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A Potential Biosynthetic Pathway for Silica Acid can be used to Increase the Sialylation of Therapeutic Glycoproteins

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Abstract

The number of therapeutic proteins has increased dramatically over the past years and most of the therapeutic proteins in the market today are glycoproteins. Usually, recombinant glycoproteins are produced in mammalian cell lines, such as Chinese-hamster-ovary-cells to obtain mammalian-type of glycosylation. The terminal monosaccharide of N-linked complex glycans is typically occupied by sialic acid. Presence of this sialic acid affects absorption, serum half-life, and clearance from the serum, as well as the physical, chemical and immunogenic properties of the respective glycoprotein. From a manufacturing perspective, the degree of sialylation is crucial since sialylation varies the function of the product. In addition, insufficient or inconsistent sialylation is also a major problem for the process consistency. Sialylation of overexpressed glycoproteins in all mammalian cell lines commonly used in biotechnology for the production of therapeutic glycoproteins is incomplete and there is a need for strategies leading to homogenous, naturally sialylated glycoproteins. This review will shortly summarize the biosynthesis of sialic acids and describe some recent strategies to increase or modify sialylation of specific therapeutic glycoproteins.

***Keywords:** Silica acid; Recombinant glycoproteins; Therapeutic proteins; Protein stability*

Introduction

Sialic acids represent a family of amino sugars with 9-carbons with over 50 members derived from N-acetylneuraminic acid Most mammals express N-glycolylneuraminic acid, the hydroxylated form of N-acetylneuraminic acid at position C5 [1]. However, humans express predominantly N-acetylneuraminic acid, due to a homozygous mutation in the CMP-neuraminic acid hydroxylase gene in the human genome. N-glycolylneuraminic acid is antigenic to humans is enriched in tumor cells and is originated most probably from the diet. This is an important issue since this is one of the reasons why the nonhuman N-glycolylneuraminic acid has to be avoided in any production process of recombinant therapeutic glycoproteins. This problem has been overcome recently by using antisense strategies to reduce the activity of the CMP-neuraminic acid hydroxylase in CHO cells [2]. The respective sialic acids possess different highly specific recognition and binding properties for a variety of cellular receptors. This structural and functional diversity of sialic acid is exploited by viruses, bacteria and toxins, and by the sialoglycoproteins and sialoglycolipids

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involved in cell-cell, cell-matrix or molecular recognition. Sialic acid is only one component out of several monosaccharide's building glycans of glycoproteins, but has an outstanding impact on the quality and stability of any therapeutic glycoproteins for several reasons: Terminal glucose residues are one of the major factors determining the serum half-life of glycoproteins. The serum half-life is regulated by the expression of liver asialo-glycoprotein receptors [3]. These receptors bind nonsialylated glycoproteins on free galactose residues and bound asialo-glycoproteins are removed from the serum.by endocytosis. As a consequence, expression of terminal sialic acid on galactose residues prevents serum glycoproteins from degradation. Sialic acids are important for masking antigenic determinants or epitopes. It is known that the receptors of the immune system (T- and B-cell receptors) [4] often prefer nonsialylated structures. Therefore, the possibility of the generation of antibodies (neutralizing antibodies) against the therapeutic glycoproteins correlates with the degree of its sialylation. Negatively charged sialic acids influence protein-specific parameters such as the thermal stability the resistance to proteolytic degradation or its solubility [5].

Biosynthesis and Activation of Silica Acid

Study area

The initial reaction in the pathway to form free sialic acid is a conversion of UDP-N-*acetylglucosamine* (UDP-GlcNAc) to *N-acetyl* D-*mannosamine* (ManNAc) since the physiological precursor of all sialic acids is ManNAc [6]. ManNAc is formed from UDP-N-acetylglucosamine (UDPGlcNAc) by epimerization of the hydroxyl-group in position 2 and cleavage of UDP by the UDP-*Nacetylglucosamine 2-epimerase*. Cardini and Leloir originally discovered this enzyme in rat liver. All ManNAc produced by the UDP-*Nacetylglucosamine 2-epimerase* is metabolized to sialic acid. The biosynthesis of sialic acid is regulated by the feedback inhibition of the key enzyme of sialic acid biosynthesis, the *UDP-Nacetylglucosamine 2-epimerase*/ManNAc *kinase* (GNE). GNE is a bifunctional enzyme, which catalyzes the conversion of *UDP-GlcNAc* to *ManNAc* and the phosphorylation of ManNAc to ManNAc-6-phosphate [7-9]. The next step is a condensation of ManNAc-6-P and *pyruvat* resulting in sialic acid-9-phosphate by the N-acetyl-D-neuraminyl-9-phosphate synthase [10-13].

Summary

Nearly each naturally eukaryotic secreted protein is a glycoprotein and therefore most therapeutic proteins in development are glycoproteins. Sialic acid is a crucial monosaccharide in mammalians. Especially in humans, glycans of glycoproteins determine functional properties of the respective protein. This review concentrates on the role of sialic acid and possibilities to increase the content of sialic acid during the production process of recombinant glycoproteins. Glycosylation and sialylation (as one part of the glycosylation) have different consequences on (therapeutic) glycoproteins and therefore one has to distinguish between glycosylation and sialylation. Glycosylation per se has major impact on solubility and resistance to proteolysis of glycoproteins. Glycosylation can be achieved by expressing the respective protein in a cell system, which is capable to glycosylate proteins, such as insect cells or mammalian cells like CHO.

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