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Review Article

Our Studies on Aberrant Glycosylation in Oral Cancer and Insights on Glycosylation as a Hallmark of Cancer

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ABSTRACT

Progression of cancer is a multi-step process and involves sequential changes during neoplastic transformation. Aberrant glycosylation, a hallmark of cancer, aids in cancer cell survival, proliferation and metastasis, thus playing an important role in tumorigenesis. The present review describes our results on sialylation (total sialic acid, α-2,3 and α-2,6 sialoproteins, α-2,3 and α-2,6 sialyltransferases and sialidase) and fucosylation (fucose, fucoproteins, fucosyltransferase and α-L-fucosidase) alterations in tissues, blood and saliva of patients with oral precancerous conditions (OPC) and oral cancer patients, as well as post treatment follow-ups samples of oral cancer patients. The results depicted correlation of sialylation and fucosylation alterations with tumor initiation, progression and metastasis. The review also describes the mechanism of cancer associated aberrant glycosylation and highlights the involvement of glycogenes, which have been linked to various hallmark characteristics of cancer. This review supports the concept of glycosylation as a major hallmark of cancer and is an enabling characteristic for other hallmarks of cancer.

Keywords: Glycosylation, Hallmark, Cancer, Sialylation, Fucosylation, Tumor antigens

INTRODUCTION

Cancer hallmarks play an important role in development of cancerous phenotype by enabling the cells to become tumorigenic and ultimately malignant. The hallmarks of cancer development are sustaining proliferative signaling, evading growth suppressors, activating invasion and metastasis, enabling replicative mortality, inducing angiogenesis and resisting cell death, avoiding immune destruction, inflammation, genomic instability and mutation, deregulating cellular energetics (metabolism). [1,2] Recent studies also depicted aberrant glycosylation as a new hallmark of cancer.

Among glycosylation, sialylation and fucosylation are the major terminal modification of cell surface glycoproteins, which are specifically involved in cancer progression. Sialylation is mainly regulated by sialyltransferases (STs) and sialidases, which regulate the formation of sialyl-glycoconjugates. STs catalyze the transfer of sialic acid to terminal glycoconjugates while sialidases are responsible for breakdown of sialic acid from complex sialyl-glyconjugates, and thus involved in release of sialic acid. In cancer, there is alteration in sialylation pattern, which is mainly accompanied through changes in sialylo-glycoconjugates by STs and sialidases. [3] Similarly, fucosylation is regulated by fucosyltransferases (FUTs) and α-L-fucosidase enzyme, which regulate the formation fucoproteins. Aberrant

fucosylation is documented to have a significant role in tumor formation and metastasis. [4]

This review summarizes our various studies on aberrant sialylation and fucosylation in oral cancer from tissues, serum and saliva. It also supports glycosylation as a hallmark of cancer, which enables other hallmarks to exert their characteristics. It further describes mechanisms associated with aberrant glycosylation.

SUBJECTS AND METHODS

Our previous studies included healthy individuals as controls, patients with oral precancerous conditions (OPC) and oral cancer patients. The oral cancer patients were followed after the anticancer treatment and also post treatment follow-up samples were collected. For studying sialylation changes (from tissues, serum and saliva), total sialic acid (TSA) was estimated by spectrophotometric method, [3,5] α-2,3 and α-2,6 sialoproteins by dot blot method, [3,5] α-2,3 and α-2,6 ST enzyme activity by ELISA [3,5] and sialidase activity was measured by spectrofluorimetric analysis. [3, 5] For evaluation of fucosylation alterations, fucose levels were analyzed by cysteine HCl method, [4] α-L-fucosidase enzyme activity by spectrophotometric method, [4] fucoproteins by lectin affinity chromatography followed by SDS- PAGE and silver staining, [4] FUTs by radioimmunoassay. [4]The transcript levels of *ST3GAL1, FUT3, FUT5* and *FUT6* were analyzed by semi-quantitative reverse transcriptase PCR. [6] For expression of glycoproteins, native polyacrylamide gel electrophoresis and Schiff's staining was performed [7] and for sialyl lewis x (sLe^x) expression, western blot was performed. [8]

RESULTS

Our earlier study [3] included 100 healthy individuals, 130 oral cancer patients and 75 patients with OPC. 75 oral cancer tissues were also collected. The levels of tissue total sialic acid were significantly higher in malignant oral cancer tissues as compared to adjacent normal tissues. Moreover, serum TSA and TSA/TP ratio was also significantly increased in patients with OPC and oral cancer patients as compared to controls. Tissue α-2,3 and α-2,6 sialoproteins were observed to be significantly higher in malignant tissues as compared to adjacent normal tissues and serum levels of α-2,6 sialoproteins and α-2,6 ST were also significantly elevated in oral cancer patients as compared to the controls. The tissue α-2,6 and α-2,3 ST activities were significantly elevated in malignant tissues as compared to adjacent normal tissues. Moreover, α-2,6 and α-2,3 ST enzyme activities were observed to be progressively increased from stage I to stage IV of the malignant disease. α-2,6 sialoproteins and α-2,6 ST depicted significant correlation with tumor differentiation. Moreover, there were 75 post treatment follow-up included in the study which were divided into 52 complete responders (CR) and 23 non-responders. It was observed that serum TSA, TSA/TP ratio, α-2,6 ST and α-2,3 ST were significantly decreased in CR as compared to pretreatment (PT) levels. The results thus depicted alterations in tissue and serum sialylation changes linked to oral cancer development and proved its utility in post treatment monitoring of oral cancer patients.

In same cohort of patients, the serum fucosylation changes were also evaluated. [4] The results revealed significantly elevated serum fucose levels in patients with OPC and oral cancer patients as compared to controls. The levels of serum fucoproteins, FUTs and α-L-fucosidase activity were significantly elevated in oral cancer patients as compared to controls. Serum FUT and α-L-fucosidase enzyme activity were also observed to be significantly increased in patients with OPC as compared to the controls. Moreover, Receiver's Operating Characteristic's (ROC) curve analysis revealed significant discriminatory efficacy of serum α-L-fucosidase in discriminating controls from oral cancer patients and

controls from patients with OPC. The results also revealed that serum fucose, fucoproteins, FUT, α-L-fucosidase activities were significantly decreased in CR as compared to PT levels, while the levels were comparable between PT and NR. The analysis revealed significant association of serum fucose levels with stepwise disease activity and tumor differentiation. Also, serum fucoproteins depicted significant correlation with progression of disease to metastasis. Overall the results indicated utility of serum fucosylation alterations in monitoring oral cancer progression and treatment response. Further, α-L-fucosidase activity proved to be an efficient marker for early detection and monitoring treatment response in patients with oral cancer.

Our another study on glycoprotein profiling which included 84 healthy individuals, 50 patients with OPC and 80 oral cancer patients revealed alterations in specific glycoproteins in patients with OPC and oral cancer patients. [7] The results revealed a significant increase in 192 kDa, 170 kDa, 116 kDa, and 44 kDa glycoproteins in patients with OPC and oral cancer patients as compared to controls. ROC curve analysis revealed significant discriminatory efficacy of these glycoproteins in distinguishing controls from oral cancer patients. Moreover, a 230 kDa protein was present in some of the subjects only and was observed higher among tobacco users i.e. in 57.8% controls, 60% of oral cancer patients and 50% of patients with OPC. Further, an increasing trend of this 230 kDa glycoprotein was observed from controls to patients with OPC to oral cancer patients.

Recently, salivary diagnostics is growing an increasing attention due to its non-invasiveness and easy availability for detection of clinically useful biomarkers. Our earlier studies on saliva included 100 controls, 50 patients with OPC and 100 oral cancer patients. Our data compared serum and salivary levels of TSA and α-L-fucosidase in patients with OPC and oral cancer patients. [9] The serum and salivary TSA/TP ratio were observed to be significantly elevated in patients with OPC and oral cancer patients as compared to the controls. The levels of serum and salivary α-L-fucosidase were significantly increased in oral cancer patients as compared to the controls. ROC curve analysis also indicated significant discriminatory efficacy of serum and salivary TSA/TP ratio and α-L-fucosidase in discriminating controls and oral cancer patients. Serum and salivary TSA/TP ratio and α-L-fucosidase were increased in patients with lymph-node (LN) metastasis as compared to patients without LN metastasis. Interestingly, the results indicated higher levels of TSA/TP ratio and α-L-fucosidase activity in saliva as compared to serum. An increase in levels of TSA/TP ratio and α-L-fucosidase activity was observed in subjects with tobacco habits as compared to non-habituates. The differential results in tobacco non-habituates and habituates groups supported the premise that carcinogens present in tobacco are involved in sequential changes leading to development of cancer. The results indicated utility of salivary TSA/TP ratio and α-L-fucosidase activity, as non-invasive tools for monitoring early events during oral cancer progression.

Our another recent study also documented salivary sialylation alterations in 100 controls, 50 patients with OPC and 100 oral cancer patients. [5] The results revealed a gradual increase of salivary TSA/TP ratio, α-2,3 sialoproteins, α-2,3 ST, α-2,6 ST and sialidase activity from controls to patients with OPC to oral cancer patients and the levels were significantly elevated in oral cancer patients as compared to the controls. Salivary TSA/TP ratio, sialidase activity, α-2,3 and α-2,6 ST activity depicted higher levels in patients with LN metastasis as compared to the patients without LN metastasis. ROC curve analysis revealed that salivary TSA/TP ratio and α-2,3 sialoproteins significantly discriminated controls from oral cancer patients and controls from patients with OPC. Moreover, follow-up analysis revealed decrease in

salivary sialidase activity, α-2,3 and α-2,6 sialoproteins and ST activity in CR as compared to pretreatment levels while the same were elevated in NR. The results highlighted the importance of monitoring salivary sialylation alterations for screening. early detection of oral cancer and treatment response .

The alterations in sialylation and fucosylation are mainly due to alterations in expression of STs and FUTs. There are many subtypes of STs and FUTs. We evaluated the mRNA expression of *ST3GAL1*, *FUT3*, *FUT5* and *FUT6* in malignant and adjacent normal tissues of oral cancer patients. [6] It was observed that *ST3GAL1* mRNA expression was elevated in malignant tissues as compared to adjacent normal tissues while a significant decrease in *FUT3* and *FUT5* mRNA expression was depicted in malignant tissues as compared to the adjacent normal tissues. However, survival analysis revealed that higher levels of *FUT3* mRNA were significantly associated with lower overall survival. *FUT6* and *ST3GAL1* mRNA expression were observed to be higher in patients with LN metastasis as compared to patients without LN metastasis and levels were also elevated in advanced disease as compared to the early disease. This study showed the utility of monitoring *ST3GAL1*, *FUT3*, *FUT5* and *FUT6* transcript levels in oral cancer patients.

Different subtypes of FUTs are also involved in formation of sLe^x. Our studies have observed significant increased sLe^x expression in malignant and OPC tissues as compared to adjacent normal tissues with good ROC curve discriminatory efficacy. [8] The results revealed that increased expression of sLe^x during early stage proves to be useful in determining metastatic potential of tumors at an early stage.

Our laboratory results thus highlight the alterations of various sialylation and fucosylation parameters as depicted in Figure 1. It proves that aberrant glycosylation is enabling characteristics for other hallmark of cancer.

DISCUSSION

Our laboratory is actively engaged in studies focused on sialylation and fucosylation alterations in cancer and the present review summarizes our significant observations of these alterations in patients with OPC and oral cancer patients. We have reported significant increase in TSA in serum, saliva and tissues of patients with OPC and oral cancer patients. Alterations in TSA have also been observed in various cancers along with oral cancer. [10-16] The results depicted correlation with stage of the disease and metastasis, which are in concordance with earlier studies in oral cancer and lung cancer. [11, 14] The increased levels of sialoproteins exhibited in our study are in correlation with early detection and treatment response monitoring of oral cancer patients. Earlier studies have also reported altered expression of sialoproteins and STs in gliomas and hepatocarcinoma playing an important role in neoplastic transformation. [17, 18]

Salivary sialidase activity was observed to be higher in patients with OPC and oral cancer patients as compared to the controls and depicted correlation with metastasis and infiltration. The altered expression of sialidase activity has been reported in upper aerodigestive tract tumors [19] and was associated with different grades of tumor in breast cancer. [20] Our data revealed increased expression of ST in patients with OPC and oral cancer patients and its role in early detection and treatment response monitoring. The alterations in STs have been also observed in other cancers. [21-24] Moreover, increased *ST3GAL1* mRNA expression in malignant oral cancer tissues depicted important role in oral cancer pathogenesis. The alterations in different subtypes of STs mRNA expression have been also observed in various cancers including breast, cervix, bladder, and multiple myeloma. [25-28] STs play a key role in regulation of overall sialylation process and thus serve as important drug targets. There is much advancement in inhibitors of STs and FUTs which play important role in

inhibiting overall sialylation process. [29, 30] Our recent review summarizes the details on inhibitors of sialylation pathway [29] along with various studies depicting alterations in various intermediates of sialylation pathway. The inhibitors included various lithocholic derivates, fluorinated analogues and other glycomimetics and inhibition using antisense or small hairpin RNA. The progress made in development of drugs inhibiting sialylation, may prove wonders in inhibition of cancer metastasis and invasion.

Our studies depicted significant increase of serum and salivary α-L-fucosidase in patients with OPC and oral cancer patients with good discriminatory efficacy by ROC curve analysis. The results also depicted its usefulness in treatment response monitoring of oral cancer patients. The results were supported by earlier studies in ovarian, hepatocellular, colorectal, liver and endometrium cancer, which depicted its role in early detection, diagnosis as well as in treatment monitoring. [31-35] Our results of serum fucose levels are in concordance with earlier studies, which observed significant increase in serum fucose levels in cancers associated with diagnosis and prognosis. [36-39] An elevated expression of serum fucoproteins was observed in patients with OPC and oral cancer patients. Earlier studies have revealed alterations in fucoproteins to be correlated with tumor burden in cancer patients. [40] Our results revealed alterations of mRNA expression of different subtypes of *FUTs*, which depicted the involvement of specific subtype of *FUT* in tumor formation and metastasis. Earlier studies have observed alterations in expression of *FUTs* in various cancers. [41, 42]

Various subtypes of STs and FUTs are involved in formation of sLe^x antigens. [43-45] Our studies have revealed increased expression of sLe^x in malignant tissues as compared to adjacent normal tissues. [8] Similarly, various studies have shown alterations in tumor antigens playing an important role in tumorigenesis and metastasis. [46, 47]

Understanding mechanisms associated with aberrant glycosylation:

As documented, from our studies and several other reports on aberrant glycosylation suggest that process of tumorigenesis has intense effects on cellular glycosylation process accompanied by disease specific alterations in glycan biosynthetic pathways leading to altered glycosylation of cell surface proteins. [48] Glycosylation is involved in formation of abundant and diverse glycans that are frequently attached to proteins or lipids. [49] The cancer associated glycan alterations leads to alterations in cell-cell and cell-environment interactions, which is a key to cancer progression. As depicted in Figure 2A, the cancer associated glycosylation changes broadly includes changes in β-1,6 branching, Sialyl Lewis antigens, T, Tn, and sialyl Tn antigens, gangliosides (sialic acid containing glycolipids) and alterations in α-2,6 sialylated lactosamine.

The mechanisms associated with altered glycosylation in cancer include altered glycosidase expression, altered expression of sugar and sugar nucleotide transporters, competition between normal and cancer associated carbohydrate structures (Figure 2A). [50] The alteration in glycosidase enzymes is depicted in various cancers. The best examples are α-L-fucosidase and sialidase enzymes. Altered sialidase expression has been known to be involved in cancer development. [51, 52] A higher level of α-L-fucosidase activity was depicted in our study and similar observations have also been documented in various cancers. [31, 32, 33] The masking of cancer associated carbohydrate antigens may be mediated by addition of sulfate groups linked to sixth position of GlcNAc residue of sLe^x generating sialyl 6-sulfo Lewis X in normal tissues. [46] Previous reports have suggested that UDP-galactose transporter is the limiting factor in sugar antigen biosynthesis and have depicted the involvement of UDP-galactose transporter in the regulation of the expression of cancer associated antigens, T, sLe^a, and sLe^x. [53,54]

A competition between normal and cancer associated carbohydrate structures exist and is shown to be regulated by the level of enzymes synthesizing alternative structures. [50] There are also genes referred as 'glycogenes' whose products are involved in the biosynthesis, degradation or recognition of carbohydrate chains. The mechanism of regulation of these glycogenes is by oncogenes and tumor suppressor genes, hypoxia and epigenetic regulation (Figure 2A).

Aberrant glycosylation enables other hallmarks of cancer. Also, our recent review considers the various aspects of considering glycosylation as a new hallmark of cancer and has summarized various studies on glycosylation alterations in various cancers. It also highlights the correlation of glycosylation with other various hallmark capabilities involved in tumor progression and malignant transformation. [55] Recently, a study has also put forth the idea of considering glycosylation a hallmark of cancer. [56] It has been suggested that the relationship between altered glycosylation and altered signal transduction is bidirectional. The cancer associated alterations in signal transduction pathways leads to increased expression of specific glycosyltransferase, which is responsible for altered glycosylation pattern. On the counter side, cancer associated glycans expressed on cell membrane receptors can modify cell signaling resulting in alterations in fundamental properties of cancer cell. [49] Glycosylation is also involved in controlling cancer cell phenotype like angiogenesis, apoptosis, cell growth, cell survival, cellular adhesion and metastasis. [49, 57-61] It has been shown to be correlated with other hallmark capabilities like invasion and metastasis, proliferation, angiogenesis, evading tumor suppressors, evading apoptosis and replicative immortality (Figure 2B).

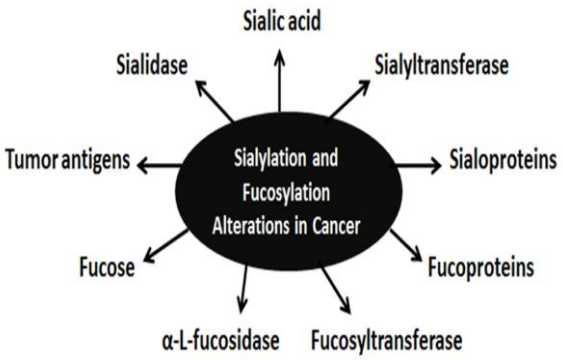


Figure 1. Various forms of aberrant sialylation and fucosylation in cancer as documented in reports [3-9].

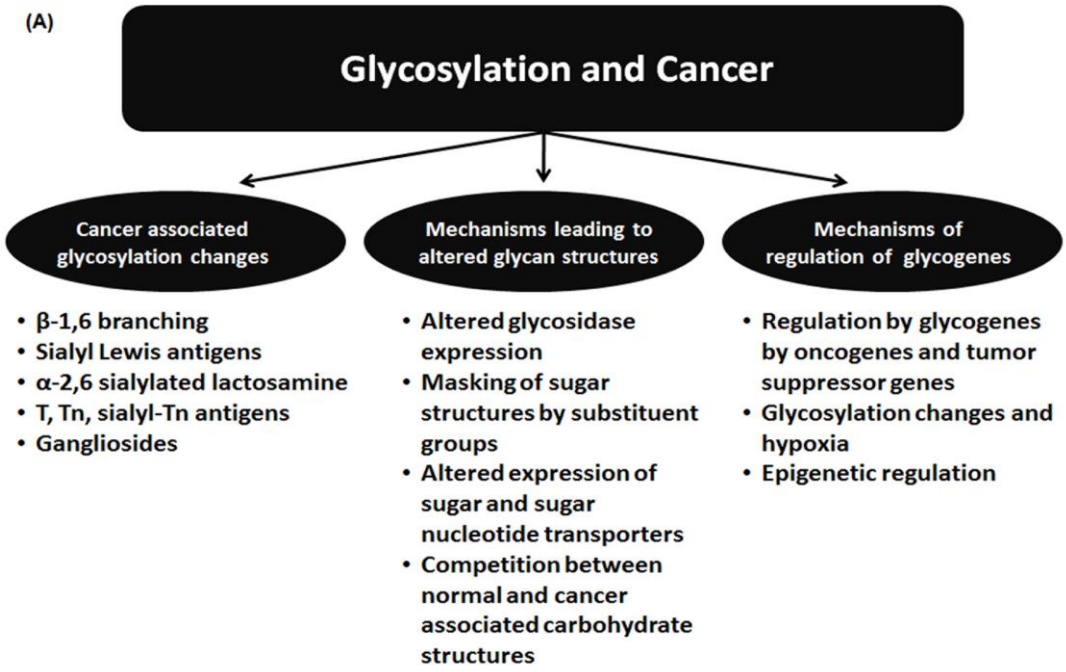
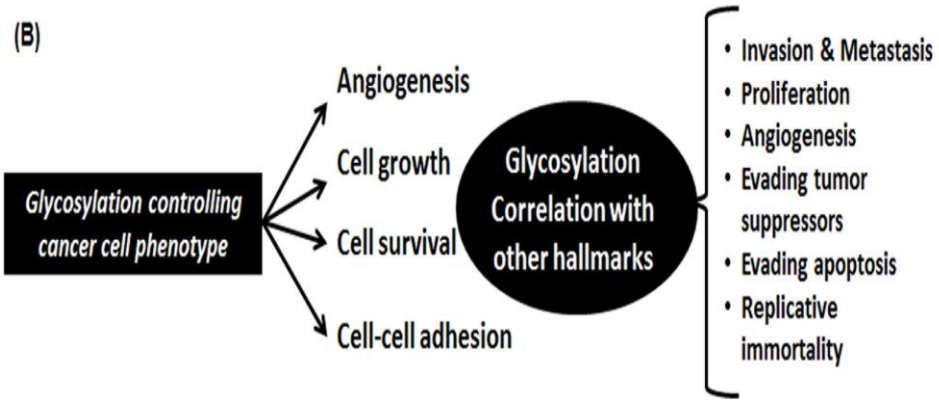


Figure 2(A): Glycosylation and development of cancer: cancer associated glycosylation changes, mechanism leading to altered glycan structures, mechanism of glycogens regulation.



(B). Role of glycosylation in controlling cell phenotype and correlation with different hallmarks of cancer.

Thus, considering various aspects of cancer associated glycosylation changes as observed in our studies in tissues, serum and saliva linked to diagnosis, prognosis and treatment monitoring, mechanisms leading to altered glycan structures, mechanisms of regulation of glycogenes, and involvement of glycosylation in controlling cellular phenotype and association with various hallmarks, suggests the ideality for considering glycosylation as a new hallmark of cancer which also enables other hallmarks to exert their oncogenic characteristic.

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