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Smoking and Cryptococcosis

Aline Beatriz Mahler Pereira and Alexandre Paula Rogerio*

Laboratory of Experimental Immunopharmacology. Departamento de Clínica Médica, Universidade Federal of Triângulo Mineiro, Brazil

*Corresponding author: Alexandre Paula Rogerio, Laboratory of Experimental Immunopharmacology, Universidade Federal do Triângulo Mineiro, Rua Manoel Carlos, 162, 38025-380 – Uberaba – MG, Brazil, Tel: +55 34 3318 5814; Email: alexandre.rogerio@uftm.edu.br

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Cryptococcus is an invasive fungus that causes cryptococcosis in both immunocompromised and immunocompetent hosts. The two species of *Cryptococcus* that are commonly associated with infections in humans are *C. neoformans* and *C. gatti* [1]. *C. neoformans* is commonly recovered from avian droppings while *C. gattii* is recovered from decayed woods inside trunk hollows of diverse tree species. Infection with *C. neoformans* and *C. gattii* starts with inhalation of the fungus that can establish pulmonary infection and subsequently spread to other organs of the body especially to the central nervous system causing inflammation of the meninges and consequently the fatal cryptococcal meningoencephalitis [2]. Cryptococcus has several virulence factors, especially the capsule that consists of high molecular weight polysaccharides, mainly glucuronoxylomannan (GXM) and, to a lesser extent, galactoxylomannan (GalXM) and mannoproteins (MP). The capsule acts as a barrier against the host's defenses. Other virulence factors include the ability to grow at 37 ° C, melanin production, which protects against phagocytosis, and the production of various enzymes such as proteases, ureases, superoxide dismutase and phospholipase B, which facilitates tissue invasions [3-6].

The severity of the disease and the prognosis in cryptococcosis are largely dependent on the integrity of the host immune system and on the characteristics of each variety of *C. neoformans* and *C. gattii* [7]. Studies investigated the correlation of immunity in human immunodeficiency virus-infected patients to cryptococcal infection and analyzed the rate of clearance of infection by serial quantitative cerebrospinal fluid fungal cultures through the measurement of cytokines, and the results demonstrated that pro-inflammatory mediators (IL-6, IFN-γ, TNF-α, and IL-8) were significantly higher in survivors compared with nonsurvivors. In addition, the increased cytokine production was associated with increased macrophage activation, more rapid clearance of fungal from cerebrospinal fluid and survival [8-9]. In common with a number of other chronic fungal and bacterial infections, the protection to cryptococcosis is associated with an active inflammatory response with a pattern of Th1-cytokine released [10]. The role of Th1 response is also reinforced by studies showing that patients who survived neurocryptococcosis have higher levels of IFN-γ in cerebrospinal fluid than patients who died [11].

C. neoformans can cause infection in immunocompetent individuals but preferentially infects immunocompromised hosts, especially human immunodeficiency virus-infected patients, but also other underlying disorders, including malignancy, collagen vascular disease, transplantation and, immunosuppressant usage [12]. In addition, tobacco smoke is also considered a risk factor for cryptococcosis [13]. Cigarette smoking is a worldwide epidemic, and it is one of the main preventable causes of morbidity and mortality worldwide. Cigarette smoke contains about 45,000 chemical substances, with several of them showing toxic effects, including mutagenic and carcinogenic properties [15]. Of the numerous smoking-related disorders the most common is chronic obstructive pulmonary disease (COPD) and the most deadly is lung cancer [16]. COPD is characterized by a chronic inflammatory process and progressive airflow obstruction. Pathological changes that are induced by chronic exposure to cigarette smoke are observed more early in airway epithelium [17]. The most pronounced changes are hyperplasia of goblet-producing goblet cells and basal cells, metaplasia of squamous epithelial cells, shortening of the cilia (resulting in less mobility of the mucus produced by goblet cells and less elimination of pathogens) and loss of tight junctions that impairs the protection the respiratory tract against pathogens, xenobiotics and other harmful particles [16,17]. In addition, the cigarette smoking causes activation and damages of epithelial cells, which induce the secretion of chemical mediators (chemokines, cytokines and others), and consequently the recruitment of leukocytes (mainly neutrophils and macrophages) to the lungs. The migration and activation of leukocytes in the inflammation zone intensify the airways inflammatory process increasing the secretion of several pro-inflammatory (cytokines, chemotactic factors, oxygen radicals and others) and enzymes providing an uncontrolled inflammatory response. The continuous inflammatory process of the airways causes also the destruction of the lung parenchyma with consequent loss of the alveolar attachments of the airways leading to obstruction or limitation of airflow [16-18]. The inflammatory response in patients with COPD involves both innate and adaptive immune responses and could be amplified during acute exacerbations or precipitated by bacterial or viral infection [18]. Interesting, there are components from cigarette such as nicotine that demonstrate immunosuppressive effect in innate cells, including bronchial epithelial cells, macrophages, neutrophils and lymphocytes, of the host might cause increase of the susceptibility to infections [15,19,20]. Interesting, immunodeficiency virus-infected individuals who were current smokers had at increased risk for *C. neoformans* infection [21,22], which can favor the invasive fungal disease. In another study, MacDougall et al. 2011 [23] observed an increase of *C. gattii* infection in smokers in an immunosuppressive state, induced by oral corticosteroid use or with invasive cancers. Although most cases of *C. gattii* infection occur in healthy individuals, it may also occurs in immunosuppressive individuals. These increased susceptibility to *C. neoformans* and *C. gattii* infection could be associated to the adversely effects of smoking in the respiratory system (smoking impairments the protective barriers in airways and inhibition of mucociliary clearance). Furthermore, chronic inflammation of the airway may well contribute to impaired immunity and to a predisposition to criptococcosis [21,24]. Additionally, the tobacco contains a large number of chemicals and the consequent absorption of tobacco ingredients directly into the lungs or bloodstream during smoking could provide compounds that serve as precursors for synthesis of several

substances including melanin [13,25]. Interesnting, melanized cells of *C. neoformans* are more virulent and exhibit increased resistance to host defenses and thus survive longer [26] as well as reduced susceptibility to antifungal agents [27]. Additionally, the fungus has tropism by the central nervous system, since this organ has optimal concentrations several nutrients assailable by it such as the presence of melanin precursors [14].

Taken together, smoking weakens pulmonary function and provides substances associated to fungal resistance mechanisms that contribute towards enhancing the risk of cryptococcosis in smokers but mainly those affected by immunosuppressed conditions.

References

1. Negroni R. Cryptococcosis. Clin Dermatol.2012; 30: 599-609.
2. Taylor-Smith LM, May RC. New weapons in the *Cryptococcus* infection toolkit. Curr Opin Microbiol. 2016; 34: 67-74.
3. Chayakulkeeree M, Perfect JR. Cryptococcosis. Infect Dis Clin North Am. 2006; 20: 507-544.
4. Perfect JR, Casadevall A. Cryptococcosis. Infect Dis Clin North Am. 2002; 16: 837-874.
5. Dylag M. Etiological factors of cryptococcosis - what makes them pathogens? Med Dosw Mikrobiol. 2015; 67: 221-231.
6. Andrade JCBN, Gatto M, Rodrigues DR, Soares ÂMVC, Calvi SA. *Cryptococcus neoformans* and *gattii* promote DNA damage in human peripheral blood mononuclear cells. Med Mycol. 2017.
7. Wormley FL Jr, Perfect JR. Immunology of infection caused by *Cryptococcus neoformans*. Methods Mol Med. 2005; 118: 193-198.
8. Siddiqui AA, Brouwer AE, Wuthiekanun V, Jaffar S, Shattock R, et al. IFN-gamma at the site of infection determines rate of clearance of infection in cryptococcal meningitis. J Immunol. 2005; 174: 1746–1750.
9. Jarvis JN, Meintjes G, Bicanic T, Buffa V, Hogan L, et al. Cerebrospinal fluid cytokine profiles predict risk of early mortality and immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis. PLoS Pathog. 2015; 11: e1004754.
10. Gibson JF, Johnston SA. Immnunity to *Cryptococcus neoformans* and *C. gatti* during cryptococcosis. Fungal Genet Biol. 2015; 78: 76-86.
11. Siddiqui AA, Brouwer AE, Wuthiekanun V, Jaffar S, Shattock R, et al. IFN- gamma at the site of infection determines rate of clearance of infection in cryptococcal meningitis. J Immunol. 2005; 174: 1746-1750.
12. Chuang YM, Ho YC, Chang HT, Yu CJ, Yang PC, et al. Disseminated cryptococcosis in HIV-uninfected patients. Eur J Clin Microbiol Infect Dis. 2008; 27: 307.
13. ZU Khan. Smoking, Melanization, and Cryptococcosis: Is There a Connection? J Clin Microbiol. 2006; 44: 1207.
14. Polacheck I, Platt Y, Aronovitch J. Catecholamines and virulence of Cryptococcus neoformans. Infect Immun. 1990; 58: 2919-2922.
15. Mehta H, Nazzal K, Sadikot RT. Cigarette smoking and innate immunity. Inflamm Res. 2008; 57: 497-503.
16. Houghton AM. Mechanistic links between COPD and lung cancer. Nat Rev Cancer. 2013; 13: 233-245.
17. Barnes PJ. Cellular and molecular mechanisms of asthma and COPD. Clin Sci (Lond). 2017; 131: 1541-1558.
18. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2016; 138: 16-27.
19. Drannik AG, Pouladi MA, Robbins CS, Goncharova SI, Kianpour S, et al. Impact of cigarette smoke on clearance and inflammation after Pseudomonas aeruginosa infection. Am J Respir Crit Care Med. 2004; 170: 1164-1171.
20. Gaschler GJ, Skrtic M, Zavitz CC, Lindahl M, Onnervik PO, et al. Bacteria challenge in smoke-exposed mice exacerbates inflammation and skews the inflammatory profile. Am J Respir Crit Care Med. 2009; 179: 666-675.
21. Hajjeh RA, LA Conn, DS Stephens, W Baughman, R Hamill, et al. Cryptococcosis: population-based multistate active surveillance and risk factors in human immunodeficiency virus-infected persons. J. Infect. Dis. 1999; 179: 449-454.
22. Olson PE, Earhart KC, Rossetti RJ, Newton JA, Wallace MR. Smoking and Risk of Cryptococcosis in Patients With AIDS. Jama. 1997; 277: 629-630.
23. MacDougall L, Fyfe M, Romney M, Starr M, Galanis E. Risk factors for Cryptococcus gattii infection, British Columbia, Canada. Emerg Infect Dis. 2011; 17: 193-199.
24. Boelaert JR, E Blasi. Cryptococcosis and smoking: the potential role of smoking. J. Infect. Dis. 1999; 180: 1412-1413.
25. Pryor WA, K Stone, LY Zang, E Bermudez. Fractionation of aqueous cigarette tar extracts: fractions that contain the tar radical cause DNA damage. Chem. Res. Toxicol. 1998; 11: 441-448.
26. Casadevall A, AL Rosas, JD Nosanchuk. Melanin and

virulence in Cryptococcus neoformans. Curr. Opin. Microbiol. 2000; 3: 354-358.

27. van Duin D, A Casadevall, JD Nosanchuk. Melanization of Cryptococcus neoformans and Histoplasma capsulatum reduces their susceptibilities to amphotericin B and caspofungin. Antimicrob. Agents Chemother. 2002; 46: 3394-3400.