Healthy Living, Good Food and the Gut Microbiota

CarboMet

Relevance and Problem

The promotion and maintenance of a healthy relationship with our gut microbiota is increasingly understood to be important for human health and well-being, through every stage of life. The 100 trillion symbiotic microorganisms that reside in the human gut fulfils several vital biological functions and these imbalances in the microbial populations are associated with a number of inflammation and infection conditions, such as gut disorders (e.g. Irritable Bowel Syndrome, and the Irritable Bowel Diseases, Ulcerative Colitis and Crohn's disease) and non-communicable diseases (e.g. diabetes, cardiovascular diseases and cancers). In Europe, an estimated 2.5 - 3 million people are affected by Irritable Bowel Disease (IBD) with a direct healthcare cost of more than EUR 4 billion per year.[1] In conjunction with other related disease, the total cost of healthcare will likely reach tens of billions by 2030.

Challenges and Opportunities

Carbohydrates play a number of crucial roles in maintaining microbial communities. For example, dietary fibre has a major influence on overall gut health and carbohydrates are the main modulators of the gut microbiota structure and function.[2] Carbohydrates are also found in the human gut lining and are the first point of contact between the microbiota and the host. Alteration of the carbohydrates in the lining give rise to several disease profile and are associated to gut disorders such as IBD. Therefore, a comprehensive understanding of the role of carbohydrates in the gut is essential to elucidate the interactions between the human host and gut microbiota in order to exploit these relationships for the benefit of human health. The ageing population and the growing prevalence of non-communicable disease is continuously adding strain to the healthcare system and it is vital to develop new strategies to improve health outcomes and to reduce healthcare costs. To stimulate growth in microbiome research, CarboMet identified 5 key areas[3] that will expedite the development of new treatments and preventative measures.

- **Elucidating the relationship between microbiota and human health**
- **Biotechnological production of carbohydrates**
- **New metrology and analytical tools**
- **Data management and integration**
- **New strategies to promote healthy diet**

Social and Economic Impact

IBD is generally managed through anti-inflammatory drugs or through supplements to reduce inflammation. As a last resort, surgery can be used but this results on removing the entire colon. As a result, the quality of life for patients suffering from IBD is drastically reduced and the negative effect on the patients emotional and social life is estimated to cost the European industry EUR 1.5 billion per year.[4]

Impact on human health - HMO case study

At the end of the 19th century physicians observed that breast-fed infants had a higher survival rate than those who were bottle-fed in cases of infection and other disease. To date more than 150 of the 200 different human milk oligosaccharide (HMO) structures have been identified, 30 of which have been successfully synthesized and used in formula milk.

The most abundant of these is 2-fucosyllactose commercialised by a European biotechnology company and was granted the first EU approval of a HMO as a novel food ingredient.

References

1. Lakatos et. al., *J. Crohn's and Colitis*, **2013**, 7, 322-337.
2. Juge et. al., *Biochem. J.*, **2017**, 474, 1823-1836.
3. Microbiome Briefing paper - Carbomet.eu
4. Calculated from the average cost to industry per patient per year of EUR 500 taken from Canavan et. al. *Aliment Pharmacol Ther.*, **2014**, 40, 1023-1034.

CarboMet is a four-year Collaborative Support Action ['CSA'] funded by the EC Horizon 2020 Future and Emerging Technologies initiative

E-mail: projectmanager@carbomet.eu
Website: carbomet.eu
Twitter: @CarboMet_EU

CarboMet

Healthy Living, Good Food and the Gut Microbiome

European Commission

Metrology of Carbohydrates for Enabling European Bioindustries

A horizon 2020 coordination and support action (CSA) 2017-2021 funded by the European Commission under FET-OPEN

Background

CarboMet is a four-year Collaborative Support Action ['CSA'] funded by the EC Horizon 2020 Future and Emerging Technologies initiative. The primary aim of the CSA is to mobilise the European academic and industrial community to identify measurement, data management and metrological challenges that need to be addressed in order to advance and exploit carbohydrate knowledge and applications. The vast diversity and complexity of the gut microbiome is a major challenge to identify the mechanism of how it influences the bodies immune system to fight infection, development of chronic diseases and the change in emotional state. Therefore as a first stage CarboMet has organised some open, Europe-wide workshops to identify key topics where our understanding needs to be advanced urgently, and where current limitations in our measurement, data management and metrological capabilities are hindering progress. Workshop participants were asked to recommend appropriate work programmes that should be supported by Horizon 2020 and its successor, Horizon Europe. One of these workshops addressed the topic of the role of carbohydrate molecules in the gut microbiome. This paper reports on the technological challenges that were identified at this workshop and lists a set of recommended areas as high priority research for funding to enable a better understanding of the role of microbial and dietary carbohydrates.

Executive Summary

The presence of diverse microbial community in the gut and how it interacts with the human body has been well described in recent years. However, there has been increasing evidence to suggest gut microbiota is associated with chronic disease such as gastrointestinal inflammatory, cardiovascular, neurological and even respiratory illness. The World Health Organisation has estimated by 2020 three-quarters of all death will be related to chronic illness. There is an urgent need to elucidate the role and mechanism of the gut microbiota in disease progression to identify novel therapeutic interventions. The aim of the report is to highlight the importance of the gut microbiome and the complex interplay between the microbial community in the gut and the host body mediated by carbohydrates as food or on the cell surface as a communication tool. Five research areas are highlighted in the report which are essential to further develop new capabilities to facilitate our understanding of the microbiome.

Introduction

The promotion and maintenance of a healthy relationship with our gut microbiota is increasingly understood to be important for human health and well-being, through every stage of life. The 100 trillion symbiotic microorganisms that reside in the human gut fulfils several vital biological functions and these imbalances in the microbial populations are associated with a number of inflammation and infection conditions, such as gut disorders (e.g. Irritable Bowel Syndrome, and the Irritable Bowel Diseases, Ulcerative Colitis and Crohn's disease) and non-communicable diseases (e.g. diabetes, cardiovascular diseases and cancers). In Europe, an estimated 2.5 - 3 million people are affected by Irritable Bowel Disease (IBD) with a direct healthcare cost of more than EUR 4 billion per year.[1] In conjunction with other related disease, the total cost of healthcare will likely reach tens of billions by 2030.

Social and Economic Impact

IBD is generally managed through anti-inflammatory drugs or through supplements to reduce inflammation. As a last resort, surgery can be used but this results in removing the entire colon. Consequently, the quality of life for patients suffering from IBD is drastically reduced and the negative effect on the patients emotional and social life is estimated to cost the European industry EUR 1.5 billion per year.[2]

Glossary

Microbiome — The collective genetic material of the microorganism in a particular environment.

Microbiota — Smaller community of microorganism

Carbohydrates — Also known as sugars and oligo-, polysaccharides.

Prebiotic — non-digestible food ingredient which promotes growth of good bacteria in the gut.

Challenges

Carbohydrates play a number of crucial roles in maintaining microbial communities. For example, dietary fibre has a major influence on overall gut health and carbohydrates are the main modulators of the gut microbiota structure and function.[3] Carbohydrates are also found in the human gut lining and are the first point of contact between the microbiota and the host. Alteration of the carbohydrates in the lining give rise to several disease profile and are associated to gut, autoimmune and inflammatory bowel disease. The promotion and maintenance of a healthy relationship with our gut microbiota is increasingly understood to be important for human health and well-being, through every stage of life. Recent studies suggest intestinal microbiota even affects distant organs and is involved in skin homoestasis.[4] Between 2013 and 2017 12,900 research papers were published on the microbiome which represents 80% of the total publication in this field over the last 40 years[5] and with 2400 clinical trials in 2018 related to the microbiome[6] highlights the immense interest in this area. Current therapies look to replace the bad bacteria by introducing beneficial bacteria orally. The complex mutualistic relationship between the gut microbiota and the human body makes it an ideal target for elucidating this complex mechanism and exploiting for novel therapies. For example, the microbiota is responsible for the metabolism of drugs, production of important vitamins, maturation of the immune system and protection against pathogens.

Role of carbohydrates in the gut

- Food derived polysaccharides: These are dietary fibres and prebiotics from fruit and vegetable. The gut bacteria consume these sugars to produce chemicals that are beneficial to the human body.
- Carbohydrates on gut lining: Mediates the interaction between microbiota and the host body. Also prevents infections and dehydration in addition to lubricating the wall. Changes in the glycan structure can lead to gut disorders and disease.[7]

The composition of the gut microbiota and the structure-function capability of the microbes largely depends on the dietary carbohydrate intake of the host. Western diets today are typically high-fat, high sugar compared to the relatively low fat, high polysaccharide diets of the past, resulting in the typically modern lower diversity of microbial composition in the gut. This loss of diversity or unbalance, also referred to as ‘dysbiosis’, has been associated with a number of diseases affecting westernized or “developed” countries. These include neurological diseases (e.g. autism, Parkinson’s, Alzheimer’s), metabolic diseases (mainly diabetes and obesity), gut diseases (e.g. Irritable Bowel Syndrome, Inflammatory Bowel Diseases (Ulcerative Colitis and Crohn’s disease), Coeliac disease, liver disease, colon cancer), food allergies or cardiovascular diseases. Many risk factors have been implicated in the perturbation of the gut microbiota such as mode of delivery, lifestyle, eating behaviours, disruption of biological clock and antibiotic over-use.[8] Increasing the complex carbohydrate content in the diet rapidly leads to an increase in microbial diversity with the associated health benefits.[9] This provides an opportunity in terms of developing carbohydrate-based strategies to promote or restore gut homeostasis.

Impact on Human Health—HMO Case Study

Around the end of the 19th century observations indicated that breast-fed infants had higher survival rates than those who were bottle-fed in cases of infection and other diseases. It was later discovered these were a class of compounds called human milk oligosaccharides (HMO). 2’-Fucosyllactose (2’-FL), an oligosaccharide (made up of the 3 sugar units fucose, glucose, and, galactose) is the most abundant HMO in breast milk. While these prebiotics pass through the infants gut undigested, the ‘good’ bacteria in the intestine consume it to promote immunity, digestion and cognitive health benefits.

In 2017, Jennewein, a German biotechnology company, was granted the first EU approval of a HMO as a novel food ingredient.[10] Since then, other companies have entered into the EUR 20 bn market releasing 2’-FL as a functional ingredient in infant formulas.

Therefore, a comprehensive understanding of the role of carbohydrates in the gut is essential to elucidate the interactions between the human host and gut microbiota in order to exploit these relationships for the benefit of human health. The ageing population and the growing prevalence of non-communicable disease is continuously adding strain to the healthcare system and it is vital to develop new strategies to improve health outcomes and to reduce healthcare costs. To stimulate growth in microbiome research, CarboMet identified 5 key areas[3] that will expedite the development of new treatments and preventative measures.

Elucidating relationship between microbiota and human gut

The European glycoscience community is leading the development of new analytical tools and knowledge to understand the mechanisms behind the interactions between our gut, the microbiota and diet. To study the impact of host, microbial or dietary carbohydrates, it is necessary to analyse directly what carbohydrates and glycoconjugates are present. To do this, it is essential to integrate and develop glycobiology, glycosynthesis and glycometrics approaches to provide mechanistic insights to determine: 1) How gut microbiota influence human health 2) Identification and validation of novel biomarkers 3) Development of novel microbiome targeted strategies.

Biotechnological production of carbohydrates

The carbohydrates involved in microbiota-host interactions need to be available as validated, high quality pure standards, both for allowing high-throughput analysis and for providing materials as probes for functional studies. Significant advances in carbohydrate synthesis and analysis have been made to produce a range of bespoke carbohydrates. However, there is an urgent need to be able to produce these on scale, economically and efficiently in sufficient quantities that will allow their assessment for health benefits and safety which require multi-gram to kilogram quantities for commercial success (see box on 'Impact on human health - HMO case study'). Four main approaches have been identified:

- Isolation of naturally occurring carbohydrates: Fermentative production from microbes/naturally producing microorganism or in genetically modified strains. Require technologies in biomanufacturing with accurate monitoring and purification systems.
- Chemical synthesis: Traditionally very challenging and largely carried out by specialist academic groups and SMEs. Require development of new and routine synthetic methodologies for rapid access to sugar building blocks.
- Enzymatic synthesis: A sustainable approach compared to traditional synthetic approaches. However, a major limitation is the availability of carbohydrate-active enzymes with the required properties and chemical activities. Therefore there is an urgent need to build an arsenal of more glycoenzymes showing an expanded repertoire of chemistries.
- Combined integrated approach: Using combinations of some or all of the above for chemical and/or enzymatic modification of naturally occurring carbohydrates. Such integrated approaches require cross-disciplinary strategies including chemistry, biochemistry, molecular biology and computation, and machine learning.

New metrology and analytics

Core to the success of developing new targeted therapies for the microbiome is the development of new standards for measurements and analysis including ISO standards. The subtle differences in surface carbohydrates of bacteria will make classification and identification of 'good' and 'bad' bacteria easier. ISO standards will aid the safe development and production of bespoke carbohydrates for human intervention; through to the safe design of clinical trials and targeted drug design and delivery.

Data management and integration

Data management is central to the development, sharing and dissemination of research. With new tools that can collect enormous amount of data (glycomics, metabolomics and genomics), new data management systems are needed that can store and process this data. Perhaps what is urgently required is the development and integration of artificial intelligence (AI) to analyse vast amounts of data and identify novel mechanistic insights.

New strategies to promote healthy diet

The above 4 topics will all contribute to the development of strategies that target the gut microbiota to restore and/or promote good health and well-being for all at all stages of life. Double-blinded, placebo controlled clinical trials will need to be carried out, exploiting the mechanistic knowledge and capacity building from 1-4, to provide evidence for the health benefits in humans. There will also need to be a strong engagement with consumers to ensure not only that the development of new functional food products is palatable but that consumers are informed on their health benefits and that the consumers' needs and expectations are taken into account.

Conclusions

This report emphasises the importance of the microbiome in the human body and how the interplay between carbohydrates in food and on the surface of the gut and bacteria play a crucial role on the health and disease. Disruption or imbalance in these systems can lead to chronic diseases such as IBD. Elucidating the mechanism and the extent to which the microbiota harness carbohydrates and communicate with the host body will lead to novel therapeutic interventions targeting the microbiome. The five priority areas highlighted in this report directly address 3 of the 5 research missions for Horizon Europe; Digitisation, Health and Food.

References

1. Burisch, J.; Jess, T.; Martinato, M.; Lakatos, P. L. *J. Crohn's and Colitis*, **2013**, 7, 322-337.
2. Calculated from the average cost to industry per patient per year of EUR 500 taken from Canavan et. al. *Aliment Pharmacol Ther.*, 2014, 40, 1023-1034.
3. Thursby, E.; Juge, N. *Biochem. J.*, **2017**, 474, 1823-1836.
4. Salem, I.; Ramser, A.; Isham, N.; Ghannoumi, M. A. *Front. Microbiol*. **2018**, 9, 1459.
5. Cani, P. D. *Gut*, **2018**, 67, 1716-1725
6. Seventure Partners, Press release, Future Prospects of Microbiome-Related Diseases and Microbiome-Directed Therapies, 2018.
7. Juge, N. *Trends Microbiol*., **2012**, 20, 30-39.
8. Thursby, E.; Juge, N. *Biochem. J*., **2017**, 474, 1823-1826
9. Lynch, C. J. *et al*. *Am. J. Physiol. Endocrinol. Metab*. **2018**, 315, 1087-1097.
10. Jennewein press release EU approval for 2'-fucosyllactose: http://jennewein-biotech.de/en/euapproval-for-2-fucosyllactose-2/