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Dendritic cell specific DNA-dependent protein kinase mediates Th2 airway inflammatory responses to house dust mite

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The innate signaling pathways for Th2 immunity activated by inhaled antigens are not well defined. DNA-dependent protein kinase (DNA-PK) is a nuclear protein serine/threonine kinase that acts as a molecular sensor in DNA damage and mediates ligation of double stranded DNA break repair, V (D) J recombination and telomere stabilization. Yet the role of DNA-PK in Th2 immune responses to allergic asthma remains to be completely elucidated. Since DNA-PK can regulate innate immunity and pro-inflammatory signaling pathways, we hypothesized that it might also modulate adaptive Th2-mediated immune responses to house dust mite (HDM) antigen. In the present study, we report that DNA-PK regulates myeloid dendritic cell (DC)-dependent allergic sensitization and Th2 immune responses to HDM. We found that HDM induces DNA-PK phosphorylation in DCs via generation of reactive-oxygen species. Next, the adoptive transfer of HDM-pulsed $CD11c^{+}$ bone marrow-derived DCs (BMDCs) from $Prkdc^{scid}$ mice or $CD11c^{+}$ BMDCs from wild-type (WT) mice that had been treated with the pharmacologic DNA-PK inhibitor, NU-7441, or the Akt kinase inhibitor, GDC0068 had an impaired ability to induce HDM-specific airway inflammation in HDM-challenged WT recipient mice. This confirms that Akt is downstream of DNA-PK signaling in DCs. CD11c-specific deletion of DNA-PK in mice ($DNA\text{-}PK^{fl/fl}$; CD11c-Cre) displayed a similar phenotype of reduced allergic sensitization and Th2-mediated airway inflammation as compared to $DNA\text{-}PKcs^{fl/fl}$. In addition, adoptive transfer experiments using $CD11b^{+}$myeloid DCs isolated from mediastinal lymph nodes of HDM-challenged $DNA\text{-}PK^{fl/fl}$; CD11c-Cre mice to WT mice demonstrated impairment in antigen presentation that limits their ability to induce allergic sensitization and Th2-mediated airway inflammation. Moreover, feeding NU7441-containing chow before and after HDM-challenges to WT mice suppressed mucous cell metaplasia as well as airway inflammation and airway hyper-responsiveness. Our findings highlight a novel function for DNA-PK in myeloid DCs where it mediates antigen presentation and the induction of Th2 immune responses to HDM in the lung. Collectively, these data suggest that DNA-PK contributes to airway inflammation and that targeting DNA-PK kinase activity may be a noveltreatment approach for allergic asthma.

Biography

Amarjit Mishra has completed his PhD from Oklahoma State University and postdoctoral studies from NHLBI, NIH. He has published more than 13 papers in reputed journals including Nature Communications and got the Orloff Science Award this year by Division of Intramural Research, NHLBI, National Institutes of Health and has been serving as an editorial board member of repute.

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