GUT MICROBIOTA COMPOSITION IMPACTS HOST GENE EXPRESSION BY CHANGING CHROMATIN ACCESSIBILITY

The gut microbiota is highly complex and host specific, displaying a strong variation across individuals. It has been associated with several diseases, although the mechanism of action is not well understood. In this context, it is crucial to understand the role of the microbiome in host physiology, in order to further develop targeted therapies on gut microbiome (1).

The paper here highlighted is focused on the effects of the gut microbiome on human gene regulation, specifically the authors aimed to understand the mechanism by which variation in microbiome composition induces differences in gene expression in the host cells, by using an *in vitro* approach based on human epithelial cells inoculated with live gut microbiota extracted from human individuals (2).

The authors started by analyzing changes in gene expression and microbial composition following 1, 2 and 4 hours of exposure (Figure 1A). They observed the overall changes in each microbiome treatment occurred at 2 hours, compared to untreated colonocytes (Figure 1B). Furthermore, meta-analysis was used to identify genes that consistently changed across the time-points, showing they are enriched for genes involved in protein translation, supporting a biological function for consistent changes in gene expression that may relate to the host cell interaction with the microbiota. The authors also accessed the relation between microbiota abundance and differentiated gene expression. Several host genes exhibited changes in expression associated with the abundance of 46 taxa, and a considerable number responded to particular microbes. This suggests that it is not the general exposure to the entire gut microbiota that leads to changes in gene expression, but rather the exposure to specific microorganisms. To validate this hypothesis, the authors explored the specific effect of *Collinsella aerofaciens* in colonocytes. Increasing amounts of *Collinsella* were added to human cells co-cultured with microbiota without *Collinsella*. This experiment lead to changes in gene expression in a fashion dependent of *Collinsella* amount, indicating that besides the presence or absence of a specific microbe, its relative abundance also plays a role in the physiological effect on the host.

The next step was to elucidate the mechanism responsible for the altered gene expression by exploring the effect of the microbiota in the chromatin accessibility of the host genome. Using ATAC-seq, 234 regions in the treated samples exhibited different chromatin accessibility when compared to the controls. Additionally, and as a follow up of the *C. aerofaciens* experiment, it was observed that the genes which expression was related with the abundance of this microbe had different chromatin availability in their neighbouring, when compared to controls.

In conclusion, these results revealed that an inter-individual variation in microbiome composition correlates with differences in gene expression response. In particular, the abundance of a specific microbe can lead to changes in the expression of host genes involved in a large variety of phenotypes, through a mechanism of modulation of chromatin accessibility. This could be instructive for the design of therapies, since an introduction of a single microbe could manipulate the composition of the gut microbiome inducing a cellular regulatory response in a predictable way.

The major drawback we identified in the paper is that we cannot directly correlate the level of transcripts of the differentially expressed genes with the level of product actually formed. To truly access what is the impact of the altered gene expression in the epithelial cells, we would need to investigate how this alteration translates in real physiological effects to the cell (e.g protein overexpression that leads to dysregulation of a certain cell function or to an altered crucial feature). Only with that knowledge we can walk towards targeted therapies for microbiome dysbiosis-associated diseases.

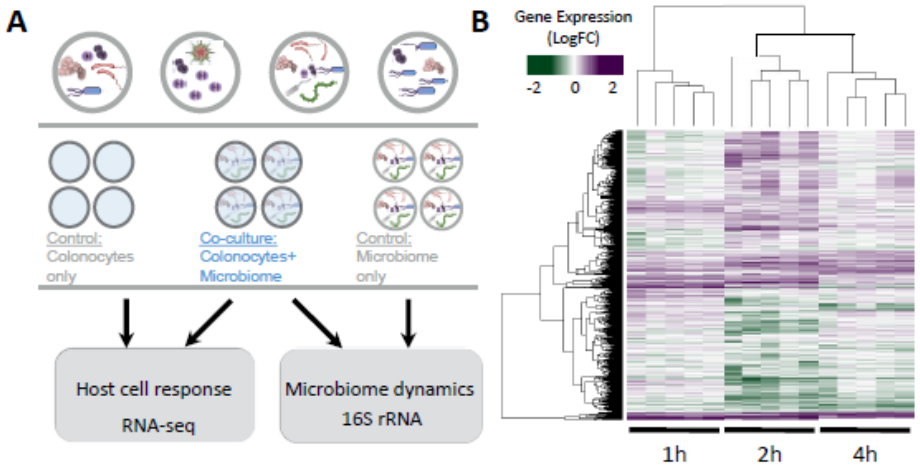

Figure 1: Gene expression changes in colonocytes treated with microbiota from five unrelated individuals. **A)** Study design. Human colonocytes were inoculated separately with five microbiota samples from unrelated individuals. **B)** Heatmap of gene expression changes induced at each time point by the individual microbiota samples. Purple denotes an increase in gene expression (green shows a reduction) compared to the gene expression in the control (colonocytes cultured alone). Only genes that are differentially expressed in at least one sample are shown.

References:

1. Huttenhower, C., et al, (2012). Structure, function and diversity of the healthy human microbiome. Nature, 486(7402), 207-214.
2. Richards, A. L., et al, (2016). Genetic and transcriptional analysis of human host response to healthy gut microbiota. *mSystems*, 1(4).