Increased frequency of IL-7 and IL-15 receptor alpha chain (CD127, CD215) co-expressing CD4+ T cells in granulomatosis with polyangiitis (Wegener's)

Sirs,

One of the striking alterations within the T-cell compartment in granulomatosis with polyangiitis (GPA / Wegener's) is the expansion of circulating effector memory T-cells (T_{EM}) with a concomitant decrease in the number of naïve T cells (T_N) (1). GPA is a rare chronic inflammatory disorder of unknown etiology characterised by a predilection for chronic granulomatous inflammation of the upper and/or lower respiratory tract and a systemic autoimmune vasculitis associated with highly specific anti-neutrophil cytoplasmic autoantibodies with a specificity for proteinase 3 (PR3-ANCA) (2). Th1-type cells infiltrate granulomatous and vasculitic lesions suggestive of a role of T-cells in maintaining chronic inflammation in GPA. Circulating memory T cells are persistently activated and display a skewed mixed inflammatory cytokine response to PR3 *in vitro*, whereas the suppressor activity of regulatory T cells is impaired. Oligoclonality and shortened telomers suggest clonal expansion and antigen- and/or cytokine-driven replicative senescence and differentiation of T cells in GPA (3-7).

To address the question what drives memory T-cell expansion in GPA, we analysed the expression of the interleukin-7 receptor alpha chain (IL-7Rα, CD127) and IL-15Rα (CD215) on peripheral blood $CD4^+$ T-helper-cells in 15 GPA-patients and 15 healthy controls from a cohort which we have analysed with regard to the phenotype and function of regulatory T cell previously (5). Cell preparation, staining of cellular surface markers with previously determined optimal concentrations of fluorochrome-conjugated monoclonal antibodies and flow-cytometric analysis with a four-colour flow cytometer was performed as described earlier (3, 5). In the present study we found no difference in the frequency of $CD4^+IL\text{-}15R\alpha^+$ T cells between GPA and healthy controls (8.2±5.6% *vs*. 5.3±2.5%, not significant, Mann-Whitney U-test). The percentages of $CD4^+IL\text{-}7R\alpha^+$ T cells were higher in comparison to the percentages of $CD4^+IL\text{-}15R\alpha^+$ T cells both in GPA and healthy individuals (24.2±10.0% *vs*. 8.2±5.6% $p<0.001$ and 42.7±12.7% *vs*. 5.3±2.5%, $p<0.0001$, Mann-Whitney U-test). However, there was a significant difference in the percentage of $CD4^+IL\text{-}7R\alpha^+$ T cells between GPA-patients and healthy controls (24.2±10.0% *vs*. 42.7±12.7%, $p<0.01$, Mann-Whitney U-test). Analysis of the co-expression of IL-7Rα and IL-15Rα on $CD4^+$ T cells showed a significant increase in the percentage of $IL\text{-}7R\alpha^+IL\text{-}15R\alpha^+$ co-expressing $CD4^+$ T cells in GPA in comparison with healthy controls (Fig. 1). Thus, while there was no difference in the percentages of $IL\text{-}15R\alpha^+$ T cells between GPA and healthy controls and even a decreased frequency of $IL\text{-}7R\alpha^+$ T cells in GPA as compared with healthy indviduals, co-expression of both receptors was found in a higher percentage on $CD4^+$ T cells in GPA-patients.

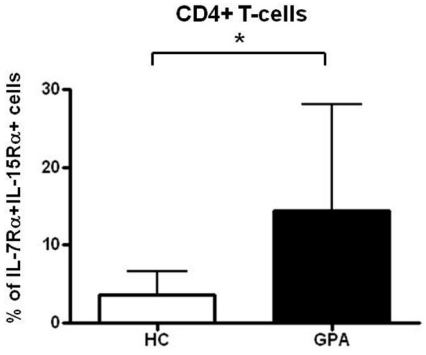

Fig. 1. Increased frequency of IL-7Rα (CD127) and IL-15Rα (CD215) co-expressing $CD4^+$ T cells in GPA. Percentages of $CD4^+IL\text{-}7R\alpha^+IL\text{-}15R\alpha^+$ T cells in GPA and healthy controls (HC). Percentages of positive cells as assessed by flow cytometry (mean±SD, $*p\leq0.05$, Mann-Whitney U-test).

Expansion of circulating T_{EM} has been reported in GPA previously (1, 3, 7, 8). Genetic and environmental factors may play a role in driving T-cell differentiation in GPA (6, 8, 9). Of note, T_{EM} and IL-15-producing cell are present in granulomatous lesions in GPA (3, 8). Proliferation and differentiation of $CD4^+$ memory T cells is driven by IL-7 and IL-15. The responsiveness of $CD4^+$ T cells to IL-7 and IL-15 is progressively acquired as naïve T cells (T_N) differentiate to central memory T cells (T_{CM}) and effector memory T cells (T_{EM}) and up-regulate the IL-2/IL-15Rβ chain (CD122) and the common γ chain (CD132) to form the IL-7R heterodimer and IL-15R heterotrimer together with the IL-7Rα and IL-15Rα subunits, respectively (10). In the present study, we found an increased percentage of circulating $CD4^+$ T cells co-expressing the IL-7Rα and IL-15Rα in GPA-patients. An increased frequency of $CD4^+$ T cells co-expressing both receptors could favour the expansion of T_{EM} in GPA. Further studies will have to define the conditions driving the up-regulation of IL-7R and IL-15R and expansion of T_{EM} in more detail.

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