FoodBioSystems DTP - PhD Project Advertisement Text

Project Title: FOODBIOSYSTEMS - Gut bacteria and their DNA as elicitors of host beneficial responses

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Research Group: FOODBIOSYSTEMS BBSRC DTP
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Project Description: The incidence of gut inflammatory disorders such as such as the post-infectious irritable bowel syndrome (PI-IBS) is increasing globally, with devastating consequences in animal production and public health. These disorders are caused by gut microbiota alteration and a dysfunctional mucosal barrier that allows the penetration of large amounts of microbes into inner parts of the gut, where immune cells such as macrophages gather to cope with this microbial invasion (**Fig. 1**). The macrophage response results in the production of pro-inflammatory cytokines such as TNF-□, a molecule that, before the onset of PI-IBS, helps with infection clearance; but once the syndrome has developed, is completely adverse as it causes a perpetual cycle of inflammation due to the continuous recruitment of macrophages. In this respect, the use of probiotics that induce other cytokines such as type-I interferons (IFN-I) has been proposed as an alternative therapy against PI-IBS. On the one hand, IFN-I inhibits the production of TNF-□ in macrophages, thereby limiting inflammation. On the other hand, probiotics help reset the gut microbiota and restore appropriate immune responses. However, the oral administration of probiotics able to activate IFN-I has also resulted in the production of TNF-□ due to the fact that, as any other bacteria, probiotics are extracellularly recognised by macrophages (**Fig. 2A-B**).

Here we present the exciting discovery that a particular probiotic bacterium (*Lactobacillus plantarum*) evades the extracellular response of macrophages. By contrast, we have observed that macrophages sense the intracellular presence of *L. plantarum*, resulting in IFN-I production at the expense of TNF-□□(**Fig. 2C**). We also know that this *L. plantarum* possesses proteins on its surface that are important for macrophage adhesion, which facilitates internalization for the subsequent activation of IFN-I.

Based on our preliminary observations, this study will address the following questions:

1) Are the adhesion proteins what make *L. plantarum* so appealing for macrophage internalization?
2) Are intracellular pathways the main drivers of IFN-I activation following the internalization of *L. plantarum*?
3) Would *L. plantarum* trigger a protective immune response against PI-IBS in the long term?

The data resulting from the first two questions will help us understand the mechanisms that *L. plantarum* utilizes to activate IFN-I production. The identified mechanisms could be further exploited to trigger IFN-I-based protective responses as a tool to combat PI-IBS. The results generated from question 3 will be essential to expand the potential

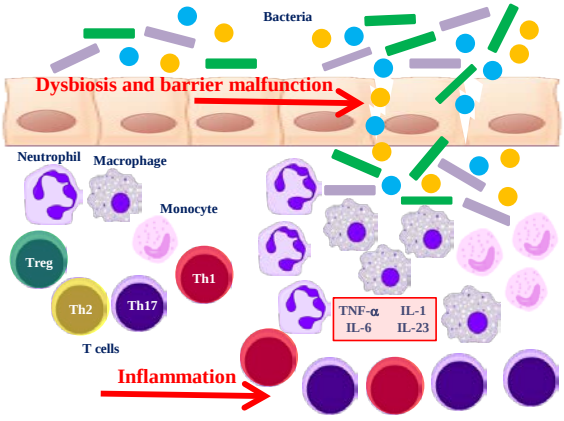

Fig. 1. Perpetual inflammation in the gut. The combination of microbial dysbiosis and malfunction of the gut mucosal epithelial barrier results in a direct interaction between large amounts of microbes and macrophages, leading to the massive production of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6 and IL-23. These cytokines promote the differentiation of $CD4^+$ T cells into pro-inflammatory Th1/Th17 effector T cells and the recruitment of more lymphocytes, monocyte-derived macrophages and neutrophils. This high level of inflammation is continuously maintained, causing cell accumulation in the lamina propria.

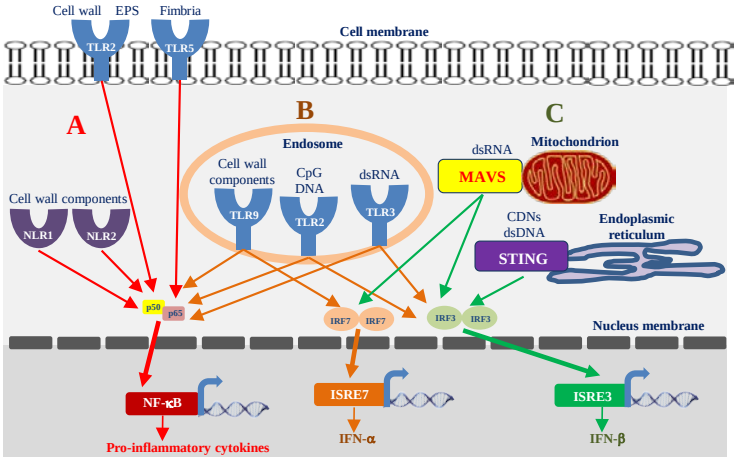

Fig. 2. Protective innate immune pathways activated by LAB. (A) NF-κB activation upon recognition of MAMPs such as exopolysaccharides (EPS), fimbria and cell wall components via TLRs and NLRs, resulting in the production of pro-inflammatory cytokines. **(B)** Activation of NF-κB and the Interferon-Sensitive Response Element (ISRE) via IRF following the recognition of cell wall components, CpG DNA and dsRNA via endosomal TLRs. This dual activation results in the production of pro-inflammatory cytokines and the IFN-I cytokines IFN-α and IFN-β. **(C)** ISRE activation upon recognition of nucleic acid (dsRNA/dsDNA) and cyclic dinucleotides (CDNs) by the cytoplasmic sensors MAVS (mitochondrial-antiviral signaling) and STING (Stimulator of Interferon Genes), leading to IFN-β production.

use of probiotics as a therapy against PI-IBS in animals and humans.

Funding Notes: This project is part of the FoodBioSystems BBSRC Doctoral Training Partnership (DTP), it will be funded subject to a competition to identify the strongest applicants. Due to restrictions on the funding, this studentship is only open to UK students and EU students who have lived in the UK for the past three years.

The FoodBioSystems DTP is a collaboration between the University of Reading, Cranfield University, Queen's University Belfast, Aberystwyth University, Surrey University and Brunel University London. Our vision is to develop the next generation of highly skilled UK Agri-Food bioscientists with expertise spanning the entire food value chain. We have over 60 Associate and Affiliate partners. To find out more about us and the training programme we offer all our postgraduate researchers please visit https://research.reading.ac.uk/foodbiosystems/.

Training opportunities: The selected PhD student will benefit from training in multidisciplinary skills, specialized for scientific research and transferable to food industry. This student will receive scientific and technical training in the area of molecular & cellular biology, advanced microscopy, high-throughput technologies and bioinformatics; as well as aiming to gain other transferable skills (e.g. project and personal management, scientific writing, supervision, ethics) and manage/supervise career progression, to ensure optimal employability. The PhD student will also have the opportunity to interact with post-doctoral researchers, MSc students and undergraduates in our laboratories, with access to state-of-the-art facilities including multi-mode fluorescent detection plate readers, microscopy, flow-cytometry and RNA/protein stations to carry out transcriptional analysis and immunoblotting.

Student profile: This project is suitable for students with a degree in biological sciences, microbiology, food science or a closely related science. The PhD student is expected to contribute intellectually to the development of the project to maximize the results obtained. This person will develop sound laboratory and scientific skill to become a well-trained molecular microbiologist with sound expertise in probiotics and gut immunology. Previous education in microbiology and innate immunology is desirable; and ideally having some experience in working with bacteria and/or immune cells.

References:

Gutierrez-Merino, J., B. Isla, T. Combes, F.O. Martinez-Estrada, C. Maluquer de Motes. 2020. Beneficial bacteria activate type-I interferon production via the cytosolic sensors STING and MAVS. Gut Microbes.