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Adaptive immune maturation in relation to allergic disease and vaccine responses in children

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligen försvaras i föreläsningssalen våning 3, Guldhedsgatan 10A, Göteborg, torsdagen den 16 februari 2017, klockan 9.00

av **Anna Strömbeck**

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Avhandlingen baseras på följande delarbeten

I. **Strömbeck A**, Rabe H, Lundell A-C, Andersson K, Johansen S, Adlerberth I, Wold AE, Hesselmar B, Rudin A. *High proportions of FOXP3^{+}CD25^{high} T cells in neonates are positively associated with allergic sensitization later in childhood.* Clinical & Experimental Allergy, 2014;44:940-52.

II. **Strömbeck A**, Lundell A-C, Nordström I, Andersson K, Adlerberth I, Wold AE, Rudin A. *Earlier infantile immune maturation is related to higher DTP-vaccine responses in children.* Clinical & Translational Immunology. 2016 Mar 11;5(3):e65

III. **Strömbeck A**, Lundell A-C, Nordström I, Andersson K, Adlerberth I, Wold AE, Rudin A. *Delayed adaptive immunity is related to higher MMR vaccine-induced antibody titers in children.* Clinical & Translational Immunology. 2016 Apr 29;5(4):e75

IV. **Strömbeck A**, Nordström I, Andersson K, Andersson H, Johansen S, Maglio C, Rabe H, Adlerberth I, Wold AE, Hesselmar B, Rudin A, Lundell A-C. *Allergic disease in 8-year old children is preceded by delayed B-cell maturation.* Submitted manuscript.

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Adaptive immune maturation in relation to allergic disease and vaccine responses in children

Anna Strömbeck

Avdelningen för reumatologi och inflammationsforskning, Institutionen för medicin, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2017.

Abstract

Adaptive immune maturation in children is likely the result of a complex interplay between both intrinsic and environmental factors, but surprisingly little is known about how early life immune maturation is related to immune responses and subsequent development of allergic disease. The aim of the FARMFLORA birth-cohort study, including farmers' and non-farmers' children, was to visualize longitudinal patterns of adaptive immune maturation in relation to allergic sensitization and disease, vaccine-induced antibody responses, as well as to certain environmental factors in childhood.

By the use of multivariate factor analyses, we show that higher proportions of circulating neonatal regulatory T cells was strongly associated with sensitization in early childhood, and that a sustained higher fraction of these cells related to allergic disease at school age. Allergic disease at this age was also associated with higher proportions of naïve CD45RA$^+$ T cells in infancy and with higher proportions of immature/naïve CD5$^+$ B cells from birth to 8 years of age. These results indicate that allergic disease in childhood is preceded by a heightened immaturity in the adaptive immune system. Further, growing up on a dairy farm was associated with a higher degree of adaptive immune maturation, which may in part explain the lower incidence of allergic disease among farmers' children.

We further found that higher antibody levels induced by the non-live vaccine against diphtheria, tetanus and pertussis was associated with increased baseline immune maturation prior to vaccination. In contrast, higher antibody levels induced by the live attenuated vaccine against measles, mumps and rubella were generally associated with a lower degree of baseline adaptive immune maturation. Differences in the formulations of these vaccines and their respective way to induce immune responses in the host may be a possible explanation for these diverging association patterns.

Keywords: Adaptive immune maturation, children, allergic disease, farm, vaccine responses, prospective birth-cohort, multivariate factor analysis

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