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Chapter

Virulence Attributes in *Aspergillus fumigatus*

María Guadalupe Frías-De-León, Eduardo García-Salazar and Gustavo Acosta-Altamirano

Abstract

*Aspergillus fumigatus* is one of the most important opportunistic fungal pathogens. It causes various types of infections in humans, from skin, lung, and allergic infections to invasive infections. However, these stand out because their mortality rate can reach up to 95%. *A. fumigatus* is a ubiquitous fungus and, therefore, humans are in constant contact with it without major risk, except when there is a predisposing factor on the host, that allows the fungus to penetrate and invade the tissues. It is fascinating how this fungus manages to go from harmless to pathogenic as, in addition to the predisposing factors of the human, multiple attributes of the fungus intervene that favor its growth and survival in the host. Among these virulence attributes are thermotolerance, the ability to evade the immune response, some components of the cell wall, the production of secondary metabolites, compliance with nutritional requirements, and the production of melanin, among others. Furthermore, some of these virulence attributes are interrelated, making understanding the pathogenesis of aspergillosis more complex. This chapter presents a review of some virulence attributes that are known, to date, in *A. fumigatus*.

Keywords: *A. fumigatus*, virulence, pathogenesis, invasive aspergillosis, pathogenicity attributes

1. Introduction

The genus *Aspergillus* groups more than 200 species of filamentous fungi, with *A. fumigatus* being one of the most abundantly distributed species in the environment [1]. *Aspergillus* taxonomy is very complex, there are more and more species recognized as pathogenic for humans; however, *A. fumigatus* remains the most important species (Appendix 1). Being a ubiquitous and saprophytic fungus, it can grow and reproduce easily on decaying organic matter, soil, and dust in the air [2]. Until a few years ago, asexual reproduction was the only one recognized in *A. fumigatus*; it is now known to important species reproduce sexually also [3]. In the environment, this fungus reproduces mainly asexually, producing large numbers of small conidia (2–3 μm, the ideal size to go deep into the pulmonary alveoli) in structures called conidiophores, which disperse over great distances [2]. The conidia present in the air are constantly inhaled by humans (up to 5000 conidia per day), which can easily overcome the mucociliary
clearance and reach the epithelial cells of the airways, where it begins to colonize and, after approximately 24 h of hyphal growth, produce some secondary metabolites that break the endothelial epithelium (Figure 1) [4, 5].

After damaging the epithelial layer of the alveoli, the fungus can enter the endothelium of blood vessels [6]. The pathogenesis of the disease mediated by A. fumigatus occurs in a multi-step manner and involves the morphological transition of the inhaled fungal spore to a hyphae form. Epithelial damage can be considered to occur in the early (conidia) or late (hyphae) phase of the fungal interaction with epithelial cells [7]. In healthy immunocompetent individuals, the growth of hyphae is impeded by immune mechanisms, whereas, in people with immune deterioration, such as those who have leukemia or who have undergone bone marrow or solid organ transplantation, mycelial development leads to severe disease, which can be life-threatening (Figure 2) [8–11].

The respiratory tract is the main route of entry and site of infection of A. fumigatus; however, in both immunocompetent and immunocompromised hosts, other sites such as the skin, peritoneum, kidneys, bones, eyes, and gastrointestinal tract can be infected [4]. Lung diseases caused by A. fumigatus are classified according to the site affected within the respiratory tract and the degree of mycelial colonization or invasion, both of which are influenced by the immune status of the host [4]. Thus, repeated exposure to Aspergillus conidia or antigens without mycelial colonization can lead to allergic diseases, such as asthma, allergic sinusitis, and alveolitis. Patients usually show improvement when the environmental source of exposure is removed [11]. On the other hand, when there is fungal colonization and mycelial growth in the host, allergic bronchopulmonary aspergillosis (ABPA), aspergilloma, and invasive aspergillosis (IA) can develop, and patients usually require therapeutic intervention to achieve clinical improvement. Unfortunately, this is not always achieved, particularly in cases of IA, where the mortality rate is high (80–90%) [10–12]. Therefore, the pathogenicity of A. fumigatus depends not only on the host’s immune status but also on the ability of the fungus to adapt to the host environment, that is, on the virulence of the fungus strain [13]. Contrary to what happens in most primary pathogens, in which
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virulence traits develop in association with the host [14], the virulence in A. fumigatus is multifactorial and determined by a series of attributes that are under polygenetic control [13, 15, 16]. The virulence attributes that contribute to the pathogenicity of A. fumigatus are related to various processes such as thermotolerance, cell surface organization, adhesion molecules present on the conidial surface, production of secondary metabolites, compliance with nutritional requirements, interactions with the host immune system and stress response [16, 17]. Although some of these attributes do not fit the classical definition of a virulence factor, they are essential in the pathogenesis of aspergillosis. Thus, their knowledge may provide new opportunities for developing antifungals [14]. Below are some of the main virulence attributes in A. fumigatus.

2. Thermotolerance

A. fumigatus is a thermotolerant fungus that can grow at high temperatures (55°C) and even survive up to 75°C [18]. Thermotolerance is an essential characteristic of the fungus. It allows it to carry out its primary functions, degrade organic matter, exceed the thermal exclusion barrier of mammals, including humans, and cause infections [19, 20]. Therefore, genes that regulate thermotolerance are considered virulence attributes. Some genes (thtA, afpmt1, cgrA) associated with thermotolerance have been described in A. fumigatus [21–23]. These genes have different functions; for example, the afpmt1 and thtA genes contribute to fungal growth at 37 and 48°C, respectively [21, 22]. It has been seen that the deletion of these genes does not modify the virulence of the fungus. However, they indirectly influence pathogenicity, as they provide the ability to grow and persist within the human host, overcoming the thermal exclusion barrier. In the case of the cgrA gene, which is involved in the biogenesis of ribosomes at 37°C, it has been reported to have a direct influence on virulence since the mutant isolates produced by the deletion of this gene have a phenotype of low pathogenicity [23]. On the other hand, for A. fumigatus to survive human body temperature and transition from conidia to hyphae, it must resist high-temperature induced proteotoxic stress and flow in protein production demand [20]. Under these conditions, the so-called heat shock proteins (HSPs) become relevant. These proteins

Figure 2.
A. fumigatus host interaction and pathogenesis.
are upregulated with increasing temperature and stress induction, function as chaperones to facilitate proper folding and modification of proteins, and are molecules conserved between organisms. HSPs facilitate the acquisition of thermotolerance and allow human fungal pathogens to grow at human body temperature and survive after heat stroke at elevated temperatures. Several of these chaperones are necessary for morphological changes. Hsp90 and Hsp70 in human fungal pathogens contribute extensively to thermotolerance, morphological changes necessary for virulence, and tolerance to antifungal drugs [20]. In *A. fumigatus*, Hsp90 is involved in hyphal formation, so it has been suggested as a potential target of antifungal drugs [24]. Hsp70s are located on the cell surface of *A. fumigatus*, have high levels of expression at elevated temperatures, and influence morphological transitions [20, 25].

3. Adherence

After inhalation of the airborne conidia, adherence of *A. fumigatus* to host epithelial cells is essential for developing infection [16, 26]. After the conidia attach to the epithelial cells and to the extracellular matrix exposed in the airways, these cells recognize and internalize them. Some conidia manage to survive, avoiding the action of immune cells [27]. Recognition is achieved through the expression of different pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), C-type lectin (CLR), and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) that recognize fungal cell wall polysaccharides or fungal pathogen-associated molecular patterns (PAMPs) [28]. Recognizing specific PAMPs promotes the activation of antimicrobial mechanisms that help eliminate fungi. The most critical PAMPs of filamentous fungi are mannan, β-glucan, and chitin [28, 29]. During infection, the β-1,3 glucans of the cell wall are relevant PAMPs recognized by dectin-1, a type C lectin. Some studies have shown that hydrophobins hide these glucans in conidia but are exposed when the conidia swell and begin to germinate [30, 31]. After germination, exposure to β-1,3 glucan decreases due to hyphae-associated galactosaminogalactan (GAG) production, impairing the recognition of hyphae by dectin-1 [32]. There is evidence that GAG plays a vital role in mediating the adherence of hyphae to host epithelial cells. For example, GAG-deficient mutant isolates (Δuge3 and ΔmedA) reduce their adherence to lung epithelium cells of cell line A549 [27, 33]. On the other hand, the adhesion of the hyphae of the mutant Δuge3 improves notoriously when the purified GAG adheres directly to the epithelial cells A549 [32]. Thus, nullified GAG production in the mutant Δuge3 is associated with increased exposure to β-1,3 glucan in hyphae [34, 35]. This results in increased recruitment of leukocytes during lung infection and increased binding of dectin-1 to the surface of hyphae, leading to increased production of inflammatory cytokines by dendritic cells *in vitro* [31]. Inflammation and ciliary damage result in decreased mucociliary elimination, which in turn can favor adherence and germination of *A. fumigatus* conidia [26, 36].

4. Compliance with nutritionals requirements

4.1 Copper

Another virulence attribute recognized in *A. fumigatus* is copper [37]. The fungal hyphae must acquire copper from the environment and maintain the intracellular
concentration within the micromolar range. In general, copper is internalized through high-affinity uptake systems, depending on the copper concentration in the extracellular medium [38, 39]. One of the high-affinity uptake systems comprises the family of copper transporter proteins (Ctr) associated with the membrane. They are small proteins (18–30 kDa) with up to three transmembrane domains and have the Cu + ion as a substrate [40–42]. Copper-binding motifs (Mets) located in the extracellular N-terminal region or transmembrane domain are rich in methionine (MxxM, MxM, or MxxxM) [43]. The MxxxM motif is essential in the transmembrane transport of Cu+ [40]. Ctr proteins are assembled to create a pore by which the transmembrane passage of Cu + is driven. Entry is facilitated when the intracellular concentration of the metal is low [44]. Copper in its Cu2+ oxidation state can also be internalized but must be reduced first to Cu + by the action of reductases present in the plasma membrane [39].

On the other hand, copper uptake is a strictly controlled process. When the intracellular level of Cu + exceeds the toxicity threshold, in addition to generating reactive oxygen species (ROS), the mechanism of detoxification or ion sequestration is activated to restore the balance of cellular copper. This mechanism is directed by the transcription factor AceA [37, 45]. The DNA-binding domain, known as “Cu_FIST,” and the numerous cysteine residues arranged in CxC-CxxC segments throughout the protein sequence are the characteristic domains that identify this transcription factor. Within the DNA-binding domain, two different motifs are involved in binding stabilization. When there is an excess of copper, four Cu + atoms bind to the Cys-rich domain, causing a conformational change that facilitates AceA-DNA bonding. This binding allows transcription of the crpA coding gene for P-type ATPase. P-type-ATPase CrpA is synthesized in the endoplasmic reticulum and migrates to the plasma membrane, where CrpA pumps Cu + ions out of the cell to restore balance and reduce copper toxicity. AceA also activates the sod1 and cat1/2 genes, which encode superoxide dismutase (Sod1) and catalase (Cat1/2). Sod1 and Cat1/2 enzymes neutralize ROS generated by Cu + toxicity and even those generated by the host’s defense mechanisms ([Figure 3]) [37, 45]. Therefore, the mechanism of copper detoxification is a critical factor in the viability of the pathogen during infection. In addition, both Sod1 and Cat1/2 also play an essential role in fungal virulence. Interestingly, host organisms have developed defense strategies against copper-dependent fungal pathogens. For example, by removing all Cu + in the infection area, copper deprivation in the pathogen can be induced, and its growth can be limited. Likewise, the copper mobilization mediated by the host’s innate immune cells to the tissue invaded by the fungus is another defense mechanism that seeks to cause fungal poisoning by excess copper [46].

On the other hand, copper also acts as a cofactor of the laccases AfAbr1 and AfAbr2, which are involved in the melanin biosynthesis in *A. fumigatus* and,
therefore, in virulence [47]. Melanin confers a non-immunogenic state to the fungus. Therefore, if the absorption of copper in the hyphae decreases, the laccase activity is also reduced, generating melanin deficiency in the conidia, which makes them immunoreactive [48, 49]. The latter highlights the importance of copper uptake for pathogen viability within the host.

4.2 Iron

Iron is an essential nutrient for all living organisms, including *A. fumigatus* [50]. This fungus uses iron as a cofactor for fundamental biochemical activities, such as oxygen transport, energy metabolism, and DNA synthesis [51]. Therefore, during infection, iron competition is a crucial event that determines the outcome of the host-pathogen relationship [52]. While the host’s innate immune system sequesters iron to reduce its free concentration to low levels and limit availability for *A. fumigatus*, the fungus uses different strategies to adapt to low environmental iron concentration [53], and even iron overload, as it is vital to maintain homeostasis. Two transcription factors maintain iron homeostasis: GATA factor SreA and factor bZIP HapX [51, 54]. When the fungus has enough iron for cellular activities, factor SreA represses iron absorption mediated by iron-reducing assimilation and siderophores to avoid toxic effects [55]. When iron is scarce, the factor HapX activates siderophore-mediated iron acquisition and, at the same time, saves iron by preventing its consumption in activities such as heme biosynthesis and respiration. Recent research has revealed that siderophores represent essential virulence factors contributing to a host’s microbiome-metabolome dialog [56, 57]. HapX deficiency, but not SreA, attenuates the virulence of *A. fumigatus* in murine models of aspergillosis [55, 58], emphasizing the crucial role of iron-limiting adaptation in pathogenicity. It has been reported that immunocompromised patients with iron overload, after a transplant, have a high risk of developing invasive aspergillosis. Therefore, it is proposed that the pharmacological inhibition of the siderophores synthesis of *A. fumigatus* or chelating agents could favor this type of patient [52].

4.3 Zinc

In the same way as iron, zinc is an essential cofactor for many crucial metabolic processes, including the growth and virulence of *A. fumigatus* [59]. Therefore, the fungus has also developed mechanisms to capture zinc through transporters (zrfC) and maintains homeostasis through the action of a transcription factor (zafA). Thus, mutant strains lacking genes encoding a zinc transporter (ΔzrfC) and a transcription factor (ΔzafA) that regulates zinc absorption show a reduced virulence phenotype in murine models of pulmonary aspergillosis [16, 60].

5. Secondary metabolites

5.1 Melanin

Melanin is one of the most important virulence determinants in *A. fumigatus* [61, 62]. This fungus can synthesize two different types of melanin: DHN-melanin attached to the cell wall of conidia and water-soluble extracellular pyomelanin [61]. The metabolic pathway of DHN-melanin production is activated during conidiation
and may be involved in multiple mechanisms of adaptation and survival in harsh environments. DHN-melanin protects against UV rays and desiccation and neutralizes free radicals [63, 64]. In addition, it protects the fungus against the innate immune response, mainly affecting the activity of macrophages, phagocytosis, and acidification of phagosomes and phagolysosomes, which facilitates the colonization and persistence of conidia during infection. It is thought that the production of pyo-melanin is a mechanism that protects germinating hyphae when DHN-melanin has disappeared. DHN-melanin is closely associated with the adhesion of molecules such as hydrophobins that form a rod layer that provides conidial hydrophobicity, physical resistance, and immune inertia to \textit{A. fumigatus} against the host's immune system [65]. DHN-melanin is also known to bind to antimicrobial peptides, reduce the efficacy of antifungal drugs, and prevent intracellular destruction of conidia by reducing luminal acidification and resisting phagolysosomal degradation [26].

DHN-melanin biosynthesis in \textit{A. fumigatus} is a polyketide-based pigment synthesis consisting of six genes: \textit{pksP/abl1}, \textit{ayg1}, \textit{arp1}, \textit{arp2}, \textit{abr1}, and \textit{abr2}, expressed during conidiation [66]. \textit{A. fumigatus} mutants lacking any of these genes related to melanin biosynthesis have shown melanin-deficient phenotypes and decreased virulence in \textit{Galleria mellonella} [67]. Since melanin provides cell wall stability and structural rigidity [5], it has been suggested that in mutant strains, the absence of melanin causes a modification of the fungal cell wall, which in turn triggers an increased immune response in the larvae.

5.2 Gliotoxin

Gliotoxin (GT) is a hydrophobic metabolite secreted by \textit{A. fumigatus}, which belongs to the class of epipolythiodioxopiperazine compounds characterized by a quinoid fraction and a disulfide bridge across the piperazine ring, which is essential for its toxicity [11, 68–70]. GT is a recognized virulence factor in this fungus. Its functions are to inhibit the phagocytic activity of macrophages and the response to oxidative stress, decrease the cytotoxic activity of T cells, and prevent the apoptosis induction of host cells [64, 71]. The biological activity of GT is based on an internal disulfide bridge that can bind and inactivate proteins through sulfur: thiol exchange [4]. The transcription factor mtfA regulates GT biosynthesis through the \textit{gliZ} and \textit{gliP} genes. Reeves et al. [72] showed in the \textit{G. mellonella} model that there is a positive correlation between GT production and the pathogenicity of \textit{A. fumigatus}, i.e., isolates with high GT production were lethal to the larva. There is also clinical evidence of GT involvement as a virulence factor. For example, GT has been detected in the lung and the serum of cancer patients suffering from invasive aspergillosis. It should be noted that this finding was corroborated in a murine model. Other evidence is that more than 90% of \textit{A. fumigatus} strains isolated from cancer and invasive aspergillosis patients produce GT, and GT has been seen to occur much faster at 37°C under high oxygen levels, that is, under conditions similar to the host lung environment [11].

5.3 Galactosaminogalactan

Galactosaminogalactan (GAG) is a specific carbohydrate polymer consisting of galactose bound to \(\alpha\)-1,4, N-acetyl galactosamine (GalNAc), and galactosamine (GalN), which is expressed and secreted by actively growing hyphae of \textit{A. fumigatus} [10]. After being secreted by hyphae, GAG binds to the surface of the hyphae themselves, generating a polysaccharide sheath that covers the growing fungus and forms
an extracellular matrix between the hyphae [2]. Then, it can wrap cell wall polysaccharides such as β-glucans from innate immune detection and repel cationic molecules such as antimicrobial peptides associated with neutrophil extracellular traps [32, 73]. As a cationic exopolysaccharide located within the extracellular matrix, GAG is an adhesin that mediates binding to anionic surfaces, such as human cells, macro-molecules, and plastic and supports biofilm formation [32, 74]. Other vital functions of hyphae-secreted GAG are mediating neutrophil apoptosis and resistance to neutrophil extracellular traps (NETs), modulating host immune responses through platelet activation, inducing secretion of IL-1 receptor antagonists, and inflammasome activation [31, 73, 75]. Therefore, GAG is critical for host damage and fungal virulence, as studies in mouse models of invasive pulmonary aspergillosis (IPA) have shown, where GAG-deficient strains exhibit reduced adherence to lung epithelial cells, do not form biofilms, and are less virulent [7, 32]. The multiple and important functions of GAG in virulence have prompted the study of the mechanisms involved in its biosynthesis. To date, it has been seen that GAG synthesis is initiated intracellularly with the interconversion of UDP-N-acetylglucosamine to UDP-N-acetylgalactosamine and UDP-glucose to UDP-galactose by the bifunctional UDP-glucose-4-epimerase (Uge3) [76]. The polymerization and extracellular export of the GAG macromolecule are mediated by a transmembrane glycosyltransferase (Gtb3) [74]. The release of fully acetylated GAG is mediated by a glycoside hydrolase (Sph3) anchored to the membrane that retains endo-α-1,4-N-acetylgalactosaminidase activity [77]. Upon crossing the cell wall, acetylated GAG is processed by a secreted carbohydrate esterase (Agd3), making GAG cationic and biologically active [78, 79].

5.4 Fumagillin

Fumagillin (FM) is a mycotoxin produced by *A. fumigatus* during hyphae development. FM is considered an important virulence factor that inhibits angiogenesis; that is, it reduces the proliferation of endothelial cells for the formation of blood vessels, preventing the infiltration of host immune cells to the infection site [80]. It has been reported that this toxin is produced during the first 30–72 h of invasive aspergillosis, which, together with gliotoxin (GT), helps the fungus evade the immune response and favors the spread and invasion of hyphae, damaging the epithelial layer [11, 81]. Some studies in the *G. mellonella* model have reported that FM exhibits potent neutrophil inhibitory activity, destabilizing the proper immune response to infections. Inhibition of hemocyte phagocytosis is also observed, allowing the fungus to grow in the larva [64, 82]. In other studies, FM has been administered to larvae prior to inoculation with *A. fumigatus*, finding that it increases susceptibility to infection [83, 84]. Therefore, understanding the mechanism of action of FM may open paths to finding new therapies for treating invasive aspergillosis [85].

5.5 Alkaloids

Ergot alkaloids are metabolites produced by *A. fumigatus*. The festuclavine and fumigaclavine alkaloids A, B and C are present in or on the conidia of *A. fumigatus* [86]. Fumigaclavine C inhibits the production of tumor necrosis factor α in human macrophages and reduces the expression of several other inflammatory cytokines in mice [87]. In addition, several in vivo studies in the *G. mellonella* model show that this type of specialized alkaloid is involved in fungal pathogenicity [64]. The most relevant evidence has been that the mutant strains of *A. fumigatus*, generated by the
alteration of the genes involved in the biosynthesis of fumigaclavine, both PesL and pesI and dmaW, showed a hypovirulent phenotype in *G. mellonella* due to a deficient production of fumigaclavine C [64, 88, 89].

6. Fungal development

From the two *A. fumigatus* morphotypes, the hyphal morphotype predominates during invasive pulmonary aspergillosis, while the conidial morphotype is rarely observed [90]. It has been reported that during *in vitro* growth, conidia production is associated with a reduction in hyphae growth [91]. Therefore, the forced induction of conidiation during infection could decrease virulence by suppressing the growth of hyphae and invasion. The regulation of conidiation is determined by the transcription factor BrlA. This factor is sufficient to activate the conidiation pathway in *A. fumigatus*, inhibit in vitro vegetative growth, and reduce the virulence of invasive Aspergillus infection in vivo models. Likewise, it has been observed that ΔbrlA mutants of *A. fumigatus* do not produce conidia but hyphae and exhibit greater virulence. However, the effects of brlA overexpression in *A. fumigatus* are unknown [91].

On the other hand, there are studies in the *G. mellonella* model that have shown some proteins (flbA, gprK, rgsA, rax1, rgsC, and rgsD) of the G-protein signaling regulate, positively or negatively, the production of virulence factors in *A. fumigatus*, such as GT and melanin [64]. In addition, it has been observed that fungal isolates with mutant protein ΔrgsD increase conidiation, stress response, and the production of GT and melanin and, therefore, virulence in the larva. However, with ΔrgsC and ΔgprK mutants, the conidiation, growth, and tolerance to H$_2$O$_2$ and GT production are reduced, the cell wall is modified, and virulence is reduced [64, 88, 92]. In the same way, it has been observed that other GTPase proteins (srgA A, srgA B, srgA C) participate in the development and filamentation of fungi. For example, in mutant ΔsrgA isolates, the growth rate, aberrant conidiation, and virulence are reduced [93]. *A. fumigatus* has five septins or proteins with GTPase function (aspA, aspB, aspC, aspD, and aspE) involved in regulating critical cellular processes, such as septation. It has been observed that in *G. mellonella* mutant isolates ΔaspA, ΔaspB, and ΔaspC are hypervirulent, and the conidiation is reduced without alteration in the growth rate, except in the case of mutants’ ΔaspB in whom the growth rate is reduced [94].

7. Calcineurin

Calcineurin is an essential virulence factor in *A. fumigatus*. Calcineurin is a specific serine/threonine protein phosphatase that is a heterodimer consisting of a catalytic subunit, CnA, and a regulatory subunit, CnB. It is activated in the presence of calcium and calmodulin. Calcineurin signaling in *A. fumigatus* and other fungal pathogens is highly conserved and leads to the activation of virulence genes and proteins essential for organism growth at host body temperature, hyphae development, and survival [95]. These essential functions in virulence make calcineurin a target for developing antifungals. For example, FK506 (tacrolimus) is a natural calcineurin inhibitor produced by several *Streptomyces* species with potent antifungal activity [96]. FK506 acts on fungal cells by binding to FK506 binding protein 12 (FKBP12), forming a complex that binds to calcineurin and inhibits it by sterically blocking substrate access.
to the active site. FKBP12 belongs to the protein family called immunophilins that bind to immunosuppressive molecules and mediate their activity [97, 98].

So, it is fascinating how this fungus manages to go from harmless to pathogenic as, in addition to the predisposing factors of the human, multiple attributes of the fungus intervene that favor its growth and survival in the host. Among these virulence attributes are thermotolerance, the ability to evade the immune response, some components of the cell wall, the production of secondary metabolites, compliance with nutritional requirements, and the production of melanin, among others (Figure 4). Furthermore, some of these virulence attributes are interrelated, making understanding the pathogenesis of aspergillosis more complex.

8. Conclusions

*A. fumigatus* requires different strategies to infect and cause disease in different hosts and suppress resistance responses by the host. In these strategies, it uses various attributes whose expression is influenced by environmental conditions (nutrient composition and response to host defenses). Some of these virulence attributes are interrelated, which makes it more complex to understand the adaptation mechanisms of both host and fungus to adapt and survive in a hostile environment and produce an infection. However, it is essential to understand these mechanisms to help develop new therapeutic strategies against aspergillosis.

**Conflict of interest**

The authors declare no conflict of interest.
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A. Appendix 1

A.1 Aspergillus taxonomy

Aspergillus taxonomy is a complex subject. In 1965, based on phenotypic characteristics, Raper and Fennell [99] classified 150 Aspergillus species into 18 groups. In 1985, Gams et al. [100] reclassified the groups into 18 sections as a formal taxonomic status. Currently, the approximately 250 known species within the Aspergillus genus are classified into at least 16 sections [101, 102]. This classification is based on a polyphasic analysis that not only includes phenotypic but also molecular studies. The Sections of the current classification are: Aenei, Aspergillus, Bispori, Candidi, Circumdati, Clavati, Cremei, Flavi, Flavipes, Fumigati, Nidulantes, Nigri, Restricti, Terrei, Usti, Zonati. The major species known to cause disease in humans are found in five Aspergillus sections: Fumigati, Flavi, Nigri, Terrei, and Nidulante; however, the A. section Fumigati is the most frequent. The section Fumigati includes 12 species that are pathogenic for humans, several of which have been found to be in the sexual state (Neosartorya) (Table 1). The species in section Fumigati are morphologically indistinguishable from each other, but may present different antifungal susceptibility profiles.

Due to taxonomic complexity, in this chapter we refer simply to A. fumigatus.

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Table 1. Pathogenic species within the Fumigati section.
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