

Correspondence

Proficient DNA repair in house dust mite-induced asthma?

To the Editor:

Chan et al¹ recently reported that house dust mite (HDM)-induced asthma caused DNA double-strand breaks with proficient DNA repair, and NU7441, a DNA repair inhibitor, augmented DNA damage and apoptosis without affecting airway function. This study has crucial pitfalls in interpretations and study design. The authors had shown (graphical abstract) that HDM exposure leads to cell survival due to proficient DNA repair in spite of increased oxidative stress. These claims do not have proper support because they found significant cell death with HDM exposure and increase in 2 DNA repair proteins (Ku70 and Rad51) without direct demonstration of DNA repair capacity or determining these proteins in cell-specific manner.

The increase in these proteins was not interpreted properly for the following reasons: (1) oxidative stress itself reduces Ku70 expression²; we found a decrease in Ku70 in mitochondrial oxidative stress-induced human bronchial epithelia (unpublished observation, Rehman R, Mabalirajan U, et al, 2016); (2) Ku70 inhibits apoptosis via Bax sequestration from mitochondria³; (3) caspase 3 degrades Ku70²; and (4) Ku70 participates in class-switch recombination.³ The observations of proficient oxidative stress and caspase 3 in lungs along with increased TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) positivity and γ -H2AX expression in epithelial and nonepithelial cells (Fig 3, A and D) with HDM exposure indicate the necessity of determining cell-specific Ku70 expression and coexpression analysis of γ -H2AX and DNA repair proteins such as Ku70 to have a clear conclusion regarding DNA damage response in asthmatic lungs. In addition, the authors did not consider ectopic class-switch recombination and local IgE production in airways⁴ though the authors avoided lymphoid tissue and IgE measurement. These indicate that the observed increase in Ku70 could be merely due to class-switch recombination in B cells.

The authors had used NU7441 to inhibit the DNAPKcs (DNA-dependent protein kinase, catalytic subunit) activity in *in vitro* experiments without prior determination of Ku70/Ku80 in HDM-induced BEAS-2B cells. The substantial secretion of T_H2 cytokines from highly stressed, monolayer cultured dying bronchial epithelial cells is rarely reported though A549 cancer cell line has shown such secretion.⁵ It is surprising that the authors had not shown such increased T_H2 cytokines and airway inflammation in NU7441-treated HDM-induced mice. Because they found more apoptosis in the inflammatory cells (Fig 8, C) in these mice, one can expect the reduction in the inflammation and T_H2

cytokines with NU7441 treatment to corroborate with earlier reports of DNAPK inhibition-mediated beneficial effects on asthma.¹

Because the authors have used a single human asthmatic sample that does not even have bronchi, their data did not match with the earlier report⁶ that found a significant expression of Ku70 and γ -H2AX in healthy individuals with normal lung functions compared with near absence in this study. In addition, the time trends in poly [ADP-ribose] polymerase 1 and Ku70 expressions with HDM induction in Fig 5, A, were not similar in HDM alone-induced mice in Fig 6, E.

In contrast to the protective role of proficient DNA repair, harmful role of ogg1-mediated DNA repair has also been reported in pollen-induced asthma.⁷

Editor's note: There is no accompanying reply to this correspondence.

Rakhshinda Rehman, MTEch
Ulaganathan Mabalirajan, MBBS, PhD

From Molecular Pathobiology of Respiratory Diseases, Council of Scientific and Industrial Research, Institute of Genomics and Integrative Biology, Delhi, India.
E-mail: mabsome@yahoo.co.in.

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