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*Review Article*

# Significance of Altered Glycosylation in Oral Cancer

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## ABSTRACT

Cancer being a cellular disease, changes in cellular glycoproteins via glycosylation plays an important role in malignant transformation and cancer progression. Protein glycosylation is the most widely observed and structurally diverse form of post-translational modifications. Around 70% of human proteins are found to be glycosylated. Glycosylation is the enzymatic process that produces glycosidic linkages of saccharides to other saccharides, proteins or lipids. Various investigators have documented fundamental role of glycosylation in key pathological steps of tumor development, progression and metastasis. Alterations in cell surface glycosylation particularly, terminal motifs may results in altered cell-cell adhesion, cell-matrix interactions, inter and intra-cellular signaling and cellular metabolism. To study these glycosylational changes, study of glycome is required. The glycome in a cell or tissue is assembled by the synchronized action of numerous glycan modifying enzymes termed as glycosyltransferases and glycosidases. Majority of the studies have investigated protein glycosylation changes by studying these enzyme alterations in cell lines and tumors of various cancers. The present review represents an ample overview on aberrant glycosylation and associated systemic enzymes in oral cancer as well as other different cancer types. It is predicted that the understanding of these biologically relevant glycan alterations on cellular proteins will smooth the progress of the discovery of novel glycan based biomarkers which can potentially serve as diagnostic and prognostic indicators as well as newer drug targets for oral cancer.

***Keywords:*** Oral cancer, Glycosylation, Glycosyltransferases, Glycosidases, Sialylation, Fucosylation

## Oral cancer: A major health hazard in India

Oral cancer is the most common cancer in India and accounts for one third of oral cancer cases in the world. [1] 20 per 100000 populations are affected by oral cancer which accounts for about 30% of all types of cancer. [2] According to the statistics, in 2018 the incidence of oral cancer in India is 1, 19, 992 and mortality is 72,616. [3] In Gujarat, Western India, this malignancy is highly prevalent with a serious trend of increased rate in the younger age groups. [4] Additionally, chewing *mawa-masala* and *gutkha* is the predominant tobacco habit in population from Gujarat. [5] For early diagnosis and better treatment of oral cancer, it is mandatory to completely understand the molecular mechanisms of initiation, promotion and progression to identify newer biomarkers for management of cancer.

## Glycosylation: A major post-translational modification

Glycosylation is an enzymatic process that links glycan sugars to other glycans, lipids or proteins. It is one of the most common types of post-translational

modification and it is a critical determinant of protein function. It plays a major role in cell signaling, immune recognition and cell-cell interactions. [6] Glycosylation is not a template based process such as DNA, RNA or protein synthesis but is rather based on the balance achieved by the expression and activity levels of the different enzymes involved in the glycosylation process. The complete pattern of glycan modifications in a cell or tissue known as the glycome is assembled by the synchronized action of numerous glycosylation enzymes and takes place in the Golgi apparatus and the lumen of the endoplasmic reticulum. [7] Glycosyltransferases synthesize glycan chains, whereas glycosidases hydrolyze specific glycan linkages. Although glycosyltransferases are the anabolic component of glycosylation, both types of enzymes determine the structural outcome of a particular and reproducible glycan profile referred to as the glycome, which is a unique feature distinguishing one type of cell, matrix, protein or lipid from another (Figure 1). The structural variations in glycome at the cell surface produce numerous biomarkers for cell differentiation, cell activation and various diseases. [8,9] This highly increases the complexity of the protein glycosylation process and the molecular microheterogeneity of glycoproteins. [10]

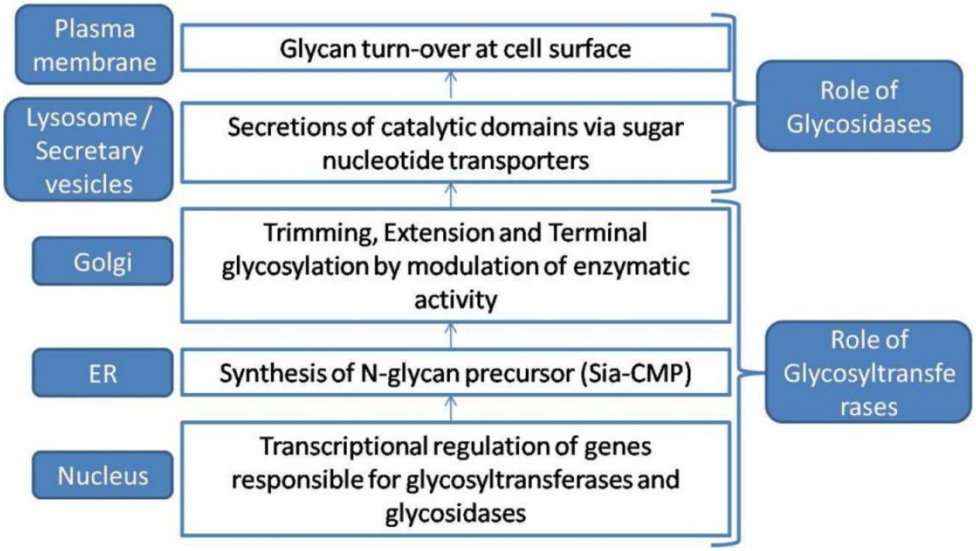


**Figure 1: Mechanisms of glycan formation via alterations in expression, structure and activity of cellular glycosyltransferases and glycosidases**

The cell surface membrane plays an important role in the social behavior of cells that is communication with other cells, cell movement and migration, adherence to other cells or structures, access to nutrients in the micro-environment and recognition by the body`s immune system. [11] Glycans exist as membrane-bound glycoconjugates or as secreted molecules, which can become integral parts of the extracellular matrix. In these locations, glycan can mediate cell adhesion and motility as well as intracellular signaling events. [12] Moreover, changes in glycan structures are associated with many physiological and pathological events such as cell growth, migration and differentiation. Aberrant changes in cellular processes are likely to result in alterations of the glycan profiles of the cell surface resulting in various diseases which are found to be associated with a distinct glycosylation pattern of a cell. For example, humans lacking a functional ST3Gal-V glycosyltransferase, also known as GM3 synthase, develop an early neurological disorder termed infantile-onset symptomatic epilepsy. [13] Consequently, aberrant glycosylation occurring in cancer cells also influence cell proliferation, adhesion and

motility as well as angiogenesis and metastasis. [14]

Recent studies have shown that glycoproteins are found on all animal cells and that their glycan structures are commonly altered upon cellular transformation. Changes in glycosylation provide new directions for understanding the molecular nature of cancer and cellular transformation and often new opportunities for identifying biomarkers of disease and developing interventional strategies for treatment. [15] Various studies have been carried out to identify changes in glycan structures. In most cancers, fucosylation and sialylation, known as terminal modification are significantly modified. Thus, aberrations in glycan structures can be used as targets to improve existing cancer biomarkers. [10]

In this review, clinical significance of aberrant protein glycosylation in cancer is discussed. In particular the major focus will be on aberrant glycosylation via altered sialylation (sialidases and sialyltransferases) and fucosylation (fucosidases and fucosyltransferases) as a new hallmark of cancer.

**Sialylation and Fucosylation: Two major aspects of glycosylation**

Sialic acids are a special series of 9-carbon backbone negatively charged carbohydrates and typically found at terminal sugar chains attached to cell glycoconjugates. They play critical roles in many physiological and pathologic processes, including inter-molecular binding that leads to microbial infections, regulation of the immune response and the progression/spread of human malignancies. [16,17] The addition of sialic acid residues also termed as "sialylation" is an important modification in cellular glycosylation as sialylated glycans mediate various roles in cellular recognition, cell adhesion and cell-to-cell signaling. [18]

Sialylation is governed by sialyltransferases (STs) and sialidases. Sialic acids are transferred from a donor substrate to terminal positions of glycoprotein and glycolipid carbohydrate groups by STs. [19] STs are categorized into four families on the basis of the carbohydrate side chain they synthesize, namely ST3Gal ($\alpha$2, 3-ST), ST6Gal ($\alpha$2, 6-ST), ST6GalNAc and ST8Sia ($\alpha$2, 8-ST). [20] On the other hand, their removal from glycan chains is catalyzed by sialidases (NEUs). The activity of these enzymes is believed to affect the conformation of glycoproteins and therefore contribute to either increased recognition or masking of biologically relevant sites in molecules and cells. [21] NEU1, NEU2 and NEU3 are now known to be localized predominantly in the lysosomes, cytosol and plasma membranes, respectively and NEU4 is found in lysosomes or in mitochondria and endoplastic reticulum. [21]

The other aspect to study altered glycosylation is fucosylation. It is one of the most common modifications involving oligosaccharides on glycoproteins and glycolipids. Fucosylation consists of transfer of fucose residue from GDP to N-glycans, O-glycans and glycolipids and is involved in many of the biological processes. [22] Fucosylation is catalyzed by a family of fucosyltransferase enzymes (FUTs), consisting of 13 members, including FUT1 to 11, POFUT1 (protein o-fucosyltransferase 1) and POFUT2. FUTs promote attachment of fucose to N-, O- and lipid linked glycans through an α 1, 2- (by FUT 1 & 2), α 1, 3- (by FUT 3 to 7 and FUT 9 to 11), α 1, 4- (by FUT 3 & 5) and α 1, 6- (by FU8) linkage or directly link to the serine/ threonine residues of EGF-like or thrombospondin repeats (by POFUT 1 & 2). [23,24]

α- L-fucosidase is a lysosomal enzyme that catalyzes the hydrolytic cleavage of terminal fucose residue that is involved in maintaining the homeostasis of fucose metabolism. It has been reported that alterations in serum and/or tissue α-L-fucosidase activity may be potentially useful in the diagnosis and management of cancer patients and as an indicator of tumor burden, metastasis and response to anticancer treatments in cancer patients. [25]

**Clinical Significance of altered sialylation and fucosylation in various cancers**

The amount and type of sialylation of tumor cell membrane depend on the activity of a number of different STs. [25] Over expression of STs and other glycogenes during malignant transformation and progression results in aberrant sialylation of cancer cells. The high expression of sialic acids can protect cancer cells from apoptosis, promote metastasis, and has been suggested to confer resistance to therapy. [26] Expression levels of lysosomal sialidase may be critical and defining factors in malignancy whereas increased expression of plasma membrane associated sialidase may be essential for the survival of various cancer cells. [27] Alterations in sialidase, STs and mRNA subtypes expression have been reported in various cancers as mentioned in table 1. Despite increasing amounts of evidence showing the involvement of STs and aberrant sialylation in cancer progression, therapeutic strategies to reduce aberrant sialylation lag behind.

**Table 1 Clinical Significance of alterations in sialyltransferases (STs) and sialidases in various cancers**

| Malignancy | Observation |
|---|---|
| Various colorectal cancer cell lines | NEU3plays a role on EGFR activation through its desialylation [28] |
| Colorectal cancer patients and cell lines | NEU3 plays a major role in maintenance of self-renewal and tumorigenic potential of colon cancer cells [29] |
| Mouse fibroblast cell line | NEU3 as an essential participant in tumorigenesis through the EGFR/Src signaling pathway and a potential target for inhibiting EGFR-mediated tumor progression [30] |
| Various Cancer cell lines | Alterations in different subtypes NEU1, NEU2 and NEU3 and NEU4 correlated with cancer progression [21] |
| Colon cancer cell line | NEU4 plays an important role in control of sialyl Lewis antigen expression and its impairment [31] |
| Prostate cancer patients and cell line | NEU3 is found to be up regulated and further plays a role in tumor progression through Androgen Receptor signaling [32] |
| Colon cancer patients and cell lines | High expression of the sialidase NEU3 in cancer cells leads to protection against programmed cell death, probably modulation of gangliosides [33] |
| Breast cancer | GALNT6 is correlated to a small tumor size and low grading and thus glycosyltransferases can identify small tumors with well-differentiated cells [34] |
| clear cell Renal Cell Carcinoma | ST3GAL-1 is an independent adverse prognostic factor for recurrence and survival of patients with clear cell Renal Cell Carcinoma [35] |
| Multiple Myeloma cell lines | High expression of ST3GAL6 is associated with inferior overall survival and knockdown of ST3GAL6 results in a significant reduction in levelsof a-2,3–linkedsialicacid on the surfaceof Multiple Myeloma cells [36] |
| Gastric cancer cell line | Over expression of ST3GAL4 leads to $SLe^x$ antigen expression in gastric cancer cells which in turn induces an increased invasive phenotype [37] |
| Human gastric cancer tissues | High levels ST3GAL4 and ST6GAL1 were observed in which ST3GAL4may contribute to the expression of a 2,3-linked sialic acid residues which is associated with the malignant behavior of gastric cancer cells [38] |
| Acute Myeloid Leukemia | Altered ST3GAL5 and ST8SIA4 presented the unusual property of association with MDR of AML cells via regulating the PI3K/Akt signaling pathway [39] |
| Colorectal Cancer | Increased ST6GAL1 and subsequently elevated levels of cell-surface α 2, 6-linked sialic acids have been associated with metastasis and therapeutic failure in Colorectal Cancer [40] |
| Pancreatic adenocarcinoma | Increased expression of ST3GAL3 and ST3GAL4 in pancreatic adenocarcinoma tissues associated with tumor progression process [41] |
| Hepatocellular carcinoma | ST3GAL6 promotes cell growth, migration, and invasion and mediates the effect of miR-26a through the Akt/mTOR signaling pathway [42] |
| Cervical cancer cell line | Loss of ST6GAL1 promotes cell apoptosis and inhibits the invasive ability of cells [43] |
| Chronic Myeloid Leukemia (CML) | a-2,8-sialyltransferases are involved in the development of Multi Drug Resistance of CML cells probably through ST8SIA4 regulating the activity of PI3K/Akt signaling [44] |
| Bladder cancer | ST3GAL1 plays the major role in the T antigen sialylation, and its expression is associated with bladder cancer malignancy and recurrence [45] |
| Gastric Cancer | high levels of ST3GAL3 and ST6GAL1 in the tumor tissue correlated with secondary local tumor recurrence [46] |
| Acute lymphoblastic leukemia | Elevated mRNA level of ST6GAL1 and ST3GAL4 positively correlates with the high risk of pediatric acute leukemia [47] |
| Hepatocellular carcinoma patients and cell lines | ST6GAL1 and ST8SIA2 regulation affects the unusual properties of invasion and chemosensitivity in HCC cells by modulating the PI3K/Akt signaling pathway [48] |

Fucosylated glycans are synthesized by a range of FUTs and can be generally divided into two subcategories, core fucosylated and terminally fucosylated glycans. Core fucosylation is the addition of fucose via α 1-6 fucosyltransferases (encoded by FUT8). Up regulation of core fucosylation and the associated FUT8 gene

is an important factor in most cancers as evidenced by its high expression in breast, colon, ovarian and liver cancer and its association with increased cell adhesion and aggregation. [49] Importantly, the presence of core fucosylated glycans on the cell surface is also largely mirrored by their presence in the sera, thereby demonstrating the potential for further use of specific protein glycoforms for early cancer detection. [49] Cell surface glycans frequently carry fucose residues in α 2-3 and/or α 2-4 linkage at the terminus of the N- and O- linked glycan structures, giving rise to the formation of specific Lewis blood group antigens, such as $Le^{x/y}$ and $Le^{a/b}$ by terminal fucosylation. Several fucosyltransferases are involved in the formation of Lewis antigens. Although terminal fucosylation is essential for normal biological functions, alterations in fucosylation can be strongly implicated in cancer and increasing metastatic potential. Alterations in fucosidase and FUTs mRNA subtypes expression have been reported in various cancers as mentioned in table 2. The results documented in the table 2 shows the importance of monitoring fucosylation changes during various stages of cancer progression which can be helpful for early detection and management of cancer patients.

**Table 2 Clinical Significance of alterations in fucosyltransferases (FUTs) and fucosidases in various cancers**

| Malignancy | Observation |
|---|---|
| Ttriple-negative breast cancer patients | High FUCA expression alters the composition and decrease the quantity of cell surface fucosylation-associated molecules, thereby limiting the invasiveness of cancer cells in early-stage breast tumors. Tumor cells expressing lower FUCA protein levels exhibit increased cell surface fucosylation, which enhances the malignant potential of the tumor cells [50] |
| Various cancer cell lines | Overexpression of FUCA1, but not a mutant defective in enzyme activity, suppressed the growth of cancer cells and induced cell death. Thus, protein defucosylationmediated by FUCA1 is involved in tumor suppression in several cancers [51] |
| Bladder epithelial cell line | Decreased expression of FUCA1 gene, which encodes Type 1 α-L-fucosidase, contributed to increased expression of fucosylated N-glycans inTGF-β induced EMT [52] |
| Thyroid cancer patients and cell line | Down-regulation of FUCA-1 is related to the increased aggressiveness ofthyroid cancer [53] |
| Human hepatocarcinoma cell lines | Altered levels of FUT8 in HCC cell lines is significantly linked to the malignant behaviors of proliferation and invasion *in-vitro* [54] |
| Lung cancer patients and cell lines | Ginsenoside Rg3 inhibits epithelial-mesenchymal transition (EMT) and invasion of lung cancer by down-regulating FUT4 [55] |
| Prostate cancer cell lines | Over expression of FUT8 was found to be associated with aggressive prostate cancerand it can serve as a promising target to differentiate between aggressive and non-aggressive prostate tumors [56] |
| Breast cancer cell lines | FUT4 has a role in EMT through activation of the PI3K/Akt and NF-κB signaling systems, which facilitate the acquisition of a mesenchymal phenotype [57] |
| CML cell lines | The altered levels of FUT1had a significant impact on the phenotypic variation of Multi Drug Resistance in CML [58] |
| Hepatocellular carcinoma cell line | FUT6 plays an important role in HCC growth by regulating the PI3K/Akt signaling pathway [59] |
| non-small cell Lung Cancer | High expression of FUT8 was associated with poor survival and was also a significantand independent unfavorable prognostic factor in patients with potentiallycuratively resected NSCLCs [60] |
| Breast cancer cell lines | FUT4 is associated with the proliferation and metastasis of breast cancer and it can also serve as novel biomarker in the diagnosis and prognosis of breast cancer [61] |
| Breast cancer | High FUT8 protein expression was correlated with lymphaticmetastasis and stage status [62] |

Above results document that glycosylation is heavily altered during malignant transformation of a cell due to differential expression of glycosyltransferases (STs and FUTs) and glycosidases (sialidases and fucosidases) which in turn cause cancer progression Hence, this fundamental changes to the glycome can be said as a classic hallmark of malignant transformation. [25,63]

**Altered glycosylation in oral cancer**

In spite of having bunch of studies on clinical significance of altered glycosylation in other malignancies, there are very few reports available particularly for oral cancer. Thus, we have been keenly involved in studying clinical significance of glycosylation changes in oral cancer as oral cancer is a major health hazard in India. Earlier, we have reported that elevations in sialic acid levels in oral cancer patients have potential utility in diagnosis as well as

determining clinical stage of oral cancer. [64] We have also reported elevated sialidase activity in patients with OPC and oral cancer patients. [65,66] We have also observed altered enzyme activities of α-2, 3 and α-2, 6 STs in serum, saliva and tissue of patients with OPC and oral cancer patients and its significance in treatment monitoring. It was also observed that levels of serum and salivary α-2, 6 ST along with salivary α-2, 3 ST were significantly decreased in complete responders (CR) as compared to pre-treatment (PT) levels. The levels of serum α-2, 6 ST were found to be significantly increased in non-responders (NR) as compared to PT levels. The levels of serum α-2, 3 ST, serum and salivary α-2, 3 ST and α-2, 6 ST were also found to be increased in NR as compared to PT levels. [66,67] Increased sialidase activity was shown to be associated with metastasis and tumor infiltration in oral cancer. [67] Shiga et al have observed that sialidase activity (NEU3) regulates the EGFR signaling and which was further associated with lymph node metastasis in HNSCC cell lines, which is in accordance with our data. [68]

Significantly higher serum and salivary α-L-fucosidase activity was also reported in oral cancer patients as compared to controls. [69] Reports from our laboratory have also documented serum a-L-fucosidase as a useful marker for close monitoring of patients during post–treatment follow-up. [70] Head and neck cancer patients having primary tumors exhibiting higher FUCA1 expression was associated with worst survival. [71] It was also reported that, increased fucosylation has a pivotal role in invasive and metastatic properties of head and neck cancer stem cells. [72] Association between altered glycosylation with the other hallmarks of cancer has also been reviewed in our recent report. [25]

Thus, understanding the molecular basis underlying these glycan modifications will further contribute to explain cancer cell interactions, extracellular communications and cancer immunology. The changes in glycosylation may provide a new direction for understanding the molecular nature of cancer and cellular transformation. Further, it will also provide opportunities to identify novel biomarkers to develop interventional strategies for treatment of oral cancer.

## CONCLUSION

Aberrant glycosylation has been identified in almost every type of cancer due to significant modification/alterations in sialylation and fucosyltion. Therefore, the broaden view of glycosylation changes during malignant transformation in various cancers suggest that glycosylation can be considered as a new hallmark of cancer or a new enabling characteristic. Thus, distinctive alterations in tumor-associated glycosylation may provide us a distinct feature of cancer cells and therefore grant novel diagnostic and even therapeutic targets. In oral cancer, altered glycosylation has been found to be progressively increased from healthy individuals to patients with oral precancerous conditions to oral cancer. Further, it is associated with stage and progression of oral cancer. Overall results emphasize glycosylation as a promising field for identification of potential biomarker and newer drug targets for better management of cancer.

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