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Title: Dose dependent effect of thrombomodulin in a murine model of allergen-induced asthma

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Body: Background: Thrombomodulin (TM), the thrombin receptor on the endothelial cell surface, plays an important role in coagulation and inflammation by inactivating thrombin and activating protein C. Previously we reported that recombinant human TM (rhTM) is protective against murine asthma. However, the effect of different concentrations of rhTM on asthmatic inflammation remains unclear. Objective: To evaluate the dose-dependent effect of inhaled rhTM on airway inflammation and hyperresponsiveness in a murine asthma model. Methods: Bronchial asthma was induced by sensitization and challenge with ovalbumin (OVA). Mice treated with saline were used as control. The effect of inhaled low dose to high dose rhTM was assessed by administering it prior to OVA exposure. Airway inflammation was evaluated by measuring the number of inflammatory cells and the levels of cytokines in bronchoalveolar lavage fluid (BALF). Airway hyperresponsiveness was measured using a plethysmograph. Particle size distribution of each different rhTM was measured by Spraytec. Results: The number of eosinophils in BALF and airway hyperresponsiveness was decreased by rhTM in a dose-dependent manner compared to saline treated mice. rhTM concentration of 3.75µg/ml was associated with the lowest number of BALF eosinophils and airway hyperresponsiveness, and with the smallest particle size. Conclusion: These results suggest that the effect of rhTM in murine asthma is dose- and particle size-dependent.