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Title: Regulatory role of antigen-induced IL-10, produced by Tr1 cells, in airway neutrophilia in a murine model for asthma

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Body: It has been suggested that IL-10 exerts immunosuppressive effects on allergic inflammation, including asthma. In a model of experimental asthma utilizing multiple intratracheal antigen challenges in sensitized mice, IL-10 production as well as eosinophilia and neutrophilia in the lung were induced by the multiple challenges. In this study, we set out to reveal the cellular source of endogenously produced IL-10, and the roles of IL-10 in airway leukocyte inflammation using an anti-IL-10 receptor monoclonal antibody. Balb/c mice were sensitized i.p. with ovalbumin+$Al(OH)_3$, and then challenged by intratracheal administration of ovalbumin 4 times. Flow cytometric analyses revealed that the cellular source of IL-10 was $CD4^+$ T cells lacking the transcription factor, forkhead box P3, which should be Tr1 cells. Treatment with anti-IL-10 receptor monoclonal antibody prior to the 4th challenge significantly augmented airway neutrophilia as well as the production of IL-1β, and CXC chemokines, keratinocyte-derived chemokine (KC) and macrophage inflammatory protein (MIP)-2, but neither airway eosinophilia nor Th2 cytokine (IL-4 and IL-5) production. Approximately 40% of IL-10 $receptor^+$ cells expressed the macrophage marker F4/80, whereas only 3-4% of the IL-10 $receptor^+$ cells were granulocyte differentiation antigen (Gr)-1^{high} cells (neutrophils). In conclusion, multiple airway antigen challenges induced the proliferation of IL-10-expressing Tr1 cells. It was suggested that IL-10 produced from the induced Tr1 cells by the specific antigen challenge suppressed macrophages to produce CXC chemokines through activation of the IL-10 receptors on the cells.