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Melanin Pigments of Fungi under Extreme Environmental Conditions (Review)

N. N. Gessler[a], A. S. Egorova[a], and T. A. Belozerskaya[b]

Bach Institute of Biochemistry, Russian Academy of Sciences, Moscow, 119071 Russia
Department of Biology, Moscow State University, Moscow, 119991 Russia
e-mail: tabinbi@mail.ru

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Abstract—This review is dedicated to the research on the functions of melanin pigments in fungi. The participation of melanin pigments in protection from environmental factors is considered. Data on the biosynthetic pathways and types of melanin pigments in fungi are presented.

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INTRODUCTION

The study of melanin pigments has over time shown their importance for the survival of fungi under extreme environmental conditions, including the protection of pathogenic fungi from the action of reactive oxygen species (ROS) in host cells. A clear understanding of the molecular mechanisms of the resistance of extremophilic fungi and fungal pathogens allows one to identify targets for new drugs.

Melanin pigments were found in representatives of all natural kingdoms from bacteria to mammals. They often color the vestiture of fish, birds, and animals. In fungi melanin is an important protective factor against the adverse effects of environmental stresses, such as UV radiation, drying, high concentrations of salts, heavy metals, and radionuclides. The presence of melanin allows fungi to exist under the influence of high electromagnetic radiation, for example, in high mountain regions, desert soils, and on plant surfaces. Under extreme conditions, the proportion of melanized fungi in mycobiota usually increases, for example, in ecotopes contaminated with radionuclides [1–4]. In aerial environments, the amount of melanized spores is higher than in the soil [5]. It was shown experimentally that dark-colored spores of many fungi are resistant to UV irradiation [6, 7]. The presence of melanin pigments ensures a high survival rate during high levels of UV radiation, while nonpigmented forms die within a few minutes. Microcolonial yeast-like fungi growing on rocks under the conditions of extreme temperatures, high insolation, drought, and low concentrations of organic compounds are strongly melanized [8–10]. Viable cells of these fungi were found in the Antarctic [11, 12]. A genetic analysis of microcolonial melanized fungi growing on the surface of stones allowed to classify many of them as the Dothideomycetes (including Eurotiomycetes) and related Arthoniomycetes classes. Among them, Capnodiales (members of the family Teratosphaeriaceae), Dothideales, Pleosporales, Myriangialis, as well as some unidentified groups related to Dothideomycetes [13], were identified. When grown under the harsh conditions of the Antarctic in cracks of rocks, the microscopic fungi *Cryomyces antarcticus* and *Cryomyces minteri* showed high resistance to UV radiation (280–360 nm, 3W/m^2), which they were able to sustain for few hours, whereas nonpigmented *Saccharomyces pastorianus* cells died after 30 min of exposure [14].

Under natural conditions, extremophylic fungi often form a community with bacteria, algae, and plants [15–16]. More than 80% of endophytic fungi that exist in the community with the herbaceous plant *Deschampsia antarctica* Desv. (Poaceae) in Antarctica produced melanin pigments [17]. These findings were consistent with earlier comments regarding the benefits of melanized fungi under the conditions of high insolation, drought, and low temperatures.

Melanized fungi also exhibit improved resistance to high concentrations of salts. *Hortaea werneckii, Phaeotheca triangularis, Trimmatostroma salinum, Aureobasidium pullulans*, and *Cladosporium* spp. live in salterns and are able to tolerate high (close to saturation) salt concentrations [18]. For some types of these fungi (*H. werneckii, R. triangularis*, and *T. salinum*), hypertonic sodium chloride solutions are their natural environment [19]. It was suggested that the presence of melanin in the cell wall of *H. werneckii* reduces the flow of salt into the cell [19].

The presence of melanin ensures the survival of microscopic fungi under the conditions of technogenic pollution. In industrial and roadside areas, an increase in the proportion of dark-colored melanin-containing fungi, which were more resistant to contamination in urban areas by heavy metals and unsaturated hydrocarbons, was observed [20, 21]. In urban conditions in air and snow samples, representatives of

the genera *Cladosporium* and *Alternaria* were dominant [22, 23].

Radionuclide contamination led to a change in fungal communities, an increased proportion of melanized fungi, and a reduced diversity of species [3, 4, 24]. Most common in contaminated zones were the species *Cladosporium*, *Ulocladium*, *Stachybotris,* and *Humicola*. The species *Cladosporium sphaerospermum*, *C. herbarum*, *C. cladosporioides, Alternaria alternata,* and *Aureobasidium pullulans* were widely available [3, 25]. Melanized fungi (mainly *Cladosporium* spp., *A. alternata*, *A. pululans*, and *Hormoconis resinae*) were found even in environs of the destroyed reactor in Chernobyl [25]. The presence of melanin was also shown in light-colored fungi, distributed in the area around the Chernobyl nuclear power plant: *A. versicolor* and *Purpureocillium lilacinum* (*Paecilomyces lilacinus*, according to the old classification) [26, 27]. The latter species, along with *Chaetomium aureum*, was recognized as a bioindicator of soil contamination within the range 3.7×10^6–3.7×10^8 Bq/kg [3]. In *P. lilacinum*, strains isolated from contaminated areas had a melanin content that was 2–2.5 times higher than in related strains that lived in areas isolated from the background level of radioactivity [26, 28]. The distribution of melanized fungi in areas with high levels of radiation undoubtedly reflects their advantage over light-colored fungal species; however, a majority of the basic mechanisms of radiation resistance of living organisms are not currently established [29].

A majority of melanized fungi that are adapted to extreme conditions, phylogenetically are similar to melanized pathogenic fungi, capable of withstanding ROS attacks in host cells [30]. Melanized opportunistic fungi have adapted to dishwashers and are able to survive elevated temperatures and the presence of detergents [31]. The melanized yeasts *Exophiala dermatitidis* and *E. phaeomuriformis* (Chaetothyriales), which may cause systemic diseases in humans, were the fungi most frequently (up to 56% of the detected mycobiota) found in dishwashers. Probably, the high temperature, high humidity, and the alkaline medium in dishwashers provide an alternative environment for these pathogenic fungi.

The presence of melanins in pathogenic fungi can have a significant impact on the development of diseases. Thus, it was shown that virulence was significantly higher in melanized strains of *Cryptococcus neoformans* [32, 33] and *E. dermatitidis* [34, 35] than in nonmelanized strains. *Aspergillus fumigatus* strains with melanin-containing conidia also showed higher virulence due to the participation of these pigments in the protection of spores of the pathogen from oxidative stress caused by ROS of host leukocytes [36–39]. Melanins may also act as an immunomodulators, reducing the ability of host immune cells to react to the presence of an etiological agent (*A. fumigatus* and *E. dermatitidis*) [35, 40, 41]. In *A. alternata*, mutational damage of melanin synthesis genes influence the development of conidia and their resistance to UV radiation [42]. Melanins in *Magnaporthe grisea*—a pathogen of rice blast—are needed as an antioxidants that protect the fungus from plant ROS [43, 44]. Lovastatin inhibits the synthesis of melanins in the pathogenic fungi *M. grisea*, *Stagonospora nodorum*, *Colletotrichum atramentarium*, and *Bipolaris sorokiniana*; this inhibition reduces the virulence of the fungi and allows recommending lovastatin as an indirect-action fungicide [45].

Melanins are one of the main factors in the pathogenesis of *Gaeumannomyces graminis*, which is a causative agent of the root rot of gramineous. Isolates, which did not synthesize melanins, were able to colonize the roots of gramineous, but any visible symptoms of the disease were not observed [46]. The lack of melanin pigments in mutant *Alternaria brassicicola* strains can not only cause a change in the color and increased sensitivity to UV radiation but also reduce the resistance to proteolytic and glycolytic enzymes [47]. Melanins protect *Rhizoctonia solani* from bacterial lysis [48]. Transformation of the entomopathogenic fungus *Metarhizium anisopliae* with melanin synthesis genes increases the efficiency of the application of this fungus against larvae of the cabbage moth (*Plutella xylostella*) [49].

Localization of melanins in fungi. Melanin pigments in fungi may be detected in the cell wall or secreted into the environment. Melanins can be seen as a dark substance in the cell wall during microscopic examination [19, 50]. Investigations of the microstructure of melanins associated with the cell wall of *C. neoformans* showed that it is represented by multiple layers of spherical granules (50–80 nm in diameter), located under the polysaccharide capsule and adjacent to the plasma membrane [54]. In the halophilic fungus *H. werneckii* with an optimal concentration of salt (0.86 M NaCl), the melanized dark layer is on the outer part of the cell wall, but the whole cell wall is smelanized when the concentration of salt is increased [19]. Dark melanin granules were found in the fibrillar matrix on the surface of the cell wall in *A. pullulans, Verticillium dahliae*, and *Phomopsis* sp. [51]. In the presence of a melanin precursor—3,4-dihydroxyphenylalanine (DOPA)—melanin granules are formed on the surface of conidia and yeast cells of the dimorphic pathogenic fungi *Histoplasma capsulatum* and *Blastomyces* dermatitidis and the cell surface becomes rilled [52, 53]. According to an electron microscopy analysis, in the soil fungus *Gaeumannomyces graminis*, the melanin layer composes almost half of the thickness of the cell wall and is located between the cell wall and the inner chitinous layer [51]. There are exogenous soluble melanins, for example, piomelanins of the fungus *Ophiocordyceps* which parasitize on insects [55]. The formation of soluble melanins is characteristic of *Agaricus bisporus* and a number of basidiomycetes [56]. Exogenous melanins were also found in culture fluids of *Cladosporium resinae* and *Aureobasid-*

ium pullulans [57]. Soluble melanins are a significant part of the extracellular matrix of *Botrytis cinerea* and are pathogenic to plants [58].

In *Sclerotinia sclerotiorum*, melanins were localized in the outer layer of sclerotia, forming a solid protective cover [59]. In the multicellular conidia *A. alternata*, melanin was localized in the outer layer of the cell wall and in septa [60].

Types of melanins. There are three main types of melanins: eumelanins (black and dark-colored polymers), pheomelanins (yellow and red polymers), and the most heterogeneous group of allomelanins, including soluble piomelanins [61]. In fungi, there are melanins of all three types [61, 62]. Eumelanins are the oxidation products of 5,6- dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) [63, 64]. Pheomelanins contain sulfur, and they are polymers of benzothiazine derivatives [65, 66]. Allomelanins are a heterogeneous group of pigments derived from metabolites of homogentisic or *p*-hydroxyphenylpiruvic acid (piomelanins), γ-glutamyl-4-hydroxybenzene, and catechols [38, 67–69] and are also very common in fungal melanins, formed from dihydroxynaphthalene compounds (DHN). Typically, allomelanins do not contain nitrogen.

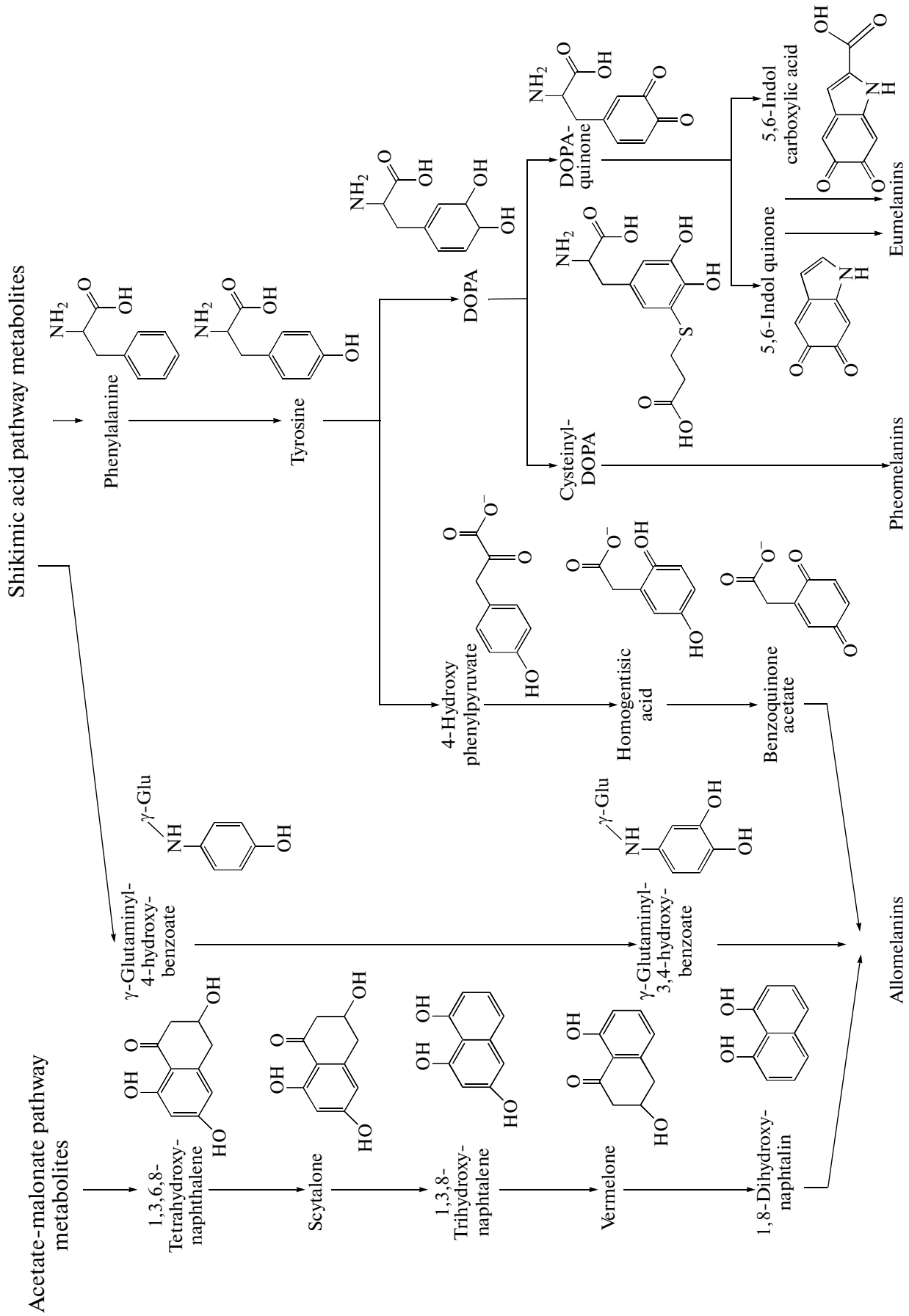
Melanin biosynthesis in fungi. Several biosynthetic pathways of these pigments were identified in fungi; the polymer structure of melanin can be formed from different precursors of phenolic nature (metabolites of both acetate-malonate and shikimic acid pathways) (figure). One of the most common melanin biosynthetic pathways in fungi is the polymerization of dihydroxynaphthalene. This pathway has not been found in bacteria, plants, and animals. Precursors of metabolites of the acetate–malonate pathway are converted under the action of type 1 polyketide synthase into 1,3,6,8-tetrahydroxynapthalene. Then, scytalone is formed in a reaction catalyzed by hydroxynaphtalene reductase (EC 1.1.1.252), and scytalone undergoes dehydration into 1,3,8-trihydroxynaphtalene, afterwards being converted into vermelon (reactioncatalyzed by reductase) and then into 1,8-dihydroxynaphthalene (DHN). DHN spontaneously polymerized with the formation of melanin. Polymerization is enhanced by phenol oxidases, peroxidases, laccases, and catalases [70–74] .

Tricyclazole is a specific inhibitor of the DHN-melanin pathway, and it also inhibits the conversion of 1,3,8-trihydroxynaphthalene into vermelon [72, 75]. DHN-melanin formation was shown in *Verticillium dahliae, Torula corallina, Aspergillus nidulans*, *A. niger*, *A. fumigatus*, *Alternaria solani*, *A. alternata*, *Aureobasidium pullulans*, *Trimmatostroma salinum*, *Phaeotheca triangularis*, *Hortaea werneckii, Sclerotinia sclerotiorum*, *Fonsecaea pedrosoi*, *Exophialla dermatitidis*, *Histoplasma capsulatum, Sporothrix schenckii*, *Magnaporte orizae*, *Ascochyta rabiei*, and many other species [50, 75–77].

In fungi, biosynthesis of melanins can also start with metabolites of the shikimic acid pathway similar to animals, plants, and bacteria. Eumelanins are formed from tyrosine or phenylalanine oxidized by tyrosinase (EC 1.14.18.1) or laccase (EC 1.10.3.2) into DOPA, and then DOPA is oxidized into quinone, followed by the cyclization and formation of 5,6-dihydroxyindole (DHI) or 5,6-dihydroxyindole-2-carboxylic acid (DHICA) (see figure) [63, 64]. The latter compounds polymerize to form brown and black pigments—eumelanins. This pathway of melanin formation was shown in *Candida albicans*, *Paracoccidioides brasiliensis*, *Cryptococcus neoformans*, and *S. schencki*.

In fungi, phenomelanins can also be synthesized from tyrosine, if during synthesis DOPA reacts with cysteine (or glutathione) with the formation of cysteinyl-DOPA. Then, cyclization of the product occurs to a benzothiazine derivative and its polymerization with the formation of brown, red, or yellow pigments (figure) [65, 66, 77]. This is the pathway of biosynthesis of sulfur-containing melanins in the truffle *Tuber melanosporum* [78]. Tyrosinase (monophenol:diphenol oxygen oxidoreductase, EC 1.14.18.1), catalyzes the formation of DOPA from tyrosin: it was found in *Agaricus bisporus*, *N. crassa, T. melanosporum*, *T. magnatum*, and many other fungi [62, 70, 78]. The expression of this enzyme is closely related to the developmental stages and pathogenesis of fungi [38, 79]. DOPA can also be converted into melanin with the participation of laccases, for example, in *Lentinula edodes* and *C. neoformans* [80].

In fungi, there are other ways that melanin can be formed from tyrozine. Thus, in the reaction catalyzed by tyrosune transaminase (EC 2.6.1.5.) occurs the formation of 4-hydroxyphenylpyruvate, which is further converted into homogentisic acid by dioxygenase (EC 1.13.11.2) and is then spontaneously oxidized to benzoquinone acetate and polymerized with the formation of soluble brown piomelanins (figure) [62]. The formation of soluble piomelanins from tyrosine via *p*-hydroxyphenylpyruvate and homogentisic acid was found in *A. fumigatus*, *A. kawachii, Madurella mycetomatis*, and *Yarrowia lipolytica* [61, 77]. In the parasitic fungus *Ustilago maydis*, polymerization of catechol dimers with the formation of fibrils of melanin was shown [81]. The precursor of melanin in *A. bisporus* and other basidiomycetes is a metabolite of the shikimic acid pathway—γ-glutaminyl-4-hydroxybenzene—oxidized under the action of peroxidase and/or phenolase into γ-glutaminyl-3,4-benzoquinone, followed by its polymerization [67, 68]. In *C. neoformans* melanins, synthesized from various exogenous substrates, e.g., D- and L-dopamine [82], homogentisic acid [83], catecholamines, and other phenolic compounds [84]. Polymerization of exogenous substrates in *C. neoformans* occurs under the action of laccase. High concentrations of exogenous substrates (more than 1 mM) inhibited the growth of



Scheme of melanin biosynthesis in fungi.

the fungus and the formation of melanins, probably due to the toxicity of the substrates themselves [85].

Melanin synthesis genes in many cases assembled into clusters, thereby coordinating their expression at different stages of development of fungi [41, 74, 86, 87]. Some fungi have more than one biosynthetic pathway of melanins in cells. For example, in *A. fumigatus*, piomelanins, synthesized from homogentisic acid, protect the cell wall of hyphae from ROS and gray-green DHN-melanins determine the structural integrity of the cell wall of conidia and their adhesive properties [87, 88]. In *A. bisporus*, melanins are formed from DOPA by tyrosinase and from γ-glutaminyl-4-hydroxybenzene by peroxidase and phenolase [89]. In *C. resinae* and *A. pullulans*, melanins were found in the cell wall and exogenous melanins were found in culture fluids [57].

Properties of melanins. The polymer net structure of melanins formed by the enzymatic and autooxidatuve polycondensation of various hydroaromatic precursors may additionally include other organic molecules. Usually, melanins are associated with proteins (melanoproteins) or with glycoproteins (melanoglycoproteins) [71]. The presence of carbohydrates and fatty acid, covalently bound to melanin, was confirmed by NMR methods [90–92]. As was demonstrated by an X-ray analysis, melanins isolated from different objects have different distances between the monomers unified in the planar structure of graphite. Probably, the distance between monomers may be an important feature of melanin pigments [93].

Despite the difference in their origins, melanin pigments have a number of common characteristics that allow them to fulfill their protective function. Melanins are very chemically stable compounds; they are not soluble in water and organic solvents. They can form a solution in an alkaline medium and are discolored in the presence of strong oxidants. The presence of quinoid groups explains the presence of paramagnetic centers and the ability of melanin pigments to deactivate free radicals and peroxides and absorb heavy metals and toxic electrophilic metabolites. These pigments exhibit strong antioxidant properties [94–96]. Melanin-containing cells are more resistant to H_2O_2 and NO [97]. The gene expression of melanin synthesis enzymes increases the resistance of fungi to oxidants [98]. Mutations in the genes of melanin synthesis reduce both oxidative stress resistance and the virulence of pathogenic fungi [41].

Melanins exhibit unusual optical and electronic properties due to the presence of mobile π-electrons [99]. Also π-electrons are responsible for the transfer of chemical and physical stimuli along polymer molecules. The presence of unpaired electrons allows for the investigation of melanins by electron paramagnetic resonance (EPR) methods. A comparison of the ESR spectra of melanin in various fungi showed that the g-factor of the signal was in the range 2.0036–2.0042 with a half-width of 4–7 eV. A study of the EPR spectra under changing power levels of microwave radiation suggests the existence of different mechanisms for the exchange of energy between the paramagnetic centers and the environment [100, 101].

Melanin pigments absorb light in a wide range of wavelengths, including the UV region, and the absorption intensity decreases slowly with increasing wavelengths [102, 103]. Melanins absorb light energy with the conversion of photon energy into heat energy [102, 104]. The mechanism of photoprotective action of melanins is of great interest. Using a monomer of eumelanin 5,6- dihydroxyindole, the possibility to transfer the hydrogen atom of the hydroxyl group on the adjacent carbon atoms of the benzene group under light excitation was demonstrated [105]. The possible transfer of protons inside a monomer as a result of energy dissipation during the photoexcitation of a pigment macromolecule was also considered by other authors [106], but the fact that the processes in heterogeneous polymer molecules of melanin may be different from those that occur in a solution of monomers should be considered. The polymerization of monomers resulted in an increase in the lifetime of the excited state of the oligomer from 100 ps to 3 ns [107].

During the interaction of melanins with hard UV radiation (240–300 nm), their photoionization and subsequent partial destruction can be observed. Under anaerobic conditions, this is confirmed by the formation of a product, which is characteristic of the interaction of a spin trap of 5,5-dimethyl-pyrroline-1-oxyl (DMPO) with a hydrogen atom or a hydrated electron. In the presence of oxygen, photoionization is accompanied by the formation of superoxide anion radicals or H_2O_2 [102]. Experiments on synthetic melanins showed that their electron emission is very low and is significantly less than 1% [103, 104]. This suggests that in melanins occurs fast thermal relaxation of absorbed radiation energy and the risk of dangerous photochemical reactions decreases [102] which allows melanins to be effective protectors against UV and solar radiation. However, the formation of cytotoxic products during hard UV radiation can still occur [108]. Although the structure of melanins was practically not affected by X-ray, γ, or UV radiation, some signal changes were detected by the EPR method, indicating an increase in the number of semiquinone radicals [102, 109]. After UV irradiation, the ability of melanin to oxidize NADH also increases [110].

Melanins exhibit high radioprotective properties, which contribute to the survival of fungi in soils contaminated by radioactive nuclides [1–4]. Early experiments on the identification of fungal resistance to γ-irradiation showed that melanized fungi were the most resistant to this type of sterilization. Representatives of the species *Stemphylium*, *Alternaria*, and *Cladosporium* survived at a dose of 625 kR, and alpine strains were more resistant to radiation in comparison to related strains of the sod- podzolic soils in the Moscow region [111]. For some fungi, exposed to radiation

(premises and soils of the Chernobyl Nuclear Power Plant) for a long time, a number of previously unknown properties were characteristic. Among them, radiotropism (directed growth of hyphae toward sources of radiation), radio stimulation (activation of growth processes under the influence of ionizing radiation), and the radio-adaptive response increased resistance to high doses of radiation after preexposure to low doses [112]. A hypothesis that melanins trap free radicals formed during the radiolysis of water by radiation was suggested for the mechanism of radioprotective action [113, 114]. It was also assumed that melanin pigments, participating in redox reactions, are able to perceive the energy of radiation (UV, visible light, and radiation) and make it available for metabolic processes [3, 110, 115]. Probably, this explains the activation of metabolic processes and the growth of fungal hyphae under the influence of different types of radiation, found in melanin-containing fungi [110, 112]. It was also shown that irradiating melanin caused its oxidation, which was more expressed in the presence of reducing agents, such as ascorbate [116]. This confirms the possibility of participation of melanin in active electron transfer in living cells and the existence of a hypothetical mechanism of transfer of radiation energy for the maintenance of metabolic processes. Further research in this area can provide a better understanding of the nature of the radio- and UV-protective effect of melanin.

The ability of melanin pigments to transform the energy of radiation for use in metabolic processes was confirmed by their semiconductor properties, which were found by Blois in the 1960s [117, 118]. Later, the possibility of tunneling electrons between photoinduced paramagnetic centers was shown [119]. Recent studies have demonstrated that, in addition to the ability of transferring electrons arising under the action of radiation, melanins also possess ionic conductivity, which facilitates the binding of water to the pigment [120]. Probably, this is achieved by the unique ability of melanins to transform any type of radiation energy not only into heat but also use it for the maintenance of redox processes in cells. The presence of these unique properties makes melanin a promising material in bioelectronics, especially when one takes into account its strength, resistance to high temperatures, and hypoallergenicity.

Thus, the presence of unpaired electrons in the highly polarized structure of melanin pigments and their ionic conductivity determines a wide range of properties: the ability to convert all types of heat radiation, adsorb electrophilic compounds, exhibit antioxidant properties, and, probably, to use the energy of radiation in the redox reactions of living cells. These properties contribute to the survival of fungi under extreme conditions, such as high insolation, low temperature, a low content of water and organic substrates, high concentrations of reactive oxygen species, and increased radiation.

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