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Introductory Chapter: Glimpses of Glycosylation

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1. Introduction

Glycosylation refers to the post translational modification of proteins, lipids and nucleic acids in the presence of enzymes. The common post translational modifications of biological importance include N-linked glycosylation, O-linked glycosylation, phospho-serine glycosylation, as well as C-mannosylation and glypation (addition of glycoposphatidylinositol. Glycosylation reaction is mediated by glycosyltransferases that conjugate carbohydrate to proteins, lipids and nucleic acids. Glycosylation is a biological mechanism that aids the protein folding and help in protein signaling along with cell-cell interaction. Recently mass spectrometry technique is recently gained attention in quantitative estimation of glycoproteomics. In COVID-19 infection, the SARS-CoV-2 viral proteins including spike(S), envelope (C), membrane (M) and nucleocapsid (N) undergo post translational modification of glycosylation and phosphorylation that plays important role in virulence and infectivity.

Defined in the broadcast sense, glycosylation is the conjugation process of joining carbohydrate to the protein's backbone via enzymatic reaction. Post modification after this reaction, the protein is termed as glycoprotein. In our body, the most common glycosylation reaction refers to the N-glycosylation and O-glycosylation. Among these two post modification process, the N-glycosylation is frequently occurring mechanism. This mechanism of post translation modification comes under the domain of glycobiology, which refers to the study of biosynthesis, structures and biology of saccharides (also known as sugar or carbohydrates). Glycosylation is a critical mechanism of the biosynthetic-secretory pathway that occurs in endoplasmic reticulum (ER) and Golgi apparatus [1]. It was a known fact that nearly half of the eukaryotic proteins undergo modification, which presents the covalent conjugation of sugar moieties to particular amino acids of interest [2]. Membrane-bound and soluble proteins along with secreted proteins, ligands, surface proteins that are transported from the Golgi to the cytoplasm also become glycosylated [2].

Lipids and proteoglycans are also among the susceptible targets of the glycosylation that significantly contribute in increasing the number of substrate for the post translation modification. Carbohydrate plays an important role in the regulation of multicellular organs and organism's functions as a resultant several biological macromolecules possess covalently attached saccharides including monosaccharides and oligosaccharides which are commonly known as glycans [3]. These glycans contribute a major role in modulating cell-to-cell interaction, development and function of cell, interaction between cell and host [4]. Protein bound glycans are abundant in the nucleus and cytoplasm and serve as the key regulator element there [4].

2. N- and O-glycosylation

Several proteins undergo post translational modification by N-glycosylation that denote with the attachment of the N-acetylglucosamine (GlcNAc) to the nitrogen atom present in the Asn side chain of the amino acid by a β -1 N linkage [2]. These GlcNAc₂ mannose (Man)₃ core containing glycoconjugates shows the tendency to add/remove several monosaccharides. These conjugation reactions include galactosylation, sialylation, GlcNAcylation and fucosylation [2]. Moreover, glycosylation occurs on hydroxyl functional group of the amino acids Ser and Thr. The most common sugars showing conjugation with Ser and Thr are GlcNAc and N-acetylgalactosamine (GalNAc) [5]. GalNAc associated glycans, often known as mucin-type O-glycans are abundantly found in extracellular spaces and secreted proteins like mucin [6]. Mucin is characterized with high number of Pro, Ser and Thr residues that makes it susceptible to the O-linked glycosylation. The participating sugars conjugate with the protein as it moves through the cis, medial and trans Golgi apparatus. The glycopeptide O-glycans are post translationally modified by glycosyltransferases [5].

3. C-Mannosylation

C-mannosylation is a different approach from glycosylation, as in this process there is reaction forms carbon-carbon bonds rather than carbon-nitrogen and carbon-oxygen bonds. C-mannosyltransferase is the key enzyme that is involved in the C-mannosylation. This enzyme conjugates the C1 of the mannose to C2 of the indole ring present in the tryptophan residue [7]. Moreover, this enzyme recognizes the specific sequence of Trp-X-X-Trp that further eases the transfer of mannose sugar from dolichol-P-Man to the first Trp residue present in the given sequence [8–10]. In another event of the post translational modification (PTM), the phosphoglycosylation is among the PTM mechanism that is limited to the parasites including Trypanosoma and Leishmania including slime molds. The mechanism is characterized by the conjugation of glycans to the Ser and Thr residues linked by the phosphodiester bonds [11].

4. Glycosylation vs. glycation

Glycosylation and glycation are enzymatic and non-enzymatic reactions respectively, in which glucose and other glucose metabolites show affinity with different biological macromolecules such as proteins, lipids and nucleic acids. Increased presence of glucose both intracellular and extracellular poses a threat to the human and act as a risk factor for various metabolic disorders including diabetes mellitus. Both non-enzymatic glycation and enzymatic glycosylation reactions have been shown to play an important role in human health. Non-enzymatic glycation leads to the formation of advanced glycation end products (AGEs) that generate as a resultant of protein and lipid glycation with aldose sugars [12, 13]. Prior to the formation of AGEs, the early glycation reaction occurs that forms Schiff bases and Amadori products. AGEs formed due to the non-enzymatic glycation generate reactive oxygen species (ROS), that further binds to the particular cell surface receptors and later forms cross links [12, 14].

5. SARS-CoV-2 and glycosylation

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is severely affecting the worldwide population. SARS-CoV-2 virulence and survival is

impacted by the glycans that is covalently linked to the proteins of virus through the process of glycosylation that makes alteration in the virulence of the SARS-CoV-2 virus. It belongs to the coronavirus family which exhibit protein constituted enveloped single-stranded RNA. These viral proteins undergo post-translational modifications (PTMs) that reorganized covalent bonds and modify the polypeptides and in turn modulate the protein functions. Being viral machinery, it uses host cells system to replicate itself and make their copies, their proteins are also subject to PTMs. Glycosylation, palmitoylation of the spike and envelope proteins, phosphorylation, of the nucleocapsid protein are among the major PTMs responsible for the pathogenesis of the viral infection phase. The current knowledge of CoV proteins PTMs is limited and need to be exploring for to understand the viral pathogenesis mechanism and PTMs effect of infection phase.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

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