Th1/Th2 differentiation and innate immune mechanisms in farmers' and non-farmers' children

Contribution to YSC Davos 2008
Thematic topic: Medicine

Remo Frei[1], Christian Bieli[2], Leticia Grize[2], Claudine Bommer[1], Johanna Steinle[1], Susanne Loeliger[1], Dirk Steinhoff[1], Christina Weber[1], Marco Waser[2], Harald Renz[3], Göran Pershagen[4], Bert Brunekreef[5], Josef Riedler[6], Annika Scheynius[7], Erika von Mutius[8], Felix Sennhauser[1], Charlotte Braun-Fahrländer[2], Roger P. Lauener[1,9], and the ALEX and the PARSIFAL study team

[1]*University of Zurich, Children's Hospital, Zurich, Switzerland, e-Mail: Remo.Frei@kispi.uzh.ch*
[2] *Institute for Social and Preventive Medicine, University of Basel, Basel, Switzerland*
[3] *Department of Clinical Chemistry and Molecular Diagnostics, Hospital of the Philipps University, Marburg, Germany*
[4] *Institute of Environmental Medicine, Clinical Immunology and Allergy Unit, Karolinska Institute and University Hospital, Stockholm, Sweden*
[5] *Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands*
[6] *Children's Hospital Schwarzach, Austria*
[7] *Department of Medicine, Clinical Allergy Research Unit, Karolinska Institutet and University Hospital, Solna, Stockholm, Sweden*
[8] *University Children's Hospital Munich, Germany*
[9] *Hochgebirgsklinik Davos, Davos Wolfgang Switzerland*

Key words: Th1/Th2 differentiation, immune mechanisms, population groups, farmer, non-farmer children

INTRODUCTION

The European cross sectional study ALEX (Allergy and Endotoxin) found that growing up in an environment with elevated exposure to microbial components, such as lipopolysaccharide (LPS), reduces the risk to develop allergic diseases in children. Furthermore, peripheral blood leukocytes (PBL) of these children produced less inflammatory cytokines upon re-stimulation with LPS (Braun-Fahrländer et al., 2002). Finally, PBL of farmers' children express more CD14 and Toll-like receptor (TLR) 2, two receptors of the innate immunity (Lauener et al., 2002).
A shift towards T helper cell type (Th)-1 differentiation has been proposed to underlay the protection against allergies described in farmers' children. Here, we investigated whether such a skewing of the Th-1/Th-2 balance can be observed in farmers' children. Furthermore, we assessed whether expression of genes involved in signal transduction following TRL-triggering was related to exposure to microbial components.

METHODS

Expression of genes related to Th-1/Th-2 differentiation and to the regulation of the TLR signaling cascade was measured by quantitative PCR in peripheral blood from a subgroup of children of the ALEX (n=43) and of the PARSIFAL cohort (n=313). Furthermore, we assessed interferon (INF)-γ production of whole blood cells by ELISA following ex-vivo stimulation with LPS. For statistical analysis we calculated the spearman's correlation coefficients or used multivariate regression models, adjusted (sex, age, parental history of atopy) and expressed the

results as geometric means (GMR [95% confidence intervals]). To visualize the associations we used local nonparametric smoothing of the $\log_{10}$ transformed values adjusting for the effect of age and farming (S-Plus software).

RESULTS

In comparison to non-farmers' children, farmers' children were less often atopic, expressed more CXCR3 (Th-1-related; GMR 2.08 [1.55-2.78]), less CCR3 (Th-2-related; GMR 0.7 [0.53-0.93]), and less CCR8 (Th-2-related; GMR 0.18 [0.05-0.61]). However, comparing the expression of the transcription factors GATA3 and T-bet, governing differentiation towards Th-2 and Th-1 cells, respectively, no difference between the two populations was found for T-bet, whereas GATA3 was even up-regulated in farmers' children (GMR 1.29 [1.08-1.54]).

Considering the gene expression of molecules of the TLR signaling cascade, we found that farmers' children expressed more IRAK-1 (GMR 1.19 [1.07-1.33]), IRAK-2 (GMR 1.82 [1.5-2.2]), and SOCS-1 (GMR 1.19 [1.02-1.38]), while they had reduced IRAK-4 (GMR 0.83 [0.72-0.95]) expression. Elevated IRAK-1 and IRAK-2 gene expression was associated with less asthma of the children (IRAK-1 (GMR 0.43 [0.21-0.87]); IRAK-2 (GMR 0.48 [0.23-1.04])). Elevated SOCS-1 gene expression correlated with reduced INF-γ production of blood cells after stimulation with LPS (correlation coefficient 0.35), while enhanced IRAK-4 gene expression correlated with more antibody isotype switching to IgE (GMR 1.2 [1.03-1.41]), assessed via the expression of Cε germline-transcript.

CONCLUSION

The expression of some genes associated with Th-1/Th-2 cell differentiation correlates with environmental factors such as farming. However, as indicated by the expression of GATA3 and T-bet, protection against allergies in the farming population investigated here cannot solely be explained by a skewing of the Th-1/Th-2 balance. By contrast, the expression of some regulatory molecules of the TLR signaling cascade is regulated by environmental exposure and is associated with reduced inflammation, antibody isotype switching to IgE, or allergic diseases. We propose that environmental exposures, such as microbes, have an impact on various molecules involved in cellular activation and forming a regulatory network, finally resulting in effects on health outcome.