Early life imprinting and modulation of the risk of developing type 1 diabetes

Project outline

Many immune mediated diseases including type-I diabetes are linked to perturbed immune system development or skewed immune-microbiome relationships early in life[1–3]. Most information on immune development comes from mouse models that cannot account for environmental exposures of human newborns. Our group has performed the first longitudinal studies of immune development in human newborns and revealed immune-microbe differences with likely disease relevance [4,5]. Microbial composition is influenced by delivery mode, feeding and antibiotic exposure and the microbiome evolves through an ordered sequence of events. Abundant beneficial microbes like Bifidobacterial species protect against allergies and type I diabetes[3] but the mechanisms remain elusive. We have recently reported that metabolites such as Indole-3 Lactic acid, produced by bifidobacterial metabolizing human milk oligosaccharides, skew T-cell populations away from diseases associated states and induce immune tolerance by upregulating inhibitory factors such as Galectin 1 early in life[4]. This first example of a probiotic-mediated immunomodulation study opens several interesting hypotheses for future mechanistic study within this proposal.

Objectives

1. *Identify the epigenetic mechanisms of T-cell imprinting by beneficial microbes?*
2. *Investigate the causal metabolites and their mechanisms of action in immune cell modulation*

Methodology The general theory behind the proposed project is to use the correlative findings from the longitudinal newborn studies mentioned above and test mechanistic hypotheses in vitro. The strong associations between early-life bifidobacterial colonization, especially with subspecies B. infantis, leads us to investigate imprinting effects in immune cells collected from infants with high and low abundance of bifidobacterial using ATAC-sequencing[6]. This method allow for genome-wide assessment of open chromatin and by comparing sorted immune cell populations from children abundantly colonized with bifidobacteria and not, we hope to understand imprinting differences which could explain long-term differences in the risk of developing immune mediated diseases (**Fig. 1A**). Similar studies can be performed by comparing other microbial differences, such as the high Bacteroides seen in vaginally delivered, more than C-section delivered children and previously associated with reduced risk of developing immune mediated diseases[7]. In this way we hope to understand more about what transcriptional programs that are imprinted epigenetically by different early life exposures, effects that can be long-lasting and explain differences in the disease risks seen.

A second line of mechanistic investigation aims to identify key metabolites produced by bacteria and their possible effect on immune cells in vitro. We have obtained fecal water suspensions from newborns in our cohorts and these will be added to cultures of immune cells in vitro to screen for functional effects. Once such an effect has been determined functionally, we will use mass spectrometry-based metabolomics to search for key molecules mediating the functional effects (**Fig. 1B**). All in all, the combination of unique, longitudinal

samples and state-of the art experimental technologies as well as detailed metadata on antibiotic exposure, nutrition, vaccination and infectious disease exposures, will allow us to unravel key factors shaping human immune systems early in life.

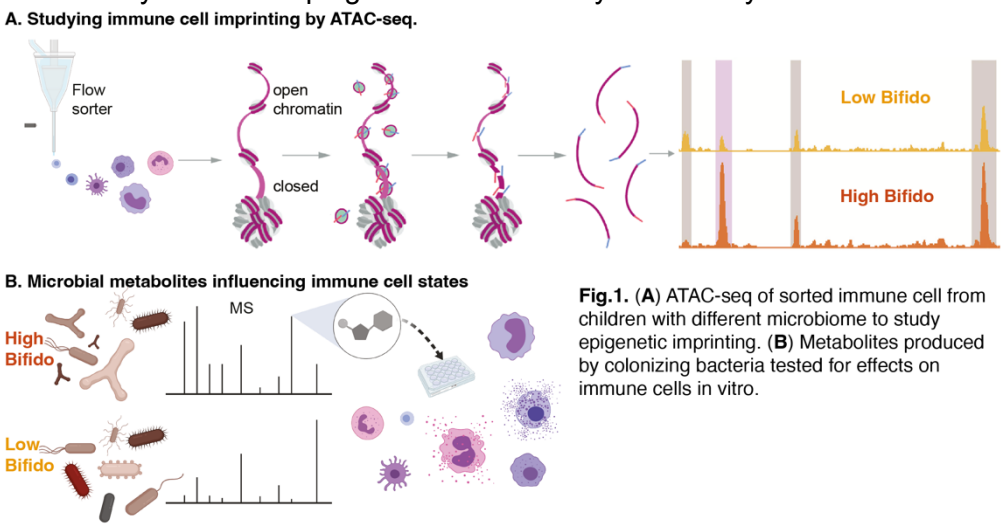

Fig.1. (**A**) ATAC-seq of sorted immune cell from children with different microbiome to study epigenetic imprinting. (**B**) Metabolites produced by colonizing bacteria tested for effects on immune cells in vitro.

Work plan The postdoctoral fellow will perform these epigenetic and functional immune cell experiments. The metabolomic screens are done together with Clarity Genomics in San Diego, US. The postdoctoral fellow will perform experiments and some basic data analysis tasks while more advanced analytics will be performed by Brodin lab computational team members.

Relevance of project for diabetes Beneficial microbes early in life have been shown to mediate some of the protective effects of vaginal delivery, breastfeeding etc on the development of type I diabetes3. In this project we hope to contribute mechanistic understanding for how this is and what the most important metabolites mediating this effect might be. This will then open the possibility of preventive treatments to be trialled in high-risk infants in future work.

References

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Contact details
Petter Brodin
Department of Women's and Children's Health, KI.
Tel: +46-(0)8-524 813 96
Email: Petter.Brodin@ki.se