The gut microbiome organ

From taxonomic association toward function, causal inference and precision microbiome medicine

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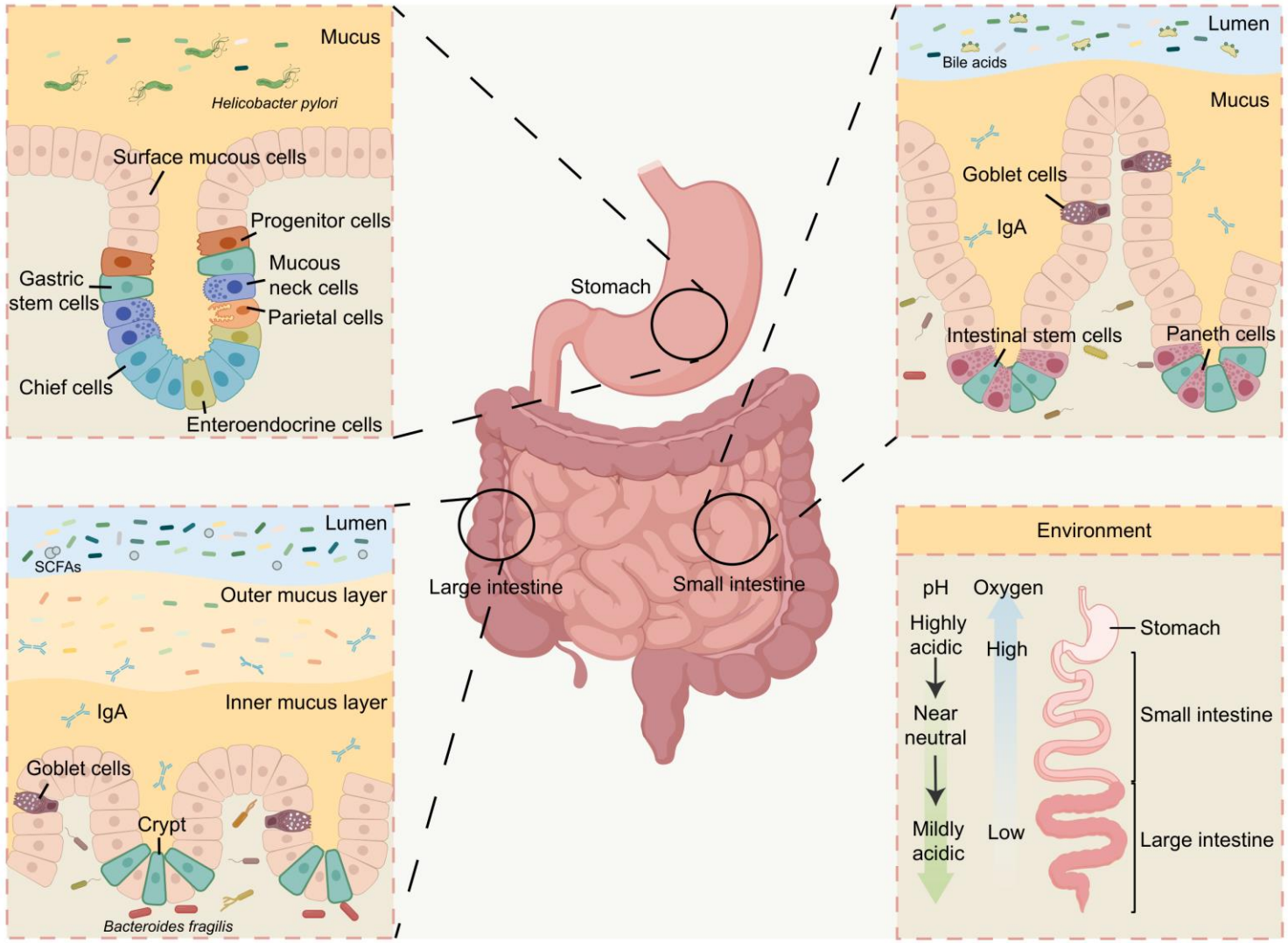
Background | From taxonomy to an organ-like framework

- Gut microbiome research is moving beyond taxonomy-centered description toward a functionally integrated systems view.
- The “gut microbiome organ” provides an integrative conceptual framework for understanding the microbiome as a distributed, organ-like functional system.
- This system exhibits spatially structured organization, broad metabolic capacity, and continuous bidirectional communication with the host.
- Through bioactive metabolites with endocrine-like, immunomodulatory, and neuromodulatory activities, it contributes to systemic homeostasis and disease susceptibility.

Highlights

- The gut microbiome can be conceptualized as an organ-like functional system that integrates spatial organization, metabolic capacity, and systemic regulatory potential.
- Microbial metabolites can act as endocrine-like mediators linking metabolic, immune, and neuroendocrine pathways.
- Multi-omics and spatial approaches are revealing functional microbiome modules and host–microbe signaling networks relevant to health and disease.
- Targeting microbiome function, rather than focusing solely on individual taxa, provides a rational framework for mechanistic investigation, causal inference, and precision therapeutics.

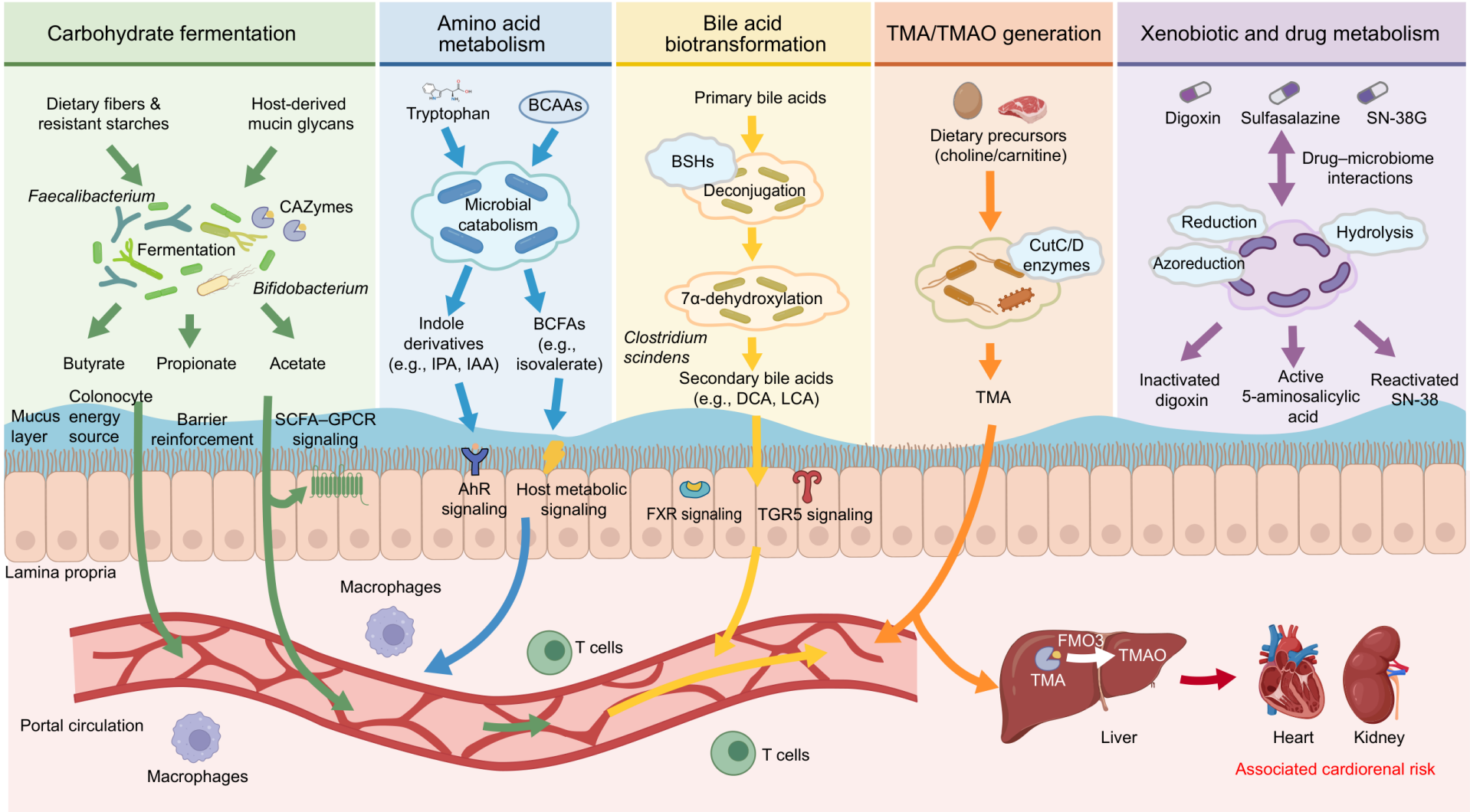
Figure 1 | A structured and dynamic organ



The gut microbiome is spatially organized along the longitudinal and transverse axes of the gut.

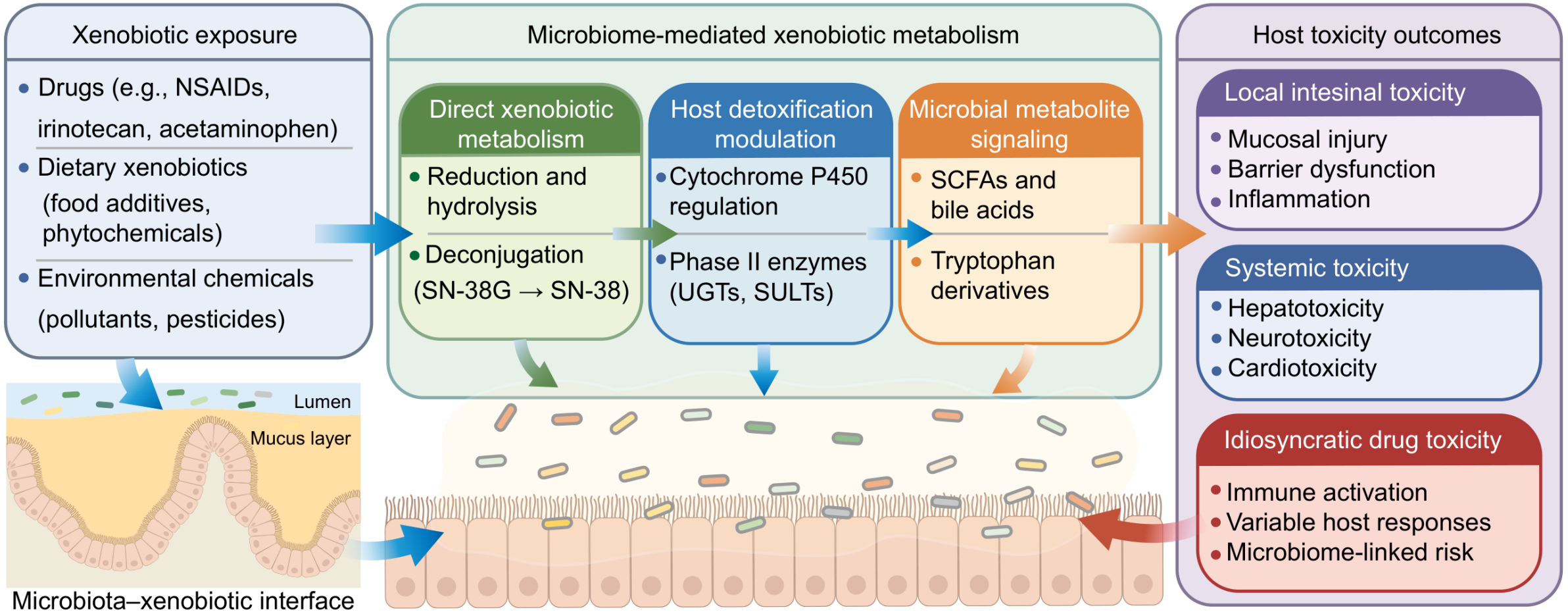
Mucus, epithelial niches, epithelial antimicrobial peptides, and IgA shape microbial colonization and host–microbe interactions, while microbial communities assemble in early life and continue to remodel across the lifespan.

Figure 2 | Functional metabolic modules



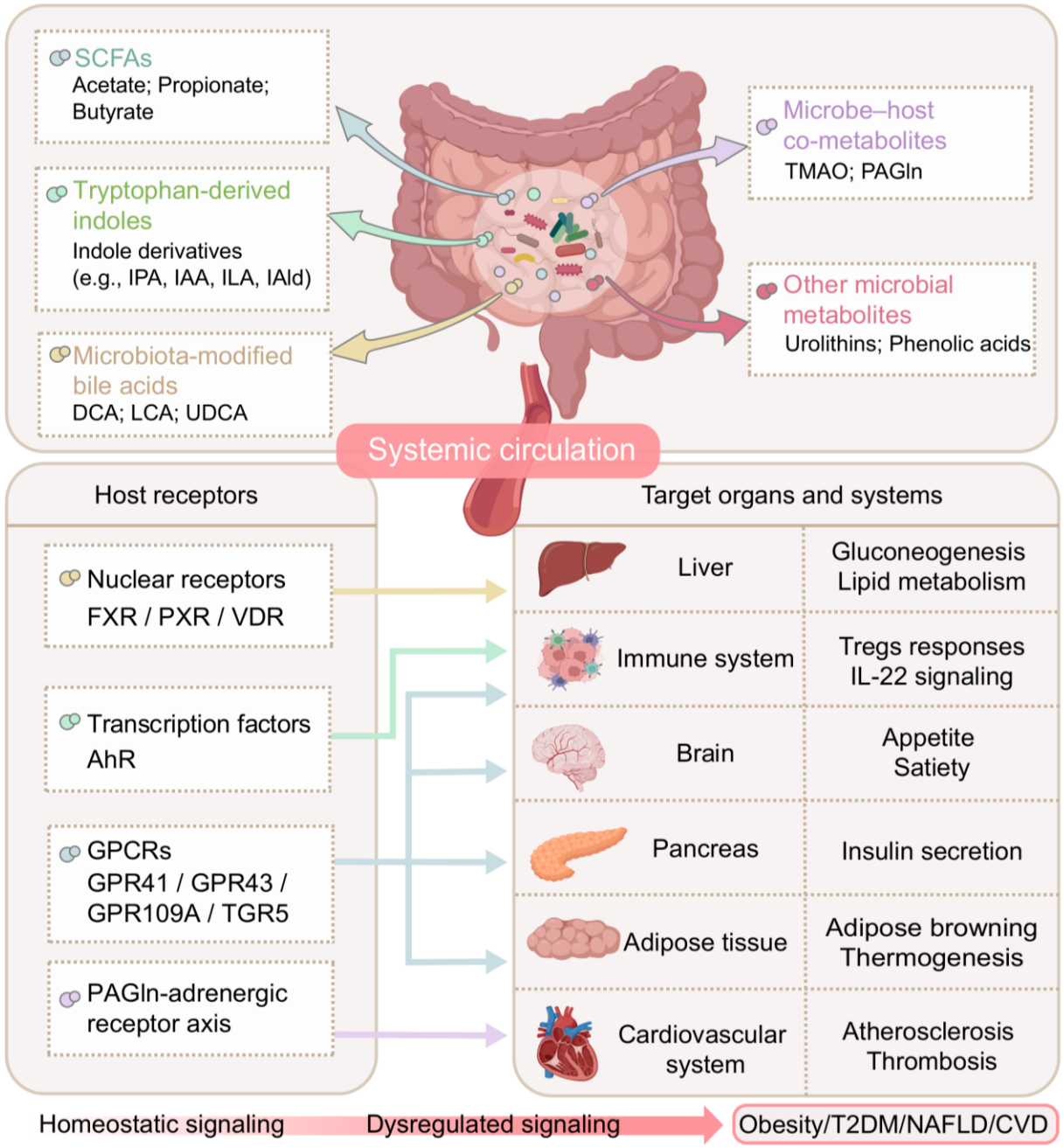
Representative metabolic modules, including carbohydrate fermentation, amino acid metabolism, bile acid biotransformation, the choline/carnitine–TMA–TMAO axis, and xenobiotic metabolism, convert dietary and host-derived substrates into bioactive metabolites that engage the barrier, immune cells, and host receptors.

Figure 3 | Xenobiotic & drug metabolism



Microbial enzymes mediate the activation, inactivation, detoxification, or toxification of drugs and xenobiotics, and modulate host metabolic enzymes, transporters, and immune responses, contributing to inter-individual variability in drug efficacy, toxicity, and idiosyncratic adverse reactions.

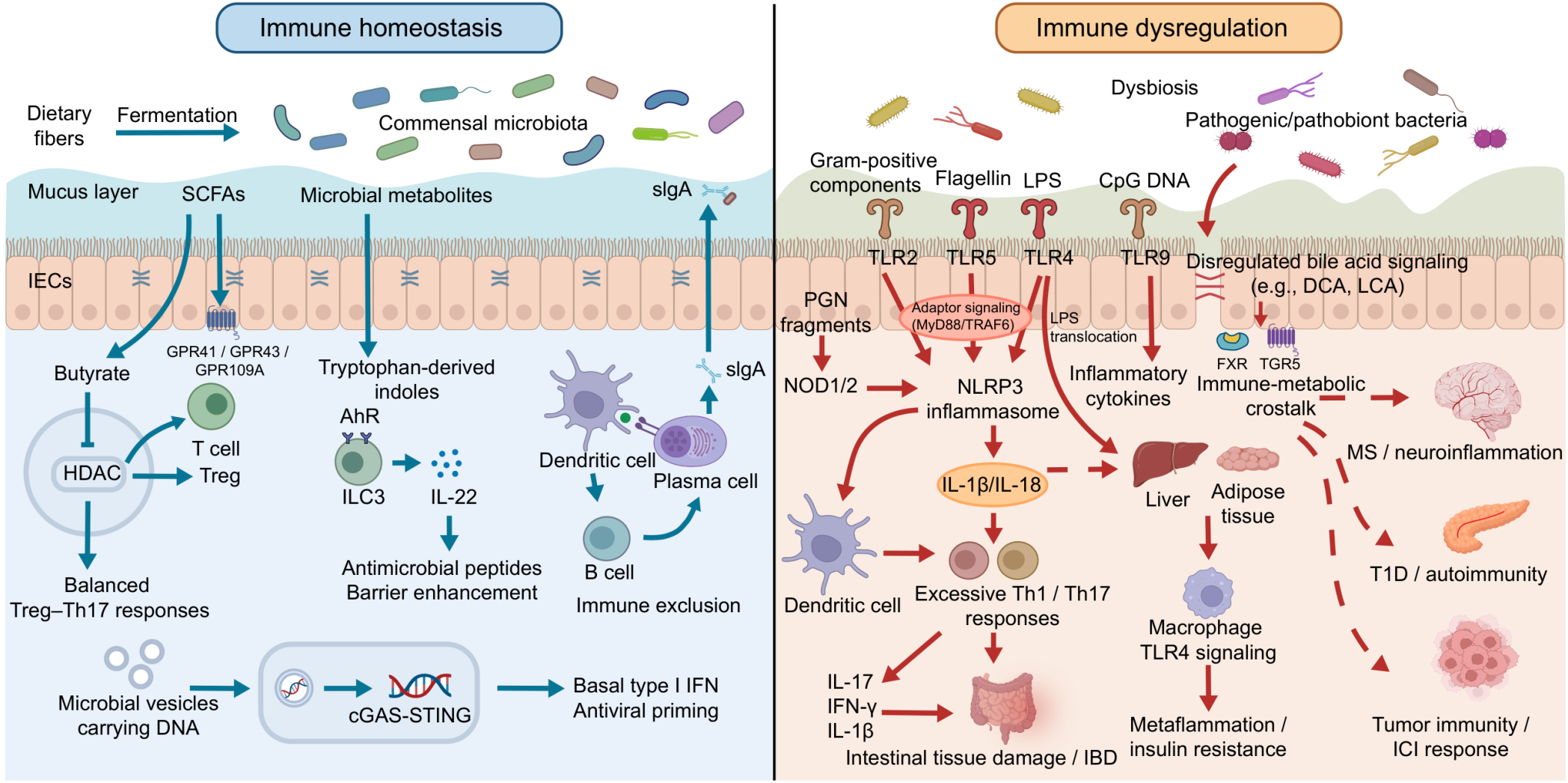
Figure 4 | A metabolic-endocrine-like organ



Microbial metabolites act as endocrine-like signals through GPCRs, nuclear receptors, and AhR, regulating energy balance, glucose and lipid metabolism, appetite, and cardiovascular function

Dysregulation is associated with obesity, type 2 diabetes, NAFLD, and cardiovascular disease.

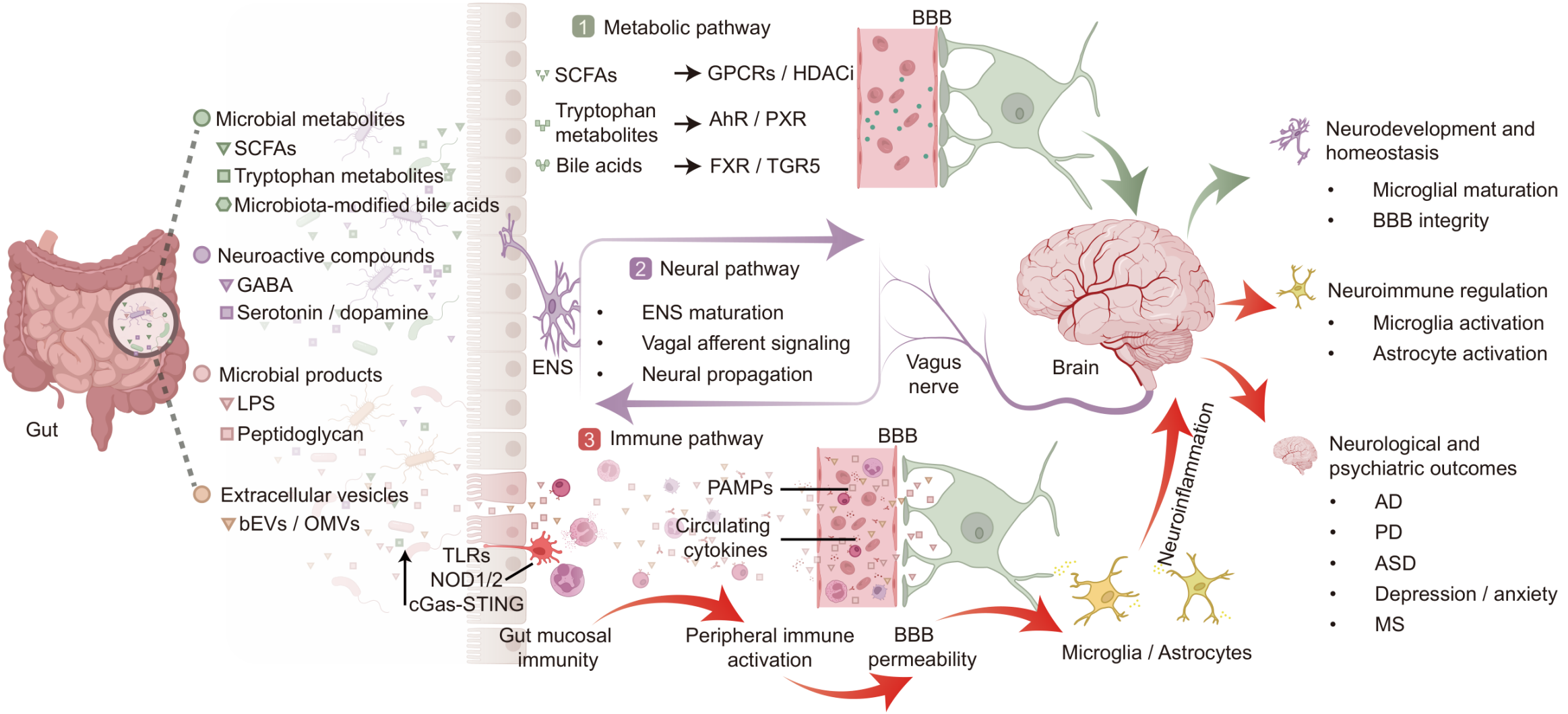
Figure 5 | A multi-layer regulator of immunity



Microbial metabolites, extracellular vesicles, and MAMPs/PAMPs signal through TLRs, NLRs, and cytosolic sensors to regulate immune-cell differentiation, cytokine production, and barrier integrity.

Dysbiosis can promote inflammation, autoimmunity, metabolic dysfunction, and cancer-associated immune dysregulation.

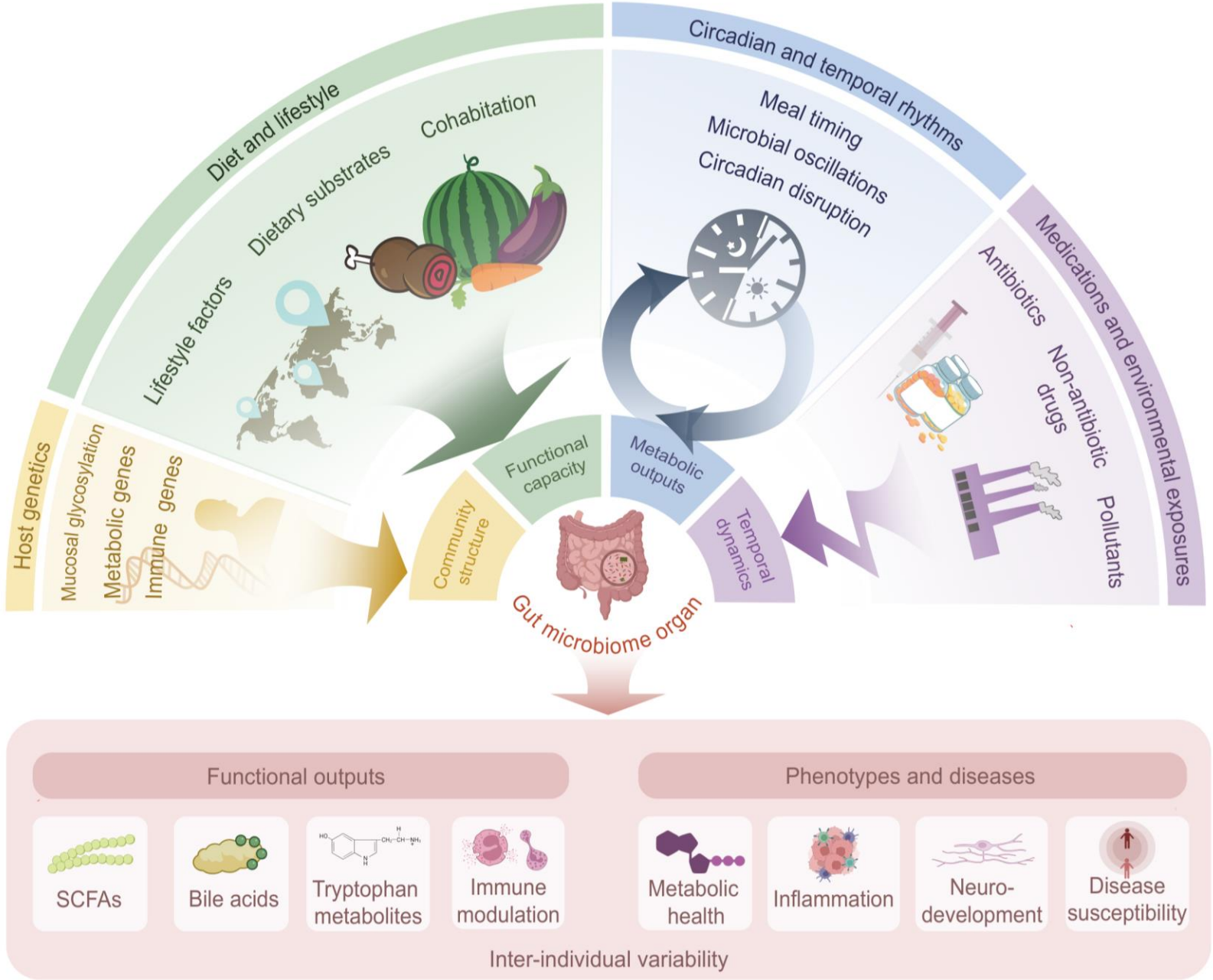
Figure 6 | The microbiome organ–brain axis



Neural, immune, and metabolic routes mediate bidirectional gut–brain communication, shaping blood–brain barrier integrity, neuroinflammation, and neuroimmune function.

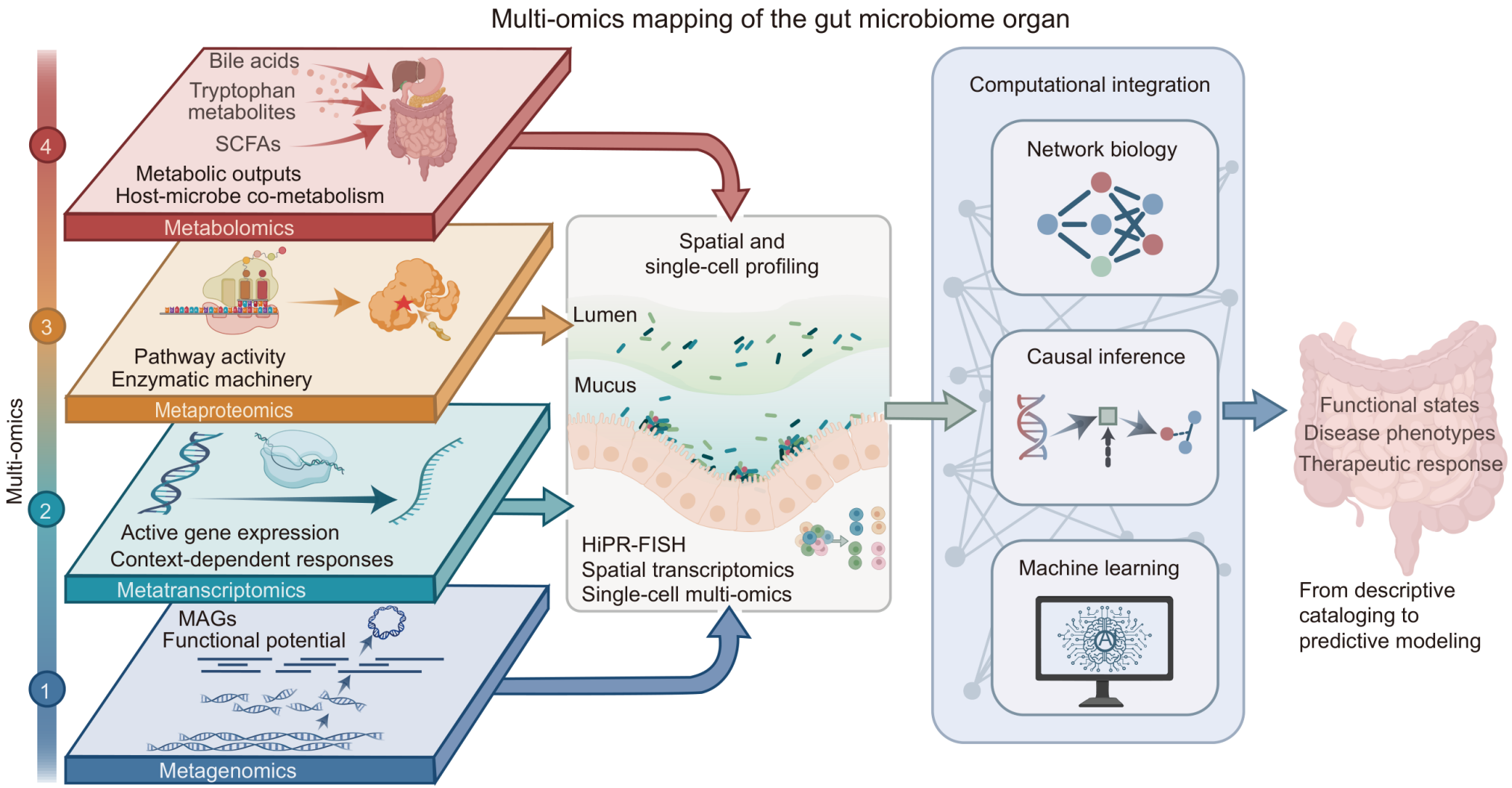
Dysbiosis has been implicated in neurodevelopmental, psychiatric, and neurodegenerative disorders.

Figure 7 | Host and environmental factors shaping the organ



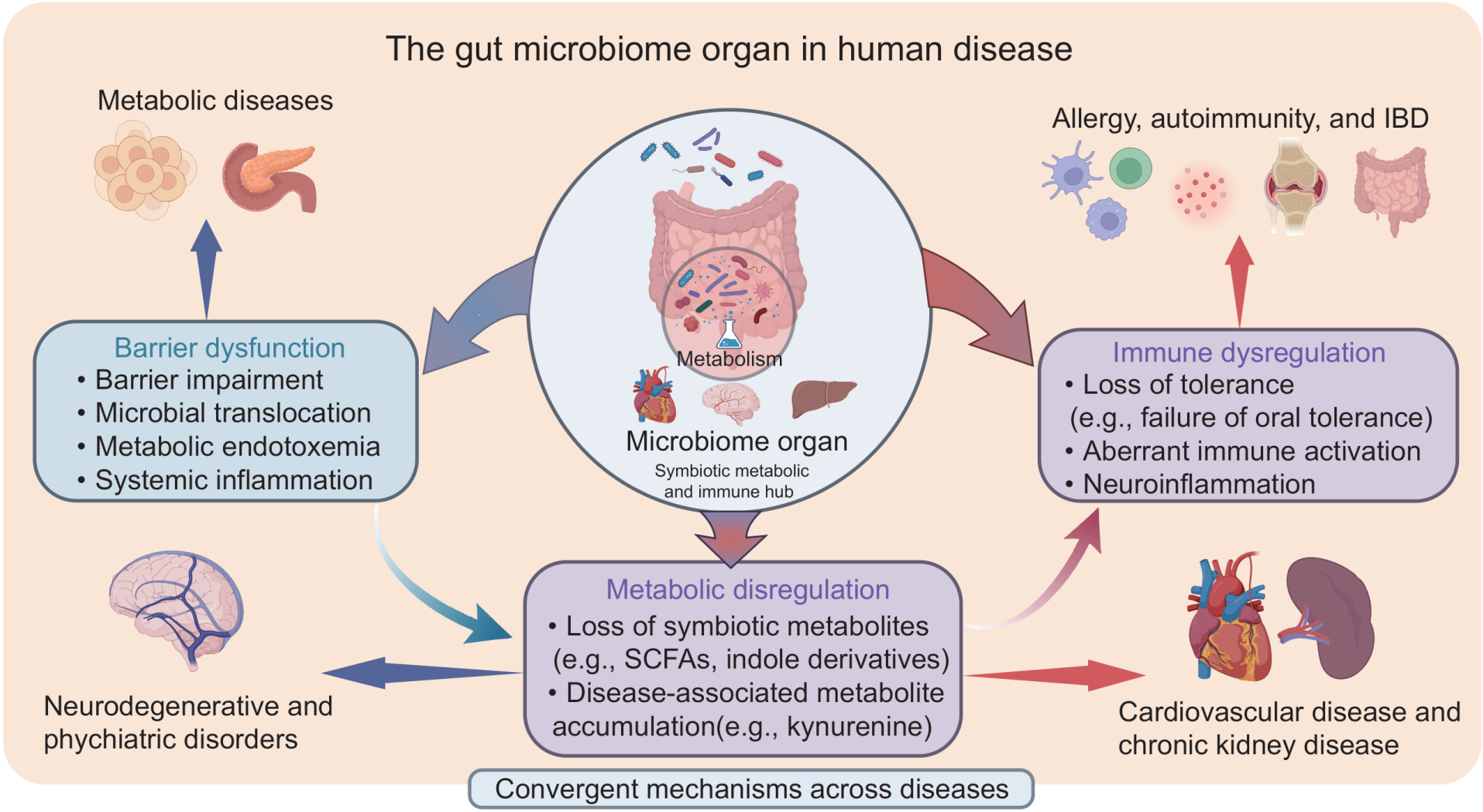
Host genetics, diet and lifestyle, circadian rhythms, and environmental exposures shape microbiome ecology and functional output, thereby contributing to differences in host physiology, metabolic homeostasis, and disease risk.

Figure 8 | Multi-omics mapping



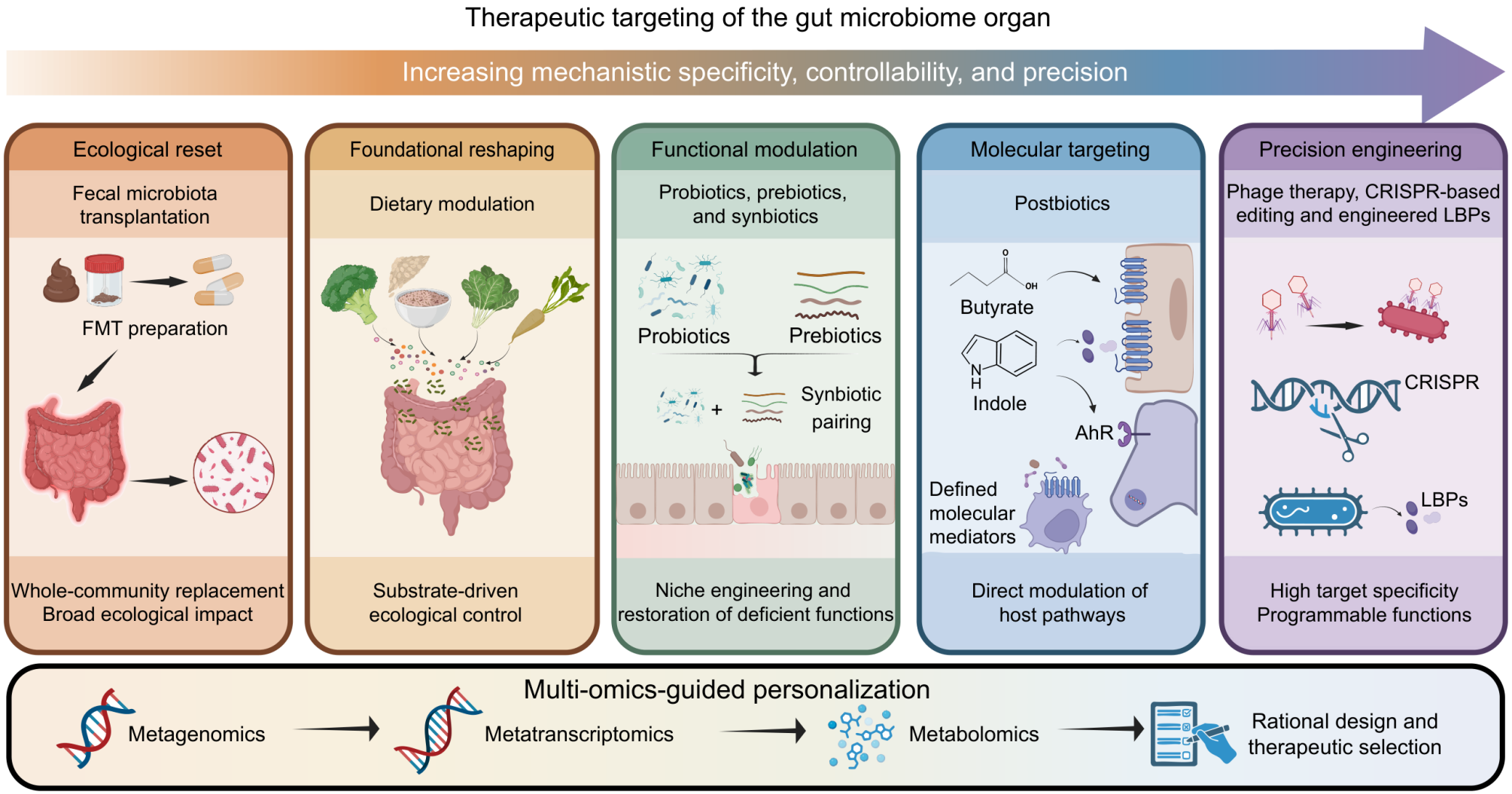
Metagenomics, metatranscriptomics, metaproteomics, and metabolomics, integrated with spatial and single-cell methods through computational frameworks, can resolve microbiome functional states and predict disease phenotypes, progression risk, and therapeutic responses.

Figure 9 | The microbiome organ in diseases



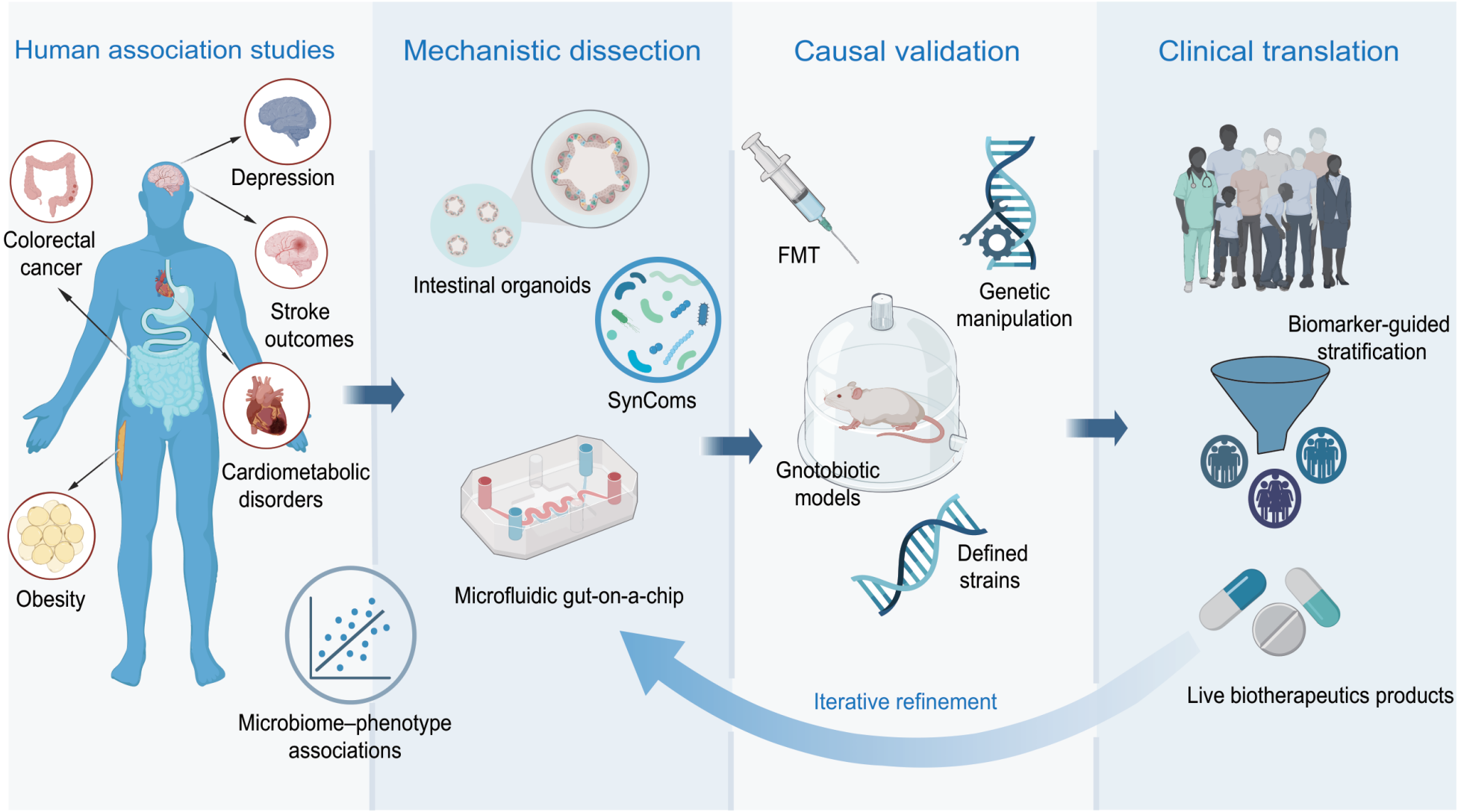
Barrier disruption, metabolic imbalance, and immune dysregulation form reinforcing feed-forward loops that connect microbiome dysfunction with metabolic, cardiovascular, kidney, neurological, allergic, autoimmune, and inflammatory bowel diseases.

Figure 10 | Therapeutic targeting



Microbiome therapeutics span a continuum from ecological remodeling to targeted engineering, including FMT, diet, probiotics, prebiotics, synbiotics, postbiotics, phage therapy, CRISPR editing, and engineered live biotherapeutics, guided by multi-omics personalization.

Figure 11 | A translational framework



Microbiome translation follows an iterative bedside-to-bench-to-bedside loop, moving from human association studies to mechanistic dissection, causal validation in gnotobiotic models, and biomarker-guided clinical translation.

Conclusions

- **The gut microbiome can be viewed as an organ-like functional system that integrates structure, metabolism, and systemic signaling.**
- **Its effects are mediated through interconnected metabolic, immune, and neuroendocrine circuits linking environment, microbiome function, and host physiology.**
- **Multi-omics, spatial/single-cell technologies, and causal modeling are defining its functional modules and regulatory principles.**
- **Precision microbiome medicine will require targeting disease-relevant functional circuits, rather than individual taxa alone.**

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