

Correspondence

Impairment of regulatory T cells in cord blood of atopic mothers

To the Editor:

Schaub et al¹ presented an interesting study showing impaired regulatory T (Treg) cell numbers, expression, and function in cord blood of the offspring of atopic mothers. This important study, although shedding light on the mechanism by which offspring of atopic mothers are at risk of the disorder themselves, also raises several questions. For example, it would be interesting to know whether this impaired Treg cell activity is related to birth order (both for the offspring of atopic mothers and those of nonatopic mothers) because a positive answer to this question would reveal at least partly the timing when this (birth order) effect takes place. It has been hypothesized by us² that a possible suboptimal Treg cell activity directed at paternal antigens in nulliparous women could explain the birth order effect. If this hypothesis is true, we could expect cord blood Treg cells, as investigated in the study by Schaub et al,¹ to be related to birth order as well. If data on birth order have been collected, an analysis of this association would be important.

Another issue is whether all forms of "atopy" can actually be lumped together. There is increasing evidence that some forms of asthma are different from other forms of atopic disease, both with respect to pathophysiology and epidemiology. It would be interesting to breakdown Tables II and III of the article by Schaub et al¹ according to type of atopy (hay fever, eczema, and nonatopic and atopic asthma).

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2. Bernsen RM, Nagelkerke NJ, al-Ramadi BK. Does paternal antigen-induced secretion of interleukin-10 by T regulatory cells mediate the birth order effect? *Med Hypotheses* 2006;67:740-3.

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Reply

To the Editor:

Bernsen and Nagelkerke¹ raised the question regarding the article "Impairment of T-regulatory cells in cord blood of atopic mothers"² of whether the impaired regulatory T (Treg) cell activity might be related to birth order. We completely agree that this is a really important question and might elucidate potential timing of immune modulation in a child's immune development. Bernsen et al³ have previously hypothesized that nulliparous women might have a lower activity of Treg cells specific to paternal antigens compared with parous women.

Although we did not examine maternal Treg cells, there was no significant effect of birth order on Treg cell markers in the 2 groups of offspring with and without maternal atopy. For Treg cell function, the groups were too small to perform subgroup analysis.

When we stratify for maternal atopy, an effect was observed for the T_H1 effector cell cytokine IFN- γ . Lipid A- and peptidoglycan-stimulated IFN- γ levels were significantly lower in offspring of atopic mothers with 1 or more previous pregnancies compared with IFN- γ secretion in offspring of nonatopic mothers ($P = .006$ and $P = .02$, respectively). However, the numbers of subjects become small in this subgroup analysis (20 vs 25 subjects) and should be interpreted with caution. Additionally, there also might be a "dose-dependent effect" of the numbers of pregnancies. Again, in this study offspring with 2 or more siblings are just too few to investigate this.

When we compared the 2 groups of offspring with and without maternal atopy, we included older siblings, miscarriage, and previous cesarean section in Table I.² They were not significantly different in offspring with compared with those without maternal atopy and had no strong effects on the outcome parameters themselves. Thus we had not adjusted for these because there were no confounders for maternal atopy.

Second, Bernsen and Nagelkerke¹ mentioned the issue of whether different forms of atopy can be analyzed together regarding Treg cell impairment in the offspring. We agree that it is truly interesting to examine the effects of Treg cells in cord blood of mothers with asthma, allergic rhinitis, and atopic eczema separately. However, as noted in our Results section,² the study population of 118 mothers includes 70 nonatopic mothers and 48 mothers with atopy. In the latter group 9 (18.8%) mothers had asthma, 36 (75%) mothers had hay fever, and 11 (22.9%) mothers had eczema (as noted in the Results section of the Online Repository). Thus subgroup analyses for Table II (CD4CD25⁺, CD4CD25⁺high cells, lymphoproliferation, IFN- γ , and IL-10) and Table III (IL-17; correlations of IL-17 with IL-13, IL-5, and IFN- γ) will not have enough statistical power to answer this question. We agree that the group presented in the study comprises a heterogeneous group of mothers and thus does not allow conclusions regarding a specific atopic phenotype.

In summary, we did not detect an effect of birth order on Treg markers. Secretion of the T_H1 cytokine IFN- γ was lower in offspring of atopic mothers with 1 or more siblings after innate lipid A or peptidoglycan stimulation. For the future, large-size population studies might be beneficial to further investigate Treg cell function, depending on immune regulation during pregnancy.

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