Nutrient sensing and acquisition in fungi: mechanisms promoting pathogenesis in plant and human hosts

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Abstract

Fungal pathogens destroy our crops and cause hazardous human infections, therefore threatening our health and food security. The ability of fungal pathogens to sense and respond to dynamic host microenvironments enables the establishment and progression of disease. Sensing nutritional cues is vital throughout fungal infection of either plants or mammals: enabling the pathogen to invade, adapt and survive in the face of host immunity. Acquiring nutrients from their host for energy, growth and repair is also essential to a fungal pathogen's success. Cell-surface proteins embedded in the fungal plasma membrane sense and transport host macro- and micronutrients, including carbon and nitrogen sources and minerals such as iron and zinc. Using examples from model crop (*Fusarium graminearum, Magnaporthe oryzae* and *Ustilago maydis*) and human (*Aspergillus fumigatus*, *Candida albicans*, *Cryptococcus neoformans*) pathogens we review the nutrient sensing and transporting roles of fungal cell-surface receptor, transporter and transceptor proteins, and their importance to plant and human fungal disease. We discuss how their cellular localisation, central role in cell signalling and importance to disease makes these fungal cell-surface proteins candidates in the search for new strategies to control fungal diseases, while highlighting the areas where further research is needed to make this possible.

Keywords:

Nutrient, sensing, uptake, adaptation, fungal pathogen

1. Introduction

Fungal crop diseases are a serious problem: even low persistent levels of fungal disease cause losses of crops sufficient to feed ~600 million people a year (Fisher et al., 2012). Epidemics are even more damaging, for example the 2016 Wheat Blast outbreak in Bangladesh (caused by the fungal pathogen *M. oryzae Triticum* pathotype) resulted in up to 100% yield losses (Islam et al., 2016). Fungi including *Fusarium graminearum, Fusarium oxysporum* f. sp. *Lycopersici and Ustilago maydis* are agents of other important crop diseases. Simultaneously, mycoses affect over a billion people globally and 150 million of these are serious or life-threatening infections, including those caused by the three major pathogens *Aspergillus fumigatus, Candida albicans* and *Cryptococcus neoformans* (Bongomin et al., 2017). This number is expected to increase in the future with more people having compromised or suppressed immune systems (Casadevall, 2018). Additionally, in both agricultural and clinical settings, populations of fungal pathogens resistant to antifungal drugs are emerging. Hence new fungal control strategies are needed to protect both our food security and human health.

Cell-surface exposed plasma membrane proteins are key to fungal cell signalling, metabolism, development and the outcome of infection, making them potential targets for disease control (Brown et al., 2018, Li et al., 2007) (Figure 1). These proteins are responsible for the sensing and uptake of extracellular nutrients and can be divided into three classes (Figure 2). **Receptors** (including G-protein coupled receptors (GPCRs), mucin receptors and Sho receptors) sense nutrients by binding to their ligands which induces a conformational change in the receptor and/or cause the endocytosis of receptor and ligand (Diallinas, 2017). These changes initiate intracellular signalling pathways that modulate fungal development and metabolism, including calcium, cAMP, protein kinase A (PKA) and mitogen-activated protein (MAP) kinase signalling (Van Dijck et al., 2017). **Transporters** move macro- and micronutrients across the fungal plasma membrane either by serving as channels or by active transport (Elbourne et al., 2017, Saier Jr et al., 2016). Importers enable fungi to take up nutrients from the host, but transporters may also be exporters (removing substances from the cell), or bidirectional (moving nutrients both in and out of the cell). Transporters lack a sensing function, although the imported nutrients may be sensed by other mechanisms once inside the cell (Diallinas, 2017). **Transceptors,** on the other hand, are proteins with both receptor and transporter functions (Conrad et al., 2014). The transport and signalling functions of transceptors are independent, as transport through a transceptor does not always trigger signalling (Van Zeebroeck et al., 2014). The ability of transceptors to transport exists on a continuum: ranging from transceptors highly effective at transport, to transporter-like receptors that have lost their transporting function at the other extreme (Thevelein and Voordeckers, 2009).

In this review, we examine how nutrient sensing and acquisition at the fungal plasma membrane influences the different stages of infection in both plant and human hosts (summarised in Table 1), giving perspectives on their potential as targets in the design of new disease control strategies.

2. Sensing and invading a host to establish infection

Fungal pathogens are dependent on their hosts for nutrition, but in order to access these resources they must find and invade a susceptible host. Most fungal pathogens arrive at their host serendipitously as spores. Commonly phytopathogens land on a plant surface and germinate before actively penetrating their host. In contrast, human pathogens *A. fumigatus* and *C. neoformans* are inhaled into the lungs from the environment (Eisenman et al., 2007, O'Gorman, 2011) whilst *C. albicans* is a commensal organism of the human gastrointestinal (GI) tract, skin, mouth and

reproductive flora that becomes pathogenic under certain conditions (Noble et al., 2017). However, despite differences in how infection commences on different hosts, the initiation of infection requires fungal pathogens to sense the host environment via cell-surface proteins in their plasma membrane.

2.1. Breaking and entering: appressorium formation upon sensing a plant host

Following landing on a leaf, conidia of the rice blast pathogen *Magnaporthe oryzae* adhere to the epidermis, germinate and produce germ tubes involved in the recognition of the plant surface (DeZwaan et al., 1999). Recognition induces differentiation into an **appressorium**: a melanised cell in which high turgor pressure is generated to force a penetration peg through the plant cuticle and cell wall, allowing hyphal invasion (Dagdas et al., 2012). On the nutrient-poor leaf surface, the *M. oryzae* conidium undergoes autophagy and mobilises stored nutrients (including lipids and glycogen) for the synthesis of glycerol needed to generate turgor pressure in the appressorium (Yin et al., 2019). *M. oryzae* senses rice leaf hydrophobicity and cutin monomers by a **GPCR**, PTH11, which acts upstream of cAMP signalling to induce appressorium formation (DeZwaan et al., 1999, Kou et al., 2017) (Figure 3). By anchoring PTH11 on endosomes, PTH11 can be mobilised to the tip of the germ tube to promote appressorium formation or targeted to the vacuole to down-regulate PTH11 signalling during vegetative growth (Ramanujam et al., 2013). PTH11-related genes exist in the genomes of many phytopathogens within the Ascomycete subphylum Pezizomycotina. In *F. graminearum* most putative PTH11-related genes have a similar expression pattern to those in *M. oryzae,* being upregulated during plant invasion (Xu et al., 2017). *F. graminearum* produces compound (multicellular) appressoria called infection cushions to penetrate wheat floral tissues (Boenisch and Schäfer, 2011). Normal formation of infection cushions in response to wheat floral tissues requires GIV1, a non-PTH11-like GPCR, which may act by inducing cAMP-PKA and Pmk1 MAPK signalling (Jiang et al., 2019), while additional PTH11-like GPCRs are required for the invasion of other wheat tissues. During the initial symptomless phase of infection, a highly expressed PTH11-like GPCR regulates the biosynthesis of secreted virulence factors, including the mycotoxin deoxynivalenol, promoting the suppression of host defences and the progression of infection throughout the wheat head (Dilks et al., 2019, Brown et al., 2017).

In addition to GPCRs, plant pathogenic fungi use **mucin** and **Sho** receptors to sense the plant surface and initiate appressorium formation and invasive infection. Mucins have an extracellular domain which senses nutrient and physical cues to activate intracellular signalling, whilst Sho receptors span the plasma membrane and interact with MAP kinases to activate signalling (Van Dijck et al., 2017, Lanver et al., 2010). In *M. oryzae* the mucin Msb2 senses hydrophobicity and cutin monomers, whilst the Sho receptor Sho1 is involved in sensing surface waxes (Liu et al., 2011) (Figure 3). Msb2 and Sho1 are conserved in many plant pathogens including *Ustilago maydis* and *F. graminearum* (Lanver et al., 2010, Gu et al., 2015). Cbp1 is another mucin produced by *M. oryzae*, which may interact with Msb2 by an unknown mechanism to mediate sensing of the leaf surface (Wang et al., 2015). The chitin-deacetylase activity of Cbp1 may account for its role in appressorium initiation (Kuroki et al., 2017) and the derived chitosan may be needed for Msb2 to localise to the cell wall (Geoghegan and Gurr, 2016). Nonetheless, collectively Msb2, Sho1 and Cbp1 activate the Pmk1 MAP kinase cascade which leads to appressorium formation and plant invasion (Liu et al., 2011, Wang et al., 2015). Therefore, fungal GPCRs, mucin and Sho receptors appear to functionally overlap in the recognition of plant surfaces, activating conserved MAPK pathways to promote infection.

2.2. Finding a natural opening: fungal chemotropism

An alternative strategy used by other pathogenic fungi is to enter through pre-existing chinks in host defences. Gaps between root epidermal cells provide a point of access without the need to produce specialised infection structures (Pérez-Nadales and Di Pietro, 2011; Kou and Naqvi, 2016). Soil borne plant pathogens must sense their host in order to reach the tubers or roots by way of motile zoospores in the case of chytrids (van de Vossenberg et al., 2019) or by orienting hyphal growth in filamentous fungi. The ascomycete causing vascular wilt of tomatoes, *Fusarium oxysporum* f. sp. *Lycopersici*, directs hyphal **chemotropic** growth towards tomato roots preceding invasion (Turra et al., 2015). *F. oxysporum* senses a component of the root exudates, resulting from the action of root peroxidases, using the Ste2 GPCR which leads to cell integrity Mpk1 MAP kinase signalling and infection (Nordzieke et al., 2019). The resulting chemotropism is enhanced by H_2O_2, which may act as an electron acceptor for plants peroxidases during the oxidation of an unknown substrate. The *F. oxysporum* NADPH oxidase B (NoxB) complex and superoxide dismutase (SOD) located at the hyphal apex produce extracellular H_2O_2, promoting peroxidase chemotropism and virulence (Nordzieke et al 2019) (Figure 3). Upon finding the tomato root, *F. oxysporum* secretes an array of effectors including the rapid alkalinisation factor (RALF) which alters the pH of the microenvironment, inducing PacC and invasive growth MAPK signalling to promote infection (Masachis et al., 2016, Fernandes et al., 2017). Ste2 is also the classical mating pheromone receptor, which upon pheromone sensing initiates Mpk1 signalling and mating, illustrating how a single receptor can be involved in sensing multiple ligands to initiate different cellular responses (Turra et al., 2015) (Figure 3). This mechanism appears to be conserved, as in *F. graminearum* Ste2 also senses a chemoattractant derived from wheat peroxidases and is required for pathogenicity on wheat coleoptiles. Ste2 may enable *F. graminearum* to locate regions of damaged cell walls, but this is yet to be determined (Sridhar et al., 2020).

2.3. Resisting human immunity: evasion and immunomodulation to establish infection

Upon arrival within the host, opportunistic human pathogens immediately encounter the host immune system and therefore must evade detection and being killed. *C. albicans* evades immune recognition by masking cell wall β-glucans when in association with its host. L-lactate produced by the host or gut bacteria is sensed by the fungal GPCR Gpr1, which induces signalling to the Crz1 and Ace2 transcription factors leading to **cell wall remodelling** (Figure 3). This β-glucan masking reduces host immune responses, including neutrophil recruitment, aiding host colonisation (Ballou et al., 2016). In *C. neoformans,* encapsulation and titan cells confer immune-evasion and immunomodulatory properties, facilitate dispersal and aid in the adaptation to the host. **Encapsulation** occurs within the first few hours of host infection (Zaragoza et al., 2008), involving biosynthesis of a thick polysaccharide capsule composed mainly of glucuronoxylomannan and glucuronoxylomannogalactan. The capsule changes in size and density in response to different host niches as an immune evasion strategy. Capsule formation is induced by host tissue properties including low iron, low glucose, low nitrogen, 5% CO_2 and pH 7 (O'Meara and Alspaugh, 2012). Within the fungus, intracellular iron may be directly sensed by the transcription factor Cir1, which regulates genes involved in iron and nitrogen source uptake and is required for capsule formation. Cir1 represses genes encoding the protein kinases Abc1 and Tda10 which negatively regulate capsule formation (Do et al., 2020). Sensing of glucose and amino acids involves the GPCR Gpr4, which interacts with the Gα protein Gpa1 to signal via the cAMP-PKA pathway to regulate capsule formation and mating, although Gpr4 is dispensable for virulence (Xue et al., 2006). *C. neoformans* **titan cells** are enlarged cells between 10 and 100 μm in diameter and are found in different host niches. Formation of titan cells is induced by environmental cues including nutrient starvation and is regulated by the GPCRs Ste3a (pheromone receptor) and Gpr5 (ligand unknown) which interact with the Gα subunit Gpa1 to trigger cAMP production and PKA pathway activation (Hommel et al., 2018).

These examples show how yeast-like fungi sense the host environment, modifying their cell wall polysaccharides to promote immune evasion and infection.

An alternative strategy is used by *A. fumigatus* conidia, which following inhalation evade immune detection by **masking** the highly immunogenic cell wall constituents, such as β-1,3-glucans and melanin, with an immunologically inert surface layer composed of hydrophobic rodlet RodA proteins (Aimanianda et al., 2009). Yet despite this strategy, conidia are still phagocytosed by mammalian host immune cells. When inside pulmonary macrophages, **melanin** in the *A. fumigatus* conidial cell wall interferes with phagolysosome acidification and inhibits macrophage apoptosis amongst other defensive functions (Heinekamp et al., 2013), promoting conidial immune evasion and survival. Melanin biosynthesis is regulated by several GPCRs. GprM signals by the MpkB pathway and into the MpkA cell wall integrity pathway to negatively regulate melanin biosynthesis (Manfiolli et al., 2019) (Figure 3). The ligands of these GPCRs are unknown, as are the cues inducing melanin biosynthesis. However, it is known that copper, delivered from the cytosol by the P-type transporter CtpA, is required for melanisation: likely to supply the copper cofactor for laccases involved in melanin biosynthesis (Upadhyay et al., 2016). **Germination** of the engulfed *A. fumigatus* conidia is induced by conditions within the macrophage phagolysosome and pulmonary environment, facilitating their escape (Aimanianda et al., 2009). As germination commences, conidia swell and shed the rodlet layer (**isotropic growth**) exposing β-1,3 glucans. However, mature hyphae synthesise the exopolysaccharide galactosaminogalactan (GAG) which masks the β-1,3 glucans to effect immune evasion (Gravelat et al., 2013). The G-protein β and γ subunits SfaD and GpgA are important for germination (Shin et al., 2009) and their homologues in the closely related *Aspergillus nidulans* induce germination by sensing carbon sources to activate independent cAMP-PKA and Ras signalling pathways (Fillinger et al., 2002).

Thus, conserved GPCR and G-protein sensory mechanisms, mostly of unknown ligands, are vital to modulating the initial interaction between an opportunistic fungal pathogen and the mammalian host, promoting adaptation, immune evasion and protection to establish infection.

3. Morphological and metabolic adaptations within the host

3.1. Switching growth form

Nutrients are important signals that induce **dimorphic switching** in plant pathogens. Low ammonium levels are sensed by the high affinity ammonium transceptor Ump2 in *U. maydis*, which is required for the switch to hyphal growth and pathogenicity on maize (Figure 4). Ump2 expression itself is induced by the Msb2 and Sho1 receptors upon sensing plant surface cues (Lanver et al., 2014). Ump2 affects expression of other transporters and secreted enzymes to induce hyphal growth (Paul et al., 2018). MAP kinase and cAMP-PKA signalling affect hyphal growth in *U. maydis*, but Ump2 has not yet been confirmed to function upstream of these pathways in the response to ammonium levels (Paul et al., 2018). The **yeast-to-hyphal growth** morphological transition is a major virulence factor for *C. albicans*, enabling invasion of the epithelium and escape from macrophages, amongst other immune evasion strategies (Cheng et al., 2012). The transition is induced by a range of host cues, including the availability of different nitrogen sources (Alves et al., 2020). Methionine is sensed by the GPCR Gpr1, which signals via the G-protein Gpa2 to activate cAMP-PKA signalling and hyphal growth (Maidan et al., 2005) (Figure 3). Since Gpr1 also senses L-lactate to regulate cell wall remodelling and β-glucan masking, this is another example of a single receptor with multiple nutritional ligands driving distinct biological responses. The methionine permease Mup1 also plays an essential role, importing methionine to be metabolised inside the fungal cell, which is required for cAMP production (Schrevens et al., 2018).

Vascular wilts such as *F. oxysporum* grow as hyphae through the host roots to reach the vasculature whereupon **conidiation** occurs. Induction of conidiation in *F. oxysporum* depends upon G-protein signalling (Jain et al., 2002). Conidia are transported in the sap, spreading the infection throughout the plant. **Yeast cells** play an analogous role in *C. albicans,* being released from fungal biofilms into the bloodstream to be disseminated throughout the host (Lohse et al., 2018). Nutrient availability and quorum sensing are predicted to regulate dispersion (Blankenship and Mitchell, 2006). **Fungal biofilms** are the principle growth form in nature, providing efficient colony organisation and resistance to external stresses including host immune responses and antifungal drugs. *C. albicans* forms biofilms on mucosal surfaces and medical implants (Chong et al., 2018). The biofilm consists of yeast and hyphal cells in an extracellular polysaccharide matrix, stabilised by cell surface adhesin proteins. Adhesin expression is regulated by nitrogen source availability and target of rapamycin (TOR) signalling. Nitrogen limitation inactivates Tor1 (Flanagan et al., 2017), releasing repression of adhesin encoding genes including ALS1, ALS3 and HWP1 required biofilm formation (Bastidas et al., 2009). *A. fumigatus* also forms biofilms, which in an aspergilloma (persistent fungal ball inside body cavity) consist of hypha in a polysaccharide extracellular matrix, predominantly galactomannan and GAG (Loussert et al., 2010). GAG is crucial for biofilm adhesion and is synthesised by five co-regulated genes (Lee et al., 2016). The expression of these genes is governed by the lim-binding nuclear protein PtaB (Zhang et al., 2018) but the upstream signals are unknown.

Evidently, fungal pathogens of both plants and humans frequently switch between growth forms in response to nutritional cues as a strategy to adapt to host environments. Hyphal growth promotes invasion, yeast-like growth or sporulation facilitate dissemination throughout the host, whilst recalcitrant fungal biofilms and titan cells confer persistence and other virulence benefits.

3.2. Nutrient sensing and acquisition in a live host

Fungal pathogens can form prolonged intimate associations with live hosts, making the ability to sense sources of nutrition, while activating mechanisms for its uptake and metabolism, vital to the establishment of infection and survival in the host. **Biotrophic** plant pathogens (rusts and powdery mildews) and those with a transient biotrophic phase (**hemibiotrophs**) keep their hosts alive in order to exploit them as a source of nutrients. In several species, the site of nutrient uptake and metabolism is a specialised feeding structure (**haustorium**) which forms following penetration of the plant cell wall and invaginates the host plasma membrane (Bozkurt and Kamoun, 2020). Establishment of these interactions and the initiation of haustorium formation likely involves sensing plant-derived chemical cues, such as volatiles and carbohydrates, by mechanisms yet to be defined (Mendgen et al., 2006, Heath, 1990). Transporters in the haustorium membrane take up host nutrients including sugars and nitrogen sources. Hexose **sugars**, namely D-glucose and D-fructose, are imported by the proton symporter Hxt1 in the Fava bean rust pathogen *Uromyces fabae* (Voegele et al., 2001). Homologues of Hxt1 exist in other species, for example in *U. maydis,* which does not form a haustorium but does invaginate host cells to form a biotrophic interface (Brefort et al., 2009). In *U. maydis* Hxt1 is the main hexose importer, transporting glucose, fructose and mannose and may also act as a sensor of glucose, thus enabling biotrophic development and corn smut disease (Schuler et al 2015) (Figure 4). Srt1 is another sugar transporter in *U. maydis* expressed upon infection and required for virulence (figure 4). Srt1 imports sucrose, which may be an advantageous sugar source compared to monosaccharides produced by secreted fungal invertases because monosaccharides can be sensed by the host as a sign of infection, triggering a reduction in photosynthesis and the induction of defences (Wahl et al., 2010). Sugar sensing and uptake at the biotrophic interface is therefore vital to fungi during infection of live plant hosts. **Ammonium** sensing and uptake is likewise vital. The ammonium transceptor Ump2 in *U. maydis* is not only

important for inducing hyphal growth (see section 3.1) but also for ammonium uptake, with roles in both transport and signalling (Figure 4). Ump2 has a high ammonium transport affinity and is also essential for the expression of the low affinity ammonium permease Ump1 (Paul et al., 2018). Ump2 is greatly upregulated during the early biotrophic phase (Lanver et al., 2018) which suggests preparation of nutrient uptake systems needed for growth inside the host.

Human fungal pathogens also require **carbon** and **nitrogen sources** from within the host. The *C. albicans* genome encodes both high and low-affinity glucose transporters. The transceptor Hgt4 senses simple sugars (including glucose at the concentrations found in human serum) to activate the expression of low-affinity glucose transporters and is required for hyphal growth, while its disruption causes hypovirulence (Brown et al., 2006, Sabina and Brown, 2009) (Figure 4). *C. albicans* also imports the sugar N-acetylglucosamine (GlcNAc), which is present in mucosal layers and induces hyphal growth, via the transporter Ngt1 (Alvarez and Konopka, 2007). The GPCR Gpr1 senses lactate and methionine, but exactly how these signals are integrated remains to be determined (Van Ende et al., 2019). *C. albicans* also adapts to nitrogen starvation. In low ammonium conditions, the ammonium permeases Mep1 and Mep2 are expressed. Mep1 is an ammonium transporter whereas Mep2 is a transceptor with lower transport efficiency that activates the Cph1 MAPK and cAMP pathways via Ras1 to regulate hyphal growth (Biswas and Morschhäuser, 2005, Brito et al., 2020) (Figure 4). Furthermore, *C. albicans* expresses six amino acid permeases (AAPs), with only Gap2 shown to be a general AAP (transporting all amino acids) and also possessing a signalling function that activates the PKA pathway (Kraidlova et al., 2011). In addition, Csy1 is an amino acid sensor which regulates amino acid uptake, induces transcription of AAP-encoding genes and is involved in the regulation of hyphal growth (Brega et al., 2004).

In *C. neoformans* Hxs1 (homologue of *Saccharomyces cerevisiae* glucose sensor Snf3) is important for glucose transport when glucose concentrations are low and is required for virulence (Liu et al., 2013) suggesting that glucose uptake is needed for survival in the host. *C. neoformans* can also use inositol, a sugar that is abundant in the human central nervous system as a sole carbon source (Xue et al., 2010). Several inositol transporters are encoded by the *C. neoformans* genome and Itr1 is predicted to be an inositol sensor that regulates other inositol transporters. Inositol uptake and metabolism is crucial for mating and virulence (Xue et al., 2010). **Nitrogen** limitation (particularly when the sole source is **ammonium**) is sensed by the ammonium permeases Amt1 and Amt2 in *C. neoformans* to induce pseudohyphal growth, although they are dispensable for virulence (Lee et al., 2012). Bioinformatic analyses predict 10 AAPs exist, with Aap4 and Aap5 needed for thermal and oxidative stress resistance, while being essential for virulence (Martho et al., 2016).

A. fumigatus senses carbon and nitrogen sources using GPCRs including two putative carbon sensors (GprC and GprD), three putative nitrogen sensors (GprF, GprG, GprJ) and three putative cAMP receptors (GprH, GprI, GprL) which may be involved in carbon source sensing (Grice et al., 2013, Brown et al., 2015, dos Reis et al., 2019). The novel hybrid GPCR GprK with both 7-transmembrane and regulator of G-protein signalling (RGS) domains may also play a role in external pentose sugar sensing and the regulation of nutrient transporters, in addition to affecting development, stress responses and gliotoxin production (Jung et al., 2016) (Figure 3). Evidently, the interconnected sensing and acquisition of carbon and nitrogen sources by fungal cell-surface proteins is important for pathogenesis and colonisation of both plant and human hosts.

4. Micronutrient acquisition when confronted by host immunity

A pathogen's need for nutrition is exploited by hosts as a mechanism of **nutritional immunity**, in which the host sequesters essential micronutrients, including copper (see section 2.3), iron and zinc

away from the pathogen to combat infection (Hood and Skaar, 2012). In response, fungal pathogens have acquired mechanisms involving cell-surface, plasma membrane and secreted proteins to scavenge micronutrients from their host.

4.1. Iron homeostasis

Regulation of internal iron levels is important for fungi: iron is needed for aerobic metabolism and is a cofactor in enzymes. However, iron has a low solubility and is usually bound to chelators, for example ferritin in mammals and plants, and nicotianamine in plants, resulting in a low bioavailability. To survive, plant and human pathogenic fungi use **siderophores**: low molecular weight organic compounds able to scavenge host iron (Oide et al., 2015).

Siderophores are produced by many plant pathogenic fungi, although their contribution to virulence varies, for example in *U. maydis* (Mei et al., 1993) compared to *M. oryzae* (Hof et al., 2009). During wheat infection *F. graminearum* transcribes and secretes two extracellular siderophores, triacetylfusarinine C (TAFC) and malonichrome (Brown et al., 2017). The siderophore-iron complex then reassociates with the fungus via plasma membrane ferri-siderophore transporters. An inability to synthesise TAFC, caused by mutation in the gene *SID1*, impairs fungal growth under low iron conditions and limits infection (Greenshields et al., 2007). In addition, both plant and mammalian hosts generate **oxidative stress** as a defence against fungal pathogens (Lehmann et al., 2015, Aguirre et al., 2006) and iron is required for the activity of enzymes involved in the fungal oxidative stress response. Hence an inability to synthesise the extracellular siderophores TAFC in *F. graminearum* or coprogens in *M. oryzae* causes hypersensitivity to oxidative stress (Oide et al., 2015, Hof et al., 2009). The human pathogen *A. fumigatus* also produces siderophores: fusarinine C, TAFC, ferricrocin (FC) and hydroxyferricrocin (HFC). The extracellular siderophores (fusarinine C and TAFC) assist in iron uptake needed for growth under iron limitation and are required for hyphal tolerance of H_2O_2 and normal levels of virulence (Schrettl et al., 2007). The intracellular siderophore FC is involved in hyphal iron storage whilst in HFC is needed for iron storage inside conidia and for conidial tolerance of oxidative stress (Schrettl et al., 2007).

The other human pathogens *C. albicans* and *C. neoformans* do not produce siderophores, instead pirating siderophores secreted by other organisms. To take-up the hijacked siderophores, *C. neoformans* possesses six siderophore transporters. Of these, only Sit1 has been characterised and transports the siderophore ferrioxamine B (Tangen et al., 2007) which is important for melanisation although dispensable for virulence. A major source of iron for *C. neoformans* is haem-associated iron and acquisition is governed by the extracellular mannoprotein Cig1 and the cell-surface reductase Fre2 (Cadieux et al., 2013, Saikia et al., 2014). In addition, *C. neoformans* employs high- and low-affinity uptake systems for iron acquisition, which is carried out by cell-surface reductases and a membrane complex consisting of the permease Cft1 and the ferroxidase Cfo1 (Kronstad et al., 2013). Therefore, fungal cell-surface proteins are involved in the uptake of host iron that enables tolerance of host oxidative stress and the survival of the pathogen, enabling the development of disease.

4.2. Zinc homeostasis

Zinc is another essential micronutrient for pathogenic fungi, being a key constituent of transcription factors, a cofactor in enzymes and involved in cell signalling. Human immune cells exploit this need via nutritional immunity by compartmentalising zinc into the Golgi apparatus and releasing the zinc chelator calprotectin upon detecting *Aspergillus, Candida* or *Cryptococcus* species (Crawford and Wilson, 2015). Similarly, it is likely that zinc is not free in plants but sequestered into intracellular

compartments and bound to chelators such as shikimic acid (Gupta et al., 2016) but the significance of this as a defence against fungal pathogens is unknown.

In humans, *C. albicans* sequesters zinc from endothelial cells using the zincophore Pra1 (Citiulo et al., 2012). Analogous to siderophores mediating iron uptake, a zincophore is a secreted protein that binds zinc in the host then reassociates with the fungal cell. *C. albicans* PRA1 is expressed in zinc limiting and alkaline conditions similar to those it encounters in the host intracellular environment (Citiulo et al., 2012). PRA1 expression is regulated in response to pH by the transcription factors ZAP1 and RIM101 (Nobile et al., 2009, Bensen et al., 2004). Pra1 is required for *C. albicans* to cause host endothelial cell damage in the absence of zinc supplementation (Citiulo et al., 2012). A PRA1 gene orthologue, Aspf2, exists in *A. fumigatus* and its expression is regulated by the ZAP1 and RIM101 orthologues ZafA and PacC (Amich et al., 2010). Aspf2 is expressed and required for fungal growth in zinc limiting, alkaline conditions that mimic those encountered in the mammalian lung (Amich et al., 2010). These examples illustrate the importance of zincophore-mediated zinc acquisition to fungal pathogenesis in the human host. Putative zincophore biosynthesis genes exist in the genomes of fungal plant pathogens, but not have yet been characterised.

Reassociation of the zincophores in *C. albicans* requires the plasma membrane localised ZIP zinc transporter Zrt1 (Citiulo et al., 2012) and in *A. fumigatus* may involve its orthologue ZrfC (Amich et al., 2010). ZIPs also act as zinc transporters. In *C. albicans* Zrt2 is the main ZIP zinc transporter, being essential for growth in low zinc or acidic environments, whereas Zrt1 is sufficient for growth in neutral to alkaline conditions (Crawford et al., 2018). The number of ZIPs is expanded in the filamentous fungi such as *A. fumigatus*, which encodes eight ZIPs (ZrfA-H) that transport zinc into the cytoplasm, with ZrfC being essential for virulence (Amich and Calera, 2014). Bioinformatic analyses suggest that some ZIPs may additionally sense zinc, for example *C. albicans* ZRT1 may act as a zinc transceptor to activate the PKA pathway (Eide, 2020). Little else is known about zinc acquisition in this fungal pathogen. Homologues of these zinc acquisition systems are predicted bioinformatically to exist in plant pathogenic fungi, but have only been investigated experimentally in *F. oxysporum* f. sp. *lycopersici,* in which the transcription factor ZafA is needed for transcription of the ZIPs ZrfA and ZrfB during zinc limitation and for virulence on tomato plants (López-Berges, 2019). Thus, proteins on the fungal cell surface are important for both uptake of zincophore-bound and free zinc and sensing zinc, contributing to fungal survival and virulence.

5. Future perspectives

The emergence of fungal pathogen strains resistant to antifungal drugs is a major problem in both the agricultural and clinical contexts. Antifungals rely on few modes of action and some, including the dominant antifungal class the azoles, are used in both settings (Fisher et al., 2018). Furthermore, the use of antifungals in agriculture may drive the evolution of antifungal resistance in clinical isolates (Meis et al., 2016). Resistance is disastrous for fighting human fungal diseases because it seriously limits treatment options. Likewise, resistance in crop pathogens limits effective disease control and impacts on our food security. Currently, none of the major classes of antifungal drugs target fungal cell-surface nutrient receptors or transporters. Fungal GPCRs have been suggested as potential targets because of their low similarity to GPCRs of other organisms and, although unlikely to have a fungicidal effect (Brown et al., 2018), the examples given herein showed that the disruption of fungal GPCRs can inhibit fungal developmental or metabolic processes and the progression of disease. By extension, other fungal cell-surface nutrient receptors, transceptors and transporters known to regulate pathogenesis could be targeted. Alternately, fungal transporters could be exploited as a specific uptake route for antifungals. In *A. fumigatus* the Sit1 siderophore transporter also takes up the novel cyclic hexapeptide antifungal, VL-2397 (formerly named

ASP2397), due to its structural similarity to ferrichrome (Nakamura et al., 2019). Fungal nutrient and environment sensing pathways are also targets for antifungals (Perfect, 2017), such as the HOG pathway which is the target of the agricultural fungicide Fludioxonil (Lawry et al., 2017).

However, despite recent advances, nutrient sensing and transport at the cell surface of pathogenic fungi needs to be better understood if it is to become a valid target for the development of new disease control strategies. Firstly, the nutritional microenvironment inside both the plant and human host is understudied. Further work is needed to identify and quantify the bioavailable nutrients in the host, which of those are utilised by the pathogen and how these change with disease progression. Secondly, the environmental signals sensed by fungal cell-surface receptors are often unknown and structure-function relationship of these interactions are absent. Thirdly, although many of the downstream signalling pathways have been elucidated, the cross talk between them and how they integrate to promote pathogenesis is less well understood. Furthermore, as described herein, fungi often have multiple receptors/transporters with overlapping functions, and disruption of one protein is compensated for by the presence or even upregulation of others. Hence targeting a single fungal protein may be insufficient to affect the pathogen's virulence. Conversely, structural similarities amongst related receptors/transporters might allow one drug to target several of these membrane proteins. Determining the structures of these proteins, as was done recently for *S. cerevisiae* Ste2, will enable rational design of antifungal drugs (Velazhahan et al., 2020).

Overall, fungal nutrient receptors, transceptors and transporters at the plasma membrane enable fungal pathogens to sense and adapt to the host environment. They are vital to pathogenesis: promoting infection, immune evasion, morphological adaptation and nutrient homeostasis. Therefore, greater efforts are required to discover novel environment sensing cell-surface proteins and to dissect how these protein structures interact with their ligands to influence fungal cell biology, promoting the rational-based design of new antifungals. With further research, these proteins could be exploited as targets for much needed novel controls for crop and human fungal diseases.

Figures and legends

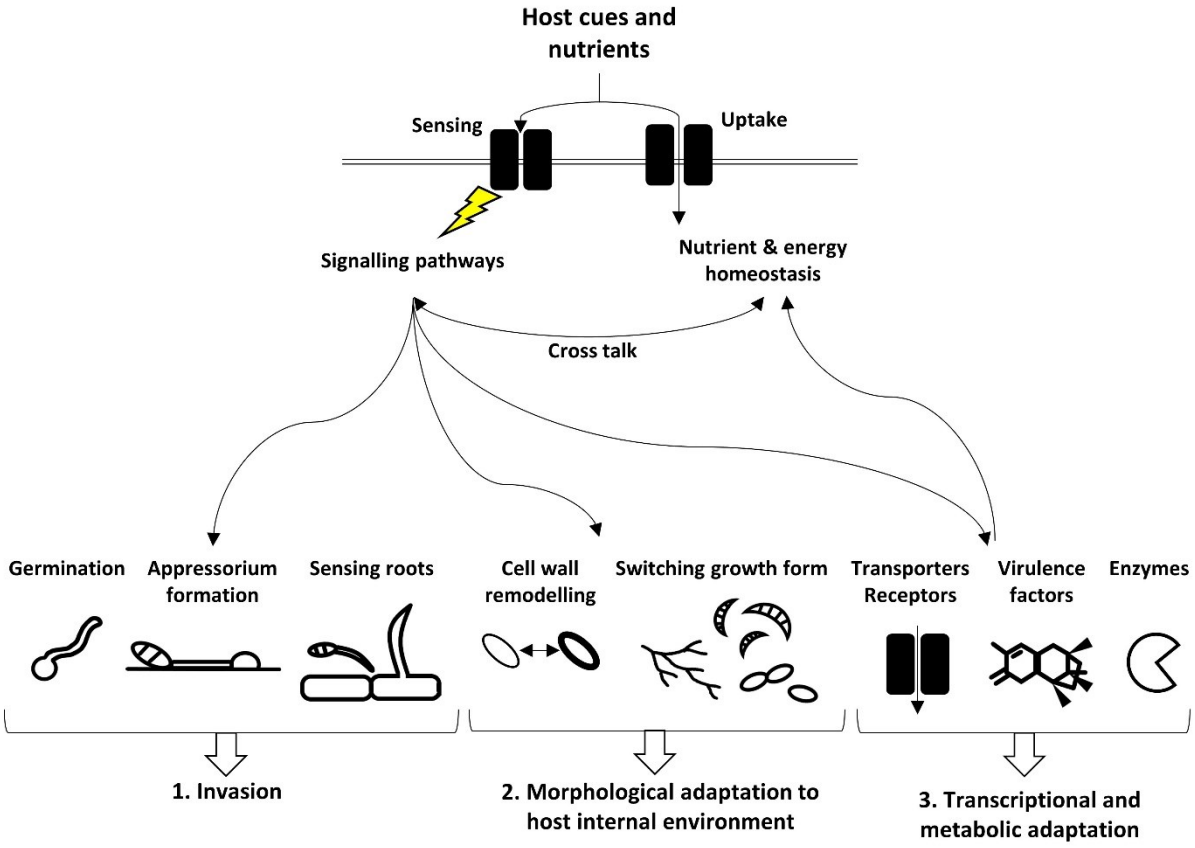

Figure 1. Overview of how nutrient uptake and sensing at the plasma membrane promotes invasion and survival in the host. Nutrients from plant or mammalian hosts provide a cue which, when sensed by proteins in the fungal pathogen's plasma membrane, promotes invasion and adaptation to the host environment. The uptake of nutrients also provides substrates for fungal metabolism. Cross talk exists by which fungal sensing of external host nutrient availability regulates expression of nutrient transporters to maintain nutrient homeostasis.

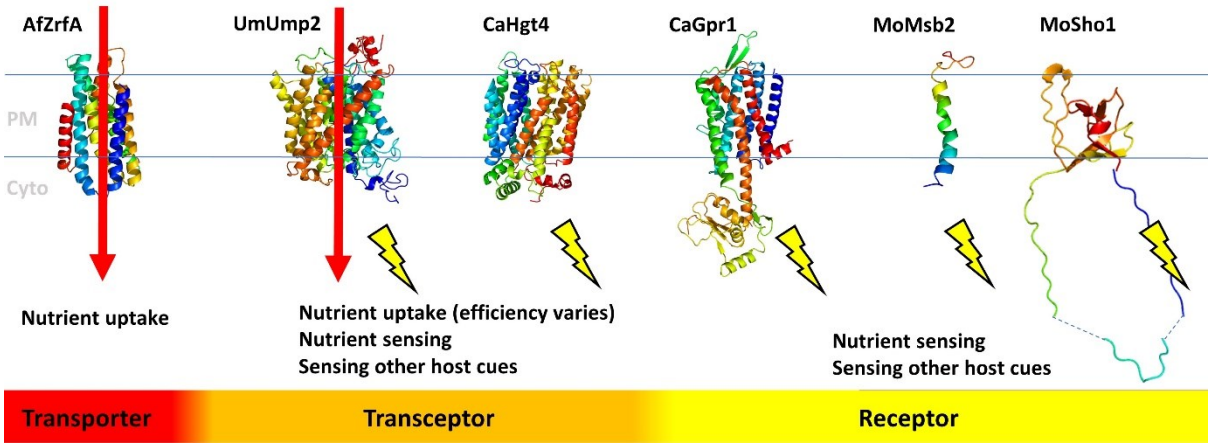

Figure 2. Functions of fungal membrane-based transporters, transceptors and receptors; and their roles in pathogenesis. Fungal transporter and receptor proteins exist on a continuum of functions ranging between transporter (red section) and receptor (yellow section). Transceptors (orange section) usually combine transport and receptor functions, as in UmUmp2. However, some transceptors, such as CaHgt4, have lost their transport function and are known as "transporter-like receptors" or "Non-transporting receptors", hence are closer to the receptor end of the continuum. Different classes of receptor exist, shown (in no particular order) are examples of GPCR (G-protein coupled receptor) (CaGPR1), Mucin (MoMsb2) and Sho (MoSho1) receptors. Nutrients include carbon and nitrogen sources and micronutrients, whilst other host cues include hydrophobicity, cutin monomers, leaf waxes, leaf topography, root exudates and plant volatiles. Solid blue lines represent the fungal plasma membrane, with the host environment above. Red arrows represent transport. Yellow lightning represents sensing. Dashed blue lines on MoSho1 indicate sections of the cytoplasmic loop that have been omitted for illustrative purposes. PM = fungal plasma membrane, Cyto = fungal cytoplasm. Af = *Aspergillus fumigatus*, Ca = *Candida albicans*, Mo = *Magnaporthe oryzae*, Um = *Ustilago maydis.* Protein models produced using Phyre2 (Kelley et al. 2015).

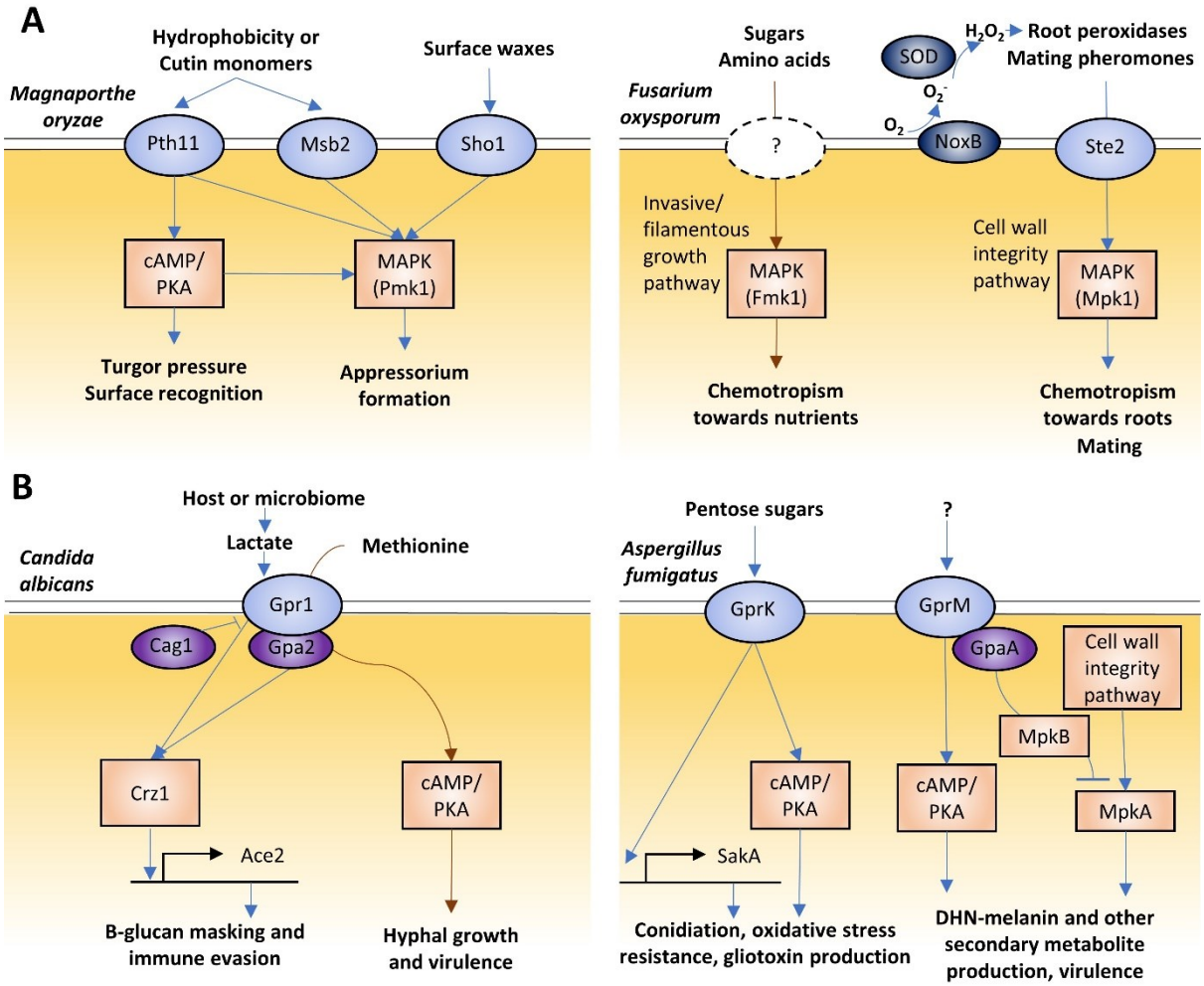

Figure 3. Receptors of (A) plant and (B) mammalian fungal pathogens involved in nutrient sensing outside and inside the host. Fungal plasma membrane based receptors (blue ovals) sense signals from the host (top of diagrams) which they transmit inside the fungus (yellow background) via conserved cAMP/PKA and MAPK pathways (red boxes) and G-proteins (purple ovals) in the case of G-protein coupled receptors, to affect gene expression (black arrows) and responses important for pathogenesis (bottom of diagrams). In *Fusarium oxysporum,* the chemoattraction induced by plant root peroxidases is enhanced by fungus-derived hydrogen peroxide (H_2O_2) produced by the fungal enzymes (dark blue ovals) NADPH oxidase (NoxB) and superoxide dismutase (SOD).

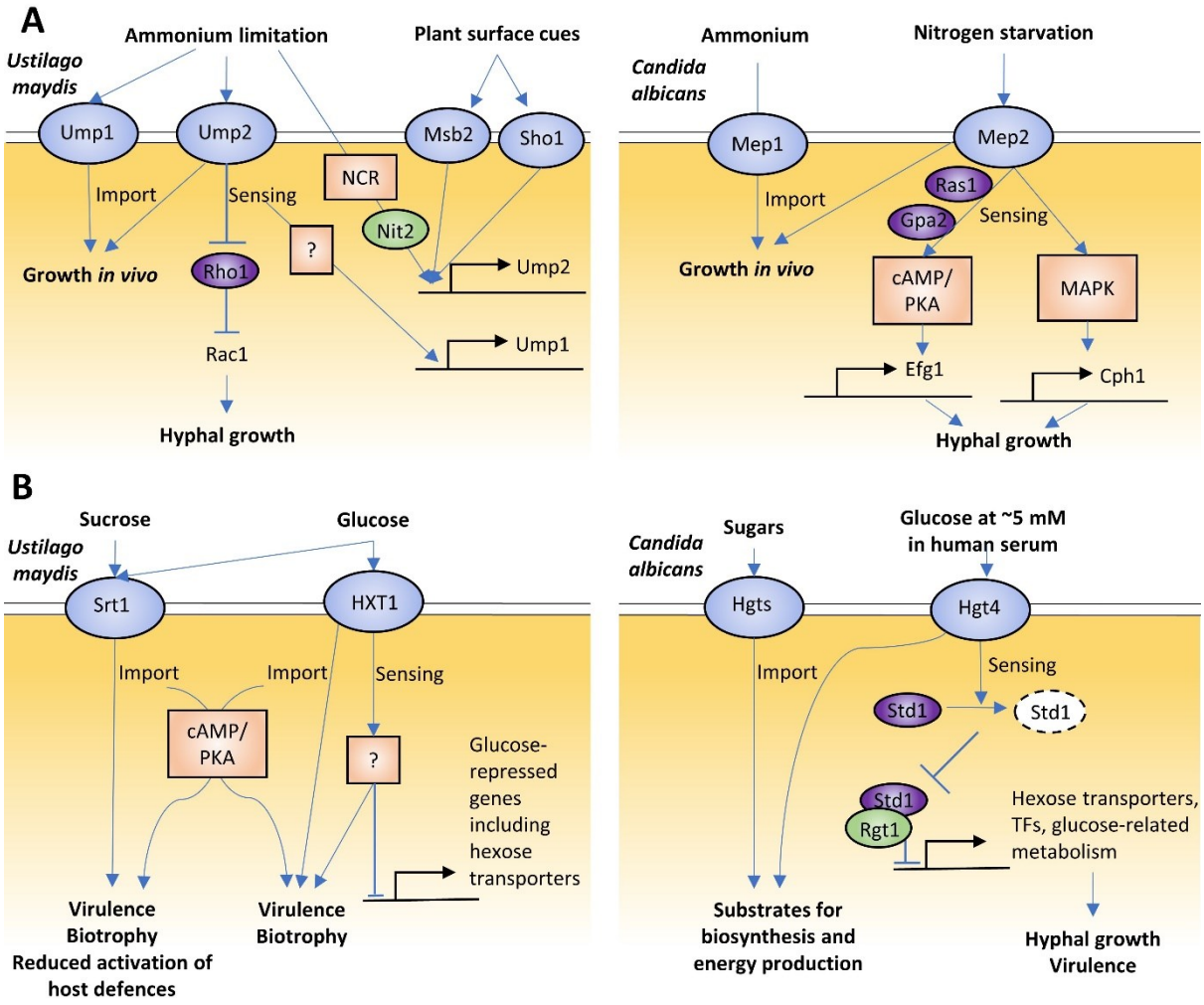

Figure 4. Transporters and transceptors of fungal pathogens involved in uptake and sensing of sources of A) nitrogen B) carbon inside plant or mammal hosts. Fungal plasma membrane based transceptors (blue ovals) sense signals from the host (top of diagrams) which they transmit inside the fungus (yellow background) via various pathways (red boxes) (including NCR = nitrogen catabolite repression), specific proteins (purple ovals) and transcription factors (green ovals) to control gene expression (black arrows) and responses important for pathogenesis (bottom of diagrams). Transceptors and transporters also import host nutrients required as substrates for biosynthesis and metabolism. In many cases sensing of nutrient availability in the host affects the expression of transporters for that nutrient. For example, sensing glucose at the concentrations in human serum by Hgt4 induces breakdown of Std1, thus Std1 cannot act with Rgt1 to repress the hexose transporter (Hgts) genes, so these are expressed.

Table 1. Summary of the key receptors and transceptors involved in fungal pathogenesis. Mo = *M. oryzae*, Fg = *Fusarium graminearum*, Ca = *Candida albicans*, Cn =*Cryptococcus neoformans*, Af = *Aspergillus fumigatus*, Um = *Ustilago maydis*, Fo = *Fusarium oxysporum.* TAFC = Triacetylfusarinine C, FC = Ferricrocin, HFC = hydroxyferricrocin, FOB = ferrioxamine B. Sources: Protein ID (Urban et al., 2020, Boutet et al., 2007); domain annotation (El-Gebali et al., 2019, Blum et al., 2020); GO (Binns et al., 2009).

Stage in pathogenesis	Protein name	Protein ID, Domain annotation	Signal sensed or transported	Biological process (GO term)
Appressorium formation upon sensing a plant host	MoPth11	Q9Y784; PF05730	Hydrophobicity, cutin monomers	GO:0009405; GO:0051701
	MoMsb2	G4N4W3; IPR039295		GO:0007232
	MoSho1	Q2KEW0; PF00018	Leaf waxes	-
	MoCbp1	Q8WZJ0; PF01522	Leaf surface component(s)	GO:0005975
Finding a natural opening: fungal chemotropism	FoSte2	A0A2H3SUP1; PF02116	Peroxidase-derived chemoattractant, mating pheromones	GO:0007186
Resisting human immunity	CaGpr1	A0A1D8PN42; PF11710; PF11970	L-lactate from host/gut bacteria, methionine	GO:0042783; GO:0036168; GO:0036170; GO:0001402; GO:0071333; GO:0009749; GO:0034605; GO:1900439; GO:0009267; GO:1900432; GO:0009593; GO:0007186
	AfGprM	Q4WGK0	Unknown	GO:0016021
Switching growth form	UmUmp2	Q6XUI3; PF00909	Low ammonium	GO:0015696; GO:0072488
	UmMsb2	Q4PHD3; IPR039295	Plant surface	GO:0007232; GO:0005034
	UmSho1	Q4P9Q7; PF00018	Plant surface hydrophobicity	GO:0005034
Nutrient sensing and acquisition in a live host	UmHxt1	Q4P4E0	Hexoses & possibly glucose	-
	CaHgt4	Q5ANE1; PF00083	Glucose	GO:0036168; GO:0019660; GO:0007165; GO:0009405 GO:0008643; GO:0010255; GO:0051594; GO:0034219; GO:1902600
	CaMep2	Q59UP8; PF00909	Ammonium	GO:0036170; GO:0006995; GO:0009267; GO:0030447; GO:0019740; GO:0072488
	CaGap2	A0A1D8PK89; PF00324	Amino acids	GO:0003333
	AfGprK	Afu4g01350	Pentose sugars	GO:0038032

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