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Glycosylation and development of atherosclerosis

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Perlecan is a major heparan sulfate (HS) proteoglycan in the arterial wall. Previous studies have localized perlecan to atherosclerotic lesions and its expression correlates with lesion progression. The retention of atherogenic lipoproteins in the arterial wall is an early step in the development of atherosclerosis and this retention is presumably mediated by the ionic interaction between the negatively charged HS and the basic amino acids of apolipoprotein B-100. Perlecan contains a core protein and three HS side chains. Its core protein has five domains (I-V) with disparate structures and domain II is highly homologous to the ligand-binding portion of low-density lipoprotein receptor (LDLR). The functional significance of this domain has been unknown. Here, we show that the perlecan domain II interacts with LDL. Importantly, the interaction largely relies on O-linked glycans that are only present in the secreted domain II. Among the five repeat units of domain II, most of the glycosylation sites are from the second unit, which is highly divergent and rich in serine/threonine but no cysteine residues. Interestingly, most of the glycans are capped by the negatively charged sialic acids, which are critical for LDL binding. We further demonstrate an additive effect of HS and domain II on LDL binding. Unlike LDLR, which directs LDL uptake through endocytosis, this study uncovers a novel feature of the perlecan LDLR-like domain II in receptor-mediated lipoprotein retention, which depends on its glycosylation. Thus, the arterial perlecan glycosylation may provide an attractive non-lipid target to decrease the progression of atherosclerosis.

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Glycans as critical quality attributes of therapeutic antibodies

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The identification of critical quality attributes (CQAs) of therapeutic antibodies is of key importance during product development. Distinct product-related variants originating from the manufacturing process or formed during storage have to be assessed regarding their bioactivity/potency, PK/PD, immunogenicity and safety. Here we present an overview on the influence of glycan structures of IgG molecules on both, their biological activity and on pharmacokinetics. Importantly, the antibody isotype as well as the antigen localization have to be considered when evaluating the glycosylation variants on the Fc part of IgGs. Depending on the primary mode of action and/or additional modes of action, N-linked glycans attached to the Fc part can significantly influence the biological activity of a therapeutic antibody. This is one reason for extensive research on glycosylation modification. In addition to N-linked glycans, glycation during the manufacturing process as well as oligosaccharides present on non-consensus amino acid sequences are discussed. Having a complete data set on both the glycan structures of an antibody and of the potential glycation sites allows for an assessment of the criticality of sugar variants regarding biological activity and pharmacokinetics.

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