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Grant Title: Unraveling the Molecular Mechanisms of Collagen Glycosyltransferases

ABSTRACT

Collagen molecules are characterized by a unique O-linked glycosylation pattern: glucosyl-(α1,2)-galactosyl-(β1,O)-5- hydroxylysine (Glc-Gal-Hyl). Covalent conjugation of glycans to collagens is a complex event which requires sequential introduction of multiple post-translational modifications (PTMs). Firstly, lysine amino acid residues located on triple helical regions are hydroxylated (LH reaction). Then, 5-hydroxylysines undergo an inverting-type glycosyltransferase reaction that relies on UDP-α-galactose as donor substrate to covalently attach β-galactose to the OH group of 5-hydroxylysine (GalT reaction). Finally, α-glucose is covalently attached to the β1,O-galactosyl-5-hydroxylysine (GlcT reaction) with a retaining-type glycosyltransferase reaction that uses UDP-α-glucose as donor substrate, leading to the final post-translationally modified product (reviewed in (1)). Thanks for the generous support offered by the Mizutani Foundation for Glycosciences, we investigated the structure-function relationships critical for the glycosyltransferase activities of multifunctional human lysyl hydroxylase-glycosyltransferase LH3 (2). With guidance from previous structural studies and insights from clinical genetics (3) we carried out an extensive mutagenesis investigation to identify critical hot spots for the enzyme's catalytic activity (summarized in (4)), and also gave the spark to new collaborations to study the structural features of LH enzymes using computational chemistry (5). The research activity then expanded to the human LH1 isoform, enabling the identification of an unprecedented glucosylgasactosyltransferase activity in this enzyme (6). Next to the work focusing on LH enzymes, we have also characterized the human collagen galactosyltransferase GLT25D1 using a integrative structural biology approach.

References:

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