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Title: Over-expression of Th17-related cytokines in bronchial and nasal submucosa in severe asthma

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Body: In severe asthma neutrophil recruitment in bronchial submucosa is associated with steroid resistance, and in addition Th17-derived cytokines are important in induction and activation of neutrophils. We evaluated the differences in inflammatory cells and Th17-related cytokine in bronchial and nasal submucosa between severe asthmatics (SA) and mild asthmatics (MA). Bronchial and nasal biopsies obtained from 20 SA and 20 MA were investigated by immunohistochemistry. Bronchial sub-mucosa (BS) of SA showed a higher number of neutrophils, CD4+ and CD8+ compared to MA. Furthermore, the number of IL17-A+, IL17-F+ e IL-22+ cells in SA was significantly higher. Forced Expiratory Volume (FEV1) negatively correlated with: CD8+, neutrophils and IL 22+ cells in BS; the number of neutrophils correlated with IL 17F+ cells and CD8+; CD4+ and CD8+ with IL22+ cells. Double staining for CD4 or CD8 and IL17F or IL22 showed that all IL 17F+ and IL22+ cells are also CD4+ or CD8+. In nasal sub-mucosa (NS) of SA we found higher number of lymphocytes CD4+, CD8+, mast cells and macrophages, but also of IL 17A+, IL17F+, IL 21+ and IL22+ cells. FEV1 negatively correlated with: IL-17A+, IL-17F+, IL-21+ and IL-22+cells in NS. Moreover, the number of CD4+, IL-17F+and IL-22+cells in BS correlated positively with the equivalent cells in NS. We showed that in SA an exaggerated neutrophil/lymphocyte infiltration in conjunction with an amplified expression of Th-17 related cytokines in both bronchial and nasal submucosa suggesting an involvement of IL-17 pathway in the progression to an irreversible steroid-resistant inflammatory process.