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Title: Increased levels of angiopoietin 1 & 2 in sputum supernatant in smoking asthma

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Body: Background: Angiopoietin-1 (Ang-1), is an essential mediator of angiogenesis by establishing vascular integrity, whereas angiopoietin-2 (Ang-2) acts as its natural inhibitor. Objective: We aimed to determine the levels of angiopoietins in sputum supernatants of patients with smoking asthma and to investigate possible associations with mediators and cells involved in both the inflammatory and the vascular remodeling process Methods: Eighty-seven patients with asthma (42 smokers) and 28 healthy subjects (14 smokers) were studied. All subjects underwent lung function tests, bronchial hyperresponsiveness assessment and sputum induction for cell count identification and Ang-1, Ang-2, VEGF, TGF-β1, MMP-2, IL-13, ECP, and IL-8 measurement in supernatants. Airway vascular permeability (AVP) index was also assessed. Results: Ang-1 (ng/ml) and Ang-2 (pg/ml) levels were significantly higher in patients with smoking asthma compared to patients with non-smoking asthma and both smoking and non-smoking healthy subjects [median, interquartile ranges 24(13-37) vs. 10 (7-14) vs. 5.3(3.7-6.5) vs 4.6 (3.8-5.7) respectively, $p<0.001$; and 168 (132-203) vs 124 (82-152) vs 94(78-113) vs 100 (96-108) respectively, $p<0.001$]. Regression analysis showed a significant positive association for Ang-2 with AVP index, and VEGF in smoking asthma. A negative association was observed between Ang-1 and AVP index, MMP-2, sputum neutrophils and VEGF in smoking asthma. Conclusions: Our results indicate that sputum Ang-1 and Ang-2 levels are higher in smoking asthma compared to non-smoking asthma and healthy subjects pointing towards a contribution of smoking through these mediators to the asthmatic angiogenesis process.