## The Proportion of FcεRI$^+$ Blood Monocytes Increases With the Degree of IgE-Mediated Sensitization in Asthma

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Atopic sensitization is an important and frequent driver of asthma, and the interaction between allergen-specific IgE and its receptor FcεRI is central to the disease. Monocytes have been shown to accumulate in the airways of children with fatal asthma, possibly as a result of recruitment from the blood [1]. A fraction of peripheral blood monocytes express FcεRI as a trimeric complex of 1 α and 2 γ chains (without the signal-amplifying ß chain). Trimeric FcεRI expression in monocytes is higher in atopic individuals and children with elevated IgE [2-4]. As IgE-mediated cross-linking induces NFκB activation and production of TNF α in monocytes in vitro [5], FcεRI$^+$ monocytes may play a proinflammatory role. However, FcεRI$^+$ monocytes might also internalize and degrade IgE, thereby contributing to IgE clearance and immune homeostasis [6]. In our study, the proportion of FcεRI$^+$ monocytes was evaluated as a potential asthma biomarker in a follow-up study of a cohort of young adults with asthma and controls without asthma based in Uppsala, Sweden.

The 39 asthma patients were aged 16-41 years (mean [SEM], 26 [1]), had total IgE levels of 14-1604 kU/L (geometric mean, 245 [1]), and well-controlled asthma with a mean asthma control test (ACT) score of 21 (0.5). The 28 controls were 15-37 years old (mean, 24 [1]), with total IgE levels of 0.05-315 kU/L (geometric mean, 13 [1]), and no asthma symptoms (see Supplemental methods and patient characteristics in Table S1). Isolated peripheral blood mononuclear cells were analyzed for FcεRI expressing CD14$^+$ blood monocytes using flow cytometry (Figure S1A).

A relationship between FcεRI expression in CD14$^+$ monocytes (henceforth monocytes) and total serum IgE levels was previously shown in children, with the highest proportion of FcεRI expression in those with both atopy and asthma [3]. In our study, total IgE levels correlated positively with the proportion of FcεRI$^+$ monocytes in adult asthma patients (Figure S1B). As expected, asthma patients had higher total IgE levels than controls (Figure, A). The asthma patients with more than 50% FcεRI$^+$ monocytes tended to have higher levels of total IgE (Figure, B) and higher levels of IgE antibodies against aeroallergens (ImmunoCAP Phadiatop; not shown; *P*=.08). Most asthma patients were sensitized to aeroallergens (Phadiatop, >0.35 kU/L) and had a higher proportion of FcεRI$^+$ monocytes than the controls (Figure, C). There was a trend towards a correlation between the degree of sensitization to aeroallergens and the proportion of FcεRI$^+$ monocytes in asthma patients (Figure S1C). A fraction of the patients with asthma (40%) were also sensitized to food allergens (ImmunoCAP fx5, >0.35 kU/L). The fx5 test measures IgE levels to hen's egg white, cow's milk, peanut, wheat, soybean, and cod allergens but does not identify which allergen an individual is sensitized to. Food allergen sensitization (fx5) correlated positively with the proportion of FcεRI$^+$ monocytes in asthma patients (Figure S1D). Furthermore, individuals sensitized to food allergens had a higher proportion of FcεRI$^+$ monocytes (Figure, D). Phadiatop$^+$/fx5$^+$ individuals had higher total IgE levels than asthma patients that were Phadiatop$^+$/fx5$^-$ or Phadiatop$^-$/fx5$^-$ (Figure, E). Furthermore, FcεRI$^+$ monocytes were more frequent in asthma patients who were Phadiatop$^+$/fx5$^+$ than in those who were Phadiatop$^-$/fx5$^-$ (Figure, F). We speculate that IgE levels are essential for the induction of FcεRI expression on human blood monocytes. A limitation is that the induction of FcεRI expression on monocytes by specific IgE was not assessed. Thus, the increase in FcεRI$^+$ monocytes in asthma patients might be due to a more pronounced atopic status.

Subsequently, we investigated whether having a high fraction of FcεRI$^+$ monocytes was associated with other parameters. Having more than 50% FcεRI$^+$ monocytes was not linked to a worse or better forced expiratory volume in 1 second, peak expiratory flow, ACT result, fraction of exhaled nitric oxide, age, or body mass index (Supplemental Table 2). However, as all patients had well-controlled asthma, a possible link between the induction of FcεRI on monocytes and disease severity cannot be excluded. While the basophil count was similar in asthma patients and controls (*P*=.13), asthma patients with more than 50% FcεRI$^+$ monocytes had slightly more basophils (Figure, G). There was a positive correlation between the proportion of FcεRI$^+$ monocytes and the blood basophil count in asthma patients (Figure S1E). This relationship was expected, since a strong association between FcεRI expression in basophils and total serum IgE levels has previously been demonstrated [3]. No relationships were found with other white blood cell counts (not shown).

The correlation between the proportion of FcεRI$^+$ monocytes and the concentration of 180 plasma proteins was analyzed for all patients using Olink Inflammation and Immune response panels and in asthma patients and controls separately. Only the aryl hydrocarbon nuclear transporter (ARNT) correlated positively with the proportion of FcεRI$^+$ monocytes in asthma patients (Figure S1F, not adjusted for

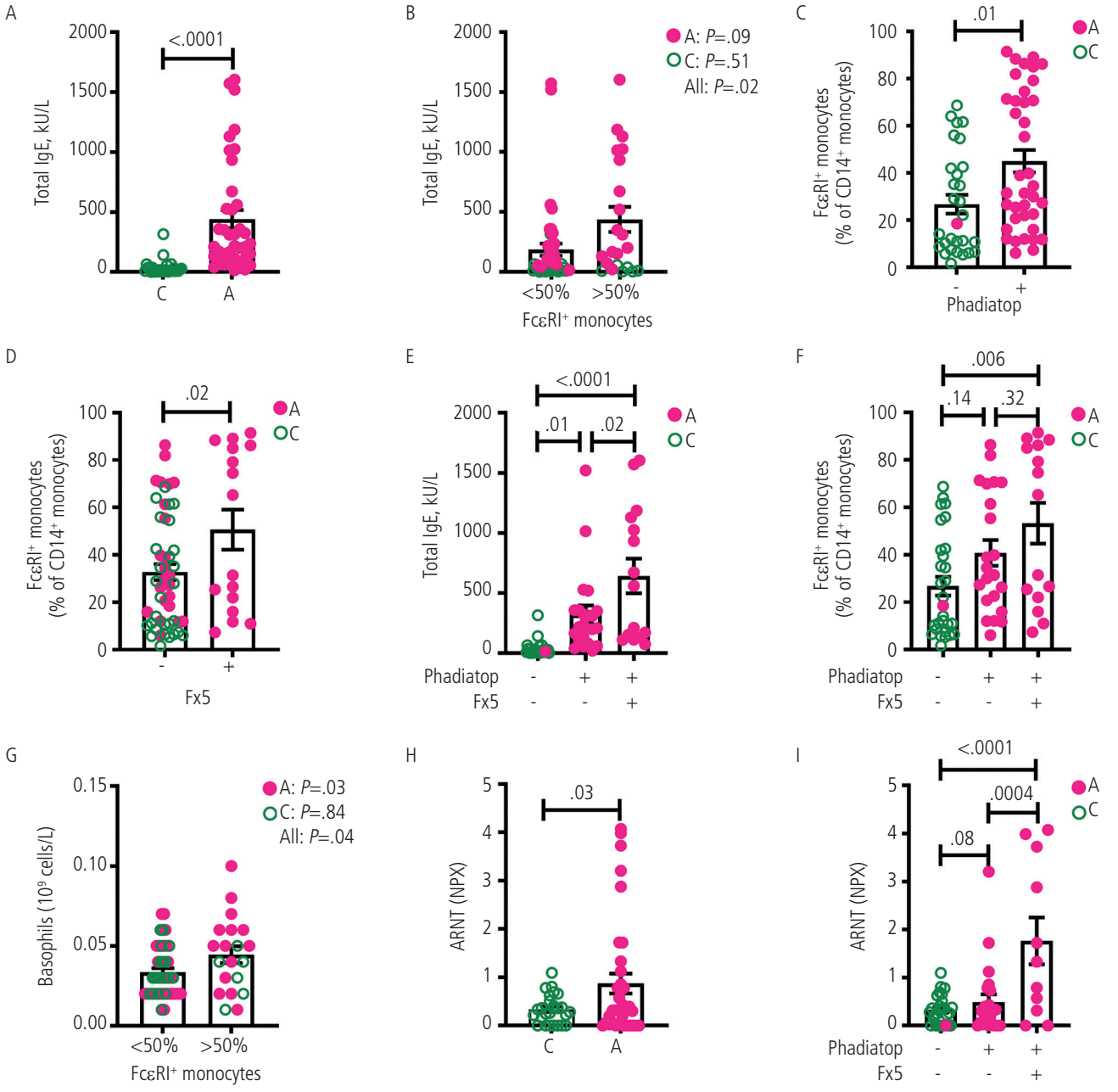


**Figure.** Multisensitized individuals have a high proportion of FcεRI⁺ CD14⁺ monocytes and ARNT levels. A-D, G-H, Groupwise comparisons of patients with asthma (A) and controls (C), based on their % FcεRI⁺ monocytes or a positive or negative Phadiatop or fx5 test. E-F, I, Multiple comparisons of patients with a positive or negative Phadiatop or fx5 test result and the specified parameters. Groupwise comparisons were tested using an unpaired *t* test, whereas multiple comparisons were assessed using 1-way ANOVA (Tukey post hoc test).

false discovery rate). There were no correlations between ARNT levels and age or body mass index (not shown). ARNT levels were higher in asthma patients than in controls (Figure, H) and tended to be higher in asthma patients with more than 50% FcεRI⁺ monocytes (*P*=.06). Asthma patients sensitized to both aeroallergens and food allergens had the highest ARNT levels (Figure, I). The nuclear protein ARNT forms a heterodimer with the aryl hydrocarbon receptor (AhR) after the activation of AhR in epithelial cells by, for example, allergens, particulate matter, or environmental toxins, and allows for nuclear translocation of AhR. The formation of the AhR/ARNT heterodimer induces expression of pro- and anti-inflammatory cytokines [7]. Interestingly, tryptophan-derived metabolites generated by microbiota can activate AhR [8]. Patients with atopic dermatitis have reduced levels of an AhR-activating tryptophan metabolite, which mediated tolerance via AhR in a mouse model of atopic dermatitis [9]. Further, AhR signaling in mice is associated with suppression of allergic

 

sensitization to egg and peanut [10]. Whether induction of AhR-mediated tolerance is related to the high levels of plasma ARNT in patients sensitized to both aeroallergens and food allergens remains unknown.

In conclusion, a high proportion of FcεRI$^+$ monocytes are associated with a high degree of IgE-mediated sensitization in young adults with asthma, suggesting that the proportion of FcεRI$^+$ monocytes is a biomarker of sensitization in these patients. Moreover, ARNT is a possible biomarker of atopic asthma with a food allergy component.

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*Conflicts of Interest*

The authors declare that they have no conflicts of interest.

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