BBA - Bioenergetics 1865 (2024) 149031

Contents lists available at ScienceDirect

BBA - Bioenergetics

journal homepage: www.elsevier.com/locate/bbabio

Alternative Oxidase – Aid or obstacle to combat the rise of fungal pathogens?

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ARTICLE INFO

Keywords:
Alternative Oxidase
Mitochondria
Fungi
Plants
Pathogen

ABSTRACT

Fungal pathogens present a growing threat to both humans and global health security alike. Increasing evidence of antifungal resistance in fungal populations that infect both humans and plant species has increased reliance on combination therapies and shown the need for new antifungal therapeutic targets to be investigated. Here, we review the roles of mitochondria and fungal respiration in pathogenesis and discuss the role of the Alternative Oxidase enzyme (Aox) in both human fungal pathogens and phytopathogens. Increasing evidence exists for Aox within mechanisms that underpin fungal virulence. Aox also plays important roles in adaptability that may prove useful within dual targeted fungal-specific therapeutic approaches. As improved fungal specific mitochondrial and Aox inhibitors are under development we may see this as an emerging target for future approaches to tackling the growing challenge of fungal infection.

1. Introduction

Fungal pathogens are responsible for over one billion human infections and over 1.6 million deaths annually [1–4], as well as a third of all global crop failures [1,5]. However, despite the threat that fungal strains present to animal species and the threat to food security worldwide, they remain under-researched [3] [6].

Human fungal pathogens can cause superficial, sub cutaneous or systemic infections, which in the case of immunocompromised individuals can be associated with high mortality. The outcome for patients is also strongly correlated with the speed and accuracy of diagnosis, a rise in antifungal resistance and socioeconomic factors that restrict treatment ability [7–9]. Antifungal resistance is likely to become a major issue, driven by factors such as a limited number of identified cellular targets for antifungal development, the over-use of agricultural fungicides and the emergence of more fungal pathogens in an ever-warming climate [10,11].

There is therefore the need to conduct research into new antifungal targets and strategies to prevent fungal infection. Mitochondria could prove to be a useful target against plant fungal pathogens [12] and growing evidence, driven by an increase in our understanding of respiratory chain physiology, suggests that inhibitors may also be developed to tackle human infection [13,14].

2. Fungal respiration

As with many eukaryotes, fungal pathogens possess a well conserved classical Electron Transport Chain (ETC) which is used to generate a proton motive force (PMF) that can drive ATP synthesis, and which is important for the numerous processes that mitochondrial function supports. Forward electron transfer through the respiratory complexes (FET) provides the thermodynamically favoured reaction that is coupled to oxidative phosphorylation and ATP production. However reverse electron transfer (RET) can occur, whereby electrons flow backwards through Complex I. RET is thought to be induced by reduction of the Ubiquinone pool (UQP) to between 40 and 60 %, requiring a high PMF, a large thermodynamic driving force, and a high ΔpH [15,16].

Sites for mitochondrial Reactive Oxygen Species (ROS) production, namely superoxide ($O_2^{\bullet-}$) generation, include Complex I and Complex III, particularly sites I_F, I_Q and III_{QO} [15]. Site I_Q is responsible for most of the superoxide production during RET, whereby electrons are forced into Complex I through a high QH_2 / Q ratio and high PMF [15]. Superoxides can be generated by both FET and RET [15], whereby production and removal depend on substrate availability (like succinate oxidation, which drives RET [17]) QH_2/Q ratio, rate of oxygen consumption, and mitochondrial dysfunction or inhibition [15]. The multifactorial nature of ROS generation and management requires

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https://doi.org/10.1016/j.bbabio.2024.149031
Received 1 August 2023; Received in revised form 16 November 2023; Accepted 3 January 2024
Available online 7 January 2024

continual homeostasis, as ROS are essential within diverse cellular processes in both host and pathogen [18], but highly inflated ROS levels have been attributed to mitochondrial disease [19]. Induction of ROS production has also been implicated in the mode of action of several antifungals [20,21] suggesting a role for mitochondria and/or redox homeostasis as a target in current therapeutic approaches. However, understanding the full signalling mechanisms of ROS within fungal pathogenesis represents a growing field of study.

Intuitively the conservation of the highly conserved classical ETC provides a barrier to its development as an attractive target for human fungal pathogens. However, fungal specific differences that are essential for function have been reported, such as alternative NADH dehydrogenases, which may bypass Complex I activity [22,23]. One key difference in the respiratory chain of many human fungal pathogens is the presence of a cyanide-insensitive alternative oxidase (Aox), which is not found in mammalian mitochondria. Aox branches from the main respiratory chain at the level of the UQP (Fig. 1*)* and has a catalytic di-iron centre orientated towards the mitochondrial matrix. Interestingly, this membrane-bound oxidase is non-proton motive, and therefore does not have a significant role in ATP production, but rather oxidises ubiquinol and reduces oxygen to water, bypassing the ETC prior to proton translocation by complexes III and IV (Fig. 1). However, there is evidence for ATP generation through the Aox/Complex I pathway in *Botrytis cinerea* [22,24], and inhibition of Aox in *Gaeumannomyces graminis* leads to a decreased rate of ATP synthesis [25], indicating that the extent of Aox involvement in ATP generation may be species specific.

While Aox is not found in mammals, it is highly conserved amongst pathogenic fungi. Some fungal species like *Aspergillus niger*, *Aspergillus flavus* and *Candida albicans* have multiple isoforms [26] [27], there are notable exceptions, for example in *Candida glabrata and Pneumocystis jiroveci,* which, like *Saccharomyces cerevisiae*, do not contain a multi-subunit Complex I or Aox. It may be the case that Crabtree positive yeasts, that primarily use aerobic fermentation for increased growth rates under high glucose availability [28], do not require an Aox for mitochondrial homeostasis, as growth is predominantly supported by fermentation rather than respiration. Crabtree negative yeast, that utilise respiration for energy generation such as *Candida albicans* and *Cryptococcus neoformans,* have retained Aox and maintain metabolic flexibility by utilising both alternative and glucose carbon sources. This flexibility may contribute to host colonisation and virulence in the nutrient-scarce host [29–32], whereby presence of Aox in fungal pathogens may also assist in the maintenance of mitochondrial function upon immune challenge, the regulation of ROS production, and pathogenesis [33–35].

Interestingly, fungi have been shown to utilise multiple respiratory pathways, for example *Aspergillus nidulans* can alternate between both classical and alternative respiratory pathways to generate sterigmatocystin, a precursor to Alflatoxin B_1 [26,36]. A third 'parallel' respiratory chain (PAR), in *Candida albicans* and *Candida parapsilosis* has been proposed [37–40], which may contribute up to 10 % of total

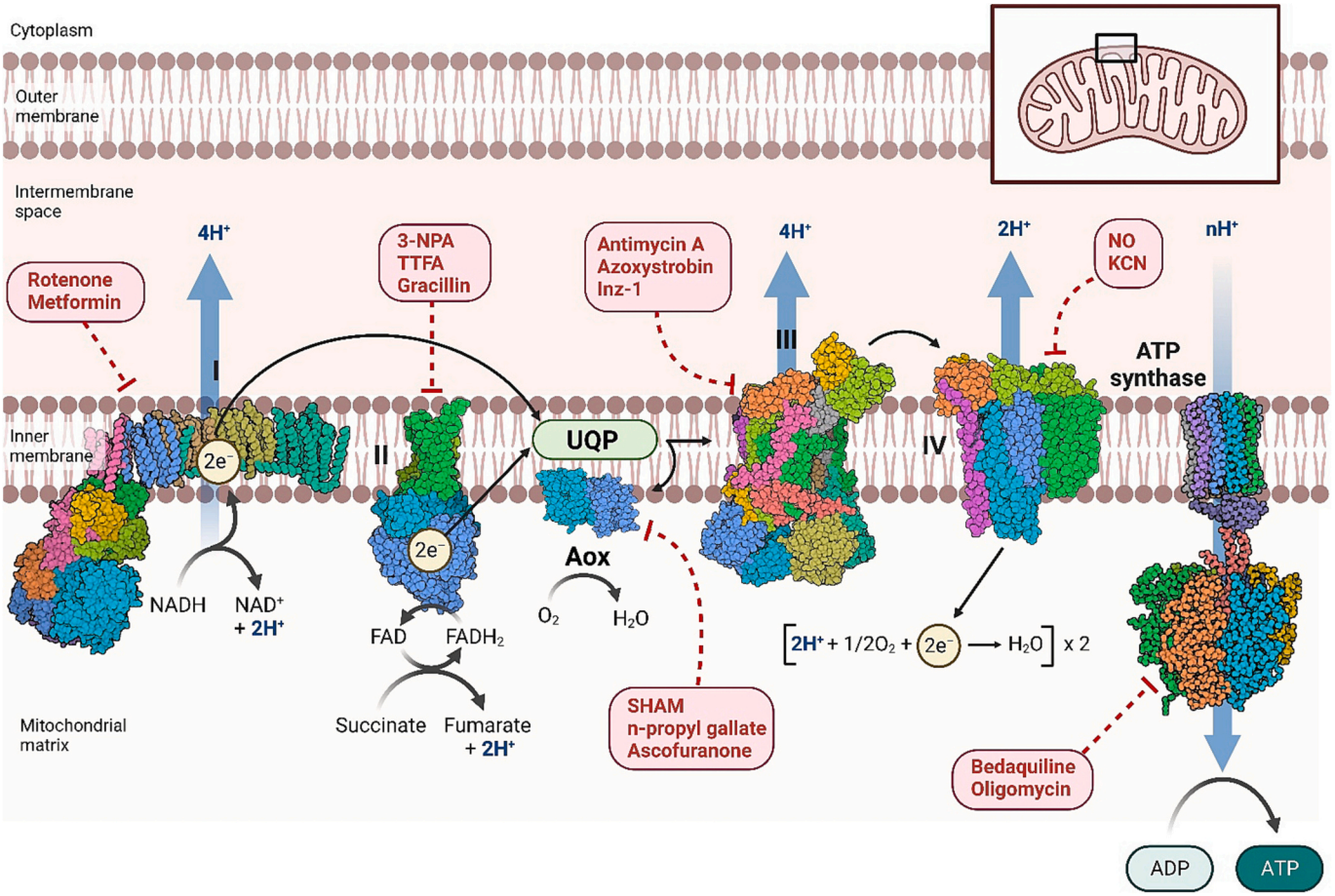

Fig. 1. *Schematic of the Electron Transport Chain (ETC) found in fungal pathogens.*
Both a classic ETC and an alternative respiratory chain are found in most fungi. Where known, crystal structures of the ETC components are shown [Complex I, Protein Data Bank (PDB) 3M9S [172], Complex II PDB 3VR8 [173], Trypanosomal Aox PDB 3VV9 [174], Complex III PDB 1KYO [175], Complex IV PDB 8DH6 (to be published), ATP Synthase PDB 1QO1 [176]]. Aox branches from the main respiratory chain at the level of the UQP. This pathway produces little ATP, but instead dissipates energy as heat and bypassing proton transfer through downstream Complexes III and IV. Known inhibitors of each ETC component are listed in red. Created with BioRender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

respiration capacity. The ability to utilise alternate routes of respiration suggests that these yeasts may have evolved within an environment that presents regular and significant challenges to electron transport. Alternately, it may be that alternate respiration supports signalling and metabolic changes that are required for adaptability within changing environments. This may include factors produced by competing or co-colonising microbes that damage or inhibit growth [41], such phenazine production by *Pseudomonas aeruginosa* [42], or detoxification of nitric oxide (NO) released by host cells during infection [43,44]. This could also involve nutritional challenges that limit access to key metabolites, co-factors that support respiration or environmental challenges such as temperature variation or oxygen availability [41,45].

3. The role of mitochondria in fungal pathogenicity

An increasing interest in fungal respiration has highlighted several mitochondrial roles which are thought to contribute to human fungal pathogenicity [46], although some of the signalling mechanisms behind this involvement are still unclear. Respiration deficiency leads to diminished virulence in mice intravenously infected with *Candida albicans* [47], and respiratory inhibition with sodium nitroprusside (SNP), an NO donor, and salicylhydroxamic acid (SHAM), an Aox inhibitor, reduces *Candida albicans* cell viability and increases phagocytic uptake by macrophages [37]. Increased phagocytosis has also been seen after treatment of *Candida albicans* with the Complex III inhibitor Antimycin A, thought to be attributable to β-glucan exposure [48]. However, pre-treatment of the cells with SHAM and SNP prior to murine infection exhibited increased virulence through transcriptional changes and cell wall remodelling, presenting a higher renal fungal burden, and increased immune infiltrate than untreated cells [37]. This data therefore indicates that mitochondrial signalling mechanisms need to be investigated further.

Active infection and dissemination inside the host is presumed to be energetically demanding for pathogenic yeasts, especially for switches to hyphal growth forms for *Candida albicans* via the Ras1/cAMP/PKA signalling pathway [49,50]. Other instances of increased respiratory demand for ATP in *Candida albicans* include escape from macrophage engulfment through catabolism of amino acids for morphogenesis [51]. This increased ATP demand could be attributed to the action of ATP-driven pumps belonging to the ATP Binding Cassette family (ABC). ABC transporters are profound influx-efflux pumps that rely on ATP hydrolysis to transport a variety of molecules, including sterols, metabolites, and drugs, proving crucial for pathogenic activity of *Magnaporthe grisea* [52,53], and are thought to contribute to the multi-drug resistant phenotype seen in *Candida auris* [54]. As well as heavy reliance on ATP production, Vacuolar ATPases (V-ATPases) generate a pH gradient through ATP hydrolysis which drives secondary transporters to maintain cellular ion homeostasis. This process requires Ergosterol for optimal V-ATPase function and is sensitive to combination treatment with both Fluconazole and Amiodarone in the *C. albicans* murine candidiasis model [55]. These investigations prove that ATP is crucial for a variety of processes that underpin fungal pathogenesis, although this could be in combination with other mitochondrial signalling pathways.

The maintenance of mitochondrial morphology for stress tolerance and virulence is highlighted in *Cryptococcus neoformans*, whereby fully functioning inherited mitochondria from the *MATa* parent are critical for growth under fluctuating temperature, low oxygen availability and iron regulation [56–60]. Defects occurring in Complex I, II or IV can impair conidiation and sexual development of the yeasts *Neurospora crassa* and *Podospora anserina,* even when alternative NADH dehydrogenases are present and respiration is maintained by Aox [61–69]. Interestingly, a mutation in the *Cryptococcus neoformans* NADH promoter region increased production of melanin, Glucuronoxylomannan (GXM) release, and ATP, virulence enhancing traits which occurred through serial passage in the *Galleria mellonella* model [70]. These studies suggest that while conservation of mitochondrial components and morphology is seen across multiple taxa, mitochondrial plasticity may have a role in enhancing virulence and host evasion.

Mitochondrial morphology is thought to have importance in the ER-mitochondria encounter structure (ERMES), which has been highlighted for cell fitness, immune evasion, and virulence in both *Candida albicans* and *Aspergillus fumigatus* alike [71]. Mitochondrial contact sites with both the ER and peroxisomes have been thought to contribute to lipid homeostasis though shuttling of tricarboxylic-acid (TCA) cycle intermediates like citrate from peroxisomes to the mitochondria, although details of metabolite transfer and regulation of contact sites is still unclear. Interestingly, although direct lipid transit pathways are yet to be elucidated, a recent study by Enkler *et. al* [72] suggested that Arf1 couples fatty acid β-oxidation to mitochondrial ATP synthesis and can regulate mitochondrial fission and fusion [72]. Adequate regulation of mitochondrial fission and fusion mechanisms is important in *Cryptococcus neoformans*, whereby mitochondrial fusion defects lead to increased ETC inhibitor sensitivity and loss of virulence in a murine model [57], and mitochondrial fragmentation seen in *Aspergillus fumigatus* is seen during human granulocyte killing as a response to oxidative stress [73]. The function of mitochondria in fungal pathogenesis is multi-factorial, with ATP production, organelle signalling and morphology underpinning virulence mechanisms. However, deeper investigations into virulence signalling pathways involving mitochondria should be explored.

4. Aox function in plant fungal pathogens

The ETC of plants has been extensively studied [74], and Aox activity has been documented in both plants and phytopathogenic fungi alike. However, evidence shows that the ETC of plants differs to that of other eukaryotes due to the number of subunits found for each mitochondrial complex. For example, the Complex I of plants has nearly 50 different subunits [75], and studies of *Pichia stipitis* and *Neurospora crassa* show that fungal Aox differs from Aox in plants in that it occurs as a monomer and is not induced by α-keto acids such as pyruvate [76]. The disparity between plant and fungal complex subunits, including additional proteins found in plant complexes [77,78] is thought to assist in antifungal therapies that target phytopathogenic respiration.

In plant fungal pathogens such as *Moniliophthora perniciosa* and *Sclerotina sclerotiorum*, Aox is reported to be more active during the mycelial growth phase, suggesting that the metabolic control provided by alternative respiration is a crucial factor in morphogenesis [79,80]. Interestingly, the activation of Aox for fungal growth has also been thought to contribute to mycotoxin production by food-colonising fungi, such as Aflatoxins produced by *Aspergillus flavus* [81–83]. It is interesting to note that Aox is activated and upregulated in *Solanum lycopersicum, Arabidopsis thaliana* and *Nicotiana attenuata* in response to bacterial and viral attack, mainly for oxidative and nitrosative stress management [84–88], although the roles of Aox in stress signalling during fungal infection of other plant species requires further research.

For other plant pathogens, such as *Botrytis cinerea, Ustilago maydis* and *Magnaporthe grisea,* Aox is required for active resistance to Quinone Outside Inhibitor (Q_oI) fungicides such as the strobilurins, Azoxystrobin and Pyraclostrobin [89–92]. This class of fungicides inhibit mitochondrial respiration through binding to Cytochrome bc_1, blocking the movement of electrons at the quinone outer binding site [93], although field resistance is becoming an increasing problem, such as in *Mycosphaerella fijiensis* and *Mycosphaerella musicola* infections of bananas [94] and *Pyrenophora tritici- repentis* infections of Argentinian wheat [95]. Increasing Q_oI resistance has been attributed to the presence of an Aox in *Mycosphaerella graminicola* and *Aspergillus flavus* [26,96], whereby Aox provides an alternative route for electron transport away from the target site of the Q_oI fungicides to maintain electron flux. In the presence of the strobilurin Azoxystrobin, *Fusarium graminearum* upregulated transcription of Aox and rapidly increased oxygen uptake [97]. To address the

emerging antifungal resistance in agricultural practices, research into new succinate dehydrogenase inhibitors (SDHIs), such as Carboxin has begun, whereby fungal respiration is inhibited through blockage of the ubiquinone binding sites of Complex II. SDHIs have been rapidly gaining interest due to their broad, high antifungal activity [98], however phytopathogenic sensitivity to SDHIs is slowly shifting [99] and evidence suggests that SDHI site-specific inhibition may give rise to resistance if not monitored correctly [100]. This may, in part, be due to the presence of fungal Aox at the level of the UQP to provide an alternative respiratory pathway under this inhibition. The potential benefits of Aox inhibitors in the agrochemical industry has been recently reviewed [81].

Although Aox has proposed functions for virulence in plant fungal pathogens, not all phytopathogens have a predicted sequence, such as the *Puccinia* species responsible for wheat rust disease and *Melampsora lini* which causes flax rust (Fig. 2). Interestingly, while resistance mechanisms of wheat and flax towards these pathogens has been documented [101,102] there are few noted instances of antifungal resistance for these pathogens themselves, which, in conjunction with these other studies, indicates that Aox may have a role in phytopathogenic resistance to antifungal drugs. While much needs to be investigated in plant-pathogen interactions, given that both plants and phytopathogenic fungi can induce Aox independently for multi-factorial stress relief, one cannot rule out the possibility that both fungi and plants may use Aox in within the environmental niche of an active phytopathogenic infection. Investigations into the role of Aox on both the host and pathogen sides of an infection could provide an insight into tackling antifungal resistance impacting food security.

5. Aox function in human fungal pathogens

Most human fungal pathogens possess at least one Aox (Fig. 3). The importance of Aox in morphogenesis and resistance to oxidative stress from the human host has been demonstrated in several fungal pathogens. Aox1 from *Cryptococcus neoformans* was shown to be induced at 37 °C and was reported to play a role in virulence in the murine inhalation model [103] and in *Paracoccidioides brasiliensis,* Aox is upregulated in response to oxidative stress and for the mycelial-to-yeast transformation, a crucial step in paracoccidioidomycosis [104,105]. *Aspergillus flavus* and *Aspergillus fumigatus* have multiple isoforms of Aox, whereby the isoform AoxA was found to attribute resistance to oxidative stress and macrophage killing [26,106,107]. Aox is also upregulated in *Candida albicans* and *Candida auris* in response to oxidative stress conditions [108–110], plays a role in hyphal growth and biofilm formation [111,112] and deletion of Aox in *Candida albicans* leads to increased Fluconazole susceptibility [113]. A recent study assessed *Candida albicans* respiratory capacity when exposed to SNP in combination with the known Aox inhibitor salicylhydroxamic acid (SHAM). *Candida albicans* treated with this combination displayed a rapid transition to hyphal growth upon relief from inhibition and *Candida albicans* treated with both SNP and SHAM also displayed a decrease in caspofungin resistance [37]. This indicated that Aox has a significant role in the hyphal switching phenotype in *Candida albicans*, and that transcription of a second alternative oxidase, Aox2, is induced in the presence of ETC inhibitors to buffer respiratory stress and increase alternative respiration capacity [37,114]. Interestingly, deletion of Aox2 also leads to decreased virulence of *Candida albicans* in the murine model through increased immune recognition [115]. However, some reports suggest that Aox1 is dispensable for virulence in *Candida albicans* [116] and *Aspergillus fumigatus* [106], this may be due to differences between experimental approaches or strain backgrounds and remains a point to be clarified.

Interestingly, both *Candida glabrata* and *Pneumocystis jiroveci* do not have a predicted Aox sequence (Fig. 3), however evidence of respiratory inhibition of *Pneumocystis jiroveci* with SHAM has been reported,

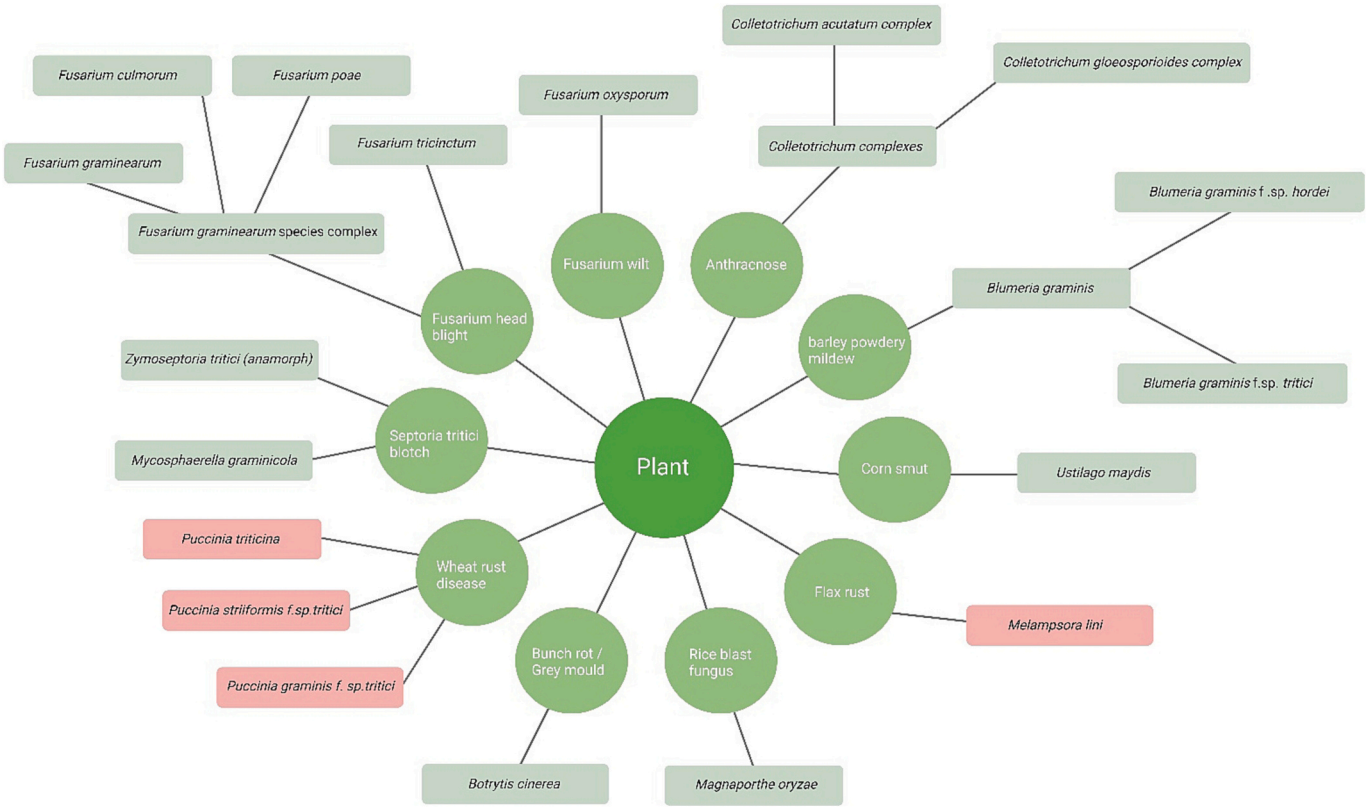

Fig. 2. *Key plant fungal pathogens.*
Schematic illustrating key plant fungal pathogens. Pathogenic species without a known or predicted Aox sequence in the UniProt database [177] are highlighted in red. Created with BioRender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

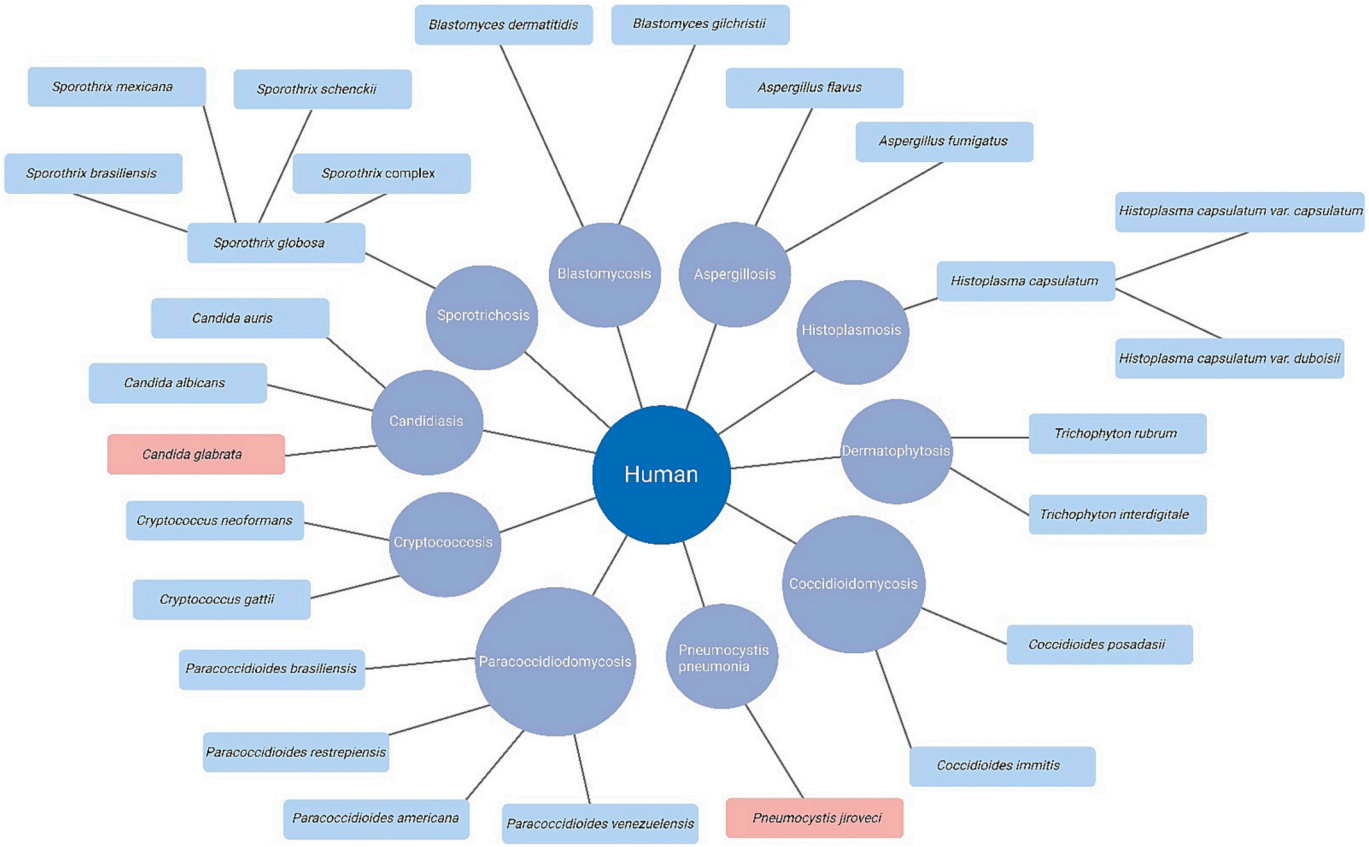

Fig. 3. *Key human fungal pathogens.*
Schematic illustrating key human fungal pathogens. Pathogenic species without a known or predicted Aox sequence in the UniProt database [177] are highlighted in red. Created with BioRender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

suggesting an Aox may be present [117,118]. While incidences of *Candida glabrata* based Candidiasis are increasing, the genetic similarity of *Candida glabrata* to *Saccharomyces cerevisiae* and differences to *Candida albicans* indicate that both species must have evolved different routes to pathogenesis, independently of Aox [119]. Unfortunately, little is known about the metabolic requirements of *Pneumocystis jiroveci* for infection, although it has been postulated that *Pneumocystis* pneumonia is based on reactivation of a latent infection, using the host an as environmental reservoir to facilitate human-human transmission [120,121] which also appears Aox independent. The importance of Aox in virulence itself appears pathogen specific, as parasitic *Trypanosoma brucei* alternative oxidase (TAO) has proven to be essential for respiration in the bloodstream form of the parasite [122,123], with intense therapeutic interest providing the only known published crystal structure of Aox [124] and evidence of TAO inhibition with ascofuranone [125]. However, while interesting links have been made for Aox involvement in parasite infection, this falls out of the scope of this review.

Although human-fungi interactions are widely investigated, direct signalling roles for Aox in fungal pathogenesis and host dissemination are still unclear. Because of its ability to maintain respiration in the presence of classical ETC inhibitors, Aox in human fungal pathogens could be proposed to relieve respiratory stresses induced by the host during infection, such as NO. In humans, NO is produced during host infection by phagocytes by nitric oxide synthase iNOS (or NOS2) as part of the arsenal of oxidants that can inhibit or kill invading pathogens [126]. While no direct links between human NO production and fungal Aox during pathogenesis have been recorded, studies on plant mitochondria show that while NO inhibits cytochrome *c* oxidase, Aox remains uninhibited [127]. The evidence presented suggests that Aox does play a role in fungal pathogenesis, although most likely as an indirect mediator of oxidative stresses induced by the host and maintenance of fungal morphology in the host environment, rather than a direct virulence component. Perhaps for human fungal pathogens, Aox activity should be seen as a latent, adaptive mechanism which activates under selective pressure for metabolic homeostasis. This would provide a background benefit to fungal pathogens in immune evasion but would be dispensable as an active component of virulence mechanisms required for dissemination in the host. However, further investigations into Aox activation and function within different human fungal pathogens is required to substantiate these postulations.

6. Problems and potential for targeting respiration in human fungal pathogens

Current antifungal therapies either inhibit biosynthetic machinery for ergosterols (e.g., azoles), nucleic acids (antimetabolites e.g., Flucytosine) or disrupt the cell membrane or wall (e.g., polyenes or echinocandins). While conservation of mitochondrial machinery between both animals and fungi presents a problem for suitable antifungal treatments, current inhibitors of the fungal ETC, highlighted in Fig. 1, include both natural and synthetic compounds. Rotenone and Metformin are known inhibitors of Complex I, investigated for their efficacy against cancer and antifungal properties against *Candida albicans* and *Aspergillus niger* [128–132], although Metformin is classically used to treat Type II Diabetes [133]. Complex II is prone to inhibition by 3-nitropropionic acid (3-NPA) or thenoyltrifluoroacetone (TTFA), although new studies have highlighted Gracillin, a natural steroidal saponin as a potential antitumour drug [134,135]. Numerous Complex III inhibitors have been identified, of which Strobilurins such as Azoxystrobin are rapidly gaining interest [83,136–138]. For example, combination treatment of

Complex III and Aox inhibition was found to enhance sensitivity to caspofungin in *C. parapsilosis* [139]. However, while Complex III inhibition is attractive for antifungal activity [13], inhibitors of this kind can often bind to both pathogenic and host complexes alike, so different applications for this inhibitor class are being investigated, such as cancer therapeutics [138,140–142]. While inhibition of yeast ATP synthase is possible using Bedaquiline [143] and Oligomycin [144], the strong conservation between fungal and mammalian isoforms of the mitochondrial ATP synthase renders this enzyme as an antifungal target obsolete, although it does provide a promising antibiotic target [145].

Prolonged reliance on treatment guidelines has presented increasing numbers of resistance in clinical cases [146–148]. Resistance patterns have begun to emerge in various fungal species, and reliance on combination therapies of azoles, polyenes, echinocandins and antimetabolites mean that monotherapies are declining in potency against rapidly adapting fungal pathogens. For example, mutations in the ergosterol pathway and sterol biosynthesis of *Candida tropicalis*, *Candida albicans* and *Candida lustiniae* leads to resistance to azoles and Amphotericin B as monotherapies [149–154] and interestingly this mutation in *Candida lustiniae ERG3* is also induced via micafungin monotherapy, which then provides cross resistance to multiple antifungal classes [155]. Treatments are now more aimed towards combination therapy to target invasive fungal infections such as the use of Caspofungins with other antifungal classes to treat Candidiasis [156], combinations of multiple triazole types such as PC945 and voriconazole for treatment of *Aspergillus fumigatus* based Aspergillosis [157] and recommended treatment for Cryptococcosis includes a combination of Amphotericin B and Flucytosine, followed by Fluconazole in a maintenance program that can last up to a year [158,159], although antifungal heteroresistance and cross-tolerance has been documented [160].

The increasing amount of antifungal resistance and the reliance on combination therapies means focus is shifting towards compounds that can re-sensitise resistant fungal pathogens to current antifungals, rather than identify novel antifungal compounds. Interestingly, a group of Indazole derivates have been identified to convert azoles from fungistatic back to fungicidal for *Candida albicans* infections through inhibition of the cytochrome bc_1 complex [161]. One compound, Inz-5, enhanced the ability of macrophages to contain *C. albicans*, and Inz-1 showed selection for yeast complex bc_1 over human bc_1, which offsets the current issues other Complex III inhibitors face in host treatment. Other synergisms are beginning to emerge, such as Tetrandrine which increased the antifungal activity of Fluconazole in the murine Candidiasis model [162] and even a combination of Fluconazole with small molecule ENOblock [163] or SHAM [164] showed synergism against *Candida albicans*. With the indication that research is moving away from monotherapeutic antifungals, inhibition of Aox could be effective in combination therapies with existing antifungal drugs such as Echinocandins and Azoles which are currently circulated for the treatment of *Candidiasis* and *Cryptococcosis,* but not as a monotherapy alone. Another postulation includes the use of known natural stressors for pathogens such as NO, which can be produced by SNP, in combination with Aox inhibitors. While using NO stress in combination with Aox inhibition is an attractive proposal, research into efficacy against fungal pathogens in vitro and in vivo is required. Research into fungal respiration machinery, especially the role of Aox, and its links to virulence, remain understudied.

In summary, due to the connection of mitochondria to pathogenesis, cell wall regulation and lipid metabolism, fungal-specific respiratory inhibitors may prove to be effective against pathogens either in isolation or in combination with current antifungals. However, the conservation of the respiratory machinery in eukaryotes and the robust and adaptive nature of fungal respiration is a challenge for drug development, so investigation into compounds that can re-sensitise drug resistant fungal pathogens to existing therapies may also provide relief from infection. Characterisation of fungal-specific respiratory chain components are needed, together with a deeper understanding of the roles of those already characterised, such as Aox.

7. Proposed roles for Aox

Studies so far suggest that Aox does not have a direct role in fungal virulence but does have a role in maintenance of oxidative stress mechanisms, ROS production, and even Complex I driven respiration in *Botrytis cinerea* [24,165] . It could be postulated that Aox, having close links and established electron transfer from the UQP, and yet no dominant role in ATP synthesis, could act as a switch between FET and RET in response to environmental cues for both ROS production and scavenging. Interestingly, this concept is supported by an investigation in murine mitochondria using xenotypic expression of Aox from *Ciona intestinalis* [166]. Aox is known to oxidise ubiquinol and reduces oxygen to water, bypassing the ETC prior to proton translocation by complexes III and IV, producing heat as a byproduct. It would make sense, therefore, if Aox acted in FET to stop electron leak through I_Q or III_{QO} by oxidation of quinone which could reduce ROS production in stress conditions induced by host dissemination. More interestingly, as RET induction requires an unfavourable thermodynamic force and high QH_2/Q ratio, one could speculate that Aox could contribute to RET induction itself through generation and release of heat energy as the RET driving force for electron movement into Complex I and maintenance of the reduced quinone state. While induction of RET and induction of ROS production seems counterproductive to fungal pathogens, certain morphological developments induce high ROS, such as capsule development in *Cryptococcus neoformans* [167] and *Aspergillus niger* and *P. penicillium* spore germination [168]. This, in conjunction with studies that show Aox as sensitive to pH changes [169] and other postulations highlighting Aox as important in ROS homeostasis [26] [170] [171] supports the idea that Aox could act a FET/RET switch to provide ROS for energy demanding virulence mechanisms in fungal pathogens or defend against host-generated ROS through induction of FET, independently of ATP production. Experiments investigating ROS production, FET/RET initiation and thermodynamics in relation to Aox activity should be considered.

8. Conclusion

While fungal pathogens present a growing threat to both human health and food security, research into antifungal therapies are still neglected. Here, we investigated the role of the electron transport chain in fungal virulence and antifungal resistance, including the Aox pathway. Interestingly, while the direct role of Aox in pathogenic virulence remains unclear, studies have showed a potential homeostatic role for metabolism under both biotic and abiotic stresses. This stress tolerance mechanism is thought to contribute to pathogenic survival in the host and contribute to current antifungal resistance through control of ROS and NO accumulation, which is uncoupled from ATP production. To address the issues faced by antifungal resistance, application of an Aox-specific antifungal may re-sensitise resistant fungal pathogens to drugs such as Fluconazole, although research into combination therapies and Aox-specific inhibitors still needs to be pursued.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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