The Emerging Link between Microbial Derived DPP-4 and Cognitive, and Metabolic Health: The Gut-Microbiome Perspective

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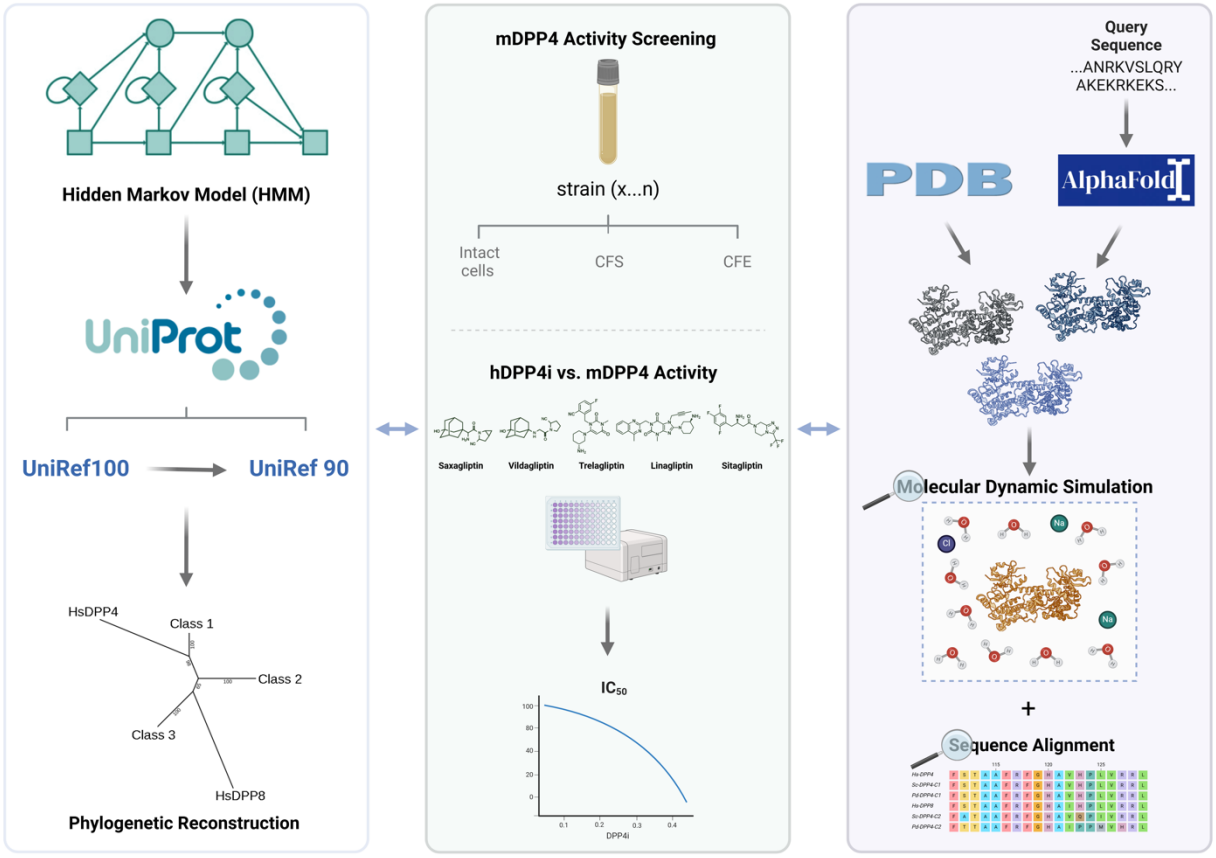
Abstract

Microbiome research has progressed profoundly over the last decades, from exploring microbial diversity to uncovering the enzymatic functions microbes share with their hosts, or microbial-host-isozymes (MHI). The study of microbially-derived dipeptidyl peptidases (mDPP-4) and their implications for human health, given their structural and functional similarities to human DPP-4 (hDPP-4), which plays critical roles in many vital processes such as glucose metabolism and immune regulation. However, research on mDPP-4 remains limited, even lacking a precise classification and nomenclature. This gap complicates the understanding and development of mDPP-4 targeted therapeutics, as early evidence indicates that mDPP-4 may not be effectively inhibited by current therapeutics designed for hDPP-4, underscoring the need for novel approaches to target these microbial enzymes. This study aimed to establish the preliminary landscape for mDPP-4 using a combination of computational and experimental methods, including in-vitro screening of activity and hDPP-4 inhibitor assays against mDPP-4 across selected bacterial strains. We propose a novel classification of mDPP-4 enzymes into three distinct classes with several clades and subclades that present changes in critical residues,

potentially making them incompatible with current hDPP-4 targeted therapeutics. Our computational studies showed molecular distinctions between mDPP-4 and hDPP-4 that explain the results of the initial in-vitro screening of hDPP-4 inhibitors across various microbial species. These findings demonstrate a high mDPP-4 diversity and highlight the need to develop personalized microbial-specific DPP-4 therapeutics that accommodate the unique characteristics of microbial enzymes.

Graphical Abstract



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