Structural Mining of Gut Metagenomes Pinpoints Therapeutically Relevant Microbial Enzymes

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The gut microbiota play key roles in human health and disease but the mechanisms the microbiota use to drive host outcomes remain unclear. Enzymes produced by the gut microbiota have been implicated in such outcomes as they directly alter the chemical structure of small molecules traversing the intestinal tract, thereby modifying their bioavailability and potential biological effects. Gut microbial enzymes have been shown by us and others to exhibit dramatic structural diversity that annotate conserved core features and make the resultant proteins highly distinct between different phylogenetic groups. Despite their prevalence and diversity, only a tiny fraction of metabolically active enzymes produced by the gut microbiota have been identified and characterized. However, recent advances in metagenomic sequencing platforms have made it possible to obtain the amino acid sequences of gut microbial enzymes residing in the GI. Furthermore, the development of targeted chemical probes has enabled the quantification of proteins present and active in human fecal samples using meta-proteomics. Here, we combine structural biology and bioinformatics to unravel the mechanistic underpinnings of microbiome-dependent metabolism influencing endobiotic bioavailability. We facilitate the functional assignment and proper annotation of orphan gene products across metagenomic datasets, then use these datasets to inform our meta-proteomic analyses. By doing so, we identify gut microbial enzymes that modulate systemic endobiotic bioavailability then describe their propensity for inhibition by FDA-approved drugs. Our structure-guided approach can be applied broadly to advance our mechanistic understanding of functional enzymology and the human gut microbiota.

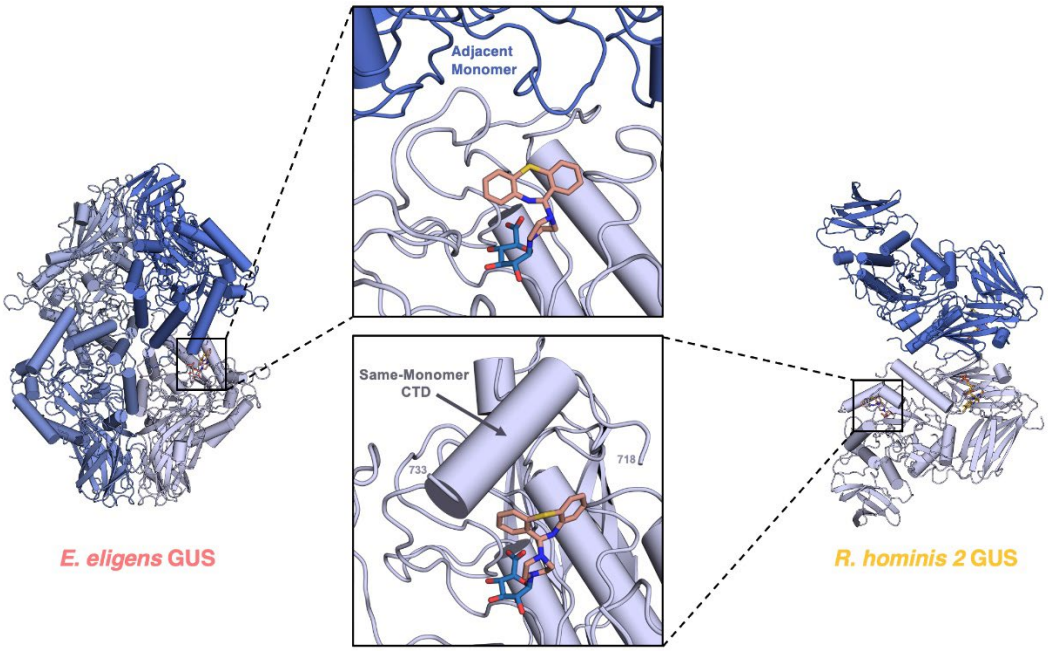

Figure 1