Identification of novel immune phenotypes for allergic and nonallergic childhood asthma.

Abstract:
Childhood asthma is classified into allergic asthma (AA) and nonallergic asthma (NA), yet both are treated identically, with only partial success. We sought to identify novel immune phenotypes for childhood AA and NA. The Clinical Asthma Research Association cohort study includes 275 steroid-naive 4- to 15-year-old German children (healthy control subjects [HCs], patients with AA, and patients with NA). In PBMCs both quantitative and functional analysis of regulatory T (Treg) and TH17 cells (flow cytometry/Treg cell suppression) before/after anti-CD3/CD28, lipid A, and peptidoglycan stimulation were performed. Cytokines and gene expression, as assessed by using Luminex or transcriptomics/quantitative real-time RT-PCR, were analyzed by means of regression analysis. Linear discriminant analysis was applied to discriminate between phenotypes. The 3 phenotypes were immunologically well discriminated by means of microarray and protein analysis with linear discriminant analysis. Patients with AA were characterized by increased Treg cells compared with those in HCs but not those in patients with NA. Treg cells from patients with AA, but not patients with NA, significantly suppressed IL-5, IL-13, and IFN-? secretion. Patients with AA had decreased expression of chloride...
intracellular channel 4 (CLIC4) and tuberous sclerosis 1 (TSC1), important innate immunity regulators. Patients with NA were characterized by increased proinflammatory IL-1β levels, neutrophil counts, and IL-17-shifted immunity. In parallel, expressions of anti-inflammatory IL37, proline-serine-threonine phosphatase-interacting protein 2 (PSTPIP2), and the neutrophil-associated genes CD93, triggering receptor expressed on myeloid cells 1 (TREM1), and regulator of G-protein signaling 13 (RGS13) were increased in patients with NA. A shared TH2 immunity was present in both asthma phenotypes. Novel immune-regulatory mechanisms in childhood asthma identified increased Treg cells in patients with AA compared with those in HCs but not those in NA and decreased innate immunity genes for patients with AA, the first potentially indicating a counterregulatory mechanism to suppress cytokines yet not sufficient to control allergic inflammation. Very distinctly, patients with NA showed an IL-17-shifted proinflammatory immunity, promoting neutrophil inflammation and less functional Treg cells. Identification of these unique pathways provides a profound basis for future strategies for individualized prediction of asthma development, disease course, and prevention.

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