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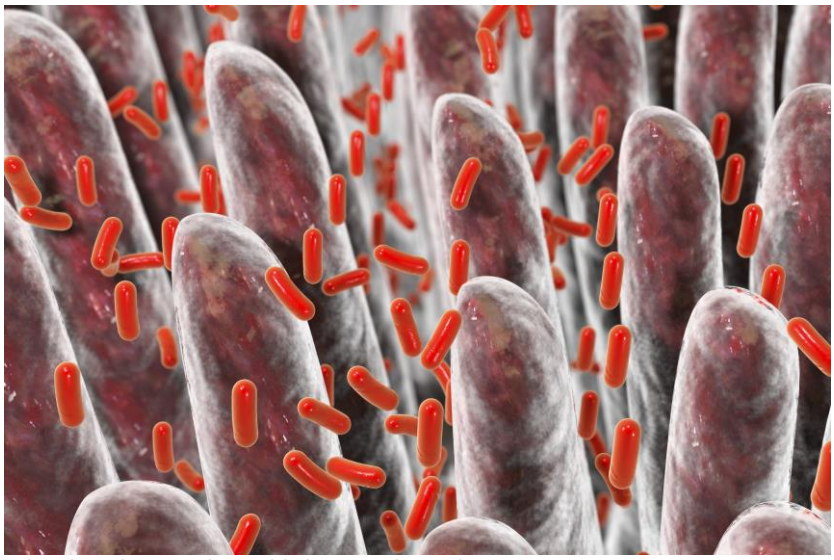
Alimentary Glycoscience Research Cluster



Microbes interacting with human intestine

Key external stakeholders:

Food for Health (functional food) manufacturers, infant formula manufacturers, Dairy and cheese industries, Dairy farmers

Practical implications for stakeholders:

The Alimentary Glycoscience Research Cluster (AGRC) is a collaboration between glycoscientists and alimentary health and microbiology experts to focus on deciphering the role of glycans in gut microbial ecology. The role of Teagasc in this this cluster was to explore the effect of milk oligosaccharides on host-microbial interactions. Teagasc researchers sought to identify milk oligosaccharides with health promoting activities for inclusion in infant and adult beverages and demonstrate that bovine milk may be an attractive commercially viable source of oligosaccharides for such applications.

Main results:

- Milk oligosaccharides were found to increase the adhesion of the prototypical infant strain, *Bifidobacterium longum* subsp. *infantis* to intestinal cells *in vitro*.
- Upon exposure to the milk oligosaccharides, a significant transcriptional response was observed in the *B. infantis* strain
- Up-regulation of a number of genes likely to enhance adhesion to epithelial cells was demonstrated
- Bovine milk oligosaccharides may contribute to the development and maturation of the intestinal immune response
- Milk from domestic animals contained a much larger variety of complex oligosaccharides than was previously assumed, and thirteen of these structures have been identified previously in human milk.

Opportunity / Benefit:

Milk oligosaccharides were shown to promote the adherence of health-promoting bacteria to intestinal cells and displayed immunomodulatory effects on intestinal cells. The inclusion of bovine milk oligosaccharides in functional foods/infant formula may benefit the newborn but also the general population, particularly immuno-compromised individuals.

Collaborating Institutions:

Teagasc, National University of Ireland Galway, University College Dublin, University College Cork

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Teagasc project team: Dr. Rita Hickey, Dr. Jonathan Lane, Dr. Devon Kavanaugh, Dr. John O' Callaghan

External collaborators of Teagasc: Prof. Lokesh Joshi National University of Ireland, Galway (PI)
Prof. Pauline Rudd, National Institute for Bioprocessing Research & Training (NIBRT)
Prof.Stephen Carrington, University College Dublin
Dr. Marguerite Clyne, University College Dublin
Prof. Douwe Van Sinderen, University College Cork

1. Project background:

The Alimentary Glycoscience Research Cluster established in 2009 is a collaboration between academic and industrial glycoscientists and alimentary microbiologists, the over-arching goal of which is to extend knowledge and understanding of the role of glycans in gut microbial ecology, with a view to develop novel approaches to combat gut pathogens, and improved probiotic/prebiotic treatments to foster and maintain a healthy gut. The AGRC also aimed to advance the application of high-throughput and combinatorial technologies to analyse glycans and to identify molecules that modulate their activities. Human milk oligosaccharides in particular have been shown to affect bacterial binding to the epithelial cell surface, either through mimetics or alteration of glycosyltransferases expression in the human intestinal epithelium. Oligosaccharides from the domestic animal milk may provide an attractive alternative to human milk glycans. Within the AGRC, Teagasc's role was to examine the effect of milk oligosaccharide fractions from various species on the host microbial interactions. The ability of milk oligosaccharide to prevent infection or promote colonisation of health-promoting bacteria may have applications in protecting formula-fed infants.

2. Questions addressed by the project:

- Do milk derived oligosaccharides influence bacterial interactions in the gut?
- If so, what is the mode of action of the milk derived oligosaccharides?

3. The experimental studies:

To investigate if milk derived oligosaccharides can influence bacterial interactions in the gut we undertook a study to test the hypothesis that milk oligosaccharides may contribute not only to selective growth of bifidobacteria, but also to their specific adhesive ability. Human milk oligosaccharides (3'sialyllactose and 6'sialyllactose) and a commercial prebiotic were assayed for their ability to promote adhesion of *Bifidobacterium longum* subsp. *infantis* to human intestinal cells. Treatment with 6'-sialyllactose resulted in increased adhesion (4.7 fold), while treatment with a mixture of 3'- and 6'-sialyllactose substantially increased adhesion (9.8 fold) to HT-29 intestinal cells. Microarray analyses were subsequently employed to investigate the transcriptional response of *B. longum* subsp. *infantis* to the different oligosaccharide treatments. The combination of 3'- and 6'-sialyllactose resulted in the greatest response at the genetic level (both in diversity and magnitude) followed by 6'-sialyllactose, and 3'-sialyllactose alone. Of particular interest is the identification of a number of genes for potential colonisation factors. The expression of these genes may give beneficial commensals such as *Bifidobacterium* the opportunity to compete with pathogenic bacteria for specific intestinal niches thereby reducing colonisation by pathogens. We also demonstrated that bovine milk oligosaccharides may contribute to the development and maturation of the intestinal immune response as several genes encoding cytokines, chemokines and cell surface receptors were differentially regulated in intestinal cells in response to bovine milk oligosaccharides. Given that human milk and animal milk are rich sources of bioactive oligosaccharides, which are of great interest to the functional food industry, we also analysed milk from a variety of important domestic animals including cows, goats, sheep, pigs, horses and dromedary camels for their oligosaccharide content. This work was done in collaboration with Prof. Pauline Rudd in NIBRT/UCD. Milk from domestic animals contained a much larger variety of complex oligosaccharides than was previously assumed, and thirteen of these structures have been identified previously in human milk.

4. Main results:

- An increased adherence phenotype was observed when *Bifidobacterium longum* subsp. *infantis* was exposed to milk oligosaccharides. The response is multi-faceted, involving transcription factors, chaperone proteins, adhesion-related proteins, and a glycoside hydrolase.
- The potential value of animal milk for the commercial extraction of oligosaccharides for use in human and animal health was determined

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5. Opportunity/Benefit:

Our studies give an insight into the role of milk oligosaccharides within the human intestine and the molecular mechanisms underpinning host-microbe interactions. The results confirm the protective effects of milk oligosaccharides which may give beneficial commensals such as *Bifidobacterium* the opportunity to compete with pathogenic bacteria for specific intestinal niches thereby reducing colonisation by pathogens. The results further validate that domestic animal milk is a highly attractive source of bioactive oligosaccharides, which once extracted can be potentially used in medical and functional foods. To justify their use, additional studies on their biological functions are required. The advanced knowledge on their structural composition will certainly help to gain new insights into the complex biochemical pathways underlying their potential health-promoting properties.

6. Dissemination:

Main publications:

- Kavanaugh, D., O' Callaghan J. C., Kane, M., Joshi, L. and R. M. Hickey. (2015). The intestinal glycome and its modulation by diet and nutrition. Nutrition Reviews. Special article. (6):359-75.
- Albrecht, S., Lane J. A., Marino K., Al Busadah K. A., S. D. Carrington, Hickey R. M. and P. M. Rudd. (2014) A comparative study of free oligosaccharides in the milk of domestic animals. British Journal of Nutrition, 111, 1313-1328.
- Kavanaugh, D., O'Callaghan, J, Buttò, L. F., Slattery, H., Lane, J. A. Clyne, M., Kane M., Joshi, L. and R. M. Hickey. (2013). Exposure of *Bifidobacterium longum* subsp. *infantis* to milk oligosaccharides increases adhesion to epithelial cells and induces a substantial transcriptional response. PLoS ONE 8(6):e67224.
- Kavanaugh, D., Kane, M., Joshi, L. and R.M. Hickey (2013). Detection of galectin-3 interaction with commensal bacteria. Applied and Environmental Microbiology. 79(11):3507-3510.
- Lane, J. A., Carrington, S. D. and R. M. Hickey (2013). Transcriptional response of HT-29 intestinal epithelial cells to Human and Bovine milk oligosaccharides. British Journal of Nutrition. 28:1-11
- Lane, J. A., Marino, K., Slattery, H., Carrington, S. D., Rudd, P. M., and R. M. Hickey (2012) Methodologies for screening of bacteria-carbohydrate interactions: anti-adhesive milk oligosaccharides as a case study. Journal of Microbiological Methods 90(1):53-9.

Thesis:

- Kavanaugh, D. (2013). The influence of milk oligosaccharides on host-commensal interactions in the gastrointestinal tract.Presented to the National University of Ireland, Galway for the Degree of Doctor of Philosophy.
- Lane, J. A. (2012). The discovery of food derived glycans for applications in promotion of human health. Presented to University College Dublin for the Degree of Doctor of Philosophy.

Popular publications:

- Marotta M. and Hickey R. M (2011) The 4th Glycoscience Ireland meeting. Moorepark news. Winter edition
- Hickey R.M. (2009) Alimentary Glycoscience Research Cluster (AGRC) Launch TResearch (Winter edition). 4 (4)

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