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Title: 4-1BBL mediated balance of Th17/Treg in patients with allergic asthma

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Body: Objective: To investigate the expression of 4-1BBL in peripheral blood of patients with allergic asthma and its role in the balance of Th17/Treg cells. Methods: We detected the plasma soluble 4-1BBL (s4-1BBL) levels with ELISA and membrane expression of 4-1BBL (m4-1BBL) on monocytes with flow cytometry in patients with allergic asthma and controls. The peripheral blood mononuclear cells (PBMCs) of patients with asthma were in vitro stimulated with or without 4-1BB agonistic mAb for 72h, the concentrations of IL-17 and TGF- β in supernatant were measured with ELISA and the percentages of Th17 and Treg cells were measured with flow cytometry. Results: The s4-1BBL concentrations of patients with asthma ($202.47 \pm 60.68 \mu\text{g/L}$) were decreased than controls ($298.29 \pm 40.32 \mu\text{g/L}$, $p < 0.01$). The m4-1BBL on monocytes of patients with asthma ($2.69 \pm 1.85\%$) was decreased than the controls ($9.06 \pm 6.79\%$, $p < 0.01$). The supernatant concentrations of TGF- β ($655.81 \pm 476.26 \text{ ng/L}$) and IL-17 ($5202 \pm 4143.74 \text{ ng/L}$) in PBMCs stimulated with 4-1BB mAb were different from the isotype controls (TGF- β : $410.50 \pm 368.03 \text{ ng/L}$, IL-17: $8377 \pm 3839.98 \text{ ng/L}$, both $p < 0.05$). There was a lower proportion of Th17 cells ($1.298 \pm 0.53\%$ vs $1.536 \pm 1.01\%$) and a higher proportion of Treg cells ($3.45 \pm 1.03\%$ vs $2.76 \pm 0.97\%$) in the 4-1BB mAb group than isotype control, but no difference between the two groups ($p > 0.05$). Conclusions: Both s4-1BBL and m4-1BBL decreased in peripheral blood of patients with allergic asthma. In vitro agonistic 4-1BB antibody stimulation enhanced TGF- β but inhibited IL-17 production by PBMCs. Thus 4-1BBL/4-BB may restore Th17/Treg balance in allergic asthma more likely by changing the function of Th17 and Treg cells.