Pros and cons of using aberrant glycosylation as companion biomarkers for therapeutics in cancer

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Cancer treatment has been stratified by companion biomarker tests that serve to provide information on the genetic status of cancer patients and to identify patients who can be expected to respond to a given treatment. This stratification guarantees better efficiency and safety during treatment. Cancer patients, however, marginally benefit from the current companion biomarker-aided treatment regimens, presumably because companion biomarker tests are dependent solely on the mutation status of several genes status quo. In the true sense of the term, “personalized medicine”, cancer patients are deemed to be identified individually by their molecular signatures, which are not necessarily confined to genetic mutations. Glycosylation is tremendously dynamic and shows alterations in cancer. Evidence is accumulating that aberrant glycosylation contributes to the development and progression of cancer, holding the promise for use of glycosylation status as a companion biomarker in cancer treatment. There are, however, several challenges derived from the lack of a reliable detection system for aberrant glycosylation, and a limited library of aberrant glycosylation. The challenges should be addressed if glycosylation status is to be used as a companion biomarker in cancer treatment and contribute to the fulfillment of personalized medicine. [BMB reports 2011; 44(12): 765-771]

INTRODUCTION

Prevention and treatment have been the main approaches adopted to improve health and, they serve as a double-edged sword in the biomedical realm. We have seen tremendous progress in both areas for the last a few decades, and an increased understanding of molecular events occurring inside diseased organisms has inarguably led to improvements in medical science. However, we still have a long way to go before we have comprehensive and efficient therapeutic options, particularly for obdurate diseases such as cancer, diabetes mellitus, etc. It is a reality that a majority of deaths still originate from cancer, stroke, and cardiovascular disease (1).

To address these challenges, increased efforts have been being made to enhance the efficiency of treatments, including combining treatment agents with diagnostics, which opened the era of ‘theragnostics (therapeutics plus diagnostics)’. This approach is based not only on the notion that every genetic identity has its suitable method of treatment, but also on the idea that the current treatment regimes can be replaced with molecular-targeted therapy. Especially, gene-based in vitro diagnostic (IVD) testing boasts unsurpassed increments in growth rate, with thousands of genes being targeted for new molecular in vitro tests (2). These IVD tests are comingled with the therapeutics in the pipeline of drug development, thereby implementing the ‘right treatment to the right patient’ strategy and producing better clinical outcomes. Nonetheless, current medications with IVDs are used in a dichotomic fashion; genetic mutation of a gene is the sole criterion for the choice of a treatment and one of the bisected groups is intended to benefit from the therapeutic approach. Because every patient identified as belonging to the ‘supposed to benefit’ group does not respond to the treatment, the current therapeutic strategy does not meet the goal of personalized medicine. To fulfill this ultimate goal in cancer, we need to know every possible molecular signature and environmental factor governing the efficiency and efficacy of a treatment.

As a case in point, we suggest in this review that the glycosylation status of a molecule can be a critical determinant for therapeutic choices in cancer. We introduce evidence that glycosylation variants are observed in cancer and affect the development and progression of diseases. In addition, we highlight the promising and limiting aspects associated with the use of glycosylation status as a companion biomarker for therapeutics.

Brief history of targeted therapy

Cancer is the leading cause of death worldwide and a tremendous effort has been made to develop anti-cancer drugs. Contrary to traditional chemotherapy which is usually intended to interfere with rapidly dividing cells, the currently used drugs are targeted at specific molecules required for tumorigenesis and proliferation, and thereby guarantee improvements in both efficacy and safety. A brief review of the history of molecular-targeted therapy in cancer will be presented to provide deeper insights for understanding companion biomarker-guided targeted...
therapies which will be discussed.

Imatinib mesylate (Gleevec, also known as STI-571) is regarded as the first success story in molecular-targeted therapy. This drug specifically inhibits ABL-BCR tyrosine kinase activity and is effective in the treatment of chronic myeloid leukemia (CML) patients who have the ‘Philadelphia’ chromosome (3-5). Rationale underlying the development of imatinib mesylate contributed to the design of ensuing kinase inhibitors and monoclonal antibodies for cancer treatment. The long development time required from the identification of the ‘Philadelphia chromosome until the approval of Gleevec was significantly shortened for the development of the ensuing tyrosine kinase inhibitors. Herceptin, which targets the Her2/neu tyrosine kinase receptor (also known as ErbB2) overexpressed in some types of breast cancer, mirrors the progress in recent drug development (6, 7). In this case, the accompanying diagnostic test for HER2 expression, known as the HercepTest, provided the treatment stratification by enabling physicians to identify the patients who are considered to benefit from the monoclonal antibody (8).

Similarly, gefitinib (Iressa, also known as ZD1839) was intended to target epithelial growth factor receptor (EGFR), which is over-expressed in non-small cell lung cancer and other solid tumors including colon and breast cancer (9). The efforts to identify target molecules to control cancer have led to an expanded list of target molecules, including not only various kinase receptors such as vascular endothelial growth factor receptor (10) and ALK (11), but also non-kinase molecules, i.e., bcl-2 (12), PARP (13), estrogen receptor (14), Janus kinase (15), and PI3K (16).

Progress in DNA sequencing and microarray techniques have made it possible to compare genome-wide studies on the relation of genetic variations with diseases. In genome-wide association studies (GWASs), whole genes were subjected to analysis for the association of person-to-person gene variation and diseases, leading to, for example, the discovery of strong associations of the deletions close to the gene encoding complement factor H (CFH), complement factor H receptor 1 (CFHR1) and CFHR3 with a reduced risk for age-related macular degeneration (17). Currently, 4,000 SNP associations are claimed for CFHR3 with a reduced risk for age-related macular degeneration (18). Along with genomic studies, we have equipped ourselves with top-notch proteomics and systems biology-based techniques to expand the spectrum of genes and proteins ‘targetable’ for diseases.

Companion biomarker as part of the drug development

The mutation study on the KRAS gene has opened a new era of targeted therapy, exemplifying the importance of discovering and testing an associated factor which affects responsiveness to a drug. After it had been reported that the HRAS gene shows a point mutation at codon 12 (19), similar mutations in KRAS and NRAS were reported (20, 21). Of note is the finding that the KRAS mutation status plays a critical role not as a drug target but as a predictive biomarker for tumor responsiveness to anti-EGFR monoclonal antibody therapies (22-24). Cetuximab and panitumumab are anti-EGFR drugs developed for the treatment of colorectal cancer and were found to produce a response only in KRAS mutation-negative patients. This case reflects the importance of a companion biomarker when devising a specific therapeutic regimen that is optimal for treatment based on the disease status of a particular patient and mirrors the future direction of diagnostics in the development of therapeutics. Directly or non-directly, the bio-molecular signature other than the target molecule will guide the treatment strategy, identify the right patients who will experience the best results in the response to a therapeutic agent, and help develop the best suited program of medication.

Pari passu with this direction, the Food and Drug Administration recently issued guidelines on ‘Companion Dx’ which support the development of innovative new targeted medicines and their corresponding diagnostic tests, and are intended to provide manufacturers with greater predictability (25). It is hoped that these guidelines will help the commercial therapeutic manufacturers develop the best suited drugs for responder populations and will spare non-responders from exposure to potential side effects of drugs that will not work for them.

There are, however, many obstacles to overcome to realize bona fide ‘personalized medicine’ with the aid of companion biomarkers in cancer. There are only a few groups into which patients can be partitioned based on available companion biomarkers. Referring to the case above, every KRAS mutation-negative patient is not responsive to a single anti-EGFR monoclonal antibody. This implies that patients with a disease should be classified into multiple groups by using multiple variables which evidently affect the pathological processes of a disease. In this sense, fulfillment of personalized medicine requires that classification of patients should be supported by sufficient information on genetic mutations beyond what has currently been discovered, as well as by expression profiles, post-translational modifications (PTMs), and time-dependent variation of molecular signatures obtained from rigorous basic research.

Alterations in the glycosylation status associated with cancer

Immature proteins are enzymatically synthesized in the endoplasmic reticulum (ER), and later undergo modification with one or more chemical moieties, termed post-translational modification (PTM). Glycosylation is typically one of several PTMs that are usually found in eukaryotic cells and produced by enzymatic catalysis, as opposed to non-enzymatic chemical reaction of glycation. Protein glycosylation can be classified into several types according to the glycan linkage site: N-linked glycosylation, O-linked glycosylation, and glycophosphatidylinositol (GPI)-anchored glycosylation (Fig. 1). N-linked glycosylation is formed at the asparagine (N) site of the N-X-S/T sequence where S and T represent serine and threonine, respectively, and X can be any amino acid except proline. Mature N-linked glycan consists of a core structure containing 2 N-acetylglucosamine and 3 mannose residues, of which 2 mannoses are elongated with antenna formed by galactose, N-acetylgalactosamine, N-acetylgalactosamine, fucose, and sialic acid. O-linked glycosylation is a relatively late-stage phenomenon.