Gut Microbes 3:5, 474-475; September/October 2012; © 2012 Landes Bioscience

Infant B cell memory and gut bacterial colonization

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Under normal conditions, the gut microbiota confers health benefits for the host. The microbiota aids in the nutrient processing and contributes to the construction of the intestinal epithelial barrier. Furthermore, animal models demonstrate the importance of stimulation from gut bacteria for a proper maturation of the immune system. In this addendum, we summarize our recent study[1] in which we demonstrate that colonization with *Escherichia coli* and bifidobacteria in the first 2 months of life was related to higher numbers of CD27-positive memory B cells later in infancy. The numbers of total B cells or $CD5^+CD20^+$ B cells, on the other hand, were not related to the bacterial colonization pattern. Thus, the gut microbiota might affect the B cell maturation also in humans, and our study indicates that an early colonization pattern that includes *E. coli* and bifidobacteria might promote this maturation early in life.

Keywords: infants, B cells, commensal intestinal bacteria, multivariate factor analysis

Submitted: 07/06/12

Accepted: 07/09/12

http://dx.doi.org/10.4161/gmic.21419

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Addendum to: Lundell AC, Björnsson V, Ljung A, Ceder M, Johansen S, Lindhagen G, et al. Infant B cell memory differentiation and early gut bacterial colonization. J Immunol 2012; 188:4315-22; http://dx.doi.org/10.4049/jimmunol.1103223; PMID:22490441.

The Gut Microbiota and Effects on the Immune System

The establishment of the commensal gut microbiota starts at birth and the list of beneficial functions attributed to the microbiota for the development of gut-associated lymphoid tissues (GALT) continues to grow.[2-4] GALT involves the mesenteric lymph nodes (MLNs), the Peyer's patches, immune cells in mucosal lamina propria and intraepithelial cells. Animals raised under germfree conditions display smaller MLNs and Peyer's patches, which lack or have fewer germinal centers, compared with conventionally raised animals.[5] They also have a decreased number of IgA-producing plasma cells in the gut mucosa.[2,5] We recently showed that the proportion of gut-homing IgG^+ and IgA^+ B cells was significantly higher in infants compared with adults. This finding could point to activation of naïve B cells in the gut, coinciding with the establishment of the gut microbiota.[6]

The Gut Microbiota in Western Infants and Potential Consequences of a Changed Colonization Pattern

In developing countries, the first bacteria that colonize the infantile gut include *Escherichia coli*, enterobacteria (other than *E. coli*) and enterococci.[7,8] Along with an increased hygienic lifestyle, it has been shown that *E. coli* colonization is delayed in Swedish infants. Instead, coagulase-negative staphylococci and/or *Staphylococcus aureus* are the first colonizers, possibly due to reduced competition from traditional fecal bacteria, such as *E. coli*.[9] Moreover, the early gut flora of Swedish infants have a lower diversity and strain turn-over rate than the flora of infants in developing countries.[8,10] Whether the changes in the bacterial colonization pattern that appear to have taken place during the last decades will influence child health is not clear, but diseases caused by deficiencies in immune regulation, including allergies, Crohn disease and type-1 diabetes, have increased in Western countries. Today, B cell-mediated allergic disorders are a major public health issue. B cells play a central role in allergy as the symptoms are initiated by IgE antibodies directed against harmless substances in the air and in foods, i.e., allergens. However, factors that regulate the misdirected IgE-response are not known and mechanisms that control

B cell maturation in children remains to be illuminated.

The Early Gut Bacterial Colonization Pattern is Associated with the Numbers of CD27+ Memory B Cells Later in Infancy

In an article published recently in *The Journal of Immunology*, we demonstrated data from our prospectively followed newborn-infant cohort.[1] In this study we had the opportunity to investigate colonization by culturable fecal bacteria in relation to counts and proportions of circulating CD20+ B cells, as well as CD27+ and CD5+ cells within the B cell population with the use of multivariate factor analysis. For the first time we show that the early bacterial colonization pattern may affect B cell maturation/activation also in humans as colonization with *E. coli* or bifidobacteria was associated to higher numbers of B cells that expressed the memory marker CD27 later in infancy. In contrast, children who harbored *S. aureus* in the gut early in life displayed lower numbers of CD27+ B cells relative to children not colonized by this bacterium. Early colonization by *E. coli* and bifidobacteria may reflect successful acquisition of maternal gut bacteria during delivery. Indeed, the classical infantile bacterial colonization pattern includes *E. coli* and bifidobacteria among the first bacteria that colonize the large bowel.[11,12] The presence of *S. aureus*, on the other hand, might reflect a gut microbiota of low complexity and the low numbers of memory B cells in these children could be because of lack of other bacterial species or groups that are normally present in a more complex microbiota. Moreover, we found no relationship between the numbers of total CD20+ or CD5+CD20+ B cells and the early bacterial colonization pattern. This indicates that the bacterial colonization patterns may be specifically associated to B cell memory differentiation in early infancy.

Conclusions and Future Perspectives

Our findings point to that the process of the gut colonization pattern in infancy needs to be further explored as is seems to influence the maturation of the immune system, which consequently may affect child health. The children in the present prospective cohort will be examined for sensitization and allergic disorders at 18 months and at 3 and 6 years of life, which will enable us to further study the relationship between gut bacterial colonization patterns, B cell maturation and development of allergy during early childhood.

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