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Assessment of the effects of aflatoxin B1 and gliotoxin on human corneal epithelial cells by continuous monitoring of cellular impedance and quantification of inflammation markers

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Background: Exposure to molds and mycotoxins is associated with asthma and chronic airway inflammation in subjects with long-term exposures, such as exposed workers in an agricultural setting. Whether molds belonging to the *Aspergillus* genus that produce numerous mycotoxins such as aflatoxins or gliotoxin contribute to the onset of respiratory disease, the exposure to molds and/or their mycotoxins also concern the ocular surface. Yet, little is known about the impact of the exposure of corneal epithelial cells to air pollutants. To test the hypothesis that the eye takes part to the onset of symptoms after the exposure to air pollutants like mycotoxins, our aim was to assess the effects of aflatoxin B1 (AFB1) and gliotoxin, two mycotoxins secreted by *Aspergillus* molds, on human corneal epithelial (HCE) cells.

Material/methods: HCE cells were exposed to different concentrations of either AFB1 or gliotoxin. Cell functionality was measured by using a 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) test. A noninvasive label-free continuous monitoring of cell viability and cell growth parameters was performed by using impedance measurement performed with interdigitated gold electrode-containing microtiter plates (xCELLigence plates). The dosage of IL-8 production was performed with ELISA kits. The gene expression of seven proinflammatory cytokines was quantified by real-time reverse transcription PCR.

Results: After a 72-h treatment with AFB1, a significant reduction of the functionality of HCE cells was noted from a concentration of 8 µg/ml. After treatment with gliotoxin, a progressive reduction of cell functionality was observed and became significant after a 72-h exposure to concentrations of 250 and 500 ng/ml. A significant increase in IL-8 production was observed from a concentration of 32 µg/ml of AFB1 for durations of exposure of 48 and 72 h. A significant increase in IL-8 production was observed from a concentration of 62.5 ng/ml of gliotoxin. Exposure to 32, 64 or 128 µg/ml of AFB1 led to a progressive but marked decrease of cell indexes measured on xCELLigence plates without subsequent recovery, reflecting cell death. Exposure to 250 ng/ml of gliotoxin induced a sharp decrease of cell indexes, followed by subsequent cell recovery, whereas exposure to 500 ng/ml of gliotoxin led to a sharp and definitive decrease of cell indexes, indicating cell death. Exposure to AFB1 induced a marked increase in IL-8, CXCL-1, and TNF-α gene expression, whereas exposure to gliotoxin induced only a moderate increase.

Conclusions: We evidenced a dose- and time-dependent increase of both the gene expression of several inflammatory markers and the production of IL-8 after exposure of HCE cells to AFB1 or gliotoxin. Continuous cell impedance measurement showed distinct profile of cytotoxicity for both mycotoxins. This is an interesting tool to evaluate cellular toxicity, with noninvasive real-time assessment of the effect on cells and an assessment of cell recovery.