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Gut Microbiota regulation of Host cell response as revealed using functional metagenomics

Herve M. Blottiere
INRA, France

Abstract

The commensal bacteria have been revealed to play key functions on Human health, however little is known on the underlying mechanisms.Each individual hosts about one hundred trillion bacteria belonging mainly to three phyla (Firmicutes, Bacteroidetes and Actinobacteria), most of them being not yet cultivable.To decipher the interactions between commensal bacteria and their hostcells, an innovative high throughput cell-based functional metagenomic approach was established (Lakhdari et al., PLoS one, 2010).Human intestinal epithelial cells (IECs) bearing the luciferase reporter gene under the control of promoter of key genes or binding elements of key signaling pathways were used to screen metagenomic libraries bearing large DNA fragments derived from human fecal microbiota, as well as cultured commensal strains. We found that short chain fatty acids produced by gut bacteria were powerful regulators of gene expression in host cells, modulating NF-kB, AP1 and PPARg pathways. It thereby impacts on *TSLP* and *ANGPTL4* transcription. Moreover, using our functional metagenomic method, we identified several bacterial genes involved in the cross-talk with host cells. As an example, we identified 2 loci derived from a Bacteroides-related strain involved in NF-κBactivation.Similarly, we characterized a metagenomic insertderived from a Firmicutes encoding for an ABC transporter, allowing the secretion of a small compound that activates NF-κB and AP1 pathways. In a co-culture system, it indirectly activated dendritic cells through IECs stimulation and further modulated T cell activity.Finally, this metagenomic fragment displayed a protective effect in a DSS colitis model in mice.

Biography

Herve Blottiere has obtained a PhD in Tumor Immunology from the University of Nantes (France) in 1989. He is presently Director of Research at INRA, the French National Research Institute for Agricultural and Food Research. He is the Coordinator of the French Research Agency-funded project, FunMetaGen and co-coordinator of the EU-funded Marie-Curie project, CROSS-TALK. He participates in other EU-projects including MetaHIT and MetaCardis. He authored 72 peer-reviewed publications and 18 reviews.He developed a Functional Metagenomics approach to study host-microbiota cross-talk and has set up a robotic platform to allow high throughput screenings, which is part of the MetaGenoPolis initiative.