UNIVERSITÀ DEGLI STUDI DI MILANO-BICOCCA

DOTTORATO DI RICERCA IN Tecnologie Convergenti per i Sistemi Biomolecolari – XL CICLO

Research Topic ID: XL – 1.13

Proponent: Prof. Simone Domenico Guglielmetti

Project Title: The role of food- and host-associated microorganisms in gut permeability: implications for the pathogenesis and treatment of non-communicable diseases

Scientific background and 'open issues'

To counteract microbial presence and proliferation in food, preservation and sanitation methods have been implemented together with constantly improved hygiene and farming practices. However, the same strategies adopted to counteract harmful microbes inevitably also eliminate numerous harmless microbial populations associated with food. The consequent loss of microbe intake through the diet is particularly relevant in the context of the so-called Microbiome Depletion Hypothesis, according to which reduced exposure to microorganisms (MOs) in the environment and through food could have caused an increase in the incidence of non-communicable diseases (NCDs) [1]. Reportedly, the intensive use of antibiotics, extensive sanitation, and widespread consumption of processed foods that occurred with industrialization have impacted the human gastrointestinal microbiota (GIM), causing a reduction in microbial diversity, alteration of the bacterial community structure, and consequently, impairment of the ecosystem services that support the mutualistic relationship with the host [2]. NCDs are associated with shifts in the inflammatory response toward chronic low-grade systemic inflammation (CLSI) [3]. CLSI is increased by enhanced intestinal permeability, which is also frequently associated with NCDs [4]. Interestingly, the GIM is widely recognized as a pivotal player in immune homeostasis [5]. It has also been demonstrated that GIM may indirectly act on intestinal permeability by modulating inflammation and directly affecting tight junctions and mucus production [6]. The precise mechanisms linking microorganisms to mucosal barrier integrity are largely unknown; nonetheless, their elucidation may significantly contribute to the understanding of the physiopathology of NCDs, permitting the identification of novel therapeutic targets or intervention strategies based on the modulation of human-associated microbiomes and/or based on the administration of "biotics" (probiotics, paraprobiotics, postbiotics, and live bioterapeutics).

Objectives

The objectives of the project can be articulated in three directions:

1. Understanding the mechanisms regulating the ability to modulate intestinal permeability by known bacteria, already studied by the research group of the proponent, namely *Collinsella aerofaciens* and *Bifidobacterium bifidum* (and related taxa).

2. Identifying new bacterial taxa, of food or human origin, capable of both positively and negatively modulating epithelial and endothelial permeability.
3. Preliminary development of strategies based on the use of beneficial microorganisms for subsequent development of dietary supplements, medical devices, and/or live biotherapeutics for the prevention, therapy, and/or management of specific conditions, with particular reference to metabolic associated fatty liver disease (MAFLD), irritable bowel syndrome (IBS), and atherosclerotic processes.

Methodologies

To achieve the above-described objectives, omics approaches of metataxonomics and shotgun metagenomics will be utilized to identify the most interesting microorganisms. Modern approaches for the cultivation of strict anaerobic and fastidious microorganisms (based on the use of an anaerobic chamber, selected micronutrients and growth cofactors, and appropriate gas mixtures) will be adopted for the isolation of microorganisms of interest. Comparative genomics and metabolic profiling will be used to characterize the microbial isolates. The use of cell lines, gene expression analysis, transcriptomics, and metabolomics will be employed to understand the molecular mechanisms linking the microorganisms of interest to the modulation of gut permeability. As a final part of the project, the use of animal models can be implemented through collaboration with the University of Toronto.

Project's Sustainability & Mobility

- The proposing laboratory has documented experience in applied microbiology related to food microorganisms and human microbiomes, microbial ecology, and the use of in vitro models to study host-microorganism interactions (see references below and here: https://orcid.org/0000-0002-8673-8190).

- References pertinent to the topic of the project (*, corresponding author):
  - Gargari G, Mantegazza G, Cremon C, Taverniti V, Valenza A, Barbaro MR, Marasco G, Duncan R, Fiore W, Ferrari R, De Vitis V, Barbara G, *GUGLIELMETTI S. *Collinsella aerofaciens* as a predictive marker of response to probiotic treatment in non-constipated irritable bowel syndrome. Gut Microbes. 2024;16(1):2298246.
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  - Taverniti V, Cesari V, Gargari G, Rossi U, Biddau C, Lecchi C, Fiore W, Arioli S, Toschi I, *GUGLIELMETTI S. Probiotics Modulate Mouse Gut Microbiota and Influence Intestinal Immune and Serotonergic Gene Expression in a Site-Specific Fashion. Front Microbiol. 2021;12:706135.
  - Peron G, Gargari G, Meroño T, Miñarro A, Lozano EV, Escuder PC, González-Domínguez R, Hidalgo-Liberona N, Del Bo' C, Bernardi S, Kroon PA, Carrieri B, Cherubini A, Riso P, *GUGLIELMETTI S, *Andrés-Lacueva C. Crosstalk among intestinal barrier, gut microbiota and serum metabolome after a polyphenol-rich diet in older subjects with "leaky gut": The MaPLE trial. Clin Nutr. 2021;40(10):5288-5297.
  - Dalla Via A, Gargari G, Taverniti V, Rondini G, Velardi I, Gambaro V, Visconti GL, De Vitis V, Gardana C, Ragg E, Pinto A, Riso P, *GUGLIELMETTI S. Urinary TMAO Levels Are Associated with the

Taxonomic Composition of the Gut Microbiota and with the Choline TMA-Lyase Gene *cutC* Harbored by Enterobacteriaceae. Nutrients. 2019;12(1):62.

- A 4- to 6-month experience is planned in the laboratory of Prof. Elena Comelli at the Department of Nutritional Sciences, University of Toronto (Canada), with whom the proposing group has long collaborated. Specifically, Prof. Comelli's research group has extensive expertise in the context of intestinal homeostasis and the role of intestinal microRNAs through the use of animal models. A shorter experience at Prof. Hanne Frokiaer's laboratory at the University of Copenhagen is also possible for specific activities in the field of immunology.

References

[1] https://doi.org/10.1073/pnas.1700688114
[2] https://doi.org/10.1126/science.aaw9255
[3] https://doi.org/10.1016/j.cell.2015.02.010
[4] https://doi.org/10.3389/fendo.2021.616506
[5] https://doi.org/10.4161/gmic.19320
[6] https://doi.org/10.3920/BM2014.0041