Neurotropic Black Yeast Exophiala dermatitidis

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The neurotropic and extremophilic black yeast *Exophiala dermatitidis* (*Herpotrichellaceae*) inhabits diverse indoor environments, in particular bathrooms, steam baths and dishwashers. It can grow at human body temperature, assimilate cyclic hydrocarbons and human neurotransmitters. Accordingly, they are capable to grow in artificial and natural environments, including synthetic/rubber hydrocarbon-rich materials. Their polymorphic nature allows them to survive environmental stress, such as UV radiation, high temperatures, pH fluctuations, low water activity and others. *E. dermatitidis* is known as extremely plastic which has evolutionarily led to adaptation on the human body. It causes numerous infections in almost all human organs, and may also be associated with Alzheimer's disease.

neurotropic fungi | black yeasts | neurotropism | hydrocarbons | extracellular vesicles | Alzheimer's disease | Exophiala dermatitidis

1. Introduction

Polyphyletic black yeasts, including the genus *Exophiala*, are melanised yeast-like fungi that populate extreme environments dominated by high or low temperatures, high salinity, aridity, low water activity, high UV radiation, fluctuating pH, and oligotrophicity [1][2][3][4][5][6][7][8]. They have a distinct extremophilic ecotype, characterized by thick, melanised cell walls, as well as slow, polymorphic growth including hyphae, yeast cells, meristematic clumps, and endoconidiation. Many black yeasts, in particular those within *Chaetothyriales*, fam. *Herpotrichiellaceae*, use the above exaptations and their unusual ability to grow at 37 °C to invade the human body, another extreme environment for fungi [3].

2. Specifics

Exophiala dermatitidis is the most clinically important and thermotolerant species of the genus *Exophiala*. It can cause various medical conditions, from cutaneous and subcutaneous infections to systemic, gastrointestinal, pulmonary, and neurotropic infections [9]. It has been isolated from the ears, sinuses, lungs, mucus of cystic fibrosis patients, blood and different catheters, and most importantly brain infections [3][10][11][12][13][14][15][16][17][18][19][20][21]. Occasionally, it can cause mildly invasive systemic infections that are associated with significant morbidity and mortality. Typical infections are seen in immunocompromised hosts such as transplant recipients, oncology, and pediatric patients, where it manifests itself as a subcutaneous disease and rarely as deep mycoses [9][22][23][24][25]

[26]. Particularly in East Asia, *E. dermatitidis* was detected in disseminated and neurotropic infections with high mortality [11][27]. Note, however, that despite infections occurring in apparently healthy humans, some authors concluded that *E. dermatitidis* and related species are opportunists rather than pathogens [28][29][30].

Its pathogenicity is probably owing to various virulence factors, including melanin pigmentation, thermotolerance, and polymorphism [9]. Melanin accumulates in the cell wall of *E. dermatitidis*. This has a protective effect against harmful substances and oxidative stress from the environment or the host cell [31]. *Exophiala* species synthesize melanin endogenously from acetate *via* the pentaketide pathway, leading to 1,8-dihydroxynaphthalene melanin. This pathway can be constrained under controlled growth conditions by addition of inhibitors, thus allowing the study of melanin's relations to morphology, physiology, and pathogenicity [32][33][34].

The polymorphic character and melanin pigmentation of *E. dermatitidis* enable its colonisation under stress conditions. *Exophiala dermatitidis* has adapted to human-made indoor environments, such as steam baths, saunas, public baths [35][36], drainpipes, and drinking water. It is most frequently (and globally) present in domestic dishwashers [37][38][39], where internal rubber seals and plastic parts can harbour up to 10^6 colony forming units/cm2 [39]. As people spend more time indoors and the number of immunocompromised people is rapidly increasing, the establishment of *E. dermatitidis* in domestic environments represents an important risk factor for human health [40][41].

Fungi normally populate parts of the human body, for example, skin, mucus of respiratory tract, oral cavity, and mucus of the digestive tract [28]. They most frequently invade through the respiratory tract by inhalation of spores or mycelium, but also enterically *via* the gastrointestinal tract or *via* traumatic injuries (e.g., accidents, surgery, interventions) [3]. After the initial infections, the fungi can spread via the haematogenous route. Fungal infections of the central nervous system occur either indirectly *via* lungs or paranasal sinuses, for example, after near-drowning episodes [42][43][44][45], *via* ocular orbits, and mastoid region of the temporal bone or retropharyngeal area, or directly as a consequence of trauma, invasive treatments, or brain surgery [41]. The potential mechanism of invasion of *E. dermatitidis* and other neurotropic fungi *via* the peripheral nervous system has not yet been described, nor have the mechanisms contributing to the spread of fungal infections to the brain.

Exophiala dermatitidis is rare in nature, but its occurrence increases in environments contaminated with cyclic or non-cyclic aromatic hydrocarbons [5][6][8] such as creosote-treated or oil-contaminated railway beams [46][47]. It can also be isolated from the cuticle of ants and ant hills [48][49], but most frequently on artificial rubber seals of dishwashers [37]. The neurotropic potential of black yeasts within *Chaetothyriales*, including *E. dermatitidis*, has been closely associated with their ability to assimilate monoaromatic and polyaromatic hydrocarbons, hypothetically including phenolic and aliphatic metabolic degradation products of catecholamine-like neurotransmitters [6][8][50][51][52]. It is known that disturbed transport or lowered concentrations of neurotransmitters can lead to neurodegenerative diseases, such as Alzheimer's [6][50][53].

According to recent investigations, systemic mycoses could be either one of the causative agents or an additional risk factor for the development of Alzheimer's. Fungal macromolecules were detected in the peripheral vascular

system and in the cerebrospinal fluid (CSF) from patients with the disease [54][55], and elevated chitinase levels were also detected in the CSF [56]. Fungal yeast cells and hyphal fragments were detected in different parts of the brain, both inside and outside the neurons. In spite of this and other evidence [57][58], there is still ambiguity regarding the etiological role of fungi in Alzheimer's [57][59].

Fungi have also been associated with other neurological diseases. Recently, an increasing number of opportunistic mycoses of the central nervous system (CNS) has been reported in healthy individuals and, in particular, in patients with sepsis, prolonged ventilation, oncological therapies, organ transplantation, overuse of antibiotics, HIV patients, and others [60]. Opportunistic mycoses of CNS are associated with higher morbidity and mortality [61][62] owing to pathogenic fungi such as *Cryptococcus neoformans*, which are able to cross the otherwise prohibitive blood-brain barrier [63].

Over the last decades, extracellular vesicles (EVs) were identified as potential mediators of intracellular and inter-organism communication in all life kingdoms [64][65]. The first evidence of fungal EVs came from the opportunistic human pathogen *Cryptococcus neoformans* [66]. From that time, studies on the roles of EVs in pathogenicity of other fungi increased significantly (reviewed in Bielska and May) [67]. Fungal EVs are heterogeneous populations of lipid-bilayer nanoparticles that harbour cargo molecules important in modulating virulence, host defence, and host immune function, as well as triggering anti-microbial activities [67]. *C. neoformans* EVs can cross the blood-brain barrier and accumulate as lesions in the brain, facilitating adhesion and transcytosis [68][69][70][71]. Thus EVs show great potential for further research regarding fungal pathogenicity in human brains.

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