Oral presentation

Unveiling the Molecular Mechanism of Tumor-Associated Antigen Recognition by *Bacteroides caccae*

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The gastrointestinal tract is home to a complex ecosystem of commensal bacteria, profoundly influencing human health. Under conditions of low-fiber diet, certain commensal bacteria adapt by utilizing host mucin O-glycoproteins as alternative substrates [1,2]. Among these, *Bacteroides caccae* has been implicated in degrading the colonic mucous layer, thereby heightening susceptibility to pathogen invasion and exacerbating intestinal diseases (Fig. 1A).

During *B. caccae* growth on mucin O-glycans, upregulation of modular enzymes, including modular M60-like metallopeptidases (commonly known as mucinases) with appended non-catalytic carbohydrate-binding modules of family 32 (CBM32), is observed. These enzymes are organized within gene clusters termed polysaccharide utilization loci (PUL), which encode the machinery required for glycan breakdown and uptake (Fig. 1B) [3].

Employing an integrative approach, we elucidated the glycan recognition pattern of a novel CBM32 (BC16100-CBM) appended to a putative mucinase within PUL53. Utilizing MUC-1 O-glycopeptide microarray analysis and affinity studies, we unveiled a remarkable specificity towards GalNAcα-Ser/GalNAcα-Thr (Tn antigen). Further molecular insights into Tn antigen recognition by BC16100- CBM were gleaned using X-ray Crystallography (Fig. 1C).

This study provides crucial insights into the molecular mechanisms underlying the recognition of tumor-associated antigens and the utilization of mucin substrates by *B. caccae*. By unraveling these intricate interactions, our findings pave the way for a deeper understanding of host-microbe interactions within the gastrointestinal tract and may inform novel therapeutic strategies targeting intestinal diseases.

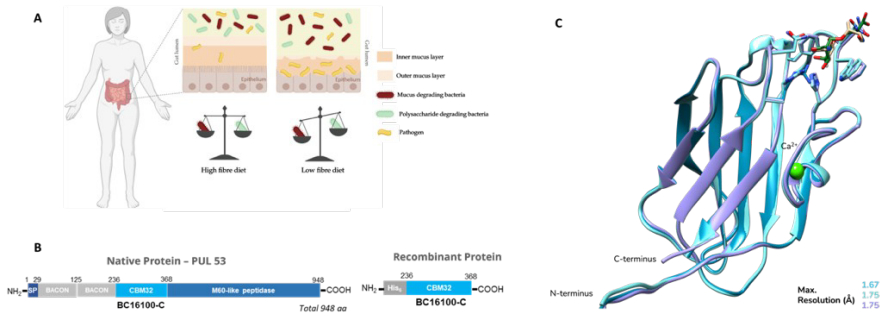

Figure 1. A. Under conditions of a low-fiber diet, certain commensal bacteria can adapt by utilizing host mucin O-glycoproteins as alternative substrates in lieu of dietary polysaccharides. B. The M60-like metallopeptidases are organized within gene clusters termed polysaccharide utilization loci (PUL). C. The figure depicts a superposition of the solved 3D structures of BC16100-CBM in its free form (blue ribbon), in complex with the Tn-Ser (GalNAcα-Ser) antigen (cyan ribbon), and in complex with the Tn-Thr (GalNAcα- Thr) antigen (purple ribbon).

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