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Biology of Glycocalyx: The Essential Role in Maintaining Epithelial Barrier. A Mini-Review

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Introduction

The glycocalyx is a forgotten structure of brush border on cellular membrane recently, leading to a new paradigm elucidating the pathophysiology of diseases that anyone previously described. Formerly, this structure is known as the apical cellular parts that selectively interact with some molecules in the extracellular compartment and responsible in the signals induction that facilitates the absorption of the nutrient; let a cell utilize it as the source required in the metabolism to produces the energy. For example, the interaction between the glycocalyx and blood glucose activates the membrane receptors let the glucose across the membrane (namely sodium–glucose linked transporters/SGLTs and facilitated diffusion glucose transporters/GLUTs, insulin receptors, sodium pump, potassium channel and the use of adenosine triphosphate (ATP) let the glucose enter the cytoplasm and changed to pyruvates.¹ The pyruvates is changed to acetyl coenzyme A and interacts with NAD entering the mitochondria let the oxidative process phosphorylation (Krebs cycle proceeded in the outer matrix of the mitochondria produces 38 molecules of adenosine triphosphate (ATP) and hydrogen ion (H⁺) and carbon dioxide (CO₂) in each cycle of the cellular respiratory chain.

Later, with better knowledge based on studies findings supported by the sophisticated technology, the glycocalyx is known to plays essential roles in a living cellular. The glycocalyx referred to 1) the mucosal interface to microbiota, 2) the outer defense layer of the cells, 3) plays the essential roles in the communication and regulation of intercell interaction. These roles have a closed relationship with the encoding structure of glycan that has no specific template let each human disease associated with the changes of glycocalyx — these somehow are leading to the new paradigm of the glycocalyx.

Biology of glycocalyx

The glycocalyx lies on the superficial layer of the villus of each cell of the human body, resembling the brush border in the apical surface. The structure interacts with the actin cytoskeleton of the cell that interacts through a dynamic bound to the cellular junctions (both cell–to–cell junctions and cell–

to–matrix junctions). To this knowledge, the molecules of the glycocalyx assembled by the glycan–binding proteins – particularly transmembrane protein and the lipid components – play an essential role in molecular transportation across the membrane and fluid exchange as well.²

The dynamic binding influenced by many factors, particularly oxygen availability, pH as well as antigen(s) derived from the microbiota. This critical role has a close relationship to the cellular barrier functions mechanism that may be interfered by microenvironmental changes, such as inflammatory mediators.³

Figure 1. The structure of glycocalyx that responsible for maintaining the gut epithelial barrier. The glycans resembling the mucin domain in villi play an essential role in maintaining the homeostasis of luminal surface and resorption, also a role as initiating the signal pathway, which involves molecules of the cytoskeleton and junction structures at the same time. Proline–Threonine–Serine sequence covered by glycans comprising by oligosaccharide and N–Glycosylation with a different character.

The 'baby bottle brush shaped' structure of glycocalyx resembled by the rod comprising a repetitive sequence of the amino acids Proline–Threonine–Serine (PTS) of 0.5 to 1 μm long. The chain of this PTS sequence is covered by the glycans, which divided into the transmembrane mucin and mucin domain; no wonder that description of glycocalyx may found in conjunction with the mucin topics.⁴ The glycans of this domain comprising of oligosaccharide bound to oxygen (namely O–linked oligosaccharides, or O–linked glycans, or simply O–glycans) and N–Glycosylation (mannose, and

specific amino acid Asn–Xaa–Ser/Thr) with a different character.⁵ Other than oxygen and N, the glycans may then be bound to transmembrane protein (namely O–glycans, and N–glycans, or glycolipid, and glycosaminoglycans. These glycans were synthesized in Golgi apparatus by xylosyltransferase and alpha–glucosidase which are the processing enzymes of endoplasmic reticulum, and GnT–I, GaINAc–T1, alpha–mannosidase II, GnT–III, GnT–V, FUT–VIII, C2GnT–I, ST3Gal–I, GaIT–1, FUT–III, ST3Gal–IV, ST3Gal–III, ST8Sia–I, and ST8Gal–I, which are the enzymes of Golgi apparatus.^{6,7}

Glycan is a preferred terminology for carbohydrate composed of hydrated carbon, $[\text{CH}_2\text{O}]_n$ — this glycan, including monosaccharide, oligosaccharide, polysaccharide, and the derivatives. In the clinical setting, the carbohydrate, saccharide, sugar, or glycan is the common terminology used alternatively. A monosaccharide is a non–hydrated carbohydrate to a simple carbohydrate. Consist of oligosaccharide and polysaccharide as the main component. The oligosaccharide is the branch of monosaccharide chain bound to each other through glycosidate bound. A monosaccharide unit might be in varies. A polysaccharide is a glycan composed of several monosaccharides, mostly ten units.³

There are terminologies; one should be familiar in the study of glycans. The terminologies are 1) glycoconjugate, which is a composition containing a glycan or more (called glycone) that bounds with a component of noncarbohydrate (aglycone), 2) glycoprotein, which is protein(s) bounds to glycan, 3) glycolipid, which is a molecule containing saccharide bound to lipid, and 4) proteoglycan, which is glycoprotein(s) bounds to glycosaminoglycan chain.³

In O–glycans group, the composition based on the conjugation is classified into four cores, namely core–1, core–2, core–3, and core–4, respectively and related to its biological roles.^{8,9} In N–glycans group, N–glycans added to protein at Asn–X–Ser/Thr sequons are of three general types in a mature glycoprotein: oligomannose, complex, and hybrid. Each N–glycan contains the common core Man3GlcNAc2Asn.⁷ In a single–core, a nonreduced end of a glycan is bound to protein(s), or lipid let the glycan to have the specific biological roles, comprising structural or modulatory, which is intrinsic– and extrinsic recognition. The intrinsic recognition meanings the ability of glycan–binding protein of the cell host to recognize self–glycans, while as the extrinsic recognition meanings the ability of glycan–binding protein of the cell host to recognize the molecular mimicry of a microorganism or toxin.⁸

Recently there were known specific glycans with their specific characteristics available as the data in bioinformatics, a specific glycan characterized by a specific shape and color. The discovery of these specific glycans with their characteristic has led to the discovery of a hundred new glycans–associated diseases. It may best elucidate further by blood type of non–ABO system approach. Nowadays, there are 35 known blood type systems; some may adequately describe why people with a particular blood type are vulnerable to a specific disease, while others not, and vice versa.¹⁰ Some studies show that H antigens of the Lewis blood system (consists of six antigens in

chromosome 19 attributed with symbol FUT3¹¹ This antigen is identical to those with blood type O, assemble a composition of glycans of those who are more resistant to plasmodium vivax and virus R. Another blood system of Landsteiner and Levine (1927) describes an MNSs antigen of Mm gene that produces glycophorin and provides a resistant to plasmodium falciparum. While as Comer antigen of CROM gene provides resistant to Escherichia coli and Enterovirus R. This approach based on the knowledge of blood type antigens expressed in the cells/tissues other than blood cells, namely secretor. In other words, one may detect these blood antigens in the procedure of blood type ascertain.

Further studies show that these antigens somehow are subjected to be influenced by the environment (namely the bio phenotype) and may further explain the role of the glycocalyx in certain diseases.^{12,13}

Using this kind of approach, the studies of the antigens and related gene, it is possible to describe the glycocalyx–associated disease through the study both of histomorphology and immunohistochemistry. First, the study on histomorphology developed well in the last ten years and leading to the discovery of new findings based on specific staining techniques using immunohistochemistry. Glycans and bound antigens were stained, and the expression observed under a sophisticated microscope (fluorescence, electron microscope). Specific morphological changes of glycocalyx were well visualized and may guide clinicians to accurate diagnostic (such as apoptosis) and prompt treatment. Physiologically, the intact glycocalyx may be detected by measuring the antigen expression using ELISA. An intact glycocalyx represented as strong– or weak expression. However, should the antibody of blood type be used, the non–secretor is not expressing. Besides, non–expressed or weakly expressed antibody denoting disassembled glycocalyx.¹⁴

Clinical implication

A most recent study in surgery was the glycocalyx in surgery were those in intraabdominal sepsis. Anyone believed that the intestinal epithelial barrier is disrupted in sepsis, allowing luminal bacteria crossing the barrier. This believes it is a logical consequence whenever not the residence micro bacteria found in the extraluminal space. There is insufficient published study focused on the epithelial barrier in association with blood group, but the endothelial barrier in sepsis. The future direction may the focus changes on the mucosal barrier as the necessary explanatory of bacterial translocation.

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