The Expobiome Map

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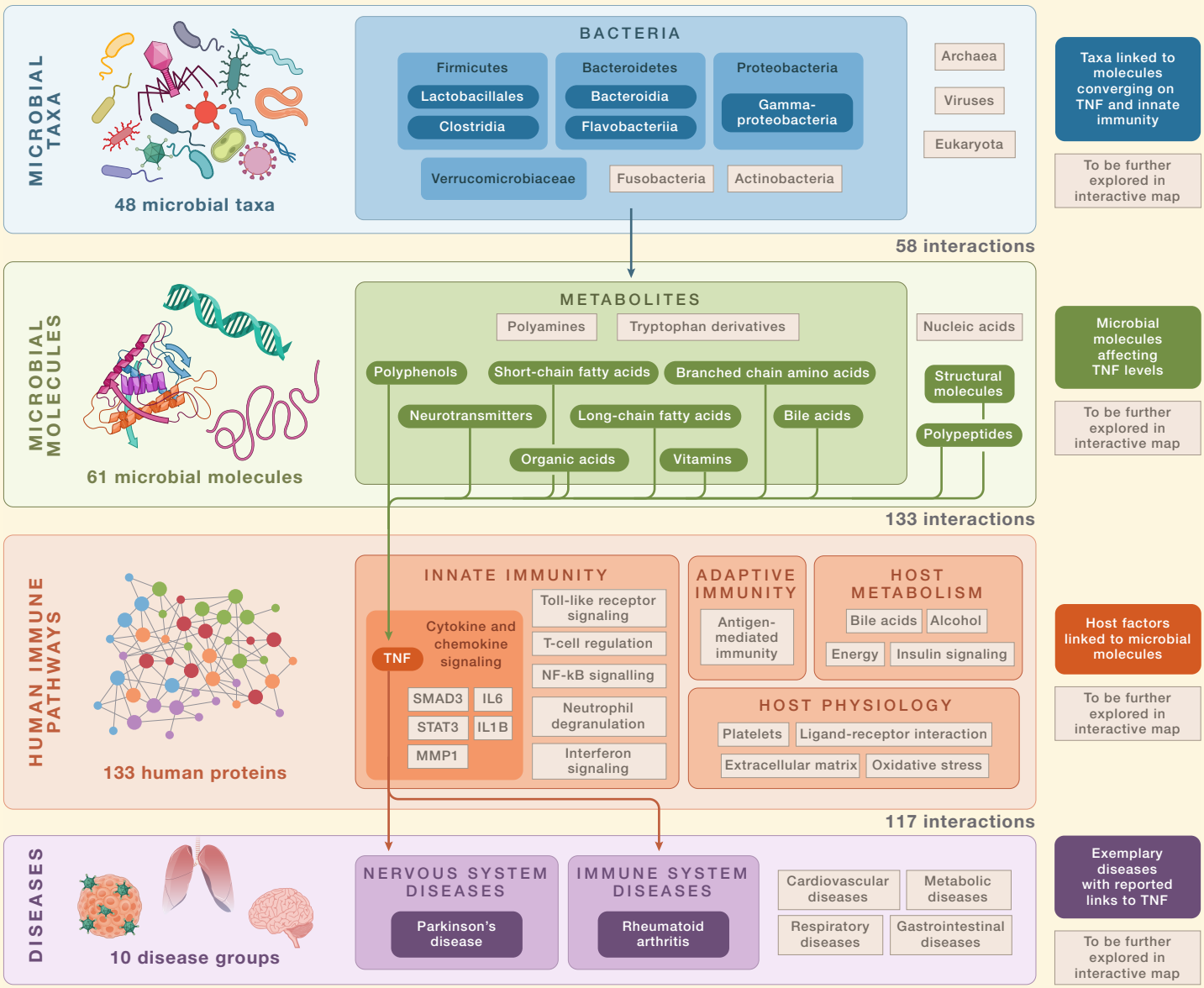
Connecting microbiome-derived molecules to chronic diseases involving inflammation



The full Expobiome Map, which is depicted in graphical form in this Snapshot with a few representative pathways linked to two exemplary diseases, can be navigated online (**https://expobiome.lcsb.uni.lu**).

Table 1. From Expobiome Map to hypothesis: Microbial taxa and microbial molecules linked to elevated TNF expression in the context of two exemplary diseases, namely Parkinson's disease and rheumatoid arthritis

	MICROBIAL TAXA	MICROBIAL MOLECULES
Parkinson's disease	↑ *Akkermansia* spp. ↑ *Bifidobacterium* spp. ↑ *Lactobacillus* spp. ↑ *Methanobrevibacter* spp. ↓ *Roseburia* spp. ↓ ***Faecalibacterium* spp.**	↑ Acetylcholine (neurotransmitters) ↑ Serotonin (neurotransmitters) ↑ Plantaricin A (polypeptides) ↑ Cyanidin (polyphenols) ↓ **Butyric acid (short-chain fatty acids)** ↑ **Deoxycholic acid (bile acids)**
Rheumatoid arthritis	↓ *Bacteroides* spp. ↓ *Haemophilus* spp. ↑ *Prevotella copri* ↑ *Collinsella* spp.	

See online version for legends, references, and declaration of interests

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The human gut microbiome is intricately connected to health and disease. Microbiome-derived molecules are implicated in many chronic diseases involving inflammation. Herein, we summarize the diverse complex of such immunogenic molecules, including nucleic acids, (poly)peptides, structural molecules, and metabolites. The interactions between this "expobiome" and human immune pathways are specifically illustrated in the context of chronic diseases.

The expobiome and its composition

The human microbiome, i.e., the ecological community of commensal and pathogenic microorganisms that live in and on our body, has emerged as a likely driver of various diseases (Duvallet et al., 2017). This is due to a diverse range of molecules that the human microbiome produces and exposes us to, herein referred to as the "expobiome". The impact of the expobiome is the most prominent in the gut, where the microbiome confers essential functionalities including digestion of dietary components, synthesis of vitamins, stimulation and regulation of the immune system, outcompetition of pathogens, removal of toxins and carcinogens, and support of intestinal function (Flint et al., 2012). The gut microbiome further interacts with human physiology via the circulatory, immune, endocrine, and nervous systems (Hill and Round, 2021).

Bacteria are the most comprehensively characterized members of the gut microbial community contributing to the expobiome. Important examples include short-chain fatty acids (SCFAs), which are primarily produced from the bacterial fermentation of dietary fibre, and structural molecules such as lipopolysaccharides (LPS), peptidoglycans (PGN), and polysaccharide A (Donia and Fischbach, 2015; Flint et al., 2012; Próchnicki and Latz, 2017; Thaiss et al., 2016). Molecules produced by gut-resident archaeal species can also be immunogenic, but the exact molecular patterns recognized by human receptors remain largely unknown (Bang et al., 2014). For microeukaryotes, there exist specific well-known examples of immunogenic molecules, such as fungal cell wall components (Iliev and Leonardi, 2017). Nucleic acids and (poly)peptides, which may originate from any domain (archaea, bacteria, and microeukaryotes), as well as viruses, can also elicit an immune response (Donia and Fischbach, 2015; Neil and Cadwell, 2018; Próchnicki and Latz, 2017). Importantly, besides the molecules of microbial origin, the expobiome also includes exogenous molecules as well as host-derived metabolites modified by the microbiome, for example drugs, environmental toxins, and bile acids (Flint et al., 2012).

From microbial molecules to immune pathways to disease

The expobiome exerts its effects on human physiology through many pathways. Beneficial SCFAs, for example, can influence the function of regulatory T cells (Donia and Fischbach, 2015) as well as gut barrier integrity (Thaiss et al., 2016). They are also used as an energy source by host epithelial cells (Flint et al., 2012; Thaiss et al., 2016). Structural molecules, such as LPS or PGN, are typically proinflammatory and are detected by innate immune receptors such as Toll-like receptors (TLRs) or nucleotide-binding oligomerization domain (NOD) receptors (Donia and Fischbach, 2015; Thaiss et al., 2016).

Perturbations of the healthy gut microbial community and related changes in the abundances of microbial molecules represent hallmarks of dysbiosis. Such perturbations have been reported in chronic diseases involving every organ system of the human body (Hill and Round, 2021), including autoimmune and inflammatory diseases (e.g. rheumatoid arthritis) as well as neurological disorders (e.g. Parkinson's disease). Connections between dysbiosis and disease are not always obvious even for conditions directly involving the gastrointestinal tract, such as inflammatory bowel disease (IBD), a condition for which no specific causal microorganisms or molecules have been identified so far. However, the depletion of beneficial microbes and linked microbial products, such as SCFAs (Duvallet et al., 2017) as well as immune dysfunction related to pathogen-sensing (Thaiss et al., 2016) have been implicated. In this context, an important consideration when seeking to establish mechanistic links is that diseases with diverse pathophysiology may reflect similar shifts in the microbiome (Duvallet et al., 2017). Since many of these conditions are associated with local or systemic inflammation, the immunomodulatory effects of microbiome-derived molecules represent a general mechanism which deserves to be explored from a systems-wide perspective and not only in a single-disease context.

Connecting the dots

To illustrate the stimulation of human immune pathways by microbiome-derived biomolecules and the shared signals across diseases, we have combined information from DisGeNET (https://www.disgenet.org), Gene Ontology (http://geneontology.org), the Human Metabolome Database (https://hmdb.ca), and the Comparative Toxicogenomic Database (http://ctdbase.org), as well as manually sourced interactions from the literature, and visualized it using the MINERVA platform (Gawron et al., 2016). The resulting Expobiome Map, which is shown in this SnapShot with a few representative pathways linked to two example diseases, can be navigated online (https://expobiome.lcsb.uni.lu). It provides an interactive tool for exploring and integrating our growing knowledge about the interactions of gut microbes and host immune pathways. It serves as a basis to contextualize and expand our current understanding of the role of the gut microbiome in human health and disease.

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