Title: Dose-dependent differential effects of thrombin in allergic bronchial asthma

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Body: Apart from its role in the coagulation system, thrombin plays an important role in the inflammatory response through its protease-activated receptor (PAR)-1, but its role in the immune response is unclear. This study evaluated the modulatory role in allergic bronchial asthma. Bronchial asthma was induced in mice by sensitization and challenge with ovalbumin. Mice with low but sustained coagulation activation had reduced allergic inflammation and allergic asthma was inhibited by low doses but worsened by high doses of thrombin. Allergic asthma was worsened by antithrombin, argatroban, hirudin and anti-thrombomodulin antibody. Mice with an increased concentration of an inhibitor of both thrombin and activated protein C had worsened disease. Heterozygous PAR-1 mice had less allergic inflammation but PAR-1 agonist worsened it. Allergic bronchial inflammation was worsened in mice that received adoptive transfer of PAR-1 agonist-treated Th2 cells compared to controls. Low concentrations of thrombin suppressed but high-dose of it enhanced maturation and secretion of cytokines in dendritic cells. The effects of thrombin on allergic asthma are dose-dependent with detrimental effects at high-dose being mediated by PAR-1 while low doses were protective via thrombomodulin. These data demonstrate that thrombin modulates the outcome in allergic bronchial asthma.