The immunoglobulin superfamily member CD200R identifies cells involved in type 2 immune responses

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Background

It is well described that type 2 immune cells as Th2, ILC2 and basophils by production of combinations of IL-4, IL-5 and IL-13 contribute to the pathologic processes associated with allergic diseases. However, surface receptors that are specifically expressed on cells with production of type 2 cytokines are less well documented. The aim of this investigation was to identify surface markers associated with type 2 immune responses.

Methods

Naïve human $CD4^+$ T cells from healthy individuals were activated with and without IL-4 for up to 60 hours. The samples were then “barcoded” and pooled following staining with >300 PE-conjugated antibodies against human cell surface proteins. Naïve CD4+ T cells were activated and stimulated under Th0, Th1 or Th2 culture conditions for one and two priming periods. *Ex vivo* isolated PBMCs from peanut allergic patients were short-term stimulated with peanut extract allowing us to identify peanut-specific (CD154+) cells and biopsies were obtained for transcriptomic analysis from healthy controls and patients with extrinsic or intrinsic atopic dermatitis and psoriasis.

Results

A systematic expression analysis of >300 surface proteins allowed us to identify IL-4 regulated surface proteins. Of importance we found for all time points an IL-4 specific up-regulation of CD90, CD108, CD109 as well as the inhibitory receptor CD200R (CD200R1). From additional analysis of naïve CD4+ T cells differentiated under Th0, Th1 or Th2 culture conditions CD200R was identified as specific up-regulated on Th2 cytokine producing cells. Moreover we found an additional increase of CD200R within cells co-producing cytokines associated with a more terminally differentiated Th2 phenotype; IL-5 or IL-31. Circulating Th2 cells (CRTh2+CD154-) in general had 7 fold higher expression of CD200R than non-Th2 cells (CD4+CRTh2-, $p < 0.0001$, MFI; 1198 vs. 183). The peanut specific Th2 (CD154+CRTh2+) cells expressed even more CD200R than the non-specific Th2 (CD154-CRTh2+) cells ($p < 0.0002$, MFI; 2455 vs. 1362). Subanalysis of the peanut-specific Th2 cells showed a relative higher CD200R expression on “inflammatory” IL-4+IL-5+ cells than IL-4+IL-5- cells ($p < 0.0018$, MFI; 2218 vs. 1227). Moreover, from *ex vivo* isolated PBMCs were we able to demonstrate that CD200R is highly expressed on type 2 cytokine producing cells as; Th2, Tc2 and ILC cells and basophils. Finally, transcriptomic analysis, of skin biopsies, revealed up-regulated CD200R gene expression in subjects with an extrinsic atopic dermatitis phenotype.

Conclusion

The inhibitory receptor CD200R was identified as specifically expressed on cells involved in type 2 immune responses. These results indicate that CD200R is strongly correlated with Th2 pathology, but the mechanism is as yes elusive.