Benzo(a)pyrene Enhanced Dermatophagoides Group 1 (Der f 1)-Induced TGFβ1 Signaling Activation through the Aryl Hydrocarbon Receptor-RhoA Axis in Asthma

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Abstract

Background: We have previously demonstrated that benzo(a)pyrene (BaP) co-exposure with dermatophagoides group 1 allergen (Der f 1) can potentiate Der f 1-induced airway inflammation. We sought to investigate the molecular mechanisms underlying the potentiation of BaP exposure on Der f 1-induced airway inflammation. Methods: BaP co-exposure with Der f 1-induced activation of TGFβ1 signaling was analyzed in airway epithelial cells (HBECs) and in asthma mouse model. The role of aryl hydrocarbon receptor (AhR) and RhoA in BaP co-exposure-induced TGFβ1 signaling was investigated. AhR binding sites in RhoA were predicted and experimentally confirmed by luciferase reporter assays. The role of RhoA in BaP co-exposure-induced airway hyper-responsiveness (AHR) and allergic inflammation was examined. Results: BaP co-exposure potentiates Der f 1-induced TGFβ1 signaling activation in HBECs and in the airways of asthma mouse model. The BaP co-exposure-induced the activation of TGFβ1 signaling was attenuated by either AhR antagonist CH223191 or AhR knockdown in HBECs. Furthermore, AhR knockdown led to the reduction of BaP co-exposure-induced active RhoA. Inhibition of RhoA signaling with fasudil, a RhoA/ROCK inhibitor, suppressed BaP co-exposure-induced TGFβ1 signaling activation. This was further confirmed in HBECs expressing constitutively active RhoA (RhoA-L63) or dominant negative RhoA (RhoA-N19). Luciferase reporter assays showed prominently increased promoter activities for the AhR binding sites in the promoter region of RhoA. Inhibition of RhoA suppressed co-exposure-induced AHR, Th2-associated airway inflammation and TGFβ1 signaling activation in asthma. Conclusions: Our studies identified a functional axis of AhR-RhoA that regulates TGFβ1 signaling activation, leading to allergic airway inflammation and asthma.

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