Fungal factors involved in host immune evasion, modulation and exploitation during infection

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Abstract
Human and plant pathogenic fungi have a major impact on public health and agriculture. Although these fungi infect very diverse hosts and are often highly adapted to specific host niches, they share surprisingly similar mechanisms that mediate immune evasion, modulation of distinct host targets and exploitation of host nutrients, highlighting that successful strategies have evolved independently among diverse fungal pathogens. These attributes are facilitated by an arsenal of fungal factors. However, not a single molecule, but rather the combined effects of several factors enable these pathogens to establish infection. In this review, we discuss the principles of human and plant fungal pathogenicity mechanisms and discuss recent discoveries made in this field.

KEYWORDS
effector proteins, fungal virulence factors, host exploitation, host modulation, human pathogenic fungi, immune evasion, plant pathogenic fungi

1 | INTRODUCTION

Among the estimated 3–5 million fungal species existing worldwide, relatively few are described as pathogens of plants, animals or humans (Blackwell, 2011). Nevertheless, these fungal species can have dramatic effects in nature, agriculture and human health. For example, many plant pathogenic fungi dramatically reduce crop yields (Doehlemann, Okmen, Zhu, & Sharon, 2017; Kohler, Hube, Puccia, Casadevall, & Perfect, 2017) and only a few hundred human pathogenic fungal species infect more than a billion people every year (Brown, Denning, & Levitz, 2012; Kohler et al., 2017). Although the hosts of these two groups of pathogenic fungi are diverse, the principles of plant and human fungal pathogenicity mechanisms are similar. In this review, we focus on recent studies dealing with factors and properties of selected plant and human pathogenic fungi facilitating infections. We will further focus on the examples of factors produced by fungi from both groups, which facilitate three key pathogenic aspects: immune evasion, host target modulation and exploitation of micro- and macro-nutrients from the host.

Annika König and Rita Müller contributed equally to this study.

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2 | PROTECTION FIRST OF ALL – FUNGAL FACTORS INVOLVED IN IMMUNE EVASION

Any initial invasive contact of plant or human pathogenic fungi with the host surface will likely induce an immune response detrimental for the fungus. Thus, escaping the host’s immune response is a general feature of all successful fungal pathogens. In fact, fungal pathogens have evolved sophisticated strategies to accomplish this, for example, by avoiding recognition and by manipulating host responses.

2.1 | Venetian masquerade ball – Shielding of immunostimulatory cell wall moieties

The fungal cell wall is the first immunostimulatory layer coming into direct contact with a host cell. It is comprised of chitin, glucans, polysaccharides (e.g., mannoproteins), waxes and pigments, depending on the pathogen (Gow, Latge, & Munro, 2017). Recognising these cell wall components cannot only alarm the host of a potential attack by a microbial invader, but also induce a targeted immune response towards a fungal pathogen. A well conserved immunostimulatory part of the cell wall of human and plant pathogenic fungi is β-glucan, which is sensed by host pathogen recognition receptors (PRRs), such as dectin-1 on human cells, subsequently initializing an immune response. Shielding is a common fungal strategy to prevent this recognition. Pathogenic Candida spp. cover β-glucan with mannoproteins, thus preventing receptor binding (Gow et al., 2017). In the airborne pathogen, Aspergillus fumigatus, the surface of hydrophobin RodA has been identified to mask the β-glucan layer (Carrion Sde et al., 2013). Cryptococcus neoformans synthesises a polysaccharide capsule to shield its β-glucan in the cell wall (O’Meara & Alspaugh, 2012), whereas Histoplasma capsulatum has been shown to shield its β-glucan layer with a coat of α-1,3-linked glucans, rendering it non-immunostimulatory (Rappleye, Eissenberg, & Goldman, 2007). This fungus also secretes Eng1, a β-glucanase, reducing the amount of exposed β-glucan on its surface (Garfoot, Shen, Wuthrich, Klein, & Rappleye, 2016).

Similarly, the plant pathogen, Colletotrichum graminicola, selectively down-regulates GLS1, a β-glucan synthase, during biotrophic growth, making hyphae non-immunogenic early on during infection (Oliveira-Garcia & Deising, 2013). Specific proteins that evolved to act exclusively during interactions with the host and thus named “effectors,” can play a role in shielding as well, as shown for the root endophyte, Piriformospora indica. This fungus secretes FGB1, which binds β-glucan, altering the fungal cell wall composition and suppressing β-glucan-triggered reactive oxygen species (ROS) induction (Wawra et al., 2016).

Chitin is a cell wall component able to activate chitin-triggered immunity (CTI) in the host plant (Gow et al., 2017). Many fungal plant pathogens secrete LysM effector proteins containing chitin-binding LysM motifs, thereby manipulating CTI in host plants. For instance, the causative agent of tomato leaf mould, Cladosporium fulvum, secretes the effector protein, Avr4, which binds to fungal chitin, thereby protecting the pathogen against host chitinases and the release of chitin fragments initiating CTI (Stergiopoulos et al., 2010).

Strategies used by human and plant pathogenic fungi to prevent recognition of immunogenic cell wall moieties by the host’s immune system are summarised in Figure 1.

2.2 | Creating confusion – Fungal activities to evade immune recognition

Immune recognition can also be actively evaded by binding or degrading host factors. For example, the human pathogenic fungus, Candida

**FIGURE 1** Shielding strategies of human and plant pathogenic fungi. Human and plant pathogenic fungi use elaborate strategies to shield immunogenic cell wall moieties from the host’s immune system. Human pathogenic fungi largely rely on shielding of the highly immunogenic β-glucan by capsule formation, a pigment, mannoprotein or hydrophobin layer, and different glucan linkage. The secretion of glucanases also ensures the reduction of surface β-glucan. Plant pathogenic fungi rather actively interfere with the immune recognition by secretion of glucan- and chitin-binding proteins. Furthermore, the down-regulation of β-glucan synthase reduces the amount of the immunogenic molecule in the fungal cell wall. Yellow – plasma membrane, red – chitin, dark green – β-1,3-glucan, turquoise – β-1,6-glucan, light green – α-1,3-glucan, purple – mannann, black – DHN melanin, dark blue – RodA, grey – capsule, scheme is modified from Gow et al. (2017).
tor proteins, secreted by symbiotic mycorrhizal fungi, can also subvert immune response to the fungus (Shi et al., 2018). Interestingly, effector proteins, which are secreted and transported into the host cell, are a very common theme for plant pathogenic fungi (Stergiopoulos & de Wit, 2009); however, so far, not a single effector, with related functions, has been found in human pathogenic fungi. Thus, human pathogens often have to live with the consequences of an activated immune response. For example, in many human pathogenic fungi, host-initiated oxidative killing mechanisms are readily detoxified. This is achieved, for instance, in C. albicans by the surface-bound superoxide dismutases (Sod) 4 and 5 (Fradin et al., 2005; Frohner, Bourgeois, Yatsky, Majer, & Kuchler, 2009) or by the glutathione reductase, Grx2, and the thioredoxin, Trx1 (Miramon et al., 2012). Very similar mechanisms are found in C. neoformans (Sod1) (Cox et al., 2003), Candida glabrata (Sod1, Yap1) (Roetzer et al., 2011) and H. capsulatum (Sod3) (Yousef, Holbrook, Smolnycki, & Rappleye, 2012). An alternative strategy is adopted by A. fumigatus, where the secondary metabolite, gliotoxin, interferes with ROS production by neutrophils (Tsunawaki, Yoshida, Nishida, Kobayashi, & Shimoyama, 2004).

These examples show that plant as well as human pathogens have evolved strategies and effectors to evade an activated immune response, for example, by detoxifying oxidative stress or through inhibition of important signalling cascades. However, secreted effector proteins that are transported into the host cell are still to be described for human pathogenic fungi.

### 2.4 | The final strike – Interference with host cell death pathways

The ultimate outcome of a fungal–host cell interaction during infection may be host cell death. This can be caused by regulated processes or by the consequence of overwhelming host cell damage and host cell death, in general, can be beneficial or detrimental for either the fungal pathogen or the host. For example, when the induction of defence mechanisms is not sufficient to limit the infection, the host can activate cell death pathways, thus sacrificing infected host cells to limit pathogen spreading and mediate fungal clearance. However, pathogens have evolved strategies and factors to interfere with this process for their own purpose. Depending on the type of pathogenic lifestyle, host cell death can either be a disadvantage or an advantage for the fungus. Some fungi (e.g., necrotrophic plant pathogenic fungi) actively induce cell death of the respective host to gain access to nutrients or to promote spreading within the host, whereas others inhibit the induction of host cell death in order to evade the immune system or due to the requirement of a living host (e.g., facultative intracellular pathogens, biotrophic plant pathogens). Furthermore, the interference with host cell death pathways can be divided into active modulation of regulated cell death pathways and indirect induction of killing due to toxin secretion or massive fungal proliferation, which overwhelm the host and, in turn, cause host cytolysis.
In the biotrophic fungus-like oomycete Phytophthora infestans, the effector protein, Avr3a, has been shown to suppress programmed cell death (PCD) of the plant host cell (Bos et al., 2010), while SNE1 inhibits necrotic cell death and interferes with other cell death inductor pathways (Kelley et al., 2010). Similarly, Phytophthora sojae Avr1b suppresses programmed plant cell death induction (Dou et al., 2008).

Necrotrophic plant pathogenic fungi, which feed on dead plant tissue, use a variety of effector proteins to induce plant cell death. This not only facilitates nutrient acquisition, but also limits detrimental ROS release by the plant’s defence mechanisms. Sclerotinia sclerotiorum, the causative agent of white mould in many plants, secretes the small protein, SsSSVP1, which relocates a protein of the mitochondrial cytochrome b-c₁ complex in the host plant, thereby triggering plant cell death (Lyu et al., 2016). Many necrotrophic fungi have been shown to elicit necrosis by activating the host plant’s PCD machinery. Exemplarily, Ecp2 from C. fulvum and its homologues in Mycosphaerella fijiensis induce necrosis in a susceptible host (Stergiopoulos et al., 2010). Furthermore, secreted toxins contribute to host cell death. Fumonisins B1, a toxin of Fusarium moniliforme is capable of inducing apoptosis-like host cell death by interfering with the jasmonate/ethylene (JA/ET) and salicylate (SA) signalling pathways (Asai et al., 2000).

Victorin, a toxin produced by the oat pathogen, Cochliobolus victoriae, similarly triggers an apoptosis-like cell death in susceptible plants but via mitochondrial malfunction (Curtis & Wolpert, 2004). Furthermore, the toxin binds TRXh5, which is sensed by LOV1, a protein which subsequently induces PCD (Wolpert & Lorang, 2016). Another inductive strategy is used by the AT toxin of Alternaria alternata, which has been shown to induce PCD in tobacco, involving caspase-like proteases and ROS accumulation in the plant tissue (Yakimova, Yordanova, Slavov, Kapchina-Toteva, & Woltering, 2009).

Interfering with host cell death pathways is not a feature limited to plant pathogenic fungi. For example, immune evasion can be accomplished by molecules from human fungal pathogens inducing apoptosis in host cells. DHN melanin of A. fumigatus suppresses the induction of apoptosis in macrophages via PI3K/Akt signalling pathways (Isaac et al., 2015) and thus inhibits the exposure of pathogen-derived antigens to dendritic cells, which bridge innate and adaptive immunity (Albert, 2004). Furthermore, the programmed, pro-inflammatory host cell death pyroptosis can be activated by fungi upon infection of macrophages. A well-studied example is given by C. albicans. Different factors and mechanisms have been discussed as triggers for pyroptosis, such as cell wall composition and the formation of hyphae (Joly et al., 2009; O’Meara et al., 2018; Uwamahoro et al., 2014; Wellington, Koseln, Sutterwala, & Kysan, 2014). In addition, secreted aspartyl proteases (Saps) have been shown to activate the NLRP3 inflammasome and could thus potentially induce pyroptosis upon C. albicans infection (Pietrella et al., 2013). Apart from these, Ahr1 and Stp2, transcriptional regulators of amino acid transport, have been reported to be involved in inflammasome activation and pyroptosis by preventing phagosomal acidification (Vylkova & Lorenz, 2017). Clearly, the induction of pyroptosis in innate immune cells is triggered by a combination of several fungal factors. The induction of this type of cell death can provide an escape route for the fungus from the hostile environment inside immune cells; however, the release of pro-inflammatory cytokines associated with pyroptosis causes attraction of neutrophils and thus contributes to pathogen clearance.

Fungal pathogens can also proliferate within immune cells for longer periods without engaging host cell death programs, but finally causing cell death due to overwhelming host cell damage. For example, the facultative intracellular pathogen, C. neoformans, resides and replicates in acidic phagolysosomes, which are maintained at an optimal pH by the buffering capacity of the fungal capsule, thus ensuring an immunological silent replicative niche for the pathogen (De Leon-Rodriguez, Fu, Corbali, Cordero, & Casadevall, 2018). Also residing and replicating, this time in non-acidified phagolysosomes, is C. glabrata, which has also been shown to manipulate macrophage cytokine profiles towards a less pro-inflammatory pattern. A constant proliferation of the fungus inside the phagocyte ultimately leads to host cell lysis and pathogen release, 2–3 days after infection (Seider et al., 2011). Recent observations propose that fungal biotin homeostasis plays a role in C. glabrata’s potential to persist and evade the host immune system (Sprunger et al., 2020). In contrast, C. albicans readily forms hyphae upon phagocytosis, which leads to mechanical damage of the phagocyte membrane starting already hours after infection (McKenzie et al., 2010).

However, host cell death is not always the ultimate outcome once a pathogenic fungus has entered a host cell. During the later stages of infection, C. neoformans favours phagocytosis and uses macrophages as a Trojan horse to cross the blood–brain barrier after replicating within immune cells (Santiago-Tirado, Onken, Cooper, Klein, & Doering, 2017). Furthermore, some pathogens are capable of escaping from the phagolysosome by inducing their own expulsion. The above-mentioned C. neoformans uses non-lytic expulsion (vomocytosis) as a side escape route (around 10–27% in the first 10 hr of infection depending on the host cell type), a process that requires actin, involves urease activity as well as autophagy mechanisms, and can still occur several hours after phagocytosis (Fu et al., 2018; Johnston & May, 2010; Ma, Croudace, Lammas, & May, 2006; Nicola et al., 2012). This non-lytic expulsion has additionally been described to occur as a rare event in C. albicans, C. krusei and C. parapsilosis–infected immune cells, however, the factors mediating this process are still under investigation (Bain et al., 2012; Garcia-Rodas, Gonzalez-Camacho, Rodriguez-Tudela, Cuenca-Estrella, & Zaragoza, 2011; Toth et al., 2014).

Apart from this non-lytic process, the induction of direct host cell lysis via toxin production can mediate fungal escape from immune cells. This has recently been reported for the C. albicans peptide toxin candidalysin, which has been shown to directly damage mononuclear phagocyte membranes, thus facilitating fungal escape without activating PCD pathways (Kasper et al., 2018). As discussed above, both human and plant fungal pathogens have evolved similar strategies to prevent recognition by the host’s immune system, to circumvent the host’s defence mechanisms, and to manipulate the immune response as depicted in Figure 2.

However, there are also clear differences between the two groups of fungal pathogens. For example, human and plant pathogenic fungi share mechanisms of interference with the host’s cell death machinery, but one striking difference between pathogens of different hosts is evident. Plant pathogenic fungi mainly interfere with host cell death pathways to facilitate their respective lifestyle (biotrophic or...
necrotrophic) and thus nutrient acquisition, whereas human pathogenic fungi usually have to cope with an activated immune response and rather use this interference to mediate evasion of immune recognition, escape from immune cells and spreading inside the host. Nevertheless, all described mechanisms of plant and human pathogens aim at the same: fungal survival.

3 | GAINING ADVANTAGES – FUNGAL FACTORS INVOLVED IN MODULATION OF HOST TARGETS DURING INFECTION

Immune evasion is a key aspect of all pathogenic fungi. Further pathogenicity mechanisms shared by plant and human pathogenic fungi include invasion strategies and, once the host has been invaded, the production of fungal factors that actively modulate host cells to their advantage. An overview of these general infection strategies of human and plant pathogenic fungi, in addition to immune evasion, is given in Figure 3 and examples are discussed below.

3.1 | Gaining a foothold – Modulation of fungal uptake

Invasion into the host can be an active, fungus-driven process, or a passive, host-driven one and can be seen as a prerequisite to optimise the manipulation of the host by effectors. In both active and passive cases, specific fungal moieties are required. Plant pathogens are known to actively penetrate plants as they have to overcome the plant’s cell wall. Many plant pathogens, therefore, build defined structures, such as appressoria and haustoria, during invasion, extensively reviewed in a study by Lo Presti et al. (2015).

**FIGURE 2**  Immune evasion strategies of human and plant pathogenic fungi. In addition to shielding (Figure 1), both human and plant pathogenic fungi need activities to evade immune recognition and/or antagonise activated immune responses. Human pathogenic fungi are usually confronted with cells of the innate immunity, such as macrophages and neutrophils. Plant pathogenic fungi have to deal with the effects of an activated immune response of the plant cell and have evolved strategies to interfere with it by either suppressing it (biotrophic fungi) or hemibiotrophs in the initial biotrophic stage) or by inducing the activation of cell death pathways in case of necrotrophic fungi.
Human fungal pathogens, which only need to breach a cell membrane during infection, can actively penetrate host cells but also, to a minor extent, induce their own endocytosis via invasins (Wachtler et al., 2012). Active penetration is a common theme of plant and human pathogenic fungi and requires hyphal morphologies. The physical forces of growing hypha per se are sufficient to penetrate many host tissues. Human pathogenic yeasts thus have to apply other invasion strategies or, as in the case of \textit{C. albicans}, switch from a yeast to a hypha morphology during invasion (Brand, 2012; Menge, Hahn, & Deising, 1996). In fact, \textit{C. albicans} is a rare example of a human pathogenic fungus, which is able to invade host cells using both mechanisms, active penetration and induced endocytosis (IE), a host-driven process. Disseminating \textit{C. neoformans} cells destabilise tight junction proteins in blood–brain barrier endothelial cells, or use macrophages as a Trojan horse (TH), thereby promoting transcellular translocation into the brain parenchyma. Upon contact with immune cells, immune evasion strategies (Figures 1 and 2) come into play. Plant pathogenic fungi, which need to breach the cell wall of plant cells, form appressoria (A), structures dedicated to generate the pressure for invasion. Biotrophic fungi (e.g., \textit{U. maydis}) usually form haustoria (H) for nutrient acquisition, secrete effectors to inhibit cell death induction and proliferate in living plant tissue. Hemibiotrophic fungi (e.g., \textit{C. fulvum}) have an initial biotrophic stage, followed by a necrotrophic lifestyle. Necrotrophic fungi like \textit{C. victoriae} secrete effectors dedicated to induce cell death pathways like necrosis for nutrient acquisition and spreading in dead plant tissue. Details are discussed in the text.

A pathogenic attribute of \textit{C. neoformans} is its urease, which has been described to be relevant for invasion into brain tissue during disseminated infections, putatively by interfering with ZO-1 protein stability thus potentially enabling paracellular invasion through the endothelial barrier (Singh et al., 2013).

One example of a plant pathogen that evolved a strategy to manipulate the host plant’s physiology after invasion is \textit{S. sclerotiorum}. This fungus produces oxalate, which mediates a permanent opening of the host plant’s stomata by increasing the amount of osmotic relevant molecules and preventing stomata closure by blocking the action of the plant hormone, abscisic acid (Guimaraes & Stotz, 2004).

### 3.2 The inside job – Host manipulation after uptake

Once inside a host cell, a pathogenic fungus might need to protect its new position, to further invade and access more nutrients (see below),
or to reprogram host metabolism to its own benefit. Plant pathogens use effectors for this purpose, whereas, up to date, no such effector molecule of a human fungal pathogen has been described. In the following paragraph, we will, therefore, discuss the examples of specific host cell manipulation by distinct effectors of plant pathogens.

In *U. maydis*, Tin2, a secreted, virulence-associated protein effector, interacts with ZmTTK1, a plant protease. This leads to the modulation of the biosynthesis of lignin by enhancing the activity of the anthocyanin biosynthesis, thus reducing the precursors for lignin. As a result, lignification of the plant cell wall is reduced, which is beneficial for massive proliferation of the fungus (Tanaka et al., 2014). Furthermore, modulation of host metabolism has been reported for this fungus, which interferes with the plant's salicylic acid pathway by secreting the chorismate mutase, Cmu1. This enzyme interacts with ZmCm2 in the cytosol of the plant cell, leading to a reduced accumulation of salicylic acid and to a changed metabolic status of the host cells, beneficial for the pathogen (Djamei et al., 2011). For biotrophic plant pathogenic fungi, the structural integrity of the host is important to obtain functional haustoria. The rust fungus, *Uromyces fabae*, effector, RTP1p, translocates into the host cell to stabilise and protect the haustorium from degradation by forming amyloid-like fibrillar structures (Kemen, Kemen, Ehlers, Voegele, & Mendgen, 2013). In addition to the examples discussed in the context of immune evasion, these examples highlight that fungal pathogens are able to manipulate their respective host to their advantage, facilitating the progression of infection.

### 3.3 Open offence – Fungal toxins

A special case of fungal pathogenicity factors are toxins, which contribute to the virulence arsenal of pathogens during infection in many ways. Some toxins were already discussed above in the context of cell death pathways. In contrast to human pathogenic fungi, the diversity of toxins in plant pathogenic fungi is immense and only a few can be covered here. Toxin production by plant pathogenic fungi is a long-known phenomenon comprising of, for example, secondary metabolites, peptides and proteins. Counting as a secondary metabolite, the already described victorin of *C. victoriae* targets the mitochondrial glycine decarboxylase complex of the host plant and thereby inhibits biosynthesis of the proteinogenic amino acid serine (Curtis & Wolpert, 2004). Other strategies are used by the *Cholobolus carbonum* HC-toxin, which inhibits the histone deacetylases and, therefore, directly interferes with the plant's gene expression, or the phytotoxic tetroxin from *Alternaria* spp., which induces an energy breakdown in certain chloroplasts due to ATP hydrolysis (Horbach, Navarro-Quesada, Knogge, & Deising, 2011). In terms of low molecular weight peptides, *Rhynchosporium secalis* secretes necrosis-inducing peptides, which probably modulate plasma membrane H⁺-ATPase function. As examples of toxic proteins, *Alternaria brassicicola* secretes AB and AP toxins, and further proteinaceous toxins have been described in the necrotrophs, *Pyrenophora tritic- repentis* (PtrToxA, ToxB) and *Stagonospora nodorum* (Sn1-4Tox) (Horbach et al., 2011).

Details about these and several other toxins of plant pathogenic fungi directly targeting specific host cell factors or proteins have been extensively reviewed by Horbach and colleagues in 2011 (Horbach et al., 2011).

Surprisingly, toxins do not seem to be common in human pathogenic fungi. The first and only cytolytic peptide toxin of a human pathogenic fungus described so far is produced by *C. albicans* and has been termed candidalysin (see also above). This toxin has been shown to be crucial for *C. albicans*-induced host cell damage on oral epithelia and during mucosal infections (Moyes et al., 2016; Naglik, Gaffen, & Hube, 2019). However, the damage caused by candidalysin is also key in activating a protective immune response via the danger response pathways (Moyes et al., 2016). Therefore, this toxin has virulence as well as avirulence functions (König, Hube, & Kasper, 2020). It is thus clear that toxins play an important role during the interaction of pathogenic fungi with the respective host, not only by inducing PCD pathways like apoptosis or pyroptosis (see above), but also by directly damaging the host cell membrane or cell wall resulting in cytolysis, by interfering with important pathways within the host cell and by inducing a protective host response. Therefore, toxins crucially contribute to processes like immune evasion or immune induction, host cell damage and thus also nutrient acquisition in both human and plant pathogenic fungi. This particular aspect of gaining nutrients from the host is discussed in the following paragraph.

### 4 FEASTING ON HOST’S EXPENSES – HOST EXPLOITATION FOR NUTRIENT ACQUISITION

During the infection process, pathogens usually face nutrient limitation. The ability of pathogenic fungi to cope with nutrient-restricted conditions is thus one of their key virulence attributes. Among others, metals, sugar and nitrogen are essential nutrients during infection. Metals, for example, are co-factors for several eukaryotic proteins. The host sequesters those resources from pathogens in a process termed “nutritional immunity.” However, fungi developed strategies to access those nutrients from their hosts (Gerwien, Skrahina, Kasper, Hube, & Brunke, 2018).

#### 4.1 Pick-pocketing – Fungi collect metals from the host environment

Pathogenic fungi have several ways to scavenge metals from the host environment, including the production of surface proteins that bind metal-rich host proteins, transporters, reductive up-take systems, metal-binding proteins and siderophores.

Although metal acquisition is essential for both plant and human fungal pathogens, this aspect of fungal pathogenicity has been more frequently investigated in human pathogenic fungi. *C. albicans* possesses a whole repertoire of iron scavenging systems, comprising proteins and hemophores for heme extraction (e.g., Rbt5, Pga7 and
Csa2), ferric reductases (e.g., Cff1 and Cff95) and the ability to capture xenosiderophores (e.g., ferricrocin), extensively reviewed in studies by Fourie, Kuloyo, Mochochoko, Albertyn, and Pohl (2018) and Gerwien et al. (2018). The already mentioned invasin Als3, required for induced endocytosis, is also crucial for acquiring iron from ferritin, which is the main iron storage protein in oral epithelial cells (Almeida et al., 2008).

Aspergillus fumigatus and A. nidulans are able to exploit iron via their siderophores, triacetylfeurcinine C and ferricrocin. In addition, it has been shown that A. fumigatus is able to utilise iron from the human serum protein, transferrin (Almeida, Wilson, & Hube, 2009; Eisendle, Oberegger, Zdra, & Haas, 2003; Haas et al., 2003; Hissen, Chow, Pinto, & Moore, 2004). Furthermore, H. capsulatum has been reported to produce siderophores comprising dimerum acid, acetyl dimerum, coprogen B, methyl coprogen B and fusarinine (Breachting & Rappleye, 2019; Howard, Rafie, Tiwari, & Faul, 2000).

Siderophore production and xenosiderophore exploitation are also described for plant pathogenic fungi. U. maydis, for example, produces ferrichrome and ferrichrome A (Budde & Leong, 1989), whereas the citrus pathogen, Geotrichum candidum, has been described to utilise iron bound by the xenosiderophore, ferroxamine B (Mor, Pasternak, & Barash, 1988).

Another important micronutrient that needs to be taken up from the environment is zinc. C. albicans secretes the zincophore, Pra1, a protein that binds zinc from host cells. The metal is then brought inside the fungus by Zrt1, a co-expressed plasma membrane zinc transporter. The system is dependent on hyphal development in alkaline pH (Citulio et al., 2012). A. fumigatus expresses a similar system comprising AspF2 and ZrtF for the exploitation of zinc (Amich, VicenteFranquera, Leal, & Calera, 2010), and so does H. capsulatum, in which the expression of Zrt2 has been reported to be crucial for zinc homeostasis (Dade et al., 2016).

The exploitation of copper requires transporters as well. H. capsulatum requires Ctr3 for growth under low copper concentrations, like in copper-depleted macrophages (Shen, Beucler, Ray, & Rappleye, 2018). C. neoformans can acquire copper through the metallothionein, Cmt, and the copper transporters, Ctr1 and Ctr4, similar to C. albicans, which expresses a protein homologous to Ctr1 (Ding et al., 2013; Marvin, Williams, & Cashmore, 2003).

Taken together, the sequestration of metals from the host by pathogenic fungi using (xeno) siderophores is a key process during infection shared by human and plant pathogenic fungi, again underlining that successful strategies and factors can evolve independently under a similar evolutionary pressure.

4.2 | Looting the host – Fungi exploit macro-nutrients

Further nutrients required for growth are carbon, nitrogen and phosphate. Plant as well as human pathogenic fungi developed transporter systems, which ensure phosphate, sugar and amino acid import.

In both C. albicans and C. neoformans, the phosphate-responsive transcription factor, Pho4, regulates the expression of phosphate transporters, such as Pho84, Pho840 and Pho89, thereby enabling phosphate acquisition (Ikeh et al., 2016; Lev et al., 2017).

During infection, fungi also crave for sugar as a carbon source. In C. neoformans, glucose is taken up by the high-affinity hexose transporter, HxS1, which is also critical for virulence (T. B. Liu et al., 2013). Furthermore, transporters have been described in haustoria, which allow biotrophic fungal pathogens to take up nutrients from their host. For example, the hexose transporter of HXT1p from U. fabae is specific for D-glucose and D-fructose (Voegele, Struck, Hahn, & Mendgen, 2001). The hemibiotrophic plant pathogen, C. graminicola, has been reported to possess five hexose transporters (CgHXT1-5) with varying affinity and expression time points, depending on the phase of infection (Lingner, Munch, Deising, & Sauer, 2011). Not only monosaccharides, but also disaccharides can be transported from the plant into the fungus. For example, U. maydis expresses the sucrose transporter, Str1, during infection, which is important for fungal virulence (Wahl, Wippel, Goos, Kamper, & Sauer, 2010).

Nitrogen is taken up by plant pathogenic fungi mostly as amino acids. U. fabae expresses Aat1 for histidine uptake and Aat3 has been described to mediate mainly leucine, methionine and cysteine uptake (Struck, Ernst, & Hahn, 2002; Struck, Mueller, Martin, & Lohaus, 2004). Fusarium oxysporum, on the other hand, produces Gap1, a general amino acid permease (Divon, Rotan-Denoyes, Davydov, A, & Fluhr, 2005). For C. albicans, it has been reported that the deletion of the amino acid transporter, Csh3, influences the amino acid uptake and virulence in a mouse model (Martínez & Ljungdahl, 2004), and transcription factors, Stp1 and 2, are regulators for amino acid and peptide utilisation (Miramon, Pountain, van Hoof, & Lorenz, 2020). In C. neoformans, only the permeases, Aap4 and Aap5, are relevant for virulence (Martho et al., 2016).

These examples show that general principles for micro- and macro-nutrient acquisition, such as siderophores, and especially transporters for sugars and amino acids, are commonly shared between pathogenic fungi independent of the host, however, adapted to their own specific niche.

5 | CONCLUSION

The tight relationship between fungal pathogens and their host, may it be human or plant, requires that such pathogens carry a whole arsenal of factors needed for survival. From immune evasion to modulation of specific targets of the host (not associated with the immune system) and host exploitation, diverse peptides, proteins and secondary metabolites enable fungi to infect their hosts in very similar ways. Independently of the respective host, plant and human fungi usually do not rely on only one factor but on several ones, all collectively contributing to the virulence of the pathogen to counteract the complex defence strategies of their host. In summary, although plants and humans are very different hosts, fungi infecting them share surprisingly similar pathogenicity mechanisms. This suggests that several of the attributes discussed in this review are essential for all established pathogenic fungi and that successful strategies have evolved independently.
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CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this Micro-Review as no datasets were generated or analysed during the current study.

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