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Title: Effect of nilotinib on airway smooth muscle thickening in a murine model of chronic asthma

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Body: Background: Asthma is characterized by airway inflammation and remodeling. The tyrosine kinase inhibitor nilotinib was developed to inhibit BCR-ABL kinase activity; however, it also has potent inhibitory activity against the c-Kit and platelet-derived growth factor receptors (PDGFR). The present study aimed to determine whether nilotinib suppresses airway smooth muscle (ASM) remodeling and whether its effect is associated with c-Kit and PDGFR pathways. Methods: We developed a mouse model of airway remodeling, which includes smooth muscle thickening, in which ovalbumin (OVA)-sensitized mice were repeatedly exposed to intranasal OVA administration twice a week for 3 months. Mice were treated with nilotinib during the OVA challenge. Results: Mice chronically exposed to OVA developed sustained eosinophilic airway inflammation compared with control mice. In addition, the mice chronically exposed to OVA developed features of airway remodeling, including thickening of the peribronchial smooth muscle layer. Administration of nilotinib significantly inhibited eosinophilic inflammation and ASM remodeling in mice chronically exposed to OVA. Nilotinib treatment significantly reduced the expression of p-c-Kit, p-PDGFRβ, and p-ERK1/2. The expression levels of genes encoding c-Kit and PDGFRβ were also reduced by nilotinib treatment. Conclusions: These results suggest that nilotinib administration can prevent not only airway inflammation, but also airway remodeling associated with chronic allergen challenge. Nilotinib may provide a clinically attractive therapy for chronic severe asthma.