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Title: Effects of combination of PI3Kγ and δ inhibitors on airway hyperresponsiveness in tobacco smoke-exposed mice

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Body: PI3K δ and γ are known to be involved in inflammatory cell functions. We recently found upregulation of PI3Kδ in lung tissue of COPD patients and ability of a PI3Kδ inhibitor on restoration of steroid sensitivity in airway inflammation in tobacco-smoke (TS) exposed mice. Superior effects of combination of PI3Kγ and δ inhibitors to each inhibitor alone on airway inflammation in TS-exposed mice were also observed. The aim of this study is to evaluate role of PI3Kγ and PI3Kδ on airway hyperresponsiveness (AHR) in TS-exposed mice. A/J mice were exposed to TS for 11 days and IC87114 (IC), AS604850 (AS) and/or fluticasone propionate (FP) were administered intranasally twice a day for 3 days after the last TS exposure. Airway responsiveness was determined as the increment of airway resistance (Δ[sRaw/TV]) before and 1 min after histamine inhalation at 24 h after the last drug dosing. The effects of the PI3K inhibitors on the contractile response to carbachol in guinea-pig tracheal smooth muscle preparation were also evaluated by the isometric tension recording. The concentration-response curve of carbachol was shifted to rightward and reduced the maximal response by AS (10-100 μM), in contrast, the effects of IC (100 μM) was limited in the tracheal smooth muscle. The AHR induced by TS was significantly reduced by AS (4 mg/ml; by 56% inhibition) and IC (4 mg/ml; 43%) alone. The inhibitory effects were enhanced by combination treatment of AS and IC (69%). Moreover, the combination of IC and FP showed stronger inhibition (96%) on the AHR.Considering with our previous findings, the combination of a PI3Kδ or PI3Kγ/δ inhibitor with corticosteroid may offer potential treatment of COPD.