Online ISSN: 2682-2628
Print ISSN: 2682-261X

IJCBR

International Journal of Cancer and Biomedical Research

https://jcbr.journals.ekb.eg

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PUBLISHED BY
EACR EGYPTIAN ASSOCIAN FOR CANCER RESEARCH
Since 2014

INTERNATIONAL JOURNAL OF CANCER AND BIOMEDICAL RESEARCH (IJCBR)

REVIEW ARTICLE

Gene-behavior theory: Behavior from nil to tangible glycosylation-implications for cancer prognosis and treatment strategies

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ABSTRACT

Increased disease susceptibility in some communities is problematic for health planners and providers. The previous gene-behavior theory outlined a causal relationship between behavior and disease susceptibility in non-coding satellite DNA. While this theoretical viewpoint requires further thought to know more about this relationship; it does provide a platform for further rigorous research. In this review, glycosylation was reviewed from a new perspective, thus we focused and tracked its association with satellite DNA and cancer susceptibility using sequential reasoning. Our model suggests glycosylation is a major tangible action of satellite DNA alterations caused by behaviors. Our model also suggests glycosylation is influenced by genetic anticipation. In addition, glycosylation patterns may function as behavioral biomarkers for the social sciences, community-targeted approaches, and early prognostic tools for behavioral-related pathogenesis. These notions open up new avenues for behavioral immunogenetics and behavioral epidemiology areas. Therefore, more in-depth and improved treatment strategies are required, especially for cancer.

Keywords: Cancer; Disease susceptibility; Gene-behavior theory; Glycosylation; MicroRNA.

Editor-in-Chief: Prof. M.L. Salem, PhD - Article DOI: 10.21608/jcbr.2022.96763.1233

ARTICLE INFO

Article history

Submitted: November 21, 2021
Revised: May 24, 2022
Accepted: May 30, 2022

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INTRODUCTION

Globally in 2020, estimated cancer numbers were approximately 16 million, with an annual incidence of 201 per 100,000 and increasing numbers year by year (Ferlay et al., 2020). Many populations demonstrate an increased tendency to be affected by specific diseases related to behavior. These studies indicate the importance of research targeting social genetic susceptibility and behavioral epidemiology. Our previous theory outlined a causal relationship between behavior and disease susceptibility in non-coding satellite DNA or microRNAs (miRNAs) (Mohamed, 2017). However, this theoretical notion requires more thought to resolve issues with this putative relationship and to provide clues for comprehensive experimental research.

Many causative factors are cited in carcinogenesis and for increased cancer susceptibility, e.g., glycosylation profiles are significantly altered during oncogenesis (Thomas et al., 2021). Additionally, miRNAs have emerged as critical regulators implicated in these changes (Thu and Mahal, 2020). Therefore, we aim to review glycosylation events and study the plausibility of intangible behaviors translated to tangible physiological /pathological glycosylation signatures. Importantly, this may open up a new era of cancer studies. Our research approach involves sequential reasoning, where theoretical reasoning begins at "cancer" and glycosylation, progresses through miRNA and ends with "behavior."

What is glycoproteomics?

Glycoproteomics is a sub-discipline of proteomics and examines protein glycosylation in different biological processes (Yang et al., 2017). "Proteomics" is defined as the large-scale, whole-protein complement of a cell line, tissue, or organism (Wilkins et al., 1995). Protein glycosylation is a common post-translational modification (PTM) where carbohydrates are

attached to proteins. Glycosylated proteins are widespread components of the extracellular milieu and cell surfaces (Hofsteenge et al., 1994).

The discovery of proteins with PTMs paved a new research pathway, with a greater emphasis on protein function and structure rather than sequence identification and analysis as conducted in basic research. Biological changes such as disease progression or "increased disease susceptibility" are usually associated with protein expression dynamics and associated glycosylation patterns/ signatures (Wei and Li, 2009).

Cancer and glycosylation

Glycosylation is considered an unfamiliar entity in many cancer related-areas, including oncogenes and anti-oncogenes, apoptosis, angiogenesis, growth factor receptors, and adhesion molecules (Hakomori, 2002). Glycosylation signatures are significantly changed during oncogenesis and in some cases, glycoproteins function as cancer biomarker targets (Peracaula et al., 2003; Thomas et al., 2021)

Cancer-associated glycan biosynthesis and its reversible reflection with the cellular milieu provides another molecular view of oncogenic pathways (Peixoto et al., 2019). Cell glycosylation is associated with oncogenesis, malignant cell-cell interactions, and metastasis (Rodrigues et al., 2018). Deviated glycosylation processes have been documented in all cancer types, making it a promising biomarker and therapeutic target (Thomas et al., 2021). For example, altered glycosylation patterns can distinguish between elevated prostate-specific antigen levels from normal and tumor origins (Peracaula et al., 2003). Recently, it was reported that plasma glycan-binding auto-immunoglobulin G biomarker levels improved the accuracy of prostate cancer diagnosis (dos Santos et al., 2021).

In lung cancer, glycoprotein expression may directly reflect the physiological and/or pathological status of lung cells (Kay Li et al., 2012). Recent research showed that five potential glycan structures were identified as unique lung cancer signatures (Liu et al., 2020). Furthermore, dramatic changes were observed in protein glycosylation levels in gastrointestinal track tumors (esophageal, gastric, and colorectal cancers), thereby generating molecular fingerprints (Fernandes et al., 2020). Similar tumor-specific glycosylation findings were also identified in ovarian, cervical, and breast carcinoma (Hu et al., 2020; Sakata-Matsuzawa et al., 2021; Lopes et al., 2021; Xu et al., 2021).

Normal glycan expression is required for cell recognition, adhesion, and signaling, which are pivotal functions for immune-hematological cells such as granulocytes, lymphocytes, and plasma cells. In terms of hematological malignancies, aberrant glycan expression was particularly identified in acute myeloid leukemia, myeloproliferative neoplasms, and multiple myeloma (MM) (Pang et al., 2018). In particular for MM, not only did serum N-glycosylation protein levels distinguish MM patients from healthy controls, but they showed strong correlations between glycan alterations and disease development (Zhang et al., 2019). These glycan changes in MM are therefore considered effective/non-invasive diagnostic biomarkers (Jin et al., 2021).

Glycosylation and miRNAs

Recently, miRNAs have emerged as key regulators of glycosylation (Thu and Mahal, 2020). Glycosylation is typically controlled by glycosylation enzymes; however, these regulatory pathways use miRNAs as proxy molecules. This strategy exemplifies the hidden function of miRNAs as protein decorators by glycogenes (Kurcon et al., 2015). Critically, modifications caused by either miRNAs or glycosylation mainly affect protein functionality (Hu et al., 2020). For example, the miRNA-mediated regulation of a glycosylation pathway in Sjögren Syndrome (autoimmune disease) strongly suggests a salivary gland insufficiency mechanism (Gallo et al., 2019). Additionally, abnormal miRNA expression promotes aberrant glycosylation in immunoglobulin-A nephron-pathy (Serino et al., 2012).

MiRNAs and behavior

MiRNAs are derived from repetitive elements including satellite DNA (Yuan et al., 2011) which

is related to cell cycle control, DNA damage, and malignancy (Jansson and Lund, 2012; Rich et al., 2014). Additionally, satellite DNA has been proposed to mediate between deviated behavior and increased disease susceptibility (Mohamed, 2017).

Increased genetic damage putatively arises from deviated behaviors (Mohamed, 2017). DNA damage is a causal factor in cancer development. Genetic defects are predisposed to cancer mutations in distinct DNA repair systems which elevate susceptibility to various cancers (Torgovnick and Schumacher, 2015). Statistical evidence has shown that increased cancer susceptibility, as reflected by genetic damage, is controlled by exposure to a deviated behavior. The effect of behavioral deviation differs according to the deviation type, which translates to a corresponding cancer type (Mohamed, 2017).

Theoretical Focus (Mohamed, 2017). **Box 1**

Gene-behavior theory

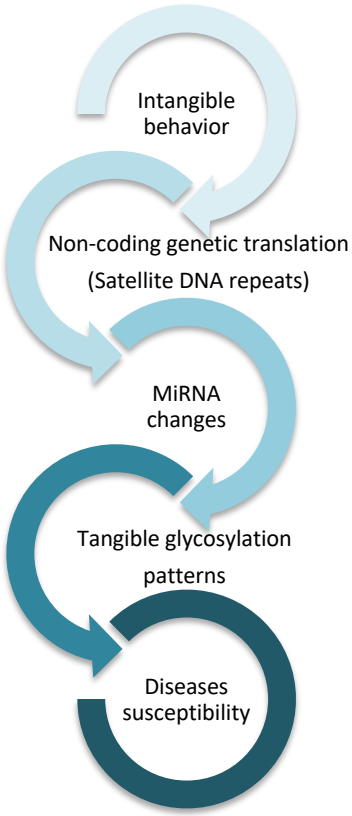
The gene-behavior theory postulates that satellite DNA functions as a mediator between behavior and disease susceptibility. Previous research showed that satellite DNA was highly, causatively related to disease, especially inherited diseases (blue arrow). Our epidemiological studies, based on a conformity approach, identified a relationship between behavior and increased selective disease susceptibility in communities (red arrow). Thus, the relationship between satellite DNA and behavior is strongly assumed (green arrow).

Our previous gene-behavior theory outlined a causal link between three different categories. The line starts with behavior as a cause, which is believed to be translated in a non-coding gene (e.g., satellite DNA) and ends with decreased/increased disease susceptibility. The relationship between the first and last categories was shown by statistical analysis but the middle gene-behavior element requires further thought and experimental data (Box 1).

Cancer from behavior to glycosylation - a novel paradigm

Our model indicated that glycosylation is a major tangible action of satellite DNA damage as affected by behavior. Our rationale proposes a connection between inherited cancer susceptibility and altered DNA (especially non-coding DNA thus miRNA) and how it affects protein functionality via glycosylation (Box 2).

Theoretical Focus **Box 2**



From nil to tangible theory

A cascade of suggested events leads to altered disease susceptibility (e.g., cancer); it starts from an intangible behavior and ends with tangible glycosylation.

Is aberrant glycosylation a result or a cause of cancer? Some studies have suggested that altered glycosylation is the result of initial oncogenic events (Hakomori, 2002). Our putative theoretic findings agreed with the notion that glycosylation resulted from initial oncogenic events (e.g., aberrant miRNA expression). Thus, being suggested as one of the tangible cancer causes (Box 2). However, further experimental studies are required to evaluate this theoretical claim.

Glycosylation as a behavior/prognostic biomarker

Cancer susceptibility is strongly influenced by inherited non-coding genetic regions (Rich et al., 2014). As a result, miRNAs are currently being used in clinical settings as diagnostic and prognostic indicators, and also treatment agents (Jansson and Lund, 2012). Consequently, glycosylation appears to be a viable non-invasive diagnostic and prognostic indicator (Fernandes et al., 2020). Glycosylation patterns have become attractive targets for personalized medicine; many studies have reported the presence of unique glycosylation patterns and repertoires associated with disease and reflect all cancer characteristics (Peixoto et al., 2019).

Glycans play roles in the molecular resistance to conventional cancer treatments (radiation and chemotherapy) as they increase tumor aggressiveness and promote the immunosuppressive milieu (Khan and Cabral, 2021). However, this apparent glycosylation disadvantage was advantageously converted to a target for drug delivery using these aberrant signatures (Diniz et al., 2022).

Satellite DNA, which is a precursor of miRNAs, is affected by genetic anticipation. A correlation was previously reported between tandem repeat size and disease severity (Rich et al., 2014; Harper et al., 1992; Richards and Sutherland, 1992; Kim et al., 2006). The glycome may *a priori* follow miRNAs as being influenced by this phenomenon. Thus, if glycome changes became more intense, this may explain the increased resistance to radiotherapy and chemotherapy.

Genetic anticipation is proposed to be the result of continuous exposure or repetition of a deviated behavior through successive generations (Mohamed, 2017). Thus, studying relationships between glycosylation patterns and corresponding behaviors will open new promising avenues for many disciplines, including behavioral genetics, behavioral epidemiology, and behavioral immunity. Additionally, glycosylation may become a behavioral biomarker for social sciences and an early prognostic tool for behavioral-related pathogenesis.

CONCLUSIONS

Our model suggests glycosylation, as a major tangible action of satellite DNA damage, may be affected by behavior and is influenced by genetic anticipation. This could be considered another step-in understanding gene-behavior theory. Of the many cellular pathways involved in cancer biology, the behavior-related genetic damage/aberrant glycosylation pathway is unique. Importantly, our theory promotes an increased understanding of behavior-related cancer susceptibility and immunity. Also, the glycome may have a role as a behavioral biomarker for the social sciences and function as an early prognostic tool for behavior-related pathogenesis. Therefore, further experimental studies are warranted to resolve the theoretical issues with our theory.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interests.

FUNDING

This research did not receive a specific grant from funding agencies in public, commercial, or not-for-profit sectors.

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