

## Smoking, Melanization, and Cryptococcosis: Is There a Connection?

Recently, it has been reported by Tendolkar et al. (9) and Khan et al. (4) that tobacco extract agar imparts brown (melanin-like) pigmentation to colonies of *Cryptococcus neoformans* and *Cryptococcus gattii*. This observation is significant in that this pigmentation may have a role in the pathogenesis of cryptococcosis (2). Since cryptococcosis is a pulmonary and meningeal disease, the absorption of tobacco ingredients directly into the lungs or bloodstream during smoking could provide additional substrates for melanin biosynthesis. Tobacco contains a large number of chemicals, including catechol, hydroquinone, and nicotine (7), some of which could serve as precursors for melanin synthesis (6). We used tobacco from a commercially available cigarette brand (Marlboro; Philip Morris Products SA, Richmond, Va.) that contained 8 mg tar and 0.6 mg nicotine to prepare the medium, which yielded brown colonies of *C. neoformans* (4). Nicotine is the most abundant of the volatile alkaloids in tobacco leaves, and it gets directly absorbed from the respiratory tract. Experimental studies have shown enhanced release of dopamine (a member of the catecholamine family) in midbrain of rats exposed to nicotine (8). The ability of *C. neoformans* to metabolize catecholamines to melanin has been suggested as an explanation for its neurotropism. Although certain areas of brain (such as the basal ganglia) are already rich in catecholamines, cigarette smoking may further enhance levels of these compounds. In this context, the recent evidence of in vivo synthesis of melanin by *C. neoformans* in patients with brain infection is noteworthy (5); this synthesis may be promoted in an environment with an increased concentration of dopamine. Since melanized cells of *C. neoformans* are more virulent (2) and exhibit increased resistance to host defenses and thus survive longer (2) and show reduced susceptibility to antifungal agents (10), these factors may contribute towards enhancing the risk of cryptococcosis among tobacco smokers.

In the above-described context, attention may also be drawn to two published studies (1, 3). In the first of these studies, which deals with cryptococcosis in human immunodeficiency virus-infected patients in the United States, Hajjeh et al. (3) found by multivariate analysis of 158 cases and 423 controls that current smoking was significantly associated with increased risk of cryptococcosis. The authors stated that this increased risk of cryptococcosis may be related to the adverse effect that smoking exerts on the respiratory system by inhibiting mucociliary clearance and disrupting the respiratory epithelium. In the second study, Boelaert and Blasi (1) suggested that the enhanced risk of cryptococcosis among smokers may also be

attributed to another mechanism, that is, smoking-related iron loading of the bronchoalveolar macrophages, which then exhibit reduced fungistasis. In conclusion, while the available evidence in the literature suggests that tobacco smoking is a risk factor for cryptococcosis, the effect which smoking might exert on in vivo melanization of *C. neoformans* could be yet another mechanism contributing to its pathogenesis. This aspect is worth investigating.

### REFERENCES

1. Boelaert, J. R., and E. Blasi. 1999. Cryptococcosis and smoking: the potential role of smoking. *J. Infect. Dis.* **180**:1412–1413.
2. Casadevall, A., A. L. Rosas, and J. D. Nosanchuk. 2000. Melanin and virulence in *Cryptococcus neoformans*. *Curr. Opin. Microbiol.* **3**:354–358.
3. Hajjeh, R. A., L. A. Conn, D. S. Stephens, W. Baughman, R. Hamill, E. Graviss, P. G. Pappas, C. Thomas, A. Reingold, G. Rothrock, L. C. Hutwagner, A. Schuchat, M. E. Brandt, and R. W. Pinner. 1999. Cryptococcosis: population-based multistate active surveillance and risk factors in human immunodeficiency virus-infected persons. *J. Infect. Dis.* **179**:449–454.
4. Khan, Z. U., S. Ahmad, E. Mokaddas, and R. Chandy. 2004. Tobacco agar, a new medium for differentiating *Candida dubliniensis* from *Candida albicans*. *J. Clin. Microbiol.* **42**:4796–4798.
5. Nosanchuk, J. D., A. L. Rosas, S. C. Lee, and A. Casadevall. 2000. Melanisation of *Cryptococcus neoformans* in human brain tissue. *Lancet* **355**:2049–2050.
6. Polacheck, L., V. J. Hearing, and K. J. Kwon-Chung. 1982. Biochemical studies of phenoloxidase and utilization of catecholamines in *Cryptococcus neoformans*. *J. Bacteriol.* **150**:1212–1220.
7. Pryor, W. A., K. Stone, L. Y. Zang, and E. Bermudez. 1998. Fractionation of aqueous cigarette tar extracts: fractions that contain the tar radical cause DNA damage. *Chem. Res. Toxicol.* **11**:441–448.
8. Rahman, S., J. Zhang, and W. A. Corrigan. 2003. Effects of acute and chronic nicotine on somatodendritic dopamine release of the rat ventral tegmental area: in vivo microdialysis study. *Neurosci. Lett.* **348**:61–64.
9. Tendolkar, U., S. Taniwala, S. Jog, and M. Mathur. 2003. Use of a new medium—tobacco agar, for pigment production of *Cryptococcus neoformans*. *Indian J. Med. Microbiol.* **21**:277–279.
10. van Duin, D., A. Casadevall, and J. D. Nosanchuk. 2002. Melanization of *Cryptococcus neoformans* and *Histoplasma capsulatum* reduces their susceptibilities to amphotericin B and caspofungin. *Antimicrob. Agents Chemother.* **46**:3394–3400.

Z. U. Khan\*  
Faculty of Medicine  
Kuwait University  
P.O. Box 24923  
Safat 13110, Kuwait

\*Phone: 965-498-6504

Fax: 00965-531-8454

E-mail: ziauddin@hsc.edu.kw

*Ed. Note:* Z.U.K. is an author of reference 4.