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Exploring the Protein Glycosylation Pathways to Find New Therapeutic Alternatives

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Abstract

After protein phosphorylation, glycosylation is the most frequent posttranslational modification found in prokaryotic and eukaryotic cells, as well as in biological entities such as viruses. The metabolic pathways involved in the elaboration of oligosaccharides and the mechanisms to add them to proteins have been extensively studied; and now this information is starting to be analyzed to find applicability in several fields. Here, we show recent examples of how basic glycobiological information is starting to be applied to solve problems in medicine, such as cancer and viral infections, and their current limitations.

Keywords: Protein glycosylation; Antiviral therapy; Cancer marker; Anticancer therapy; Metastasis marker

Description

Protein glycosylation is a universal posttranslational modification found in all life kingdoms, and has been thoroughly studied to understand the basic aspects of how organisms synthesize a wide range of protein-decorating glycans. It is now clear that this modification is not a futile accessory, on the contrary, plays key roles in the localization, function and fate of proteins [1]. Thus far, the basic mechanistic requirements that a human cell needs to generate glycoproteins are well understood, although there are some important gaps in the knowledge of these metabolic pathways. This basic information is starting to be exploit to find medical applications, and there at least four main areas where this is having a significant impact: antiviral therapies, diagnosis and prognosis of cancer, humanization of recombinant proteins, and treatment of congenital disorders of glycosylation and cancer. During *N*-linked glycosylation, there is a processing step on the glycans performed by endoplasmic reticulum glycosidases [2], and blocking of this step is currently investigated as a potential antiviral strategy. Thus far, this strategy has been successfully applied in the control of hepatitis C virus, dengue, and other hemorrhagic fever viruses [3-8]. Examples of these compounds are Celgosivir, PBDNJ0804 –a deoxynojirimycin derivative, and CM-10-18 [3-8]. Furthermore, it has been recently described that 2',3',4',6'-tetra-O-acetyl-β-D-galactopyranosyl-(1→4)-2',3',6'-tri-O-acetyl-1-thio-β-D-glucopyranosyl-(5-nitro-2-pyridyl) sulfoxide displays antiviral activity against the swine fever virus, via a mechanism involving blockage of a glycosyl transferase involved in the final elaboration of *N*-linked glycans [9].

It has been established that cancer cells have dysregulation of glycosylation pathways, and differentially express secreted and membrane glycoproteins [10,11]. The knowledge of these differences not only contributes to the understanding of the immortalization and metastasis, but can also provide molecular markers that could help in the diagnosis and prognosis of malignant processes. Glycoproteins such as AFP, DKK1, FN1, CD151 and TGFβ2 are up-regulated in hepatocellular carcinoma cells with high ability to generate metastasis, and therefore, have been proposed as metastasis markers [11]. The expression levels of the N-acetylgalactosaminyl transferase GalNAc-T5, an enzyme involved in *O*-linked glycosylation has been proposed as a prognosis marker in gastric cancer patients [12]. Moreover, proteins such as FUT1, FUCA1, POFUT1, MAN1A1, RPN1 and DPM1, involved in protein glycosylation pathways, have been found to have a prognosis value in breast cancer patients [13].

It has been recently reported that down-regulation of the gene encoding the β4-galactosyl transferase 2 (β4GalT2) is associated with developing of malignant tumors, and that gene therapy aiming to up-regulate this gene was successful in controlling tumor growth in mice [14].

It is undeniable the significant advances in this field, as above exemplified, and by a large list of reports that are daily accumulating. However, there are still limitations and lack of bridges connecting basic and applied sciences. The main challenges in the years to come are to explore the clinical value of the proposed new antiviral agents, to generate strategies to deliver chemotherapeutic drugs to cancer cells with little or no affection to normal ones, and to generate specific gene-delivery strategies to replace mutated genes in patients with congenital disorders of glycosylation. Attractive alternatives are currently under investigation, and once again, a glycobiological approach might have the answer to drug/gene delivery mechanisms based on ligand-receptor interactions [15].

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