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Editorial

Sweet secret of the multicellular life

Carbohydrates have been in the center of human interest since the very beginning of civilization, but we have only recently started to understand the importance of complex oligosaccharides (glycans) attached to protein or lipid backbones. This is perhaps not surprising, since the branched structures of sugars make analysis of glycoconjugates significantly more challenging than the analysis of linear DNA and protein sequences. A typical glycan is a complex molecule containing between 10 and 15 monosaccharides linked in a rather complicated manner that many of us have not yet learned to interpret. Two or more such glycans are attached to the protein backbone of an average glycoprotein, and since there is no genetic blueprint for glycans, individual glycan structures can vary depending on the current level of expression and intracellular localization of biosynthetic enzymes (glycosyltransferases and glycosidases). Consequently, slightly different glycan structures can be attached to the same protein backbone, and after the glycosylation of a protein is completed, proteins with the same amino acid sequence can end up in one of several hundred possible glycoforms. Because naturally glycosylated proteins still cannot be produced in vitro, structural analysis must be performed on small quantities of glycoproteins that can be isolated from nature, and considering the complexity of glycosylation, this can be a formidable task.

Glycans frequently represent a significant part of glycoproteins or glycolipids. Therefore, in order to understand the function of glycoconjugates, we have to study the structures of their glycans. For example, it is difficult to imagine that we could understand the way prion protein (Fig. 1) functions if we focus only on its protein part. Depending on the structure of a glycan and the protein to which it is attached, glycans can have many different functions: they can be important in proper folding of proteins; they can regulate function of protein backbones by differential processing of glycosylation [1]; they can be strategically placed so that they can provide protease protection without interfering with the function of the protein; they can serve as recognition motifs for specific carbohydrate binding proteins−lectins [2]; they can enable proteins and lipids to "jump" from one cell to another [3]; they can also have many other known and unknown functions. In the course of evolution, life forms learned how to use the potential for variability that glycosylation offers and the complexity of glycans exploded with the appearance of multicellular organisms. The transition from single cell to multicellular organisms required the invention of many new molecules and mechanisms needed to guide and control interactions between individual cells. Glycosylation was apparently a very useful tool in this evolutionary process, and today nearly all membrane and extracellular proteins are glycosylated [4]. Unfortunately, for most of them, we still do not know exactly how and why they are glycosylated. Many proteins appear to function (at least in some way) even when completely devoid of their glycans, but in many cases where glycosylation has been studied in more detail, glycans were found to be essential for proper function of the respective protein (Table 1).

Cells of higher eukaryotes are covered with a dense layer of glycoconjugates (glycocalyx) that mediate their communication with the outside world. Pathogens seeking access to the interior of the cell first have to bind to some of the

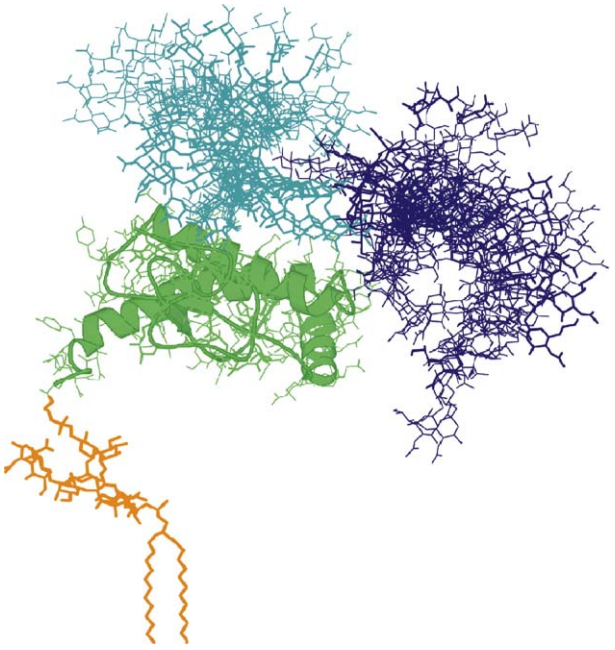

Fig. 1. Prion "furball". Prion protein is a glycoprotein composed of the amino acid backbone, two *N*-glycans, and a glycosylphosphatidylinositol anchor. The protein part of the molecule is shown in green, dynamics of the two attached N-glycans is shown in light and dark blue, and the glycosylphosphatidylinositol anchor is colored orange. Figure courtesy of M.R. Wormald, R.A. Dwek, and P. M. Rudd, Glycobiology Institute, Oxford, UK.

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Table 1
Some processes in which an essential role of glycosylation has been demonstrated

- Selectins, a family of adhesion receptors regulate inflammation through interaction with their glycoconjugate ligands [6].
- Differential elongation of *O*-fucose residues on EGF repeats of Notch modulates activation of this essential player in a wide variety of developmental cascades [1].
- Glycosylation determines half-life of recombinant erythropoietin in the circulation [7].
- Differential glycosylation of membrane cytokine receptors regulates their half-life on the membrane [8].
- Attachment of a single O-linked *N*-acetylglucosamine to protein backbones of numerous proteins is a regulatory modification that is essential for life at the level of a single cell [9].
- Addition of proper glycans to Asn297 in the C_H2 domain of IgG is necessary for efficient binding of IgG to FcγRIIIa and antibody-dependent cellular cytotoxicity [10].

glycoconjugates on the cell surface; thus, the variability of glycan structures represents a valuable tool that higher eukaryotes use to outmaneuver rapidly evolving pathogens. Using carbohydrates and their analogs to inhibit binding of pathogens to glycans on the cell surface appears to be a very successful antimicrobial strategy, and this approach promises to yield many new anti-adhesion drugs for the therapy of infective diseases [5].

With the completion of the human genome project, the focus of biomedical science is shifting to proteomics. Unfortunately, many studies are being performed on recombinant proteins, which either lack glycans altogether or are associated with some non-physiological glycans. Because over 60% of all proteins are actually glycoproteins [4], this is a significant drawback. Conversely, on the other side of the proteomics field, represented by glycobiology, it is frequently ignored that physiological functions of most glycans are defined by their exact position on a protein, and that study of isolated glycans will not give insight into functions of a native glycoprotein. In spite of differences in genealogy and biosynthetic mechanisms of carbohydrate and protein parts of a glycoprotein, once synthesized, glycoprotein functions as a single unit and other interacting molecules cannot differentiate whether they are binding to a protein or a carbohydrate part of the molecule. If we want to understand the secret of multicellular life that lies hidden in the complex process of glycosylation, we will have to use an integrative approach and study each individual glycoprotein as a functional unit composed of its protein and carbohydrate parts. Interest in glycoscience is increasing at an ever faster pace. With the current level of approximately 20,000 publications per year, glycoscience generates an impressive amount of information about this complex part of life. However, this is still only slightly above 3% of all biomedical publications (cited in the PubMed database), which is in great disparity with the extent and importance of glycosylation. Because the understanding of glycans is needed to understand life at the molecular level, it is essential to raise awareness of the importance of glycosylation in the general scientific public. Let us hope that devoting special issues in general journals to glycobiology, like this special issue on glycoproteomics, will bring us a little closer to this goal.

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