Urbanization-driven changes in the gut microbiota reveal immunomodulatory metabolites and pathways

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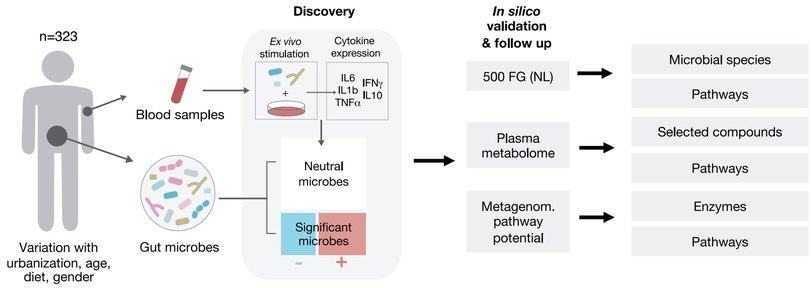
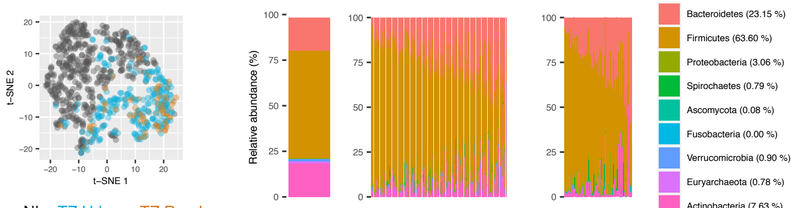
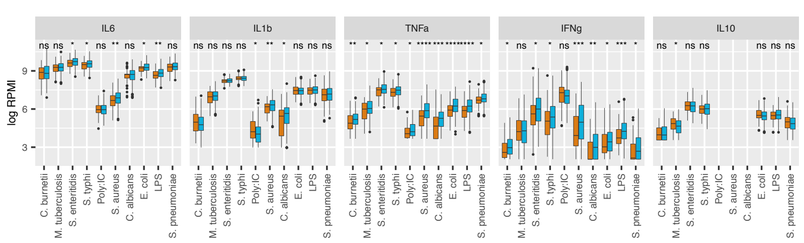
Background The human immune system maintains constant intestinal homeostasis through sensing microbial ligands and metabolites. The discovery of novel immunomodulatory factors in healthy human cohorts is challenging due to the vast number of circulating metabolites, underexplored microbial variation and limited opportunities for controlled interventions. We present a large cohort from urban and rural Tanzania (TZ) which reflects rapid urbanization, migration and related lifestyle changes.

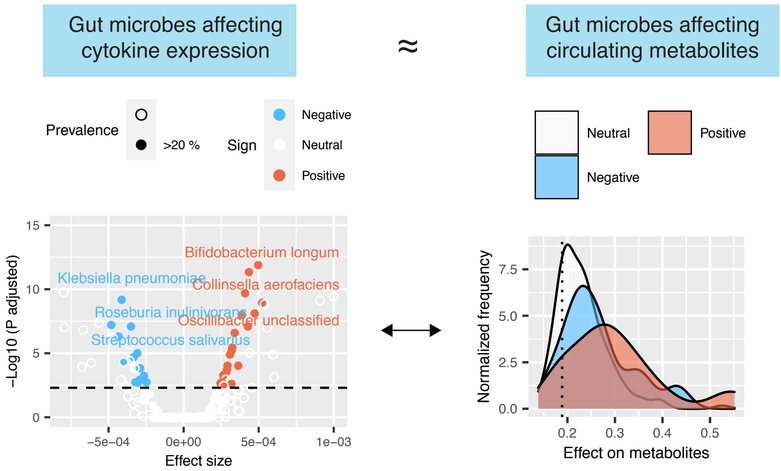


Stool metagnomes reveal an **urbanization gradient** from Netherlands (NL) through urban TZ to rural TZ detectable both in **relative abundance and strain variation**. Urban samples associate with loss of Bacteroidetes and increase in Firmicutes and Verrucomicrobia, including *Bifidobacterium longum* and *Akkermansia muciniphila*, which are more common in Western European populations.



Urban dwellers show elevated levels of *ex vivo* cytokine expression, including TNF-α and IFN-γ, in responses to multiple bacterial and fungal stimuli. The large cohort variation provides the necessary statistical power to detect 34 immunomodulatory microbes, while an integrative analysis allows us to separate microbial and host effects on the metabolome.

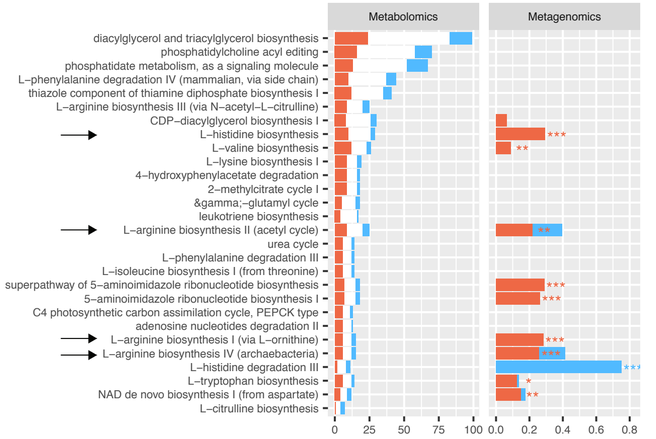




▲ Significant microbes with increased (positive species) or decreased (negative sp.) cytokine expression (FDR < 0.5%, prevalence > 20%).

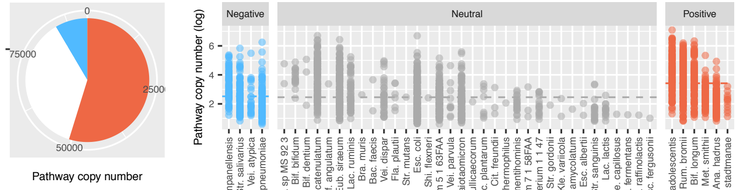
▲ Positive and negative species have larger effects on circulatine metabolites (max. Spearman correlation per species, $P < 10^{-9}$, Chi-square test.)

Multiple lines of evidence uncover that histidine and arginine metabolism compounds are mediated by *B. longum*, *A. muciniphila* and other immunomodulatory microbes.



▲ MetaCyc pathways entailed at least three metabolites with significant associations with immunomodulatory species A model of pathway copy number enrichment confirms ten of the metabolite-associated pathways enriched in immunomodulatory species' genomes, where the majority, nine, were encoded by the positive species.

▼ More than half of copy numbers from **L-histidine biosynthesis** were encoded by positive species.



Conclusion The discovered compounds and pathways aid understanding and investigating intestinal homeostasis as well as present potential therapeutic routes to modulate response to pathogen infections.