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DOI:
10.1016/j.semcdb.2018.03.004

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Warris, A & Ballou, ER 2019, 'Oxidative responses and fungal infection biology', *Seminars in Cell and Developmental Biology*, vol. 89, pp. 34-46. https://doi.org/10.1016/j.semcdb.2018.03.004

Seminars in Cell & Developmental Biology 89 (2019) 34–46

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

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

Oxidative responses and fungal infection biology

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ARTICLE INFO

Article history:
Received 5 February 2018
Received in revised form 4 March 2018
Accepted 5 March 2018
Available online 12 March 2018

Keywords:
Oxidative stress
Reactive oxygen species
Reactive nitrogen species
Fungi
NADPH-oxidase
Fungal infection biology

ABSTRACT

The balance between reactive oxygen species and reactive nitrogen species production by the host and stress response by fungi is a key axis of the host-pathogen interaction. This review will describe emerging themes in fungal pathogenesis underpinning this axis.

Contents

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https://doi.org/10.1016/j.semcdb.2018.03.004

1. Introduction

Reactive Oxygen and Reactive Nitrogen Species (ROS/RNS) arise as bi-products of cellular function and through the regulated activity of ROS/RNS-generating enzymes. In the host, mitochondrial ROS serve as markers of metabolic activity, apoptosis, and pyroptosis [1–3]. Phagocytosis and cytokine stimulation activate host NADPH Oxidase (NOX, ROS burst) and Nitric Oxide Synthase (NOS, NO^-), both of which serve to neutralise invading pathogens. The significance of the host oxidative response in the resistance to invasive fungal disease is highlighted by the susceptibility of patients deficient in this response [4]. In response to host oxidative and nitrositive stress, pathogenic fungi engage transcriptional, post-translation, and enzymatic (Superoxide Dismutase (SOD), catalase, thioreductase, glutathione) responses as part of oxidative stress responses that enable resistance to ROS/RNS toxicity and facilitate adaptation to the host. A number of recent reviews have examined our understanding of transcriptional and post-translational responses [5,6], however emerging data suggest a complex interplay between enzymatic ROS detoxification, mitochondrial function, and host pathogenicity. For example, fungi deficient in SOD exhibit reduced pathogenicity: *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus* SODs are required for full virulence, and defects in oxidative stress response pathways attenuate fungal resistance to phagocyte killing [7–10]. However, there is significant redundancy, and in most cases, loss of a single detoxification strategy has a limited impact on overall virulence [7–10]. Additionally, fungi encode an orthologous NADPH oxidase complex with an underappreciated influence on fungal infection biology and pathogenesis in the host [11–14]. Therefore, we take this opportunity to fill a gap in the literature by examining ROS/RNS generation by the host and fungus during fungal infection, focusing on the role of these two emerging aspects of infection biology in the fungal oxidative stress response.

2. Basic biology

2.1. The host

In the host, ROS/RNS production increases upon exposure to toxins and stimulation of host NADPH oxidase and iNOS pathways by micro-organisms. Polymorphonuclear and mononuclear phagocytes express both NADPH oxidase and iNOS. Neutrophils produce the vast majority of ROS, while macrophages generally produce considerably more RNS [15]. Target microbes then accumulate cell injury as a result of oxidative stress, causing DNA mutations that lead to changes in gene expression, as well as post-translational protein modification and lipid peroxidation.

Phagocyte-derived reactive oxygen and nitrogen intermediates (ROI and RNI) are of crucial importance for host resistance to microbial pathogens (Fig. 1). Their potent antimicrobial activity can be explained by their rapid and high production, a small molecular size and transmembrane diffusibility [16]. Superoxide ($O_2^{-\bullet}$) is generated by the NADPH phagocyte oxidase (phox) [17]. Superoxide alone is generally considered to be poorly toxic to microbes, although the amounts generated intraphagosomally are considered to be microbicidal [18]. However, superoxide generation leads to the accumulation of ROIs including hydrogen peroxide (H_2O_2), hydroxyl anion (HO^-) and hypochlorous acid (HOCl). Superoxide

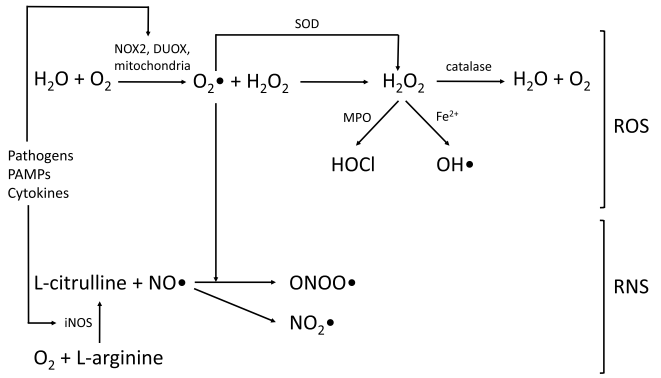

Fig. 1. Schematic representation of the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the human host. Oxygen is reduced by the NADPH oxidase in phagocytes (NOX2) or in epithelial cells (DUOX) or by the mitochondria. The superoxide ($O_2\bullet$) generated is converted by superoxide dismutase (SOD) into hydrogen peroxide (H_2O_2). H_2O_2 is either converted by myeloperoxidase (MPO) into hypochlorite (HOCl), or into water (H_2O) and oxygen, or into hydroxyl radicals ($OH^{-\bullet}$) in the Fenton reaction catalysed by iron. The production of nitric oxide ($NO^{-\bullet}$) requires L-arginine to be converted to L-citrulline driven by inducible nitric oxide synthase (iNOS) in the presence of oxygen. Subsequent spontaneous reactions involving $O_2\bullet$ and $NO^{-\bullet}$ can result in the formation of nitrogen dioxide ($NO_2\bullet$) and peroxynitrite ($ONOO^{-\bullet}$).

anions are unstable and will convert either spontaneously or via superoxide dismutase (SOD) to H_2O_2. In neutrophils, myeloperoxidase (MPO) converts H_2O_2 to the highly microbicidal HOCl, and MPO is required for antifungal defense [19]. MPO also participates in the IFNγ mediated priming of phagocytes for phox-dependent ROI production [20].

Nitric oxide radicals, including $NO^{-\bullet}$ and its derivatives (Reactive Nitrogen Intermediates, RNIs) arise via the inducible nitric oxide synthase (iNOS) pathway. The production of NO^- requires the amino acid L-arginine to be converted to NO^- and citrulline driven by iNOS activity in the presence of oxygen [21]. NADPH oxidase and MPO are constitutively expressed, while iNOS is not [16]. ROIs and RNIs react with each other as well, resulting in the generation of peroxynitrite [22]. The complex inter-relationships between ROS and RNS becomes manifest in MPO KO mice, where the augmented expression of iNOS and NO^- production results in less sepsis-induced lung injury and death [23].

In addition to the NADPH oxidases, two dual-specific oxidases (DUOX1/2) produce H_2O_2 rather than superoxide and are found predominantly in epithelial cells [24,25]. DUOX has been implicated in mucosal antimicrobial defence and the recruitment of leukocytes to the infected tissue [26]. Other ROS generating pathways are the electron transport chain in mitochondria [27], the xanthine oxidase system [28], monooxygenases and oxidases in peroxisomes, and the pseudoperoxidase or phenoloxidase activity of hemoglobulin or hemocyanin respectively[22].

2.1.1. NADPH phagocyte oxidase

Although the respiratory burst was characterized in the early 20th century, it took another 60 years to unravel the molecular mechanisms underlying this phenomenon and to demonstrate that NAPDH oxidase is the primary enzyme for generating this oxidative burst [29–32]. Five different isoforms of NADPH-dependent oxidases (NOX1-5) are known, of which NOX2 plays the most sig-

nificant role in antimicrobial and regulatory pathways (discussed further below) [28]. The NADPH oxidase in phagocytes (NOX2) consists of two membrane bound proteins, gp91^{phox} and p22^{phox} (together the cytochrome b), and four cytosolic proteins, p47^{phox}, p67^{phox}, p40^{phox} and Rac [33]. Segal et al. were the first to show that cytochrome b is responsible for the production of ROS [34]. Nowadays, mutations in the X-linked inherited CYBB and the autosomal recessive CYBA, NCF1, NCF2 and NCF4 are known, and result in chronic granulomatous disease due to a defective function of the NADPH oxidase [35].

Activation of the NADPH phagocyte oxidase occurs in response to a variety of physiological stimuli, including opsonized particles and ligation of specific pathogen recognition receptors including Dectin-1 [41,42]. *In vitro,* ROS can be stimulated by chemicals such as phorbol myristate acetate (PMA) through phosphorylation of p47-phox and activation of Nox2 [36,37].

The clinical significance of the NADPH phagocyte oxidase is well recognized as defects in the genes encoding this enzyme result in chronic granulomatous disease (CGD), one of the most significant aspergillosis patient populations [38]. CGD patients have the highest life-time incidence of invasive aspergillosis, and birth prevalence ranges from 1/250,000 to 1/120,000 in European countries and the US [16–19].

In addition to the direct antimicrobial effect of ROS, reactive oxygen molecules also play an important role in inflammation control, host-tissue injury, and numerous intracellular signalling pathways [39,40], releasing and activating cationic granule proteins (cathepsin G, elastase), autophagy and extracellular trap formation [41–44]. Key intracellular events to which ROS are linked include the activation of transcription factors including NFκB [45], induction of mitogenesis [46], and acting as substrate or cofactor for the enzymatic activity of indoleamine 2,3-dioxygenase (IDO) [47–49]. Activation of NADPH oxidase is coupled to the release of preformed antimicrobial proteases in the neutrophil that effectively prevent germination and display fungicidal activity [50]. The activation of NADPH oxidase leads to a rise in ionic strength necessary to release and activate cationic granule proteins [51]. In the CGD host, it is unclear to what extent the impaired activation of neutrophil proteases plays a role in susceptibility to invasive fungal infection, in addition to the absence of ROS. Normalisation of the phagolysosomal pH in CGD phagocytes increases the microbicidal activity of neutrophils [51]. In support of this, chloroquine (acidotrophic agent) increased the antifungal activity of neutrophils from CGD patients against *A. fumigatus* and *A. nidulans* [52].

Rac2 is a small Rho GTPase which is required for normal neutrophil function and is part of the NADPH oxidase complex. Patients with the Rac2D57N mutation have impaired neutrophil chemotaxis and superoxide production, resulting in severe recurrent bacterial infections [53,54]. As yet, no fungal infections have been described in patients with Rac2-deficiency.

2.1.2. Inducible nitric oxide synthase

Although $NO^{-\bullet}$ production has been studied most extensively in macrophages, a subset of dendritic cells and non-phagocytic cells also use $NO^{-\bullet}$ to kill microorganisms. The activity of iNOS is mainly regulated at the transcriptional level and is stimulated by microbial pathogen recognition receptors together with signalling from proinflammatory cytokines (IFNs, IL-1β, TNFα) [55]. As RNS production requires *de novo* protein synthesis, this response is less immediate than that observed for ROS production [55].

$NO^{-\bullet}$ regulates leukocyte recruitment and attachment through suppression of adhesion molecule activity, e.g. CD11/CD18 [56]. NO^{-} is consumed by neutrophils in a partly SOD dependent manner, but also other neutrophilic oxidases (including MPO) can catalytically consume NO^{-} in vitro [57,58]. Clark et al. [59] showed that CGD neutrophils, in contrast to MPO-deficient and healthy neutrophils, are unable to metabolize $NO^{-\bullet}$. On the other hand, Condino-Neto et al. [60] showed that $O2^{-\bullet}$ production is not essential for $NO^{-\bullet}$ synthesis in neutrophils and mononuclear phagocytes, as they showed $NO^{-\bullet}$ production by CGD phagocytes indirectly by inhibition of thrombin-induced washed platelet aggregation [60].

Although several iNOS promoter polymorphisms have been linked to increased iNOS expression playing a role in malaria pathology [61,62], no associations have been reported with fungal infections. iNOS deficiency in humans has not been demonstrated [61,62].

2.1.3. Myeloperoxidase

Myeloperoxidase (comprising 5% of the total protein in neutrophils) generates hyperchlorous acid (HOCl) through oxidation of chloride with H_2O_2 [38,63]. Myeloperoxidase deficiency in humans is common (1/2,000–1/4,000 in Europe and North-America) but usually asymptomatic [64]. An increased susceptibility to *Candida* infections may be observed (<5%), but often only develop if other predisposing conditions are present [64]. *Aspergillus* infections in humans with MPO deficiency have not been described, although MPO-deficient mice are more susceptible to aspergillus infection [19]. In addition, a role for MPO in the inflammatory response has been suggested. Myeloperoxidase-derived HOCl leads to oxidative degradation of foreign particles and an attenuation of the inflammatory response [65].

2.2. The fungus

2.2.1. Mitochondrial ROS

Within the fungus, the mitochondrion is the major source of ROS (Fig. 2). Classically, ROS are considered to be damaging agents generated in the cell as the necessary bi-products of cellular activity [66]. In the mitochondrion, oxidative phosphorylation enables the build-up of a proton gradient across the mitochondrial inner membrane, culminating in the conversion of ADP to ATP [67]. ROS accumulate as a direct consequence of oxidative phosphorylation and must be rapidly converted by cytoplasmic and mitochondrial SOD to hydrogen peroxide (H_2O_2), which is more stable than superoxide but can diffuse across membranes, targeting DNA [66]. Further detoxification of H_2O_2 is mediated by catalase (within peroxisomes and mitochondria), glutathione peroxidase, peroxiredoxins, and thioredoxins [68–71].

Mitochondrial Complex I and III are the major sources of O_2^- in the mitochondrion [72]. While establishing a proton gradient across the inner mitochondrial membrane, O_2^- produced by Complex I (NADH:ubiquinone oxidoreductase) accumulates within the mitochondrial matrix [73–76]. In contrast, O_2^- from Complex III accumulates primarily in the intermembrane space [77]. The distinct localisation demands distinct pools of SOD: Cu/Zn-Sod localised to the matrix, and Mn-Sod localised to the intermembrane space [66]. Complex IV also accepts electrons from Complex III, converting molecular oxygen to H_2O, thereby contributing to detoxification [78]. H_2O_2 must be further detoxified by catalase and glutathione. The Haber-Weiss reaction and Fenton chemistry convert O_2^- and H_2O_2 to highly reactive hydroxide radicals (HO^-), and oxidative stress in particular can cause the accumulation of hydroxyl anion HO^- in mitochondria [79].

2.2.2. Electron transfer in fungi

During phagocytosis, fungal Complex IV is inhibited by NO^-, a major product of iNOS-expressing macrophages [80,81]. This leads to the accumulation of Complex III-derived O_2^-. Most fungi encode an Alternative Oxidase (AOX) that bypasses Complex III and IV, allowing them to cope with accumulating superoxide [82–85]. For example, loss of Aox1 in *C. neoformans* increases killing by phagocytes [84]. Fungi additionally encode Type II NAD(P)H dehy-

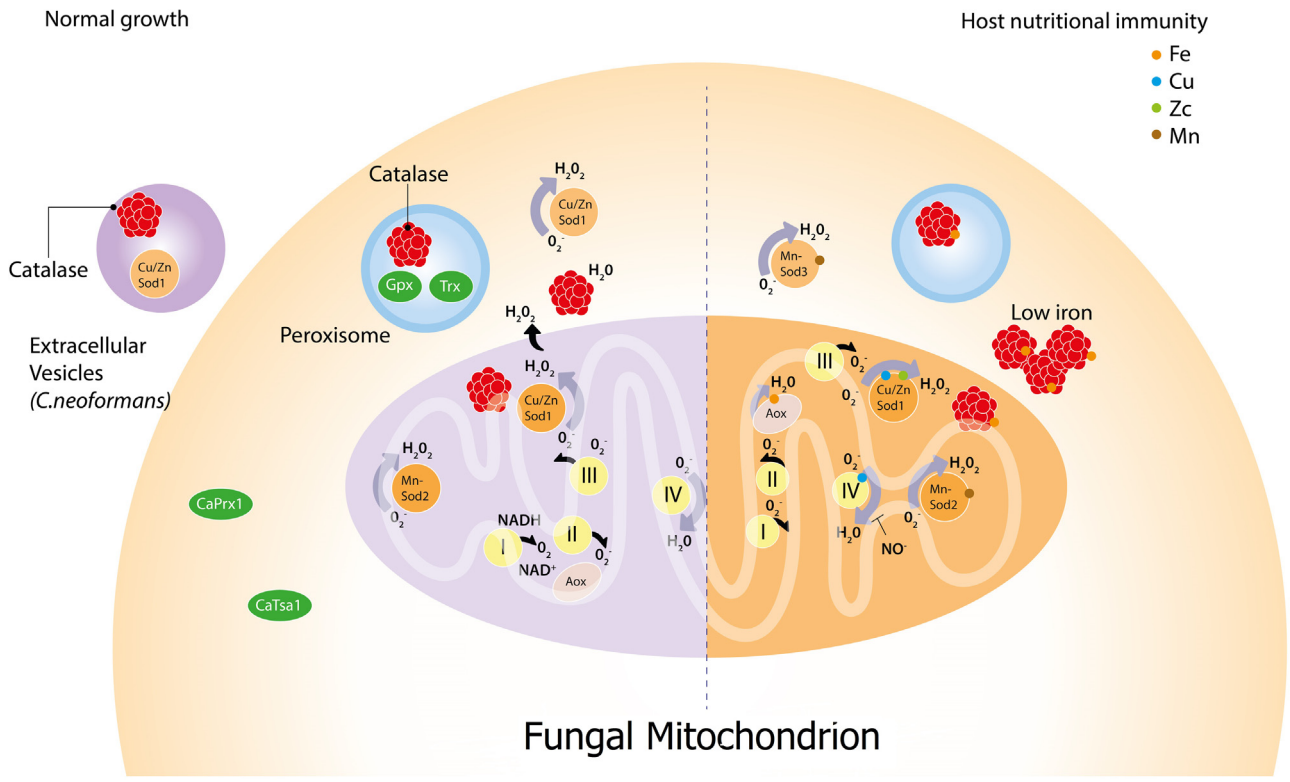

Fig. 2. In the absence of exogenous stress (normal growth, purple), oxidative phosphorylation enables the build-up of a proton gradient across the mitochondrial inner membrane (blue lines), culminating in the conversion of ADP to ATP. Superoxide (O_2^-) produced by Complex I, II and III accumulates in the matrix, where it is detoxified to H_2O_2 by Mn-Sod2. Complex III also produces reactive oxygen species (ROS) in the intermembrane space, where it is converted to H_2O_2 by Cu/Zn-Sod1. H_2O_2 can cross membranes and must be further detoxified to H_2O by catalase in the mitochondrion, in the cytoplasm, and in specialised vesicles called peroxisomes. In some species, catalase and Sod1 are also found in extracellular vesicles. During exposure to host nutritional immunity, copper, zinc, iron and manganese are limited. The metal co-factor corresponding to each enzyme is indicated. In *C. albicans*, low copper triggers the expression of Mn-Sod3 and reduction of Cu/Zn-Sod1 via the Mac1 copper-responsive transcription factor. This reduces copper requirements in the cell, enabling continued Complex IV function. Superoxide detoxification is also assisted by the activation of iron-dependent Aox1. Under low iron, constitutive expression of catalase can act as a sink for iron in the cell.

drogenases (NDE) that allows bypass of Complex I. *Saccharomyces cerevisiae* lacks Complex I entirely, relying on Nde1 and Nde2 for electron entry into the respiratory chain [86,87].

Fungal electron transport therefore constitutes a hybrid system that allows resistance to compounds that target Complex I (rotenone) and Complex IV (NO-) [88,89]. Mitochondrial function, Aox, and Nde activity are additionally linked to fungal stress response pathways. Loss of Aox in *C. albicans* increases sensitivity to fluconazole, presumably through drug induced increases in intracellular ROS [90,91]. In *A. fumigatus*, AoxA and Cytochrom C (CycA) cooperate to allow growth under hypoxic conditions, and adaptation to hypoxia is linked to virulence [92,93].

While NDE orthologs are present in the genomes of pathogenic fungi, there is limited information about their role in infection. However, loss of *C. albicans* NDH51 has been shown to abrogate filamentation [94], part of a larger emerging theme suggesting that mitochondrial ROS impacts hyphal development.

2.2.3. Superoxide dismutase

Superoxide dismutases fall into three classes based on co-factor binding and localization: Cu/Zn-Sod3 is secreted and detoxifies superoxide in the extracellular space. Mn-Sod2 is targeted to the mitochondrial matrix, where it detoxifies superoxide generated within the matrix by Complex I [95,96]. Complex III generates superoxide within matrix and in intermembrane space (IMS), where it is detoxified by a minor pool of Sod1 (~3% of total Sod1) [97]. The majority of Sod1 is cytoplasmic. In *S. cerevisiae*, Sod1 was recently shown to translocate to the nucleus upon ROS stress exposure in a Mec1 kinase-dependent manner. Further, ChIP experiments demonstrated Sod1 binding to the promoters of target genes whose regulation was lost in a *sod1*Δ mutant, suggesting that nuclear Sod1 has additional regulatory roles [98].

2.2.4. NADPH oxidase complex

The mammalian NADPH oxidase complex (NOX) is responsible for the respiratory burst (Fig. 3). Fungal NOX are well described in filamentous fungi and plant pathogens, in which a core complex comprised of an NADPH Oxidase (Nox), a Nox activator (NoxR) and Rac enable plant-fungal symbiosis and pathogenesis and fungal morphogenesis [99,100]. This has important ramifications for saprophytic *Aspergillus* species, where NoxA, NoxR, and Rac are required for differentiation, apical dominance and polarised growth [13,14,101]. Here, ROS are thought to act as signalling molecules in the cell, reinforcing a superoxide gradient that directs polarised growth (Fig. 3). Similarly, a *C. albicans* Nox complex was recently described and was shown to influence filamentation through the endogenous generation of a superoxide gradient outside the cell. *Candida albicans* Sod5 then converts superoxide to H_2O_2, enhancing polarised growth and contributing to pathogenesis [12].

2.2.5. Scavengers of reactive oxygen species

Melanin is known to be an important virulence factor by protecting fungal cells from ROS produced by phagocytic cells [102,103] and by modulating the host immune response [104]. Fungal melanin biosynthesis via either the L-DOPA or DHN pathways contributes to fungal oxidative and nitrositive stress resistance [105,106]. *C. neoformans* L-DOPA-derived melanin mediates resistance to ROS/RNS stress and also impairs phagocytosis [107,108].

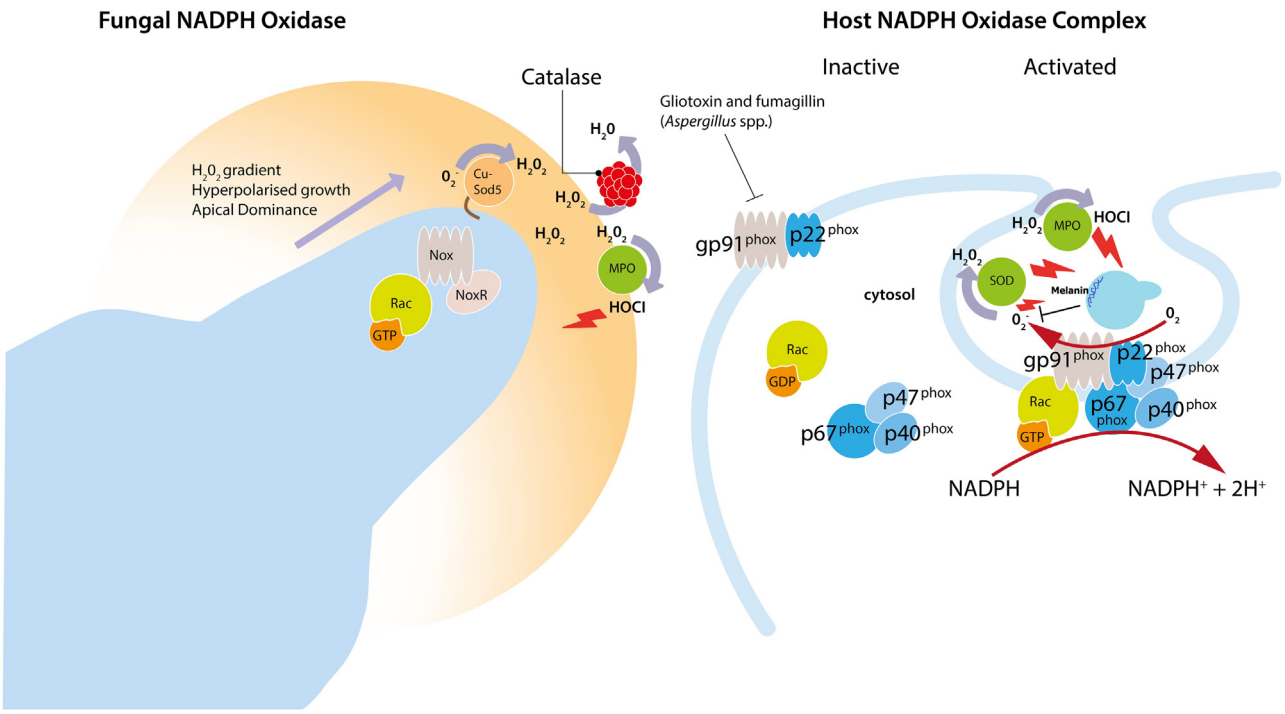

Fig. 3. The fungal NADPH oxidase complex comprises three proteins: Nox, NoxR, and Rac and has been well described in plant pathogens where it interacts with various structural proteins to reinforce apical dominance (not shown). *C. albicans* Nox (Fre8) is expressed during hyphal growth and superoxide generated at the cell wall is detoxified by secreted anchored Sod5. This results in the built up of a H_2O_2 gradient. Exogenous H_2O_2 has been shown to cause hyperpolarisation of the bud during the *C. albicans* yeast-to-hyphae transition. Exogenous H_2O_2 is a substrate for host MPO to generate cytotoxic HOCl, and it is detoxified by secreted fungal catalase. The human NADPH oxidase consists of five subunits of which 2 are localized in the plasma membrane ($gp91^{phox}$ and $gp22^{phox}$) and three in the cytosol ($gp40^{phox}$, $gp47^{phox}$, $gp67^{phox}$) in the inactivated phagocyte. Upon cell activation by recognition and binding of fungal pathogens the three cytosolic subunits form a heterotrimer which translocates to the other 2 subunits on the plasma membrane transforming to into the phagosomal membrane upon phagocytosis of the fungal pathogen. Electrons derived from NADPH are used to generate superoxide, and other reactive oxygen species including hydrogen peroxide (H_2O_2) and hypochlorous acid (HOCl). Melanin in the cell wall of various fungi acts as a scavenger of reactive oxygen species thereby protecting the fungal cell against killing.

In *Aspergillus* species, loss of melanin similarly increases sensitivity to ROS and phagocyte killing, impacting both the conidial and hyphal phases [102,109]. Despite this, *A. fumigatus* strains deficient in melanin are not reduced for virulence in vivo [110].

3. Oxidative stress responses in fungi

3.1. *Candida albicans*

3.1.1. *Regulation of mitochondrial ROS during nutritional immunity*

As mentioned above, alternate pathways for electron transport in the fungal mitochondrion enable continued respiration in the face of host stress. There have been significant advances in our understanding of this flexibility in the human commensal fungus *C. albicans* and the contribution of oxidative stress resistance to pathogenesis [6]. During dissemination, host nutrient immunity sequesters micronutrients necessary for SOD (copper, manganese, iron), Cytochrome C (COX, Complex IV; copper), and AOX (iron) function [111]. *C. albicans* cytosolic Cu-Sod1 and Mn-Sod3 are differently expressed under the control of the copper-responsive transcription factor Mac1, enabling adaptation to fluctuating copper levels in the kidney [112,113]. Cu/Zn-*SOD1* levels in the cytosol fall, while Mn-Sod3 levels rise. Aox1 is activated, and there is sufficient copper availability for continued COX function, maintaining mitochondrial homeostasis.

A similar balance between micronutrient availability and ROS detoxification is observed for *C. albicans* catalase Cat1. The conversion of H_2O_2 to water is performed by the heme peroxidase, catalase. *C albicans* Cat1, localised to the cell wall and peroxisomes, protects the fungus from acute oxidative and peroxide stress, as well as combinatorial stress [10,114–116]. However, Cat1 is tightly regulated in the cell and is dispensable for virulence in a mouse model of infection [10]. A detailed analysis of the impact of constitutive *vs.* regulated expression of Cat1 revealed that Cat1 expression depletes iron stores, and constitutive expression disrupts iron homeostasis, making the fungus vulnerable in the face of iron sequestration.

Finally, interaction with the host can alter fungal amino acid metabolism. Upon interaction with ROS-expressing macrophages, *C. albicans* specifically induces arginine biosynthesis, and this induction is dependent on ROS and host NADPH oxidase activity [117]. Fungal arginase biosynthesis is not triggered in iNOS expressing macrophages [117]. Instead, in macrophages expressing iNOS, *C. albicans* induces host arginase, which depletes L-arginine, the substrate for iNOS, and blocks NO^- production [118]. Arginine biosynthesis appears to support germ tube emergence and hyphal growth by serving as a substrate for fungal arginase Car1 and urea amidolyase Dur1/2 to produce a CO_2 gradient triggering the yeast-to-hyphal transition [119].

3.1.2. *Detoxification of exogenous ROS*

Upon exposure to acute oxidative stress or co-culture with phagocytes, *C. albicans* induces a transcriptional response including catalase, glutathione peroxidase, superoxide dismutase, and thioredoxin. However, while this response is required to survive acute stress or survival upon phagocytosis, it appears to be dispensable for long-term infection [6]. Significant effort has characterized the role of Cap1, Hog1, and Rad53 to acute oxidative stress response and virulence and this has been reviewed elsewhere [6]. However, together these data suggest that the ROS microenvironment at the host-pathogen interface is dynamic and influenced by both

host and fungal factors. Two groups have sought to visualize interactions at this interface, in mice and zebrafish models of fungal infection. Brothers et al. showed that fungal catalase expression is dependent on activation of host $p47^{phox}$ [120]. Consistent with this, Enjalbert et al. showed that *CAT1* is induced upon interaction with neutrophils, but not macrophages [121]. However, despite the clear activation of *CAT1* upon phagocytosis, Enjalbert et al. also report that only 4% of fungal cells in the kidney expressed *CAT1*. These findings may be explained by redundancy in ROS detoxification strategies: *C. albicans* has expanded its repertoire of Sods, encoding a class of GPI-anchored extracellular Cu-Sods (Sod4-6) [122–124]. These Sods, which are secreted in the apo-form, lack a zinc-binding site, but readily bind environmental copper, activating dismutase activity [124]. Sod5 is induced during the yeast-to-hyphal switch, dampens the ROS burst during co-culture with macrophages or neutrophils, and loss of Sod5 inhibits pathogenesis [123].

3.1.3. Exogenous and endogenous ROS support hyphal growth

Several *in vitro* experiments have linked the fungal oxidative stress response to the yeast-hypha transition [5,125,126]. It has also been reported that mild oxidative stress can enhance polarized growth in a thioredoxin-regulated manner *in vitro* [127,128]. Exposure of *C. albicans* yeast to an H_2O_2 gradient triggers hyperpolarisation of the new bud [127]. The physiological relevance of this finding was recently demonstrated by the discovery that *C. albicans* encodes a fungal NADPH Oxidase, Fre8 [12]. Fre8 and Sod5 together generate an H_2O_2 gradient outside the cell that supports hyphal growth [12].

3.2. Cryptococcus *species*

A growing body of data suggest mitochondrial activity is closely linked with *C. neoformans* infection biology. The glucoronylxylomannan polysaccharide capsule is well established as an antioxidant defence, and capsule growth may be influenced by mitochondrial activity [129,130]. Treatment with inhibitors of either canonical or alternative oxidase (Aox) at fungistatic concentrations prevented capsule enlargement [130]. However, capsule enlargement is also linked to cell cycle progression [131], complicating efforts to separate growth defects and capsule defects. Cryptococcal mitochondria appear to be essential, as efforts to generate *petite* mutants similar to those that enable such studies in *S. cerevisiae* have failed [132].

C. neoformans var. *grubii* and *C. gattii* encode Cu/Zn-Sod1 homologues that are required for virulence and resistance to phagocytic killing [9,133,134]. Loss of Sod1 does not impact growth, capsule, melanin, or morphogenesis in either species, but does impacts *C. gattii*, but not *C. neoformans* var. *grubbii,* expression of laccase, urease, and phospholipases, highlighting fundamental differences in how these two species respond to host stress. In both species, Mn-Sod2, predicted to detoxify ROS generated by Complex III, is required for growth at 37 °C [135,136]. Interestingly, *C. neoformans* Aox1 transcription increases at 37 °C. *C. neoformans* Aox1 is dispensable for growth, but required for full virulence [84]. Together, these findings suggest that, unlike copper-regulated *C. albicans* Aox1, *C. neoformans* Aox1 is not able to compensate for the accumulation of Complex III-derived superoxide in the host. In contrast to *C. albicans*, which has expanded its repertoire of SOD, but encodes a single catalase, *C. neoformans* and *C. gattii* encode expanded catalase families (CnCat1-4, CgCat1-3). However, a *C. neoformans* quadruple catalase mutant showed no defects in stress resistance, growth, or pathogenicity [137]. Sod3 has not been characterised in either species, although both genomes encode a single predicted Fe/Mn-Sod protein. Proteomic analysis has identified *C. neoformans* Cu/Zn-Sod and catalase within extracellular vesicles, suggesting they may have unidentified roles in detoxification of environmental ROS [138,139].

Mitochondrial morphology contributes to virulence in *C. gattii* outbreak strains [140]: virulent strains exhibit mitochondrial fusion upon phagocytosis by host cells, and this is linked to increased intracellular proliferation rate [132]. Microarray analysis found increased expression of mitochondrial genes. Further work demonstrated that tubularisation is triggered in a sub-population of cells by exposure to host ROS, and that tubularised cells are quiescent yet influence proliferation rate in their neighbors [141]. The molecular mechanisms underpinning this division of labor remain uncharacterised. Similar tubularisation has not been observed in *C. neoformans* var. *grubbii*.

3.3. Aspergillus *species*

Aspergillus fumigatus encodes 4 Sods – Cu/ZnSod1 and Mn-Sod2-4 [142]. All four are intracellular, but patients with Aspergillosis are seropositive for Sod1 [143–146], and anti-Sod3 IgE is associated with allergic response [147,148]. Consistent with their role in detoxifying mitochondrial ROS, Sod1 and Sod2 are highly expressed during conidial germination, when spores convert from a metabolically inactive to active state, and loss of *SOD1* or *SOD2* increases sensitivity to drugs that increase mitochondrial ROS (metadione) [149,150]. AfSod3, unlike other Mn-Sods, lacks a mitochondrial signal sequence, suggesting that it is cytoplasmic, and is induced during the later stages of hyphal growth, however its specific role is not known [142]. Mn-Sod4 is constitutively expressed at low levels and is essential- heterozygous diploid *SOD4/sod4* strains fail to produce *sod4*Δ spores [142].

Like *C. neoformans,* mitochondrial activity is important for *Aspergillus* thermotolerance and resistance to phagocytic attack: Sod1 and Sod2 are required for growth above 45 °C and are more sensitive to killing by phagocytes from immunocompetent mice. However, Sod1-3 are all dispensable for virulence in an immunocompromised mouse model of infection (OF1). Similarly, catalase (CatA (expressed in spores), Cat1, Cat2) [151,152], the stress responsive transcription factor Skn7 [153], and the redox responsive transcription factor Yap1 are all required for resistance to exogenous ROS stress [151], but are not required for virulence. This suggests that, similar to *C. neoformans*, there is significant redundancy in the fungal oxidative stress response. Consistent with this, loss of both mycelial catalases (Cat1, Cat2) delays virulence in a mouse model of aspergillosis [151]. In contrast, mitochondrial AfCycA is required for growth under hypoxia and for virulence, even in the presence of a functional alternative oxidase (AfAoxA) [92].

In *Aspergillus* species, the production of toxins (gliotoxin and fumagillin) that inhibit the fungicidal activity of neutrophils by blocking NADPH oxidase formation have a significant impact on survival in the host [154,155]. Inhibiting gliotoxin production reduced fungal virulence [156]. Neutrophilic NADPH oxidase activity can also impact fungal programed cell death pathways by triggering caspase activity. *Aspergillus* (and other saprophytic fungi) can express an anti-apoptotic protein, Bir1, that suppresses this programmed cell death response, enabling growth in the face of host ROS [157,158].

4. Host oxidative responses in fungal immunity

4.1. Aspergillus *species*

In the CGD host, the absence of functional NADPH oxidase has an impact on both antifungal effector mechanisms and control of the inflammatory response. Clinical epidemiological data strongly suggests a direct link between the absence of a functional

NADPH oxidase complex and infections caused by catalase-positive microorganisms. *Aspergillus* species, which require fungal Nox and endogenous ROS to maintain apical growth, are able to breakdown their own hydrogen peroxide radicals by catalases. This makes fungal-derived H_2O_2 unavailable to phagocytes for conversion into more potent fungicidal reactive oxygen intermediates. Animal studies focusing on fungal pathogenesis in the CGD host have predominantly used *A. fumigatus* as the infective fungal pathogen, and only a few have studied the virulence of *A. nidulans* in CGD mice [159–162]. Nevertheless, *in vivo* and *in vitro* studies have reported unaltered virulence of catalase-deficient *A. nidulans* in p47$^{phox-/-}$ mice [160,161]. Experimental infections with *C. albicans*, *A. tanneri* and *Neosartorya udagawae* have been compared to *A. fumigatus* infections in separate murine studies and likewise suggest roles for host NADPH oxidase in infection control [19,163,164].

Aspergillus conidia are mainly killed by non-oxidative intracellular killing mechanisms, either by macrophages or neutrophils in a phagocytosis-dependent manner. *In vitro* studies have shown that stimulation of human neutrophils (PMN) and peripheral blood mononuclear cells (PBMC) with either *A. fumigatus* conidia or hyphae results in increased production of ROS and inhibition of germination and fungal killing [165,166]. Surprisingly, the stimulation of ROS showed to be *Aspergillus* species-specific: *A. nidulans* was shown to be a weak inducer of ROS in both cell types [166]. In addition, no defect in inhibiting growth of *A. nidulans* was observed in CGD neutrophils [167].

Several studies have investigated the ability of *Aspergillus* species to modulate host phagocyte ROS and the impact of this interaction on fungicidal activity. Akpogheneta et al. [168] evaluated the activity of human PMN and PBMC against hyphae from *A. fumigatus* and non-*fumigatus Aspergillus* species. They concluded that non-opsonized hyphae from all species tested suppress the PMN oxidative burst below basal levels, while serum-opsonization abrogated this suppression. However, opsonised *A. fumigatus* was more stimulatory than non-*fumigatus Aspergillus* species. Similarly, PMN induced less hyphal damage to non-*fumigatus Aspergillus* species, particularly *A. flavus* and *A. nidulans*, than to *A. fumigatus*. [168]. In contrast, we found that non-opsonized hyphae of *A. nidulans*, being poor ROS inducers, were more effectively damaged than those of *A. fumigatus*, which did induce a robust respiratory burst [167]. A more recent study showed unopsonized *A. fumigatus* hyphae not being killed by healthy human neutrophils over a 4 h period. Opsonization of *A. fumigatus* hyphae with heat-inactivated serum or immunoglobulin-G preparations resulted in effective hyphal killing [168].

The exact role of NADPH oxidase activity in macrophages with respect to fungicidal properties is less clear, and studies have produced conflicting results. Experimental studies with alveolar macrophages (AM) from gp91$^{phox-/-}$ mice showed phagocytosis and killing rates of *A. fumigatus* and *A. nidulans* conidia comparable to AM from normal mice [159,167,169,170]. In contrast, AM from p47$^{phox-/-}$ mice were unable to kill *A. fumigatus* conidia [171,172]. Furthermore, healthy murine AM pre-treated with inhibitors of NADPH oxidase were not able to kill *A. fumigatus* conidia [171]. Indirect evidence of NADPH-independent resistance in alveolar macrophages was found by Shibuya et al., who showed that killing of catA conidia by alveolar macrophages and conidial virulence in an animal model were similar to those with wild-type conidia [173].

Microarray data of murine C57BL/6 and gp91$^{phox-/-}$ AM exposed to *A. fumigatus* conidia *in vivo* showed that the most marked early transcriptional changes did not indicate obvious NADPH oxidase involvement but instead implicated genes involved in PMN recruitment [170]. An examination of invasive pulmonary aspergilosis in an experimental murine model showed that early PMN recruitment is crucial in preventing hyphal proliferation and tissue invasion early after infection [169]. Neutrophil recruitment was slower in gp91$^{phox-/-}$ mice, resulting in increased germination despite the formation of extensive neutrophilic aggregates in the lungs at later time points. ROS seem to act as chemo-attractants early in the infection, but are also involved in the inactivation of chemotactic molecules, downregulation of IL-8 and clearance of neutrophils, once sufficient neutrophils have arrived at the site of infection [174,175].

It is clear that the almost exclusive contribution of NADPH oxidase to microbial killing is a justified subject of debate, and recent studies have indicated a critical role of the NADPH oxidase as regulator of immune homeostasis at multiple levels [17]. We have shown that the absence of the respiratory burst is associated with dysregulated inflammation, characterised by uncontrolled IL-1β release in the CGD host, and further contributes to the pathogenesis of Invasive Aspergillosis (IA) in CGD patients [52,176]. Exaggerated IL-1α production has been demonstrated in CGD murine models of sterile inflammation and is associated with excessive and prolonged inflammation and significant host damage [177]. *Aspergillus* provides a potent stimulus for IL-1β production in CGD, with X-linked CGD mice exhibiting a 5-fold increase in pulmonary IL-1β mRNA expression compared with wild-type mice following respiratory challenge with *A. fumigatus* [159]. The role of ROS as mediators/regulators in inflammation has also been underscored by van de Veerdonk et al. [178]. They showed that ROS appear to dampen inflammasome activation. As a consequence, the absence of ROS in CGD monocytes may partly explain the inflammatory complications seen in CGD patients. A recent study by Segal et al. [179] supports the occurrence of NADPH oxidase-dependent, redox-mediated signalling which is critical for termination of lung inflammation. By challenging NADPH oxidase-deficient p47$^{phox-/-}$ mice and gp91^{phox}-deficient mice with intratracheal zymosan, they showed that NADPH oxidase limits lung inflammation by attenuating the proinflammatory transcription factor NF-kB and by activating Nrf2, a key redox-sensitive anti-inflammatory regulatory transcription factor.

Studies in mice have shown an important role of NADPH oxidase in IL-17 regulation. Overproduction of IL-17 was observed in CGD mice and has been linked with defective L-tryptophan metabolism due to the finding that ROS are crucial for indolamine-2,3-dioxygenase activity, the enzyme responsible for conversion of L-tryptophan to L-kynurenine [180]. However, in humans with CGD, tryptophan metabolism has been shown to be intact, indicating that the mechanism of fungal susceptibility is different in humans and in mice [181–183]. Although it seems that an efficient anti-*Aspergillus* defence relies more on a Th1 immune response [184], the absence of an adequate IL-17 response, as observed in our study [183], might contribute in the CGD host to the inability to clear fungal infections.

Using a transgenic zebrafish line expressing the dominant negative Rac2D57N mutation in neutrophils, Knox et al. were able to show its importance in antifungal immunity [185]. Rac2 plays a role in neutrophil migration and the generation of reactive oxygen species forming a complex with the NADPH oxidase. Zebrafish larvae with this mutation were highly susceptible to *A. fumigatus* infection with a mortality of 50% by day 7, while survival was 100% in wild-type larvae. Only 2 cases of primary phagocytic immunodeficiency caused by Rac2 mutation have been reported in humans [53,186–188].

MPO-deficient mice are more susceptible to the development of pulmonary infection following the intranasal instillation of *A. fumigatus* [189]. The killing of *Aspergillus* hyphae by MPO-deficient human neutrophils is defective; however, the neutrophil-mediated inhibition of *Aspergillus* conidia germination has shown to be normal [190]. This may explain why MPO-deficient patients are not prone to develop *Aspergillus* infections,

and those infections have not been reported in MPO deficiency [191].

Resting and swollen conidia of *A. fumigatus* are relatively resistant to peroxynitrite *in vitro* and only a moderate fungistatic effect was observed [192].

4.2. Candida *species*

One of the earliest studies reporting a role for oxidative responses in an effective immune response against *C. albicans* was performed by Lehrer in 1970 [193]. Using isolated neutrophils from 7 healthy controls, 1 MPO-deficient patient and 2 children with CGD, he showed that both myeloperoxidase and hydrogen peroxide are required for candidacidal activity. However, MPO-deficient neutrophils cells exerted a demonstrable candidastatic effect, in contrast to CGD neutrophils.

In vitro, both yeast and hyphal forms of *C. albicans* can trigger ROS production in bone marrow-derived macrophages as well as myeloid dendritic cells, with a five times higher oxidative burst in murine dendritic cells compared to bone marrow-derived macrophages [194]. Expanding on the *in vitro* data, the first *in vivo* evidence that the phagocyte NADPH oxidase regulates filamentation of *C. albicans* within the intact host, results from an experimental zebrafish model. An intact NADPH oxidase proved to be crucial to limit fungal proliferations and limiting filamentous growth after zebrafish larvae were injected with *C. albicans* yeast cells into the hindbrain [120]. That NADPH oxidase has other functions than antifungal killing per se during invasive candidiasis, as has been nicely shown in following studies performed by the same group. They showed a mechanistic role of NADPH oxidase in promoting neutrophil and macrophage chemotaxis and intracellular containment of *C. albicans* to limit filamentous growth [195]. Remarkably however, if *C. albicans* cells were blocked in the yeast phase, NADPH oxidase activity was no longer required for effective fungal containment. In addition, their results suggest a role for non-phagocyte-expressed DUOX (in epithelial cells) in promoting efficient chemotaxis of phagocytes to the site of infection [195].

The role of NO^- in macrophage candidacidal activity has been well-established, although NO^- itself is not directly candidacidal for *C. albicans* [196–199]. Peroxynitrite ($ONOO^-$) is candidacidal *in vitro* and has been shown to be responsible for the candidacidal activity of NO^--producing macrophages [199]. Mice deficient in both iNOS and NADPH oxidase showed increased susceptibility to invasive candidiasis [200]. However, the data showed that this was unrelated to decreased fungal killing but due to an excessive inflammatory response.

Neutrophils use both oxidative and non-oxidative effector mechanisms to kill *Candida* spp. [201]. Although both mouse and human granulocytes that are deficient in either NADPH oxidase or MPO are incapable of efficient *Candida* killing *in vitro* [193,202]. *In vitro* studies have shown that MPO-deficient neutrophils exhibit a defect in candidacidal activity. For example, MPO-deficient leukocytes kill phagocytosed *C. albicans* much more slowly compared to normal leukocytes [202,203]. In addition, MPO-deficient mice were shown to be increased susceptible to intratracheal *C. albicans* infection [204]. In a study comparing the susceptibility to fungal infection with WT, MPO-deficient, and CGD mice, it was concluded that when the fungal load is low, ROS formed by the NADPH oxidase of neutrophils are adequate to control infection in the absence of MPO. But at high fungal load, products of the respiratory burst and MPO are needed [19,205].

Similar survival of wild-type and MPO-deficient zebrafish was observed after *C. albicans* infection [206], being somehow in contrast with the previous findings obtained in a murine model of MPO-deficiency. However, a significant higher fungal load was found during the early phase of infection in the MPO-deficient compared to wild-type zebrafish. Neutrophil migration was not affected in the MPO-deficient zebrafish. Remarkably, MPO-deficient zebrafish showed an increased inflammatory response characterised by an increased number of neutrophils at the site of infection and gene expression of IL-1β and IL-8, at later time points after infection. In addition, basal gene expression of IL-1β and IL-8 was significantly elevated in MPO-deficient zebrafish, comparable to observation in NADPH oxidase deficient patients [183].

More recent studies have reported distinct and independent mechanisms of human neutrophils to kill *C. albicans* [190]. Unopsonized *C. albicans* yeasts are killed by non-oxidative mechanisms depending on complement receptor 3 (CR3) signalling via Syk, phosphatidylinositol-3-kinase (PI3K) and caspase recruitment domain-containing protein 9 (CARD9). Phagolysosomal killing of serum opsonized *C. albicans* yeasts is dependent on Fcγ receptors, protein kinase C (PKC), Syk and ROS production by NADPH oxidase [207]. Using neutrophils from patients with inborn errors of neutrophil function (e.g. Dectin-1 deficient, CARD-9 deficient and CGD patients) those differential mechanisms were elegantly shown [207].

NADPH oxidase deficiency in patients with chronic granulomatous disease is associated with significantly increased susceptibility to invasive mould infection, but it has only little effect on susceptibility to *Candida* infection [4]. This suggests that alternative mechanisms *in vivo* can compensate for a defect in NADPH oxidase-dependent killing mechanisms. Similarly, MPO deficiency in humans does not predispose to *Candida* infection, unless there are concomitant risk factors (such as diabetes) [208].

4.3. Cryptococcus *species*

The very first study demonstrating a role for oxidative killing mechanisms in the resistance to cryptococcosis was made by Diamond et al in 1972 [209]. By inhibiting MPO activity in neutrophils from healthy donors and using neutrophils from CGD patients, defective killing of *C. neoformans* was observed [209,210]. By neutralizing specific ROI and using a *C. neoformans* isolate impaired in mannitol production, it was shown that OH^- and HOCl are critical anti-cryptococcal effector molecules [211].

The role of MPO in an effective immune response against cryptococci has been shown in experimental murine models. MPO-deficient mice are more susceptible to the development of pulmonary infection following the intranasal instillation of *Cryptococcus neoformans* [212]. Higher fungal burdens were observed in the lung and spleen, but not in the bloodstream of the MPO-deficient mice. Whereas cryptococci were hardly recovered from brain tissue in wild-type mice, significant fungal burden were found in $MPO^{-/-}$ mice on days 34 and 60 post-infection as well has higher IL-1β release [212]. Granulocyte colony-stimulating factor (G-CSF) treated neutrophils from HIV-infected patients showed an enhanced killing of *C. neoformans* isolates closely related to an augmented ROS production [213,214].

More recently, Davis et al. showed that neutrophils with a mutation in Rac2 (component of the NADPH oxidase complex) were less able to control fungal burden in a zebrafish larvae model of invasive cryptococcosis [215]. This effect was most pronounced after infection with the yeast form, supporting a protective effect of neutrophils late in the infection.

4.4. Pneumocystis jiroveci

Three case reports have been published in the English literature describing the occurrence of *Pneumocystis jiroveci* pneumonia (PCP) in 3 patients with CGD [216–218]. Although this may suggest that a functional NADPH oxidase is required in the host response against PCP, in more recent epidemiological studies, PCP is not observed

as a significant infectious complication in patients with CGD [219]. If a defective NADPH oxidase leads to other immunological consequences, specifically to T-cell function and thereby increasing the risk for PCP, is not well studied. Reactive oxygen species do have an impact on several signalling pathways in T-lymphocytes, including redox-sensitive proteins, transcription factors and Ca^{2+} channels [220,221]. Two separate studies have shown that patients with CGD have diminished T-cell numbers compared to healthy controls [222,223]. Lower CD3+ T-cell counts were associated with the development of fungal disease, but differences didn't reach statistical significance [222]. T-lymphocytes do express a $gp91^{phox}$- and $p47^{phox}$-dependent NADPH oxidase and contributes to the sustained production of H_2O_2 after TCR engagement [224]. Studies performed with T-cells derived from $gp91^{phox-/-}$ and $p47^{phox-/-}$ mice and humans (CGD patients) demonstrate a defect in TCR-induced production of hydrogen peroxide [224]. Nevertheless, the importance of the NADPH oxidase in T-lymphocytes in antifungal immunity remains to be clarified.

5. Concluding remarks

Here we have discussed the influence of host and fungal-derived ROS and RNS on fungal infection biology with a focus on three major human fungal pathogens, *A. fumigatus, C. neoformans,* and *C. albicans.* Throughout, an emerging theme is that ROS production, regulation, and response are a central axis of the host-pathogen interaction. Both host and fungi produce ROS, use conserved mechanisms to detoxify ROS, and leverage ROS in their local environment to mediate defence mechanisms. ROS production and detoxification also intersect with host nutritional immunity, and in at least one instance, host ROS stimulate altered amino acid biosynthesis in a fungus. The significance of ROS for fungal killing is clear, however there are several examples of host ROS either not being required to control the growth of fungi (*A. nidulans* in CGD) or contributing to fungal pathogenesis by providing signals for the yeast-to-hyphal switch (*C. albicans* hyperpolarised buds). A greater understanding of both the dynamics of oxidative attack and the consequences of defective phagocyte ROS and RNS production on fungal growth and morphology *in vivo* could have an impact on the treatment of patients with invasive fungal infections.

Acknowledgments

AW is supported by the Wellcome Trust Strategic Award (grant 097377) and the MRC Centre for Medical Mycology (grant MR/N006364/1) at the University of Aberdeen. ERB is supported by an Anniversary Future Leaders Fellowship from the UK Biotechnology and Biological Research Council (BB/M014525/1) at the University of Birmingham.

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