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Tunicamycin - A Born Fighter against Corona

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ABSTRACT

One of the perilous threat to humans are Viruses. A greater risk of mortality and morbidity in mankind are caused by most of the viruses. Unfortunately, corona virus stood as a monster in the present scenario. The external envelope of the viruses are comprised of proteins namely glycoproteins. The primary target in viral replication is to interrupt the n-glycosidic linkage thereby obstruct the signals from endoplasmic reticulum to the envelope. This particular area has gained more scope in scientific research. The drug namely tunicamycin has grabbed scientist's attention in prohibition of viral propagation by showing its effect on endoplasmic reticulum resulting in stoppage of the signals, envelope breaking and inhibiting the interactions with cellular membrane.

KEYWORDS

Tunicamycin; Coronavirus; Viruses

INTRODUCTION

To a greater extent almost all the viruses are contagious and causing terrific mischief to human and animals. As viruses illustrate a wide variety regarding their structure and arrangement of envelope their differentiation occurs on envelope basis. Lipid bilayer and glycoproteins are components of viral envelope out of which glycoproteins consists of external hydrophilic part and internal hydrophobic segment by which the spikes are strongly associated with the lipid bilayer [1]. Viral spikes play an important role in the interaction between viral envelopes and cellular membrane. Here the primary initiation of the cellular level. It also been demonstrated that glycoproteins of this viruses are important determinants for the spread of infection and thus for pathogenicity. Most of the viral glycoproteins studied to date contain oligosaccharide side chain that are attached by n-glycosidic linkages to the polypeptide such as glycoprotein has recently been characterized in corona virus where it is presented together with another glycoprotein of the n-glycosidic type [2,3]. The biosynthesis of viral glycoproteins with N-glycosidic linkages has been studied in detail it involves translation at membrane-bound ribosomes, insertion into the membrane of the rough endoplasmic reticulum, and transport to the site of virus assembly, which is usually the plasma membrane. In the course of transport, the glycoproteins are processed by glycosylation, proteolytic cleavage, and the covalent binding of fatty acids. At the

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co-translational level, proteolytic cleavage in many instances removes the signal sequences required for insertion of the nascent polypeptides into the membrane of the rough endoplasmic reticulum. Posttranslational cleavage is involved in the processing of a series of these glycoproteins, such as the influenza hemagglutinin and the glycoproteins of paramyxoviruses, alphaviruses, and oncoviruses. In the case of the myxovirus glycoproteins, posttranslational proteolytic cleavage was found to be a precondition for biological activity [4]. The biosynthesis of glycoproteins can be inhibited by interfering with the intracellular transport, with proteolytic cleavage, and with glycosylation. This article will be confined to the inhibition of glycosylation. To date, only glycosylation inhibitors interfering with the biosynthesis of N-glycosidically linked oligosaccharides are known. Thus, only observations made on glycoproteins containing this type of side chains will be reviewed.

Viral spikes play an important role in the interaction between viral envelopes and cellular membrane.

THE BIOSYNTHESIS AND STRUCTURE OF CARBOHYDRATE SIDE CHAINS LINKED BY N-GLYCOSIDIC BONDS TO THE POLYPEPTIDE

The oligosaccharide side chains of the viral glycoproteins are assembled through the biosynthetic machinery of the host cell by the same general principles as the carbohydrates of cellular glycoproteins. Glycosylation of glycoproteins with N-glycosidic linkages is initiated in the rough endoplasmic reticulum by the attachment of preformed oligosaccharides to asparagine residues in the polypeptide chain. The attachment sites have the sequence asparagine-X-threonine or asparagine-X-serine, with X being a variable amino acid. The oligosaccharides transferred to the nascent polypeptide are synthesized via the dolichol pathway of glycosylation which recently has been reviewed in detail elsewhere [5] and can be summarized as follows (Figure 1). The carbohydrate chains are assembled on the phosphate ester of the isoprenoid alcohol dolichol with UDP-N-acetylglucosamine, GDP-mannose, mannosylphosphoryldolichol, and glucosylphosphoryldolichol as sugar donors. After the en bloc transfer of the oligosaccharide to the polypeptide and cleavage of the pyrophosphate linkage dolichol phosphate is available for a new assembly cycle. The oligosaccharide synthesized in this way is usually a tetra-disaccharide of the structure (glucosyl)3-(mannosyl)9-(N-acetylglucosamine)2. Under certain conditions to be described below a disaccharide of the structure (glucosyl)a-(mannosyl)s-(N-acetylglucosamine)2 can be transferred. Glycosylation via the disaccharide lipid is called the alternate pathway. The enzymes involved in the assembly of the lipid-linked oligosaccharides are membrane-bound and appear to occur mainly in the rough endoplasmic reticulum [6]. After the transfer to the polypeptide the oligosaccharide side chains are further processed (Figure 2). First, the three glucose residues are removed by specific glycosidases to yield a mannose-rich carbohydrate side chain [7,8]. At this stage, processing of the oligosaccharide may cease. In most instances, however, it continues by a trimming process resulting in the release of all the mannoses but three. By the subsequent addition of N-acetylglucosamine, galactose, fucose, and neuraminic acid the complex oligosaccharides are formed [9]. The available evidence indicates that the enzymes involved in this last step in the glycosylation sequence are located in the Golgi apparatus [4].

From this review on the carbohydrate synthesis it is clear that complex and mannose-rich side chains of the general structures shown in (Figure 2) exist in mature viral glycoproteins and that both types are derived from a common precursor. It is also evident from what has been said above that the number and the position of the oligosaccharides on the polypeptide is determined by the presence of appropriate amino acid sequences that can act as attachment sites. The number of side chains attached to different glycoproteins varies therefore over a wide range; e.g. the G protein of vesicular stomatitis virus has only two oligosaccharides [10,11], whereas as many as seven side chains can be observed on the influenza hemagglutinin. The studies on the influenza hemagglutinin revealed also that the many variants of this glycoprotein vary widely in the distribution of the glycosylation sites and the oligosaccharide types attached to them [12-15]. These results indicate that the structure of the polypeptide plays an important role in determining whether a mannose rich or a complex oligosaccharide is attached to a given glycosylation site. Despite of the high variability of most glycosylation sites of the hemagglutinin, some of them appear to be conserved. It is interesting to note that according to the three-dimensional model of the hemagglutinin all conserved side chains are located in close vicinity to each other at the base of the spike [16]. This may indicate that these side chains have a special function in maintaining the proper implantation of the glycoprotein in the lipid bilayer [12].

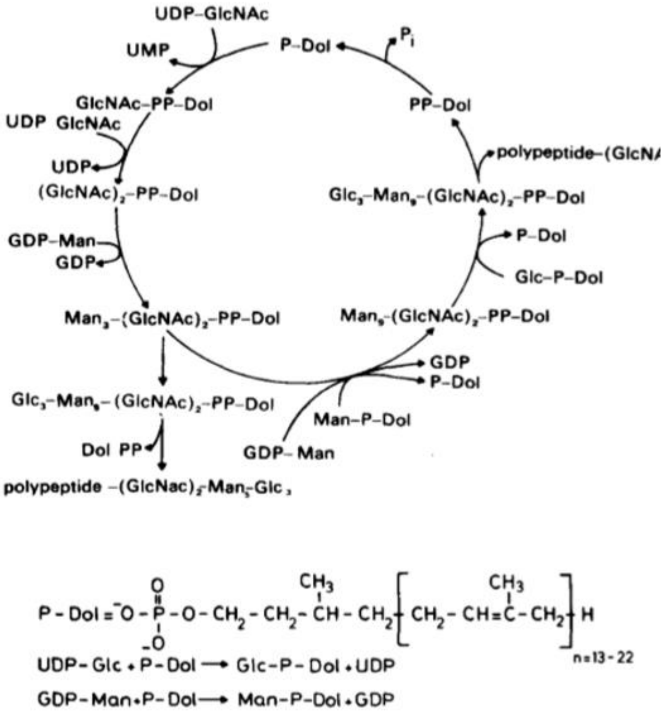

Figure 1: The biosynthesis of the dolichol-linked oligosaccharide precursors of the asparagine-linked carbohydrate side chains. **Note:** Where, Dol: Dolichol; GlcNAc: N-acetylglucosamine; Man: Mannose; Glc: Glucose.

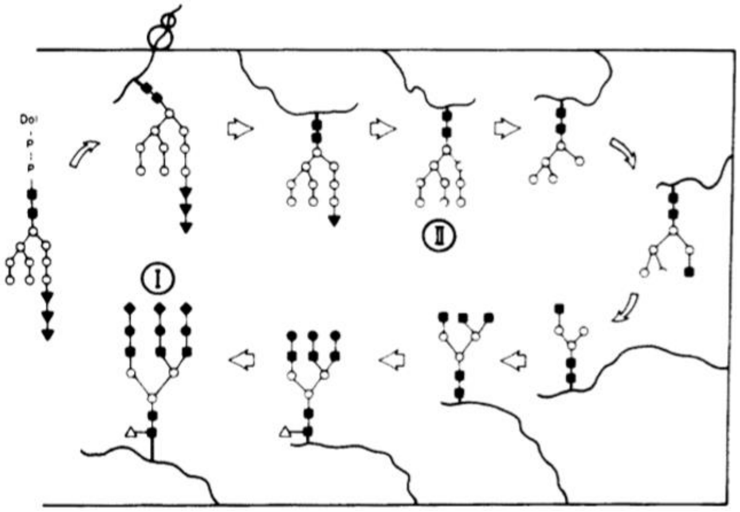

Figure 2: The processing of the protein-bound oligosaccharides. The structures of the complex (I) and of the mannose-rich (II) side chains found in mature glycoproteins are indicated. **Note:** Where, (■): Mannose; (○): Glucose; (●): Neuraminic Acid; (♦): Fucose (Δ): Galactose.

INHIBITOR OF GLYCOSYLATION

Tunicamycin

Corona virus (Figure 3) (virus group) tunicamycin (inhibitor of glycosylation).

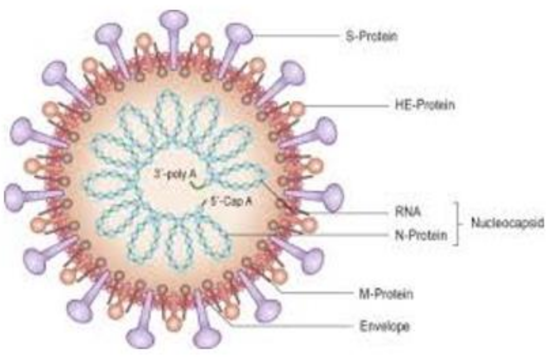

Figure 3: Structure of coronavirus.

A nucleoside antibiotic extracted from Tamura's group of micrococcus lysodeikticus was Tunicamycin (Figure 4) which is a tight-binding, competitive inhibitor of the enzyme transferring phosphoryl-N-acetylglucosamine from UDP-N-acetylglucosamine to phosphoryldolichol. Therefore N-acetylglucosaminylpyrophosphoryldolichol formation is inhibited [17-19].

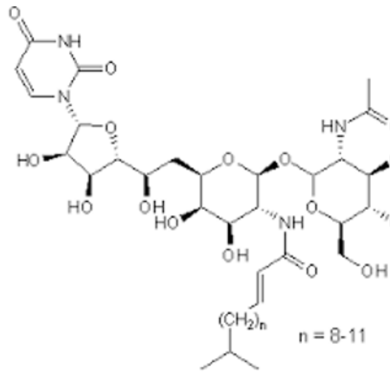

Figure 4: Structure of tunicamycin.

In order to obtain glycosylation inhibition, maximum concentrations of tunicamycin is required. Apart from this other effect includes inhibition of glucosylphosphoryldolichol formation and protein synthesis are seen in human fibroblasts.

BIOLOGICAL EFFECTS OF GLYCOSYLATION INHIBITOR TUNICAMYCIN

Tunicamycin forestalls the addition of core oligosaccharides to nascent polypeptides by inhibiting n-linked glycosylation and thereby blocks protein folding and transit through ER from: Methods in enzymology, 2011.

Nucleosides

Both *in vitro* effects of ER stress in various cell types and impact of nucleoside antibiotics on kidney are studied by widely recognized drug namely Tunicamycin. Intraperitoneally tunicamycin is administered at a dose of 0.5 mg/kg - 1.0 mg/kg for 3 days to inhibit protein glycosylation [20].

Tunicamycin

The major mechanism of tunicamycin includes inhibition of protein N-glycosylation, peptidoglycan biosynthesis and binding of teichoic acids and teichuronic acids to peptidoglycan. The above mechanisms are seen even at low concentrations of drug in both the cells with and without membrane. Translocation of a derivative of an N-acetylhexosamine-1-phosphate residue from the uridine diphosphate sugar to monophospho polyprenol is considered as a common step in the above 3 process which is inhibited by tunicamycin at minute doses. Residues of uridine and N-acetyl glucosamine are linked by N-fatty acyl galactosamine residues. It binds irreversibly to the translocase due to its structural analogue with substrate.

Inhibition of peptidoglycan synthesis and N-glycosylation of proteins marks this drug as an antibiotic and antiviral respectively. Therapeutic usage of tunicamycin in animals is avoided as it causes toxic to the cells due to inhibition of N-glycosylation of essential glycoprotein. Certainly, biological activities of different glycoproteins respond differently. The sensitivity of cells from different sources to the antimetabolite varies markedly. Even though the tunicamycin blocks glycosylation the production of transferrin and VLDL apo-B-protein (both normally N-glycosylated) by hepatocytes remains neutral whereas the low-density lipoprotein receptor activity is declined. Along with these a small change is observed in receptors that are present in fibroblasts [21].

EFFECTS ON THE SUSEPTIBILITY OF VIRAL GLYCOPROTEIN TO PROTEOLYTIC CLEAVAGE

The difference between the sugar analog and tunicamycin in the effect on the proteolytic stability of the non-glycosylated hemagglutinin it has to be pointed out [22].

SIDE EFFECTS AND ADVERSE EFFECTS OF TUNICAMYCIN

GI symptoms, peripheral neuropathy, fatigue, and thrombocytopenia are generally observed. One study suggested that bortezomib-induced ER stress could be involved in peripheral neuropathy, possibly by impairing myelin synthesis [23].

CONCLUSION

As viral infections are threatening human existence with infections, there an urgent need in focusing anti-viral drugs. The present paper is focused on the drug namely tunicamycin which had grabbed scientist's attention in prohibition of viral propagation by showing its effect on endoplasmic reticulum resulting in stoppage of the signals, envelope breaking and inhibiting the interactions with cellular membrane. This outbreak Investigations can lead to the development of novel drugs.

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