Biochimica et Biophysica Acta xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagen

The promise of protein glycosylation for personalised medicine☆

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ARTICLE INFO

Article history:
Received 22 December 2015
Received in revised form 4 March 2016
Accepted 5 March 2016
Available online xxxx

Keywords:
Serum tumour markers
IgG
Cancer
Glycomics
Glycoproteomics
Personalised medicine

ABSTRACT

Background: Complex diseases such as cancer are a consequence of numerous causes. State of the art personalised medicine approaches are mostly based on evaluating patients' individual genetic background. Despite the advances of genomics it fails to take individual dynamic influences into account that contribute to the individual and unique glycomic and glycoproteomic "configurations" of every living being.
Scope of review: Glycomic and glycoproteomic-based personalised medicine diagnostics are still in their infancies, however some initial success stories indicate that these fields are highly promising to mediate novel early diagnosis and disease stratification markers, subsequently resulting in improved patient well-being and reduced treatment costs. In this review we not only summarise current protein glycosylation based examples that substantially improve or possess great potential for personalised medicine, but also describe current limitations as well as future perspectives and challenges associated with establishing protein glycosylation aspects for this purpose.
Major conclusions: Many protein biomarkers currently in clinical use are glycoproteins, however, their glycosylation status is seldom evaluated in a clinical context. To date just few examples have already been successfully translated into clinical practice, making protein glycosylation a highly promising diagnostic target with humongous potential for personalised medicine.
General significance: There is an urgent need for markers that enable the establishment of an individualised and optimised patient treatment at the earliest disease stage possible. The glycosylation status of a patient and/or specific marker proteins can provide important clues that result in improved patient management. This article is part of a Special Issue entitled "Glycans in personalised medicine" Guest Editor: Professor Gordan Lauc.

1. Protein glycosylation influences protein function in health and disease

Protein glycosylation represents a highly interesting but still underutilised target for disease diagnosis, prognosis, therapy response and follow-up analysis since changes in glycosylation are a hallmark of various diseases [1]. Personalised medicine aims to individualise diagnosis and treatment based on an individual's medical history, physiological status and molecular characteristics. Extensive research applying genomics and proteomics has already shown some advances in personalised medicine [2], nevertheless the potential embedded in protein glycosylation signatures to be used for this purpose has to date not been fully utilised. In this review we want to provide a concise overview on current developments and efforts to employ aspects of protein glycosylation for personalised medicine.

1.1. Glycoproteins are essential key molecules in health and disease

The continuously growing interest in protein glycosylation and its consequences on protein function has catalysed a tremendous growth and improvements in glycomic and glycoproteomic technologies in recent years [3]. Numerous examples impressively demonstrated that addition of these -omics science flavours often overturned traditional knowledge on protein function [4–7]. As changes in protein glycosylation are frequently identified in the context of diseases such as cancer or inflammatory conditions, it does not come as a surprise that glycoproteins and their respective glycan signatures are considered attractive marker targets [4,8–12]. Disease associated glycosylation

Abbreviations: β-hCG, β-human chorionic antigen; AFP, α-fetoprotein; AFP-L3, core fucosylated α-fetoprotein; ALC, heavy alcohol consumption; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; EGF, endothelial growth factor; EGFR, endothelial growth factor receptor; ELISA, enzyme-linked immunosorbent assay; HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; Hp, haptoglobin; HNF1A, hepatocyte nuclear factor 1-a; IgG, immunoglobulin G; MODY, maturity-onset diabetes of the young; MUC, mucin; NeuAc, N-acetylneuraminic acid; PSA, prostate specific antigen; SLe^a, Sialyl Lewis A; SLe^x, Sialyl Lewis X; STn, Sialyl Tn; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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http://dx.doi.org/10.1016/j.bbagen.2016.03.012
0304-4165/

changes can derive from a huge number of molecular causes as glycan biosynthesis is, unlike the synthesis of DNA, RNA and proteins, a non-template-driven process involving numerous different participants [1]. Thus glycosylation signatures provide a global reflection on an individual's health/disease status that can in principle be utilised in the context of personalised medicine, given that the associations between glycan signatures, particular diseases and their treatment are understood (Fig. 1).

1.2. Glycoconjugates are crucial for recognition events

N- and O-glycans represent the best studied (and also most abundant) types of posttranslational modifications found on plasma membrane and secreted proteins [1]. They are crucial for a wide range of processes such as protein folding within the endoplasmic reticulum and conformational stability of glycoproteins [13], but have also been linked to numerous events outside the cell where they are involved in adaptive and innate immunity responses [14]. Glycans can also act as ligands for glycan binding proteins, such as galectins and selectins, where they mediate cell trafficking, angiogenesis, adhesion and signalling events [9,15,16]. Commensal and pathogenic organisms also continuously exploit such recognition events. *Helicobacter pylori* for example uses specific adhesins to adhere to mucosal glycan epitopes and subsequently colonises the gastric mucosa [17]. Individual genetic polymorphisms in the host glycosyltransferase genes that result in a distinct expression profile of histo-blood group antigens determine the susceptibility for an infection with *H. pylori* [18,19]. Subsequently, the infection and the resulting host inflammatory responses can induce gastritis, which in the worst case can result in gastric cancer. This example shows that glycosylation plays a major role in interaction and recognition events and is having substantial influence on the individual disease history [9].

1.3. Glycosylation requires a complex biosynthetic machinery

Roughly 1–2% of the entire genome are dedicated to produce enzymes such as glycosyltransferases, glycosidases and transporters that form the complex glycosylation machinery spanning various cellular compartments [1]. The majority of glycosylation processes happen within the endoplasmic reticulum and the golgi apparatus, however key steps such as the synthesis of nucleotide sugar precursors are mostly executed within the cytosol with exception of CMP-sialic acid, which is only synthesised in the nucleus [1,20–22].

Several factors contribute to the huge diversity associated with glycan structures: (1) expression levels of glycosyltransferases [11]; (2) substrate competition between glycosyltransferases for glycan acceptors [1]; (3) trafficking of glycosyltransferases and glycosidases to the ER and Golgi [1]; (4) protein and nucleotide sugar substrate availabilities; (5) expression and localisation of specific glycosidases [1,20]; (6) protein folding and its quaternary structure [23] as well as (7) variations in micro-environmental stimuli such as oxygen levels [24]. Protein glycosylation is furthermore tissue-specific, as individual components of the glycosylation machinery differ between tissues, resulting in glycoproteins sharing the protein sequence but differing in their individual glycosylation. Thus glycoprotein macroheterogeneity (degree of site occupancy) and microheterogeneity (type and relative distribution of glycans on individual sites of glycosylation) have the intrinsic potential for providing crucial information on the health and/or disease status (Fig. 2) [25].

The involvement of so many individual cellular components required for glycosylation processes increases the probability for the occurrence of disease associated glycan alterations. It also poses additional challenges for identifying the causative cellular events and subsequently interpreting its disease associated relevance. Other factors such as age, sex, and epigenetic background also influence the glycosylation machinery and thus its products, which can impede differentiation of

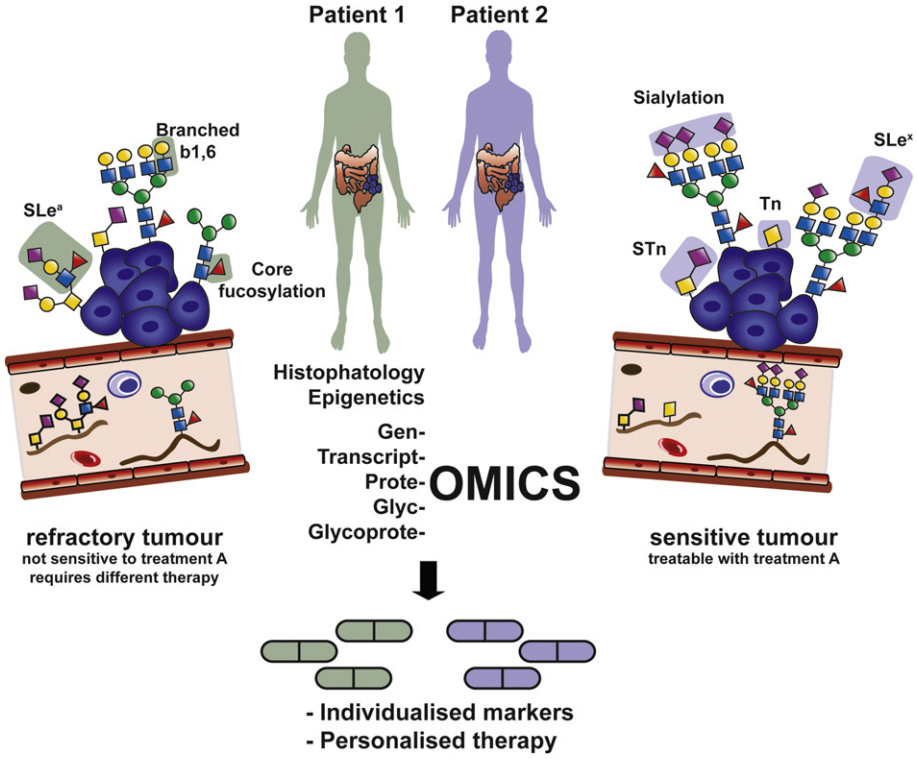

Fig. 1. Glycosylation signatures provide a global reflection on an individual's health/disease status and can function as predictive indicators for treatment success. Differences in presence, quantity, and specific localisation of glycan features such as sialylation, core fucosylation, N-glycan branching, Lewis epitope andTn/Sialyl-Tn antigen expression are frequently described in association with diseases. A combination of different -omics strategies including glycomics & glycoproteomics will be essential for improving diagnosis and treatment personalisation.

Please cite this article as: A. Almeida, D. Kolarich, The promise of protein glycosylation for personalised medicine, Biochim. Biophys. Acta (2016), http://dx.doi.org/10.1016/j.bbagen.2016.03.012