with subunit II of CIV by electrostatic interactions, simultaneously transmitting electrons to the Cuβ site of subunit II, and then the electrons are passed from heme a to the binuclear center of subunit I (29,39), where the O2 is reduced to H2O. A total of four electrons at a time from cytochrome c are almost simultaneously transferred to bind dioxygen; eight protons in total are removed from the matrix, of which half are used to form the two water molecules and the other four are pumped across the membrane into the IMS (40).

Complex V (CV). CV is normally called F1F0 ATP synthase and consists of two functional domains: F0 and F1. The F0 domain, located in the inner mitochondrial membrane, contains a subunit c-ring, including one of each of the subunits α, β, δ, ε, F6 and oligomycin sensitivity-conferring protein (OSCP) as well as the accessory subunits e, f, g and A6L (41,42). The subunits b, d, F6 and OSCP form the peripheral stalk, which is located on one side of the complex. A number of additional subunits (e, f, g and A6L), which all span the membrane, are associated with the c-ring subunit. The F1 domain, situated in the mitochondrial matrix, consists of soluble subunits: Three α subunits, three β subunits and one of each of the γ, δ and ε subunits (42,43). The three α and three β subunits make up the catalytic head of F1, and the γ, δ and ε subunits constitute the central stalk that connects the F1 head and F0 subunit c-ring (41,43,44). The ETC transfers two electrons at a time to monooxygen to generate one H2O molecule, which is accompanied by the pumping of four, four and two protons from the matrix to the IMS through CI, CIII, and CIV, respectively (or zero, four and two protons through the CI, CIII, and CIV, respectively). Then, the protons pass from the IMS to the matrix through F0, which transfers the stored energy created by the proton electrochemical gradient to F1, causing a conformational change in F1F0 ATP synthase so that ADP can be phosphorylated to form ATP (41).

In conclusion, the entire composition of each individual complex has been well described over the past century and it is now widely accepted that these complexes must establish interactions and form supercomplexes to perform their function. Due to the application of cryo-electron microscopy, a greater understanding of the high-resolution structure of these complexes has been gained (45-47).

3. ROS generation in the ETC

The sites of ROS production in the ETC. Mitochondria are a main source of cellular ROS. Under physiological conditions, 0.2-2% of the electrons in the ETC do not follow the normal transfer order but instead directly leak out of the ETC and interact with oxygen to produce superoxide or hydrogen peroxide (48,49). A total of 11 sites that produce superoxide (O2) and/or hydrogen peroxide (H2O2) that are associated with substrate oxidation and the ETC have currently been identified in mammalian mitochondria (50). Sites O6, P7, B8 and A7 are in the 2-oxoacid dehydrogenase complexes, sites I3 and I0 are in CI, site III0 is in CIII, and sites II2, G2, E2 and D2 are linked to the Q-dependent dehydrogenases in the QH2/Q pool (50). The occurrence of numerous diseases and hypoxia are closely related to the increase of ROS production. CI and
CIII, especially CI, are considered to be the main sites of ROS production in mitochondria (51,52).

ROS can be generated in the matrix at both site Iₚ (FMN site) and site Iₒ (CoQ binding site) during the transfer of electrons from NADH to CoQ in CI (Fig. 1). Rotenone and piericidin are site Iₒ inhibitors that interrupt the electron transfer to CoQ and increase ROS production at site Iₚ. Hernansanz-Agustin et al (53) found that acute hypoxia produces a superoxide burst during the first few minutes in arterial endothelial cells and CI mainly participated in this process.

CII produces ROS at site Iᵢ (Fig. 1), which is associated with succinate dehydrogenase. The level of ROS produced by site Iᵢ under normal conditions is negligible, but the increases in ROS observed in CIII mutation-related diseases are mainly derived from site Iᵢ (54,55). The study of isolated mitochondria from rat skeletal muscle also indicated that the maximum capacity for ROS production of site Iᵢ is very high, exceeded only by site IIIQₒ, and perhaps site Iₒ (50,56). The capacity of site Iᵢ to produce ROS is closely related to the quantity of reduced flavoprotein, whose FAD is a potent site of electron leakage to generate ROS. ROS are exclusively produced in the matrix, because the flavoprotein is located on the matrix side of the inner mitochondrial membrane (56). In addition, any contribution by site Iᵢ can be dampened by the occupation of the CIII flavoprotein site by dicarboxylic acids, particularly oxaloacetate, malate and succinate, which blocks the access of oxygen to site Iᵢ, where it would form ROS (21,57).

CII produces small amounts of ROS, which could be overlooked compared to the ROS production of CI (52). CIII transfers electrons through the Q-cycle. In this process, ubisemiquinone (QH⁻) of the Qₒ site carrying a single electron can move freely in CIII, directly leaking the single electron to coQ and increase ROS production at site Iₚ.

ROS as signaling molecules in physiological or pathological conditions. In the past, it was believed that ROS were exclusively harmful to cells. However, recent studies have demonstrated that ROS appear to be very important second messengers that mediate different intracellular pathways (50,61,68). ROS act through the oxidative modification of numerous types of proteins, particularly receptors, kinases, phosphatases, caspases, ion channels and transcription factors (68). The ROS produced from CIII are necessary for HIF-1α stabilization and consequently, for the proliferation of cells, including vascular smooth muscle cells, endothelial cells and erythroid progenitors (69). There is ample evidence that ROS are also involved in different protein kinase signaling cascades, such as the protein kinase B (Akt), AMP-activated protein kinase (AMPK) and mitogen-activated protein kinase kinase kinase/mitogen-activated protein kinase 8 pathways, changing the fate of cells between autophagy and apoptosis ([Table I and (70)]. Under hypoxic conditions, ROS activate AMPK, which can upregulate cytoprotective autophagy by inhibiting downstream mammalian target of rapamycin activity (71). ROS have also been demonstrated to regulate synaptic plasticity-related signalling molecules, receptors and channels, including N-methyl-D-aspartate receptor (72), Ca²⁺ channel (73,74), Ca²⁺/calmodulin kinase II (CaMKII) (75), extracellular signal-regulated kinase (76) and cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) (77,78). ROS are also necessary for long-term potentiation, a phenomenon of synaptic plasticity widely regarded as one of the main molecular mechanisms that form the basis of learning and memory (77,78). Physiological levels of ROS can promote the establishment of neuronal polarity and regulate neuronal cytoskeletal organization and dynamics by regulating intracellular Ca²⁺ release (79-81).

The amount of ROS generated as a result of a stimulus determines whether ROS play beneficial or harmful roles, which means different physiological or pathological pathways are activated. A large amount of ROS cause lipid peroxidation, DNA damage, protein oxidation, irreversible impairment of mitochondria, insufficient ATP generation and, eventually, cell death (82). The ROS-mediated activation of NHE-1 is implicated in cardiac hypertrophy (83). In addition, the activation of CaMKII by ROS contributes to an increase in cardiomyocyte death and the development of heart failure (84). ROS are involved in a number of chronic inflammatory diseases, particularly atherogenesis, through activating the NF-κB pathway (85). In addition, it is widely known that the ROS burst during reperfusion plays a critical role in ischemia-reperfusion
4. Mitochondrial proton leak

The overview of proton leak. OXPHOS is not completely coupled. Under routine circumstances, a small number of protons do not pass through ATP synthase and instead flow directly into the mitochondrial matrix across the inner mitochondrial membrane, without the generation of ATP, in a process known as proton leak. In the concept of ‘respiratory state’ proposed by Chance and Williams (16), mitochondrial respiration persists in the absence of ADP (state 4) and reflects the oxygen consumption of proton leak. The existence of proton leak can also be proven by the collapse of the proton gradient (Δp) in the presence of the ATP synthase inhibitor oligomycin in isolated mitochondria (137).

It was found that the proton leak of the inner mitochondrial membrane demonstrated nonohmic conductivity (137). According to Ohm’s Law (R=U/I), the resistance of a conductor is fixed and the electric current increases linearly with increasing voltage. However, the rate of proton leak increases exponentially with increasing ΔΨ. That is, the proton conductivity increases when ΔΨ is high. The existence of nonohmic conductivity indicates that there is a bidirectional self-regulatory mechanism between electron transport and proton re-entry: Protons are pumped out of the matrix into the IMS driven by the electron transport in CI, CII, CIV, and ΔΨ is gradually elevated. On one hand, the elevated ΔΨ inhibits the transfer of electrons to further elevate ΔΨ, through which the inner membrane is protected from electric shock and maintains suitable ΔΨ. On the other hand, the exorbitant ΔΨ can cause the increase in proton leak to decrease.
Proton leak consists of two parts: Basal proton leak and inducible proton leak. Basal proton leakage is not regulated and is related to the lipid bilayer of the inner mitochondrial membrane and the adenine nucleotide translocase (ANT). Induced proton leak is precisely regulated and can be catalyzed or suppressed by uncoupling proteins (UCPs) and ANT.

Basal proton leak has an important relationship with the basal metabolic rate (BMR) in mammals at rest. The lower the BMR of a species, the weaker the basal proton conductance. Studies have demonstrated that the extent of basal proton leak among species has a phylogenetic relationship (138,139). Although the lipid bilayer can significantly increase proton conductivity, only ~5% of basal proton leak is mediated by lipid bilayers (140) and most of the basic proton leak is correlated with ANT (141). UCP1, which is abundant in brown adipose tissue (BAT), may also be involved in basal proton leak (142), although there remains controversy (143). In particular, proton leak through ANT or UCP1 is independent of protein activity, as proton leak still occurs in the presence of the ANT inhibitor carboxyatractylate and the UCP1 inhibitor GDP (141,144).

The majority of the induced proton leak is catalyzed by UCPs. UCPs belong to the family of mitochondrial anion carrier proteins, through which the protons can reflux into the matrix. To date, five UCPs have been identified in mammals, UCP1, UCP2, UCP3, UCP4 and UCP5, and all are present in the form of dimers in the inner mitochondrial membrane (145). These UCPs have a purine nucleotide binding site located on a projection in the IMS (146). The purine nucleotides (ATP, ADP, GTP and GDP) are inhibitors of UCP-mediated proton flux, whereas ROS and fatty acids are activators (147,148). In addition to the role of uncoupling, UCPs may also participate in other processes, such as the regulation of calcium homeostasis, ion transport or synaptic plasticity (149,150).

**UCP1-5.** UCP1 is mainly expressed in BAT, which converts stored energy in ATP into heat for thermogenesis (151). UCP1 can also be detected in the beige adipocytes of white adipose tissue (WAT) during thermal acclimation under specific conditions (152). The genetic deletion of UCP1 severely inhibits cold adaptive thermogenesis and diet-induced adrenergic thermogenesis, and UCP1-null mice develop fatal hypothermia upon cold exposure (153,154). Interestingly, WAT can exert nonsnghering thermogenesis with a UCP1-independent pathway (155,156). UCP1 has also been found in thymocytes and demonstrated to be involved in the maturation and fate determination of developing T-cells (157-159). Sale et al (160) found that UCP1 is expressed in islets and associates with the acute insulin response to glucose.

UCP1-catalyzed proton leak could be activated by long chain free fatty acids and inhibited by purine nucleotides (161). Acute cold or overfeeding stimuli induce the release of norepinephrine by sympathetic nerves and then induce cAMP-responsive pathways through β3-adrenergic receptors on brown adipocytes, which could further promote the transduction of UCP1 and lipolysis for more free fatty acids (162). There are currently three models for the regulated mechanism of UCP1-implicated proton leak (162-169).

UCP2 and UCP3, paralogues of UCP1, exhibit ~60% sequence identity with UCP1 and ~70% identity with each other (170,171). UCP2 is rather ubiquitous, expressed in WAT, BAT, macrophages, erythroid cells, thymocytes and pancreatic β-cells as well as heart, brain, lung, kidney and lymphocytes (172-176). The UCP3 gene is mainly expressed in skeletal muscle, BAT and heart (177,178) and has also been detected in the thymus, spleen (179) and skin cells (180). Studies with UCP2/3-ablated mice have demonstrated that UCP2 and UCP3 are not implicated in adaptive thermogenesis or the regulation of body weight (170,181). However, the role of UCP2 and UCP3 in inhibiting the production of ROS in mitochondria by reducing ΔΨ is widely accepted (182). A strong correlation between ROS production and mitochondrial membrane potential (ΔΨ) has already been confirmed (183). Experiments have demonstrated that ROS production is increased in UCP2/3-ablated mice (184-186). ROS-induced lipid hydroperoxides such as hydroxyxynonenal can activate UCP2/3-mediated proton leak, but the mechanism remains uncertain (178). By reducing ΔΨ, the transfer of electrons in the ETC can be accelerated and the likelihood of electrons being directly transferred to O2 can be minimized. Therefore, mild uncoupling is a feedback mechanism adopted by the body to prevent excessive ROS in the mitochondria, which was termed ‘uncoupling to survive’ (187). However, whether UCP1 is implicated in the regulation of ROS in BAT is still controversial (175,188,189). In addition to the function of reducing the generation of ROS, UCP3 has been demonstrated to be involved in exporting mitochondrial fatty acid anions to the cytoplasm, thereby protecting the mitochondrial against lipid peroxide-induced damage (190,191).

UCP4 and UCP5 (also called brain mitochondrial carrier protein 1), which have 30% homology to UCP1 (192), are primarily expressed in the central nervous system of mammals (193,194). Although UCP4 and UCP5 are more widely distributed in the brain than UCP2, less is known about their function. UCP4 was first detected in the brain, but it has recently been found in adipocytes (195). In addition, UCP4 also plays a predominant role in insect mitochondria (196). On the other hand, UCP5, which is not limited to the brain, is also expressed in the testis, uterus, kidney, lung, stomach, liver and heart (149). It has been demonstrated that neuronal UCP4 and UCP5 share similar conformational and proton transport activities with UCP1-UCP3 (149,197). Although UCP4 and UCP5 may play an unconfirmed role in the neural system, their function for reducing oxidative stress is clear (195,198). Hoang et al (149) speculated that UCP4 acts in a neuroprotective role during early neuronal development, while UCP2 and UCP5 provided the protective function of restricting ROS production in developed neurons and other tissues, based on the observation that UCP2 and UCP5 displayed higher proton transport rates than UCP4. Oxidative stress has been proven to be involved in both neurodegenerative diseases and aging, so the UCP-dependent reduction of ROS in the nervous system has the potential to be neuroprotective in diseases such as Alzheimer’s disease, Parkinson’s disease and amyotrophic lateral sclerosis (199,200). Certain evidence indicates that protein-protein interactions exist between UCP4 and CII: UCP4-overexpressing neuroblastoma cells increase ATP synthesis via increasing the succinate-induced respiration mediated by CII (201). Pfeiffer et al (202) demonstrated that the Caenorhabditis elegans UCP4 plays a novel role in the regulation of CII by controlling succinate transport into...
mitochondria. UCP4 was also deemed to regulate calcium homeostasis in neuronal cells (203).

**UCPs and diseases.** Regardless, as an inner mitochondrial membrane protein, UCP1 mainly plays a role in the maintenance of body temperature in a cold environment through non-shivering thermogenesis and UCP2-5 can protect cells from oxidative stress by reducing the mitochondrial membrane potential via mediating uncoupling. Due to their wide distribution, UCPs have different physiological significance in specific tissues. Therefore, abnormal changes in UCPs in each tissue will lead to tissue-specific diseases (Fig. 2).

The ubiquitous UCP2 is associated with a number of metabolic diseases, such as diabetes, obesity, cardiovascular disease and even cancer, which has created immense interest in exploring the relationship between UCP2 and these diseases. Since UCP2 can regulate fatty acid and lipid metabolism, a number of studies have confirmed that UCP2 overexpression is associated with diet-induced obesity (204-206). UCP2 is highly expressed in pancreatic β-cells and has a negative regulatory effect on insulin secretion. Robson-Doucette et al (207) in 2011 demonstrated that the overexpression of UCP2 could reduce the secretion of glucose-induced insulin and subsequently induce type II diabetes (T2DM). Moreover, UCP2 knockout mice exhibited hyperinsulinemia and hyperglycaemia (208). Briefly, glucose is metabolized through the ETC to increase ATP production, which leads to the release of insulin and the production of ROS. Chronic elevated glucose status can lead to the excessive expression of UCP2 to reduce the overproduction of ROS, resulting in reduced ATP production, reduced insulin secretion and, eventually, progression to diabetes (209,210). Chronic inflammation, including atherosclerosis, hypertension, diabetic vasculopathy and ischemia-reperfusion injury, is accompanied by excessive ROS production, which means that UCP2 can play a protective role in these diseases by reducing oxidative stress. The signaling pathways, such as nuclear factor (NF)-κB and p53, that can lead to cellular senescence, inflammation, and irreversible vasoconstriction can be inhibited by reducing ROS production. A study showed that the protein levels of UCP2 were significantly higher in human tumor tissues from the head and neck, skin, prostate and pancreas (211). Although the role of UCP2 in tumors is intuitive, the regulatory effects of UCP2 on cellular glucose and lipid metabolism, as well as the regulation of cellular oxidative stress, may be related to the development of tumors. Several studies have confirmed that UCP2 overexpression provides protection for tumor cells and leads to chemoresistance (212-214).

UCP3 has been verified to be associated with exercise intolerance in chronic obstructive pulmonary disease (COPD) patients. COPD patients have exhibited impairment in the form of exercise intolerance, which was linked to increased levels of intramuscular lipid peroxidation products (114,215). Given the fiber-type-specific expression of UCP3, researchers have examined UCP3 levels in muscle biopsies from COPD patients and found that UCP3 content was reduced in COPD (216). It can be speculated that low muscle UCP3 levels contribute to impaired exercise tolerance in COPD patients based on the function of fatty acid anion transportation. In addition, a number of studies have demonstrated that the accumulation of lipid peroxide damage, resulting from decreased UCP3 in skeletal muscle, leads to excessive oxidative stress and is a crucial aspect in the development and progression of obesity and T2DM (191,217,218).

UCP4, UCP5, together with UCP2, are expressed in the nervous system and are implicated in several neurological...
disorders, such as schizophrenia (SCZ), Alzheimer’s disease (AD), and Parkinson’s disease (PD). Various studies link UCP2 with neurodegeneration and aging (123,124,219). The three UCPs exert neuroprotective effects mainly through the alleviation of oxidative stress. The results from selected single nucleotide polymorphism markers within the neuronal UCPs showed that UCP2 and UCP4 are important in the genetic etiology of SCZ (219). Surprisingly, despite the downregulation of UCP2 mRNA levels in SCZ patients, Gigante et al (220) found that there were no differences in UCP2 protein between patients and controls. Future studies will be necessary to clarify whether the mechanism of UCP2 is protective and opposes SCZ progression. Furthermore, in the brains of AD patients, the expression levels of UCP2, 4, and 5 were significantly reduced, which limited the activation of cytoprotective mechanisms to slow the progress of AD (124). UCP5 and, especially, UCP4 are linked to PD. UCP4 is regulated by the oxidized DJ-1 and partially via the NF-kB pathway and can protect against oxidative stress and stabilize Ca\(^{2+}\) homeostasis in PD, as demonstrated by Ramsden et al (148) in 2012. Drugs that induce neuronal UCP expression might represent another effective strategy to ameliorate PD.

5. Concluding remarks and perspective

In conclusion, the ETC is the core component of mitochondria. The OXPHOS process in the ETC, coupled with the generation of ATP, also results in ROS production. As a double-edged sword, ROS can play a role in signaling pathways, but ROS overproduction can cause cellular damage. The ROS produced by complex III is not only released into the matrix but also released into the IMS. The ROS released into the IMS can be converted to H\(_2\)O\(_2\) in a reaction catalyzed by SOD1, and the H\(_2\)O\(_2\) may diffuse out of the mitochondria and play an important role in physiological and pathological pathways. Therefore, the artificial regulation of ROS at the complex III site (site IIIQo) may be of great significance. Although the precise mechanism of ROS production is still unclear, the use of specific ROS inhibitors to reduce the excessive production of ROS under pathological conditions has ameliorated oxidative stress-mediated diseases. UCP-mediated proton leak is a positive feedback mechanism for the protection of cells against oxidative stress due to the rapid production of ATP. The proper activation of UCPs can reduce the production of cellular ROS without causing a decrease in ATP; however, when the expression of UCPs becomes too high or too low or the UCP genes are mutated, pathological effects that are involved in various diseases can occur. UCP1 mediates the inducible proton conductance that is responsible for non-shivering thermogenesis in BAT, a critical response to prolonged cold exposure. UCP2 is involved in a variety of diseases, such as diabetes, obesity and cardiovascular disease. In addition, UCP2, UCP4 and UCP5 play an important role in neuroprotection and are associated with neurological diseases such as SCZ, AD and PD. Drugs targeting UCP expression and activity might represent an effective strategy to ameliorate these diseases. However, the detailed mechanisms of the role of UCPs and the regulation of UCP expression under normal and stressful situations warrant further exploration.

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Authors’ contributions

ZBY and LZ conceived the review and analyzed the relevant literature. RZZ and SJ collected and reviewed the literature related to the topic of this manuscript and drafted the main part of this manuscript. RZZ, LZ and ZBY critically revised the manuscript. RZZ and SJ produced the figures. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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