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Title: Activin-A expression is increased in severe asthma and is involved in tissue angiogenesis

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Body: Background: Our recent studies show that Activin-A (Act-A), a cytokine belonging to the TGF-β superfamily, suppresses mouse allergic responses; however its effects on human asthma remain unknown. Objectives: To determine Act-A expression in healthy controls (CTRL) and asthmatics, identify its cellular sources and signaling mediators, and examine correlations with disease severity and airway remodelling. Methods: Serum samples were obtained from 46 mild-to-moderate asthmatics (MMA), 27 severe asthmatics (SA) and 41 CTRL. 55 subjects (18 CTRL, 18 MMA, 19 SA) underwent bronchoscopy with endobronchial biopsy and BALF collection. Act-A levels in the serum/BALF were examined. Expression of Act-A and its principal signaling mediator ALK4 in the bronchial tissue were assessed by confocal microscopy. Basement membrane thickness, goblet cell hyperplasia and angiogenesis (vessels/mm2) were also determined. Results: Act-A levels were significantly increased in MMA in the serum and in MMA and SA in BALF. Serum Act-A was further increased during asthma exacerbation. Bronchial tissue Act-A expression was significantly increased in asthmatics, especially in the subepithelium in SA, while ALK-4 expression decreased with disease severity. Act-A was mainly expressed by mast cells, neutrophils, macrophages and smooth muscle cells. Act-A and ALK-4 were also localized in endothelial cells, particularly in SA. Subepithelial Act-A expression correlated with angiogenesis and disease severity. Conclusions: Our data suggest that Act-A plays a crucial role in asthma inflammation and participates in the regulation of angiogenesis in SA. Ongoing in vitro studies will further elucidate its specific role.