

# DEVELOPMENT OF THE MUCOSAL IMMUNE SYSTEM **OF THE NEWBORN INFANT**\*

Proper development in the first 3 years of an infant's life is crucial to promote the maturation of the immune system and support protection against infections or allergy

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Human milk is considered the optimal nutrition for all infants and provides the best level of protection

The WHO recommends exclusive breastfeeding for at least 6 months of life however, according to recent European studies, only 25% of the newborns are exclusively breastfed for the first 6 months of life.

Human milk contains many (bioactive) components such as Human Milk Oligosaccharides (HMOS), which are highly abundant in human milk



The HMOS structures present in human milk are diverse with multiple functions

ved allergy development



Specific HMOS structures can interact with Intestinal epithelial cells and immune cells modulating mucosal immune development early in life



Continued research into the (bioactive) components in human milk is important to better understand the underlying mechanisms in the maturation of the immune system and development of an infant.

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### **IMMUNE ASPECTS** STUDIED:

Intestinal epithelial cells

Innate and adaptive immune cells

Extracellular vesicles

Non digestible oligosaccharides, postbiotics, Gos/ Fos, 2'FL, 3'GL



Intestinal Epithelial cells (IECs) are important cells involved in the regulation of immune responses upon a viral trigger and during inflammation



Exposure of IECs to 2'FL enhances galectin release within an inflammatory condition and instruct dendritic cells to drive Th1 and regulatory-type immune development<sup>7</sup>

**Dendritic cells** 

#### AN OVERVIEW OF THE EFFECTS PROMOTED BY NDOS AND POSTBIOTICS **MUCOSAL VIRAL DEFENSE MUCOSAL IMMUNOMODULATION** ₿-3'GL VACCINATION LvpIC RESPONSE GOS DP GF 2F'L FP CpG ↑ DTH IEC C 36 DC C CCL20 🕇 Gal-3/Gal-9 **†**Gal-4/Gal-9 ↑ Galectin-4 ↑ Galectin-9 🕇 Galectin-4 🕇 Galectin-9 ↑ Galectin-3 CXCL10 T cell † IFNγ **1** IFNγ **1** IFNγ CIRCULATION DC **†** IL-10 **↑** TNFα **†** IL-10 Activated innate and T-cells ↓IL-13 **†** IL-17A MUCOSAL IMMUNE DEVELOPMENT $\overline{\phantom{a}}$

Exposure of IECs to a viral trigger and 2'FL promote the secretion of chemokines (CCL20 and CXCL10) capable of attracting important immune cells<sup>5</sup>

In addition, 2'FL was shown to condition Dendritic Cells to instruct Th1 and regulatory-type immune responses indicating the ability of 2'FL to support mucosal immune development

The mucosal immune modulation seen by specific oligosaccharides was associated with increased secretion of specific galectins

Within inflammatory conditions, the epithelial cells secrete specific vesicles containing Galectin 4 and 9 upon exposure to NDOs, which can signal to distant organs<sup>8</sup>

Within the unique diversity of human milk oligosaccharides, specific structures show immune modulatory capacity

Small structures (incl 2'FL) support Th1 and regulatory-type immune modulation by increasing IFN- $\gamma$  and IL-10 while reducing Th2-type IL-13<sup>6,7</sup>



## CONCLUSIONS

Based on the PhD Thesis entitled: Shaping mucosal and systemic immunity by non-digestible oligosaccharides and postbiotics: **GROWING ROOTS WITH FOOD** 

New insights are generated regarding the development of mucosal immunity early in life IECs provide not only a physical barrier, but also support the mucosal immune system, regulating innate and adaptive immune responses.

Small oligosaccharides including 2'FL support Th1 and regulatory-type immune modulation.

Within inflammatory conditions, the epithelial cells secrete specific vesicles containing Galectin 4 and 9 upon exposure to NDOs, known to be able to signal to distant organs/cells.

Non-digestible oligosaccharides (incl 2'FL) are important for shaping mucosal and systemic immunity.

In addition, human milk components such as non digestible oligosaccharides, postbiotics, GOS/FOS and 3'GL also have an important role to play in shaping the mucosal and systemic immunity.



The PhD Thesis entitled: "Shaping mucosal and systemic immunity by non-digestible oligosaccharides and postbiotics: GROWING ROOTS WITH FOOD" by Veronica Ayechu Muruzabal is part of the long lasting collaboration between the Pharmacology division of Utrecht University and Danone Nutricia Research. With specific focus on understanding the role of human milk oligosaccharides, non-digestible oligosaccharides and postbiotics on mucosal immune development.

### References

1. Munblit D, Peroni DG, Boix-Amorós A, Hsu PS, Van't Land B, Gay MCL, et al. Human milk and allergic diseases: an unsolved puzzle. Nutrients. 2017 doi: 10.3390/nu9080894.

2. Lawrence RM, Lawrence RA. Breastfeeding: more than just good nutrition. Pediatr Rev. 2011;32(7):267–280.

3. Walker WA, Iyengar RS. Breast milk, microbiota, and intestinal immune homeostasis. Pediatr Res. 2015;77(1-2):220-228.

4. Duijts L, Jaddoe VW, Hofman A, Moll HA. Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy. Pediatrics. 2010;126(1):e18–25.

5. Ayechu-Muruzabal, V.; Poelmann, B.; Berends, A.J.; Kettelarij, N.; Garssen, J.; van't Land, B.; Willemsen, L.E.M. Human Milk Oligosaccharide 2'-Fucosyllactose Modulates Local Viral Immune Defense by Supporting the Regulatory Functions of Intestinal Epithelial and Immune Cells. Int. J. Mol. Sci. 2022, 23, 10958. doi: 10.3390/ijms231810958.

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6. Ayechu-Muruzabal, V.; van de Kaa, M.; Mukherjee, R.; Garssen, J.; Stahl, B.; Pieters, R. J.; van't Land, B.; Kraneveld, A. D.; & Willemsen, L. E. M. (2022). Modulation of the Epithelial-Immune Cell Crosstalk and Related Galectin Secretion by DP3-5 Galacto-Oligosaccharides and  $\beta$ -3'galactosyllactose. Biomolecules, 12 (3), 384.

7. Ayechu-Muruzabal, V.; Overbeek, S. A.; Kostadinova, A. I.; Stahl, B.; Garssen, J.; van't Land, B. & Willemsen, L. E. M. (2020). Exposure of intestinal epithelial cells to 2'-fucosyllactose and CpG enhances galectin release and instructs dendritic cells to drive Th1 and regulatory-type immune development. Biomolecules, 10 (5) (784).]

8. Ayechu-Muruzabal V, de Boer M, Blokhuis B, Berends AJ, Garssen J, Kraneveld AD, van't Land B and Willemsen LEM (2022) Epithelial-derived galectin-9 containing exosomes contribute to the immunomodulatory effects promoted by 2'-fucosyllactose and short-chain galacto- and long-chain fructooligosaccharides. Front. Immunol. 13:1026031. doi: 10.3389/fimmu.2022.1026031

9. Ayechu Muruzabal V, Shaping mucosal and systemic immunity by non-digestible oligosaccharides and postbiotics. Growing roots with food, 2022