

Summary

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Early childhood is a critical period where the maturation of the immune system occurs while it receives various challenges from the environment shared with the mother. Children growing in an environment rich in microorganisms and parasites are thought to have a different pattern of immune response compared to those children growing in a more hygienic environment. This difference might contribute to the lower prevalence of

allergic and autoimmune disorders in developing countries compared to affluent countries. Within this context, a number of cohort studies mostly performed in developed countries have focused on finding the link between the pattern of immune responses in early life and health outcomes in later life. In this thesis, we studied child's innate and adaptive responses during the first 4 years of life in a helminth-endemic area in Indonesia.

Chapter 1 provides a general introduction to the development of immune responses in early childhood. It describes and reviews how the maternal environment and exposures (for example farming environment or parasitic infections) during pregnancy might affect the child's immune responses in later life. The immune system of a child, in turn, is an important determinant of responses to vaccinations, allergens or parasitic and other infections. This chapter also describes the aim, the study population and the longitudinal design of the study.

In **Chapter 2**, we measured the different immunological patterns. Put in a very simplified way, the immune system can be characterized by two types of immune responses: TH₁ and TH₂. We analyzed TH₂-type cytokines and antibodies in young children from 2 months to 4 years of age. TH₂ responses increased significantly with age and to higher levels compared to what was seen in children of developed countries. Maternal education and socioeconomic status influenced the production of child's general TH₂ responses, while maternal filarial infection was more associated with the child's helminth-specific TH₂ responses. Maternal education was also shown to affect the child's skin prick test reactivity to allergen more strongly compared to other factors such as maternal helminth infection. Although both helminth infection and allergy are known to induce TH₂-type immune responses, our findings show that measured maternal helminth infections were not the most prominent contributors to the development of TH₂ responses in early life, indicating that more attention should be paid to find out what specific stimuli can skew immune responses toward TH₂.

In **Chapter 3**, we compared the development of innate and adaptive responses in children before and after BCG vaccination. While innate responses (early cytokines taking part in innate responses: IL-10 and TNF- α) induced by PPD & LPS were not affected, both TH₁- and TH₂-type responses against PPD were increased after vaccination and only TH₁-type was sustained into later age. BCG vaccination was also shown to stimulate child's general adaptive responses in response to mitogen-stimulation of whole blood, which correlated with PPD-specific responses till 1 year of age. All these in vitro findings still need to be studied further in relation to

the effect of BCG on the maturation of innate and adaptive immune responses *in vivo*, in order to explain the reported beneficial bystander effects of BCG on morbidity and mortality of children. Surprisingly we found that maternal intestinal protozoan infection (*Blastocystis hominis*) but no other measured factors during pregnancy, was associated with lower child's immune responses to mycobacterial antigen, again stressing the importance of exploring the contribution of a wide range of factors during early life for shaping immune responses later in life.

Chapter 4 described the relationship between maternal and child's cytokine responses at the age of 2 months, before any vaccination was given. The high production of IL-10 and IFN- γ in mitogen-stimulated whole blood from the mother was significantly associated with higher corresponding child's cytokine production. On the other hand the child's innate responses, represented by LPS-induced IL-10 and TNF- α , were more associated with area of residence than with maternal cytokines. We conclude that mother-child cytokine relationship at early infancy is seen in the adaptive responses but not in innate immune responses. Again maternal *B. hominis* infection was found to affect child's cytokine responses, warranting further research on the contribution of this particular parasitic infection on the developing immune system of the child starting from *in utero* period.

In **Chapter 5**, we followed the mother-child cytokine relationship up to 4 years of age and related this to gene polymorphisms as well as other factors. Our finding of strong mother-child cytokine relationship in early age was consistently found till 1 year of age, albeit in a decreasing strength. The genetic factors, either maternal or child's gene polymorphisms, were shown to be more associated with child's cytokines at later life. We concluded that during the first year of life the child's cytokine responses were more affected by cytokine responses of mothers, possibly through *in utero* preconditioning or breastfeeding which over rules the genetic influences. Larger studies are needed to dissect this in more detail with sufficient power.

Chapter 6 discusses the findings in this thesis, together with previous studies in both developed and developing countries. Emphasis was put on the contribution of maternal parasitic infections and other environmental factors to the child's immune responses and atopy, as well as to mother-child cytokine relationship. At the end, the possible consequences of the findings and future research have been discussed.

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Altogether, this thesis has provided a case for the importance of studying early life events not only in affluent countries but also in low to middle income countries where the changes in life style and environmental factors are the most dynamic and therefore informative for understanding development of diseases later in life.