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Abstract

Melanins are secondary metabolites made up by a group of complex heterogeneous polymers like phenolic and/or indolic monomers. Several classes of fungal melanins have been described like γ-glutaminyl-3,4-dihydroxy-benzene (GDHB)-, L-DOPA , DHN, catechol-, pyomelanin, p-aminophenol (PAP)- and also the heterogeneous melanins as well as the recently reported 5-deoxybostrycoidin-based melanin. They have been mostly localized in cell walls in different structures of fungi, which suggest that they play different biological roles. They have been related mostly with morphogenesis, stress resistance, virulence and energy transduction. Still much work remains to be done in order to clarify the role melanins play in fungi

Keywords	melanins; stress resistance; wall deposition; synthesis; biological role
Taxonomy	Biological Science Research Methodologies, Agriculture, Biochemistry

Corresponding Author	Pedro Balatti
Corresponding Author's Institution	Cerntro de Investigaciones de Fitopatologia (CIDEFI)
Order of Authors	Andrea Toledo, Mario Emilio Ernesto Franco, Silvina Marianela Yanil Lopez, María Inés Troncozo, Mario Saparrat, Pedro Balatti
Suggested reviewers	Rodrigo Almeida-Paes, Carlos Taborda, Joshua Daniel Nosanchuk, Marc Stadler

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December 28th, 2016

Editor in Chief

Physiological and Molecular Plant

Pathology

Dr. Brad Day

Dear Dr. Day:

I am sending herewith the review about melanins I suggested we can contribute to the journal.

The review deals with the different types of meanins that have been described in fungi, their localization and putative roles as well as the pathway of their synthesis. We tried to keep it as short as possible.

I will be looking forward to hearing from you.

Dr. Pedro A. Balatti

PhD Plant Pathology

Melanins in Fungi: types, localization and putative biological roles

Andrea Toledo[1], Mario Emilio Ernesto Franco[1], Silvina Marianela Yanil Lopez[1], María Inés Troncozo[2], Mario Carlos Nazareno Saparrat[2,3] and Pedro A. Balatti[1,2,*]

1-Centro de Investigaciones de Fitopatología CIDEFI (UNLP-CICBA). 2-Curso de Microbiología Agrícola, Facultad de Ciencias Agrarias y Forestales, UNLP. 3-Instituto de Fisiología Vegetal INFIVE (UNLP-CONICET).

*Corresponding author pbalatti@gmail.com CIDEFI, Facultad de Ciencias Agrarias y Forestales, Universidad Nacional de La Plata. Calle 60 y 119 La Plata (1900) TE 54-221-4236758 Int 423.

Keywords melanins-stress-wall deposition-synthesis

Abstract

Melanin is a secondary metabolite made up by a group of complex heterogeneous polymers like phenolic and/or indolic monomers. Several classes of fungal melanins have been described like γ-glutaminyl-3,4-dihydroxy-benzene (GDHB)-, L-DOPA , DHN, catechol-, pyomelanin, *p*-aminophenol (PAP)- and also the heterogeneous melanins as well as the recently reported 5-deoxybostrycoidin-based melanin. They have been mostly localized in cell walls of fungi of different structures which suggest a different biological role. They have been related mostly morphogenesis, stress resistance, virulence and energy transduccion. Still much work remains to clarify the role malanins play in fungi

What do we define as melanin?

Melanin is a secondary metabolite made up by a group of complex heterogeneous polymers like phenolic and/or indolic monomers. Recent NMR studies demonstrated that melanins are a complex network of aliphatic and aromatic (such as pyrrole structures) moieties. Sun et al. [1] by 1D-NMR spectroscopy and the 1H–13C HSQC correlations found, in the crude extracellular melanin of *Auricularia auricula,* signals of both aliphatic and aromatic regions. Therefore the condensed molecular formula of this melanin might be $[C_{18}\ (OR)_{3H7O4N2}]_{n}$.

Melanins synthesis and localization in fungi

Although melanins structure increases in complexity along the ontogeny of fungal cultures, they have carbon-containing covalent linkages between pyrroles and either chitin-derived N-acetylglucosamines or membrane glycerides. Solid-state NMR data support a stacking of indole-based aromatic units through covalent cross-linking, which generates a material ordered at microsites but globally amorphous [2]. Unfortunately, these experiments were performed only on *Cryptococcus neoformans* and should be made with other types of melanins synthetized by many different fungi. Recently, Beltrán-García et al. [3] reported that the melanin isolated and purified from the mycelium of *Mycosphaerella fijiensis* is constituted by 50 units of 1, 8-dihydroxynaphthalene (DHN). Further analysis using solid-state NMR and physical/imaging techniques should provide the bases to characterize the pigment architecture in the cell wall, which will be useful to disregard artefacts derived from the harsh chemical treatments that are frequently used to extract DHN-melanin.

Sometimes soluble melanins such as pyomelanin and heterogeneous melanins as well as insoluble ones mostly, immobilized in the cell wall, also are released in culture supernatants. So additional studies should be aimed at clarifying the places of melanin deposition and the way they are released in liquid cultures. In any case, melanins deposition and localization in the cell wall vary in fungal species, culture conditions and/or the structures differentiated by each fungus. This basically suggests that melanin might be playing more one biological role in fungal biology.

While some fungi present a layer of melanin on the inner side of the cell wall, tightly associated to the plasma membrane, like in the appressorium of *Magnaporthe grisea*, other melanins are deposited throughout the cell wall or in the outermost layers such as in the hyphae of *Pseudocercospora griseola*, or as granules on the surface of the cell walls [4]. Although in fungi melanin is an extracellular molecule, the polymer is synthetized in specialized vesicles (analogous to the mammalian melanosomes) and is transported out of the cell and anchored to the wall. Therefore it is possible that environmental conditions as well as metabolic processes might alter the extrusion of melanins in different fungi.

Many fungi differentiate vegetative and reproductive structures with melanins such as those belonging to the dematiaceous (brown-pigmented) group. The type of melanin like 1,8-DHN and L-3,4-dihydroxyphenylalanine (L-DOPA) has been associated to certain fungal groups such as ascomycetous and basidiomycetous respectively. However, recently it has been found that phylogenetically relate d fungi synthetize different dark pigments in specific structures. In , several types of melanins can be synthetized by the same fungus depending upon the environmental conditions as well as on its development stage (**Table 1**). The presence of melanins in fungi adapted to different environments and in some cases in the same organism growing under different conditions suggests that they play different crucial biological roles in nature. However, more studies should be performed at identifying the role of the different types of melanins on biological processes.

Table 1. Type, localization and putative role of melanins in different fungi.

Types of melanins synthetized by fungi

While many fungi synthetize melanins constitutively, others do so only under certain culture conditions and/or if specific precursors are available. While several fungi synthesize melanin endogenously via a DHN intermediate, others, like *Tetraploa aristata* [26], synthetize an undefined set of soluble blackish pigments that are known as heterogeneous melanins. They are present in fungal secretions and their synthesis has been related to mechanisms of detoxification. Based on their biochemical precursors, pathways and/or components several classes of fungal melanins have been described like γ-glutaminyl-3,4-dihydroxy-benzene (GDHB)-, L-DOPA-, which is referred to as eumelanin, DHN-, catechol-, pyomelanin, *p*-aminophenol (PAP)- and also the heterogeneous melanins as well as the recently reported 5-deoxybostrycoidin-based melanin (**Figure 1**). This latter dark pigment forms part of the periderm of perithecia differentiated by fungi belonging to the *Fusarium graminearum* group and its monomers have been suggested be the result of the reaction of anhydrofusarubin derivatives and ammonia [14]. Additionally, fungal melanins as well as those of plants also may be (or has been) called as allomelanins, an unclear term that include all the dark pigments synthesized from nitrogen-free precursors such as those derived from catechol and DHN [27]. Furthermore, if the pigments incorporate cysteine during their synthesis within the L-DOPA, such as it occurs in *Auricularia auricula*, they are referred as pheomelanins [1]. Although the polyketide synthase pathway is involved in the synthesis of DHN-melanins, phenoloxidases have been related to both DHN- and DOPA-one. Interestingly, disruption of genes of melanin synthesis has been done in several pigmented fungi and while this resulted in mutants that developed albino colonies, complementation of mutants with native genes fully recovered the wild type phenotype. However the key enzymes and mechanisms involved in polymerization reactions still remain unknown.

Figure 1. Pathways for the synthesis of different types of melanins in fungi. PPO, polyphenol oxidase. GHB, γ-L-glutaminyl-4-hydroxybenzene. GDHB, γ-L-glutaminyl-3,4-dihydroxybenzene. γ-GT, γ-Glutaminyltransferase. GBQ, γ-L-glutaminyl-3,4-benzoquinone.

Biological role of melanins in fungi

Fungal melanins are unique in that they play a myriad of biological roles, in morphogenesis, virulence, energy transduction and/or C storage. Also their role in cell protection against stresses seems to be a common mode of action in fungi though not the only one.

In terms of morphogenesis, in *Aspergillus fumigatus* melanin was found to be a key structural component of conidial cell wall. Also, it has been related to the expression of adhesins as well as other virulence factors [28], therefore it appears that melanin play a critical role very early just before infection occurred. In *Bipolaris sorokiniana* melanin has been associated to the development of aerial hyphae and conidiogenesis [9].

Melanins also have been associated with fungal virulence, since it is required for pathogenicity in many plant pathogenic fungi, as well as animals and human pathogens. The radical and chemical nature of melanins works as a shield against hydrolytic enzymes that may affect fungal cell wall. In addition to this, melanins also might sequestrate host defensive proteins and metals or trap single electrons or acts as a photoactivated ''toxin'' that generate singlet molecular oxygen, which has been shown for the DHN-melanin of *M. fijiensis*. In several plant pathogens melanin plays a pivotal role in generating osmotic pressure within the appressorium, when hyphae penetrate plant cell walls, which was described for *Magnaporthe* and *Colletotrichum* species. In these pathogens, mutations aimed at inhibiting melanization led to a reduction in pathogenicity.

Melanins enhance tolerance of fungi to environmental stresses. This is to say melanins are involved in fungal survival. Melanins protect fungal structures from UV radiation, temperature, oxidizing agents and antibiotics [29]. Melanins might be playing the role of an extracellular redox buffer that can neutralize oxidants generated by environmental stresses. Furthermore, melanins protect fungi from solar radiation and UV light. In fact the pigment dissipates light energy either as heat or in chemical reactions or by scavenging active oxygen species, e.g. superoxide, and singlet oxygen, which results in the consumption of molecular oxygen. Therefore, melanin works as a protective shield of fungi against a broad range of environmental stresses as well as toxic molecules, improving in this way the survival ability of fungi.

Melanized fungal cell walls are relatively resistant to decomposition, because of this melanins might be a storage source of C in the soil. Organic matter derived from *Cenococcum geophilum*, which is drought tolerant and abundant in water-stressed habitats, may represent as much as 50 % of organic C in soils [11].

Dark pigments like melanins might also function in energy transduction, which might enhance growth of melanized fungi suggesting a role for melanin in energy capture and utilization [30].

The broad functional spectrum of fungal melanins suggests that they might have several applications in medicine as well as pharmacology, cosmetics and other fields [19]. The knowledge of the biosynthesis as well as the role melanins play in pathogenic fungi as well as the enzymes involved in melanization are crucial to design strategies to manage plant pathogens of crops.

Final considerations

Data regarding the structural organization of melanins in fungi whether they are located in cell walls or elsewhere, including extracellular medium, are scarce. Such studies have only been performed in *Cryptococcus neoformans*. In agreement with this, there is no information regarding the mechanisms involved in melanization in different fungi. It is known that while some synthetize one type of melanin, others synthetize two or three different types, suggesting either that each one plays a different biological role or that the pigment plays such a key biological role that fungi assure its presence by possessing different pathways. In line with this Frandsen et al. [14] found that in *Fusarium* pigmentation is sustained by conservation, replacement and development of redundant pigments. However, different melanins have been found in fungal structures, which can be additionally altered by the environment that also might differentially regulate their synthesis. All this together strongly suggest first of all that melanins play several crucial roles in fungi mostly related with survival and also that each different type probably plays a specific biological role.

It is also important to consider that melanins are present in phylogenetically unrelated fungi that belong to different taxonomic as well as ecological groups, which might be due to adaptation to different ecological niches, again suggesting that they might work differently.

Also additional studies should be performed aimed at clarifying the synthesis and role these pigments play in fungi such as in representatives of the Mucoraceae, Neocallimastigaceae and Synchytriaceae, which should be easier considering the availability of genomes of related fungi. This will allow to perform a comparative analysis of genes coding for the enzymes involved in melanin synthesis as well as their expression levels under different environmental conditions. This should also be a complement with site directed mutations that together with phenotype evaluation and complementation studies will allow researchers to elucidate the specific role each type of melanin play in fungi. These lines of research are obvious but even though researchers are aware of the importance of melanins in nature for unknown reasons, their role in fungal biology remain unknown.

Financial Support

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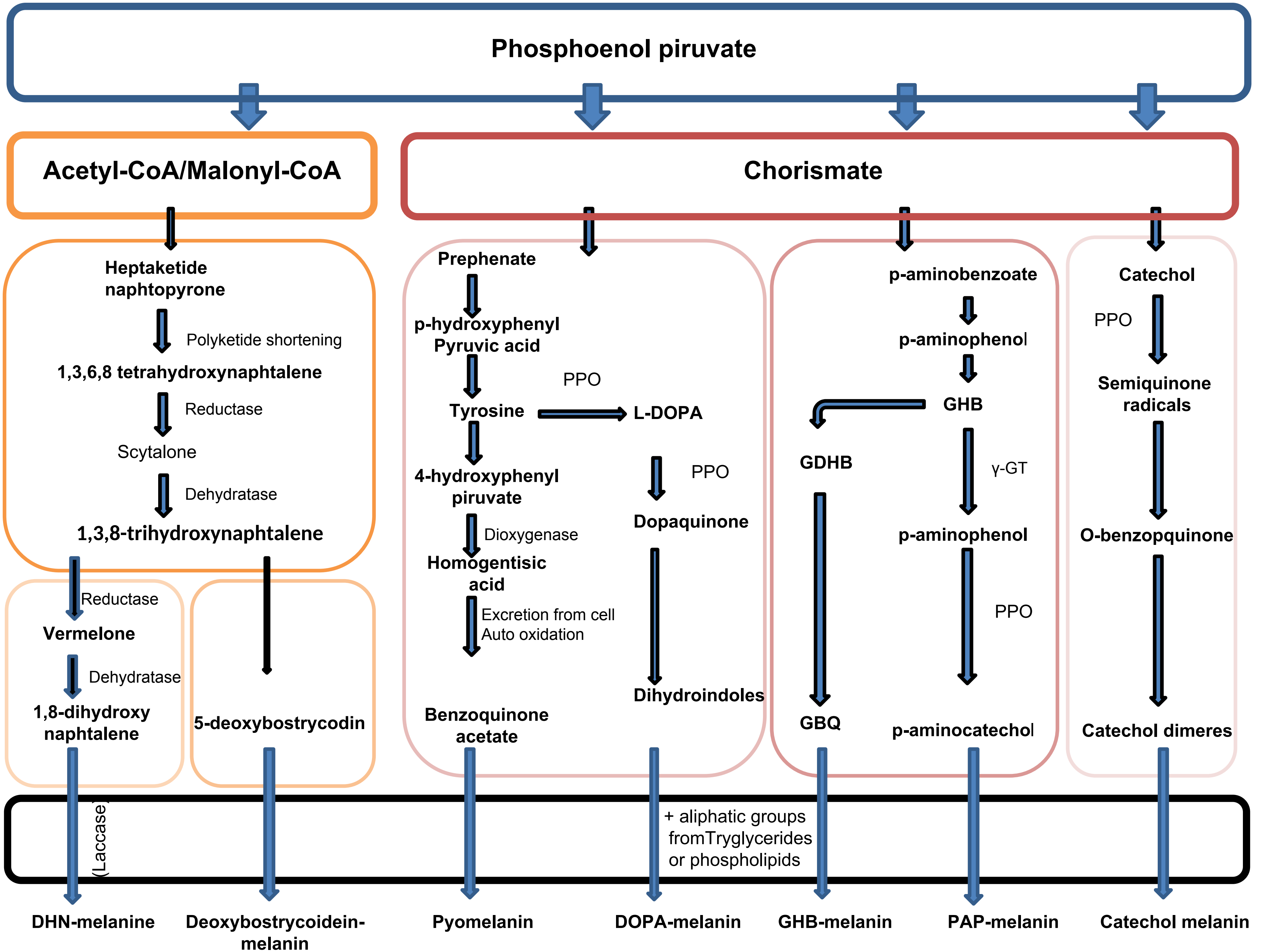

Phosphoenol piruvate
Acetyl-CoA/Malonyl-CoA
Chorismate
Heptaketide naphtopyrone
Polyketide shortening
1,3,6,8 tetrahydroxynaphtalene
Reductase
Scytalone
Dehydratase
1,3,8-trihydroxynaphtalene
Reductase
Vermelone
Dehydratase
1,8-dihydroxy naphtalene
5-deoxybostrycodin
(Laccase)
Prephenate
p-hydroxyphenyl Pyruvic acid
PPO
Tyrosine
L-DOPA
4-hydroxyphenyl piruvate
Dioxygenase
Homogentisic acid
Excretion from cell
Auto oxidation
Benzoquinone acetate
PPO
Dopaquinone
Dihydroindoles
p-aminobenzoate
p-aminophenol
GHB
GDHB
γ-GT
p-aminophenol
PPO
GBQ
p-aminocatechol
Catechol
PPO
Semiquinone radicals
O-benzopquinone
Catechol dimeres
+ aliphatic groups fromTryglycerides or phospholipids
DHN-melanine
Deoxybostrycoidein-melanin
Pyomelanin
DOPA-melanin
GHB-melanin
PAP-melanin
Catechol melanin

Table 1. Type, localization and putative role of melanins in different fungi.

Taxa*	Melanin type	Localization	Putative role	Reference
Agaricus bisporus[b] (Agaricaceae)	GHB- PAP- DOPA- Catechol-	Basidiospore wall ? ? ?	? ? ? ?	[5,6]
Auricularia auricula[b] (Auriculariaceae)	Pheomelanin DHN- Eumelanin-type	Fruiting bodies Fruiting bodies Extracellular medium	? ? ?	[1,7,8]
Bipolaris sorokiniana[a] (Pleosporaceae)	DHN-	Wall in hyphae and conidia	Development, fitness and survival	[9,10]
Cenococcum geophilum[a] (Gloniaceae, Mytilinidiales)	DHN-	Hyphae wall	Tolerance to water stress	[11,12]
Cladosporium cladosporioides[a] (Cladosporiaceae)	DHN-melanin like compounds	Wall in hyphae and conidia	Tolerance to stresses imposed by fungicides or the environment	[13]
Fusarium graminearum[a] (Nectriaceae)	5-Deoxybostrycoidin-	Perithecial wall	Tolerance to UV radiation and reactive oxygen species	[14]
Metarhizium anisopliae[a] (Clavicipitaceae)	DHN-	?	Virulence factor. Hydrophobic attraction, water absorption, adhesion, conidia germination and tolerance to water and oxidative stress	[15]
Monilinia laxa[a] (Sclerotiniaceae)	DHN-	All structures differentiated	Pathogenicity. Sporogenesis. Survival. Tolerance to environmental stresses and autolysis	[16]
Mucor spp.[d] (Mucorales)	?	Outer wall of sporangiospores	?	[17]
Neocallimastix sp.[e] Isolate MC-2 (Neocallimastigaceae)	?	Wall of mature resistant sporangia	Survival	[18]
Ophiocordyceps sinensis[a] (Ophiocordycipitaceae)	DOPA-	Fermentation broth of submerged cultures	?	[19]
Penicillium chrysogenum[a] (Trichocomaceae) .	Pyomelanin	Extracellular medium	Survival under nutrient and water stress	[20]
Pseudocercospora griseola[a] (Mycosphaerellaceae)	DHN-	Wall in hyphae and conidia	Morphogenesis	[4,21]
Sporothrix schenckii[a] (Ophiostomataceae)	DHN- DOPA- (eumelanin) Pyomelanin	Constitutively in conidial and yeast cells Wall of conidia, yeast cells, and hyphae if L-DOPA is available during fungal growth Extracellular medium if L-tyrosine is available during fungal growth	Virulence related to infection and against phagocytosis Virulence related to infection and against phagocytosis. Protection against antifungal drugs Quencher of oxidative stress. Protection against antifungal drugs	[22,23,24]
Synchytrium endobioticum[c] (Synchytriaceae, Chytridiales)	Allomelanin like compounds ?	Resting spores	Survival	[25]

Table 1. Type, localization and putative role of melanins in different fungi.

***a, phylum Ascomycota; b, phylum Basidiomycota; c. phylum Chytridiomycota; d, subphylum Mucoromycotina; e, phylum Neocallimastigomycota. GHB, γ-L-Glutaminyl-4-hydroxybenzene. PAP, *p*-Aminophenol. DOPA, L-3,4-dihydroxyphenylalanine. DHN, 1,8-dihydroxynaphthalene.**

December 28th, 2016

Editor in Chief

Physiological and Molecular Plant

Pathology

Dr. Brad Day

Dear Dr. Day:

I am sending herewith the review about melanins I suggested we can contribute to the journal.

The highlights of the review can be summarized in the following phrases

1. We discuss were melanins are located in fungi and by doing this we inferred their possible role
2. We also discuss the different type of melanines that are synthesized by different fungi
3. We present the different known routes of synthesis
4. We discuss the roles that are known they play in fungi
5. We made based on the review prospects for the future

Dr. Pedro A. Balatti

PhD Plant Pathology