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

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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.
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 nephropathy (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).

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 (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).

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.

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