Aberrant Glycosylation, a New Hallmark of Cancer has a Vital Translational Value

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Summary

As normal cell progress to neoplastic state, it acquires distinctive and complementary capabilities, which are called as the hallmark of cancer. In the course of noteworthy progress in cancer research, newer observations have modified the original formulation of the hallmark capabilities. Rising evidence supports vital role of altered glycosylation during all steps of tumor progression. Our data as well as other reports have documented aberrant glycosylation as a new hallmark of tumor proliferation, invasion, metastasis and angiogenesis. Protein glycosylation is the most widely observed and structurally diverse form of post-translational modifications after phosphorylation. It is the enzymatic process that produces glycosidic linkages of sachharides to other sachharides, proteins or lipids. 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. We have reported that the understanding of biologically relevant aberrant glycosylation can serve as clinically importamt biomarker for various cancers. The review presented here symbolizes an ample overview of literature on translational glycobiology. The results also provide the evidence of aberrant glycosylation linked with other hallmarks of cancer leading to a conclusion that glycosylation is a new hallmark of cancer.

Keywords: Glycosylation, Sialyltransferase, Sialidase, Fucosyltransferase, Fucosidase

Hallmarks of Cancer

In 2000, a highly influential review article entitled "The hallmarks of cancer" was published by Hanahan and Weinberg which proposed six hallmarks of cancer that provides a logical framework for understanding the biology of cancer. It included sustaining proliferative signaling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis and resisting cell death. (Figure: 1a) [1] Almost after a decade they have reworked on the hallmarks of cancer and proposed another two emerging hallmarks: "Deregulating cellular energetics" and "Avoiding immune destruction" and two enabling characteristics: "Genome instability and mutation" and Tumor-promoting inflammation". (Figure: 1b) [2] The evidences indicate that tumorigenesis in humans is a multistep process and that these steps reflect genetic alterations that drive the progressive transformation of normal human cells into highly malignant derivatives. The hallmarks of cancer are characterized by functional capabilities that allow cancer cells to survive, proliferate and disseminate during tumorigenesis. Further, they have also proposed that refinement of these organizing principles will surly come in the foreseeable future which will continue in the remarkable conceptual progress in the hallmarks of cancer.

Glycosylation as a hallmark of cancer

Glycans exist as membrane-bound glycoconjugates or as secreted molecules, which become integral parts of the extracellular matrix. Changes in these glycan structures are associated with many physiological and pathological events such as cell growth, migration and differentiation. Consequently, aberrant glycosylation occurring in cancer cells influence cell proliferation, adhesion and motility as well as angiogenesis and metastasis.[3,4] Our laboratory is working on several aspects of glycosylation in cancer since 1985. Based on our experience, we have came to a conclusion that aberrant glycosylation interfere with almost all the steps involved in malignant transformation and therefore can be said as classic hallmark of cancer[5]. In support of this notion, several authors have also reported glycosylation as a new hallmark of cancer. [6,7] 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 such as glycosyltransferases and glycosidases and on the availability of the nutrient resources and expression of enzymes responsible for their synthesis and interconversion.[8] The study of the changes in the enzymes associated with altered glycosylation provides new directions for understanding the molecular nature of cancer, cellular transformation and often new opportunities for identifying biomarkers of disease and developing interventional strategies for treatment of cancer.[9] Increased sialylation and fucosylation of cell surface glycoconjugates is among the key molecular changes associated with malignant transformation and cancer progression. Therefore the present review is mainly focused on clinical significance of aberrant glycosylation via altered sialylation (sialidases and sialyltransferases) and fucosylation (fucosidases and fucosyltransferases) in various cancers. In particular, aberrant protein glycosylation as a new hallmark of

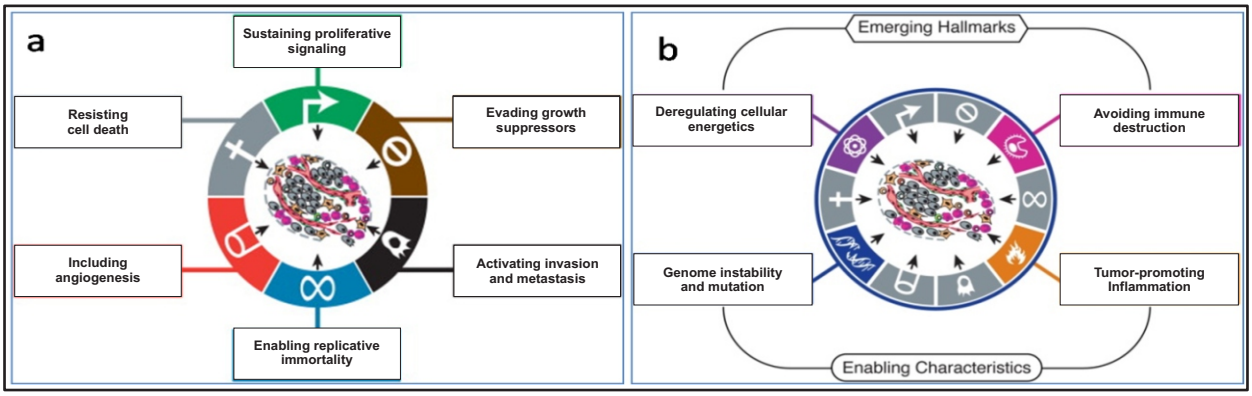

Figure 1: Hallmarks of Cancer (Reproduce from Hanahan and Weinberg RA, 2000,[1] 2011[2])

cancer will be conversed in relation with various human cancers.

Sialylation

Sialylation affects the half-lives of many circulating glycoproteins and plays a role in a variety of biologic processes such as cell-cell communication, cell matrix interaction, adhesion, and protein targeting. The transfer of sialic acids from CMP sialic acids to the acceptor carbohydrates is catalyzed by the sialyltransferase (ST) family. Aberrant sialylation in cancer cell is a characteristic feature associated with malignant properties including invasiveness and metastatic potentials.10 Sialic acid is linked either through α-2, 3 or α-2, 6 linkage to subterminal galactose or α-2, 8 linkage to another sialic acid forming polysialic acid catalyzed by specific ST. The different STs can be distinguished on the basis of oligosaccharide sequence used as acceptors and anomeric linkage formed with the penultimate sugar residue.[11, 12] Sialylation is governed by Sialyltransferases and sialidases. Sialic acids are transferred from a donor substrate to terminal positions of glycoprotein and glycolipid carbohydrate groups by STs.[13] STs are categorized into four families on the basis of the carbohydrate side chain they synthesize, namely ST3Gal (α2, 3-ST), ST6Gal (α2, 6-ST), ST6GalNAc and ST8Sia (α2, 8-ST).[14] On the other hand, their removal from glycan chains is catalyzed by sialidases. Sialidases also called neuraminidases (NEU) are glycosidases catalyzing the removal of α-glycosidically linked sialic acid residues from carbohydrate groups of glycoproteins and glycolipids. They are classified according to their major intracellular locations as intra-lysosomal, cytosolic, lysosomal membrane and plasma membrane associated NEUs. NEU1, NEU2 and NEU3 are 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.[15] The amount and type of sialylation of tumor cell membrane depend on the activity of a number of different STs.[5] The activity of these enzymes affects the conformation of glycoproteins and therefore contributes to either increased recognition or masking of biologically relevant sites in molecules and cells.[15] Alterations in sialidase, STs and mRNA subtypes expression have been reported in various cancers.

Our laboratory has reported elevated sialidase activity in patients with OPC and oral cancer patients.[16] A study has observed alterations in different subtypes NEU1, NEU2 and NEU3 and NEU4 which was found to be correlated with cancer progression in various cancer cell lines.[15] NEU3 was also found to be up regulated in prostate cancer which plays a role in tumor progression through androgen receptor signaling.[17] In colon cancer, high expression of the sialidase NEU3 in cancer cells leads to protection against programmed cell death by modulation of gangliosides is documented.[18] In addition, NEU3 also plays a major role in maintenance of self-renewal and tumorigenic potential of colon cancer cells.[19] In various head and neck squamous cell carcinoma (HNSCC) cell lines, NEU3 has been reported to regulate the EGFR signaling through ganglioside modulation which is further associated with lymph node metastasis.[20] In colorectal cancer, NEU4 is implicated as an important player in control of sialyl Lewis antigen (sLe) expression and its impairment.[21] Our laboratory has reported significant over expression of sLe^X in malignant tissues as compared to adjacent normal tissues which is further associated with disease progression and poor prognosis of the patients.[10]

Earlier studies from our laboratory have reported 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. Figure 2 depicts levels of serum and salivary α-2, 3 and α-2, 6 ST in Pre treatment (PT), Complete responders (CR) and Non responders (NR) during post treatment follow-ups. It was observed that levels of serum and salivary α-2, 6 ST along with salivary α-2, 3 ST were significantly decreased in CR ($p=0.012$, $p=0.001$ and $p=0.010$ respectively) as

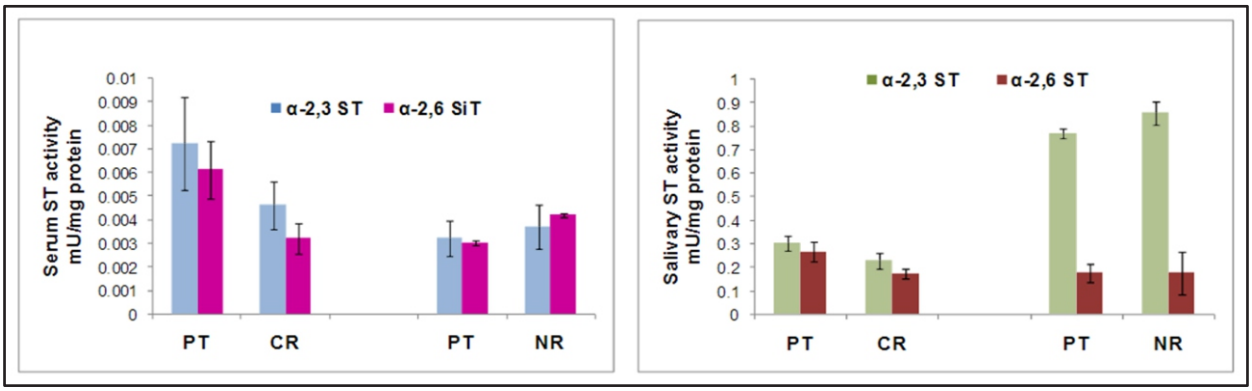

Figure 2: Levels of serum and salivary α-2, 3 and α-2, 6 ST in PT, CR and NR[22]

compared to PT levels. The levels of serum α-2, 6 ST were found to be significantly increased (p=0.024) in 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.[10,22]

During neoplastic transformation, the activity of the Golgi localized STs is usually increased and as a consequence, cancer cells express more heavily sialylated tumor associated carbohydrate antigen (TACA) at their surface. Various STs play role in formation of TACA in various cancers.[23] ST3GAL1 plays role in formation of sT antigen, ST3GAL4 in sLe^X formation, ST6GAL1 in CD75s and ST2H formation, ST6GALNAC1 in sTn antigen etc. The common glycan alterations observed in various cancers are increased $sLe^{x/a}$, increased Tn epitopes, increased sialyl Tn epitopes, increased sialyl T antigens and increased α-2,6 sialylation.[24] A study has reported ST3GAL1 as an independent adverse prognostic factor for recurrence and survival in clear cell renal cell carcinoma patients.[25] Further, it was observed that ST3GAL1 plays the major role in the T antigen sialylation, and its expression is associated with progression and recurrence in bladder cancer.[26]In cervical cancer, loss of ST6GAL1 has been showed to promote cell apoptosis and to inhibit the invasive ability of cancer cells.[27] Increased ST6GAL1 and subsequently elevated levels of cell-surface α 2, 6-linked sialic acids have found to be associated with metastasis and therapeutic failure in colorectal cancer.[28] In hepatocellular carcinoma, ST6GAL1 and ST8SIA2 regulation has been shown to affect unusual properties of invasion and chemosensitivity by modulating the PI3K/Akt signaling pathway.[29] Further, over expression of ST3GAL4 leads to SLe^X antigen expression in gastric cancer which in turn induces an increased invasive and aggressive phenotype.[30, 31] ST3GAL4 has also been reported as a biomarker for diagnosis and prognosis of multi drug resistance in acute myeloid leukemia.[32] In addition, elevated mRNA level of ST6GAL1 and ST3GAL4 are found to be positively associated with the high risk of pediatric acute lymphoblastic leukemia.[33] Hence, expression of STs are often found to be de-regulated in various cancers like colorectal, liver, gliomas, gastric and oral cancer.[10, 5] However, despite of increased amounts of evidence showing the involvement of STs and aberrant sialylation in cancer progression, therapeutic strategies to reduce aberrant sialylation lag behind.

Fucosylation

Fucosylation 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.[34] Fucosylation is catalyzed by a family of fucosyltransferase enzymes (FTs), consisting of 13 members, including FUT1 to 11, protein o-fucosyltransferase 1 (POFUT1) and protein o-fucosyltransferase 2 (POFUT2). FUTs promote attachment of fucose to N-, O- and lipid linked glycans through an α 1, 2- (by FUT 1 and FUT2), α 1, 3- (by FUT 3 to 7 and FUT 9 to 11), α 1, 4- (by FUT 3 and FUT5) and α 1, 6- (by FU8) linkage or directly link to the serine/ threonine residues of EGF-like or thrombospondin receptor (by POFUT 1 & 2).[35, 36] Fucosylated glycans can be generally divided into two subcategories, (i) core fucosylated and (ii) terminally fucosylated glycans.

Core Fucosylation: Core fucosylation is the addition of α 1-6 fucosyltransferases (encoded by FUT8). Up regulation of core fucosylation and the associated FUT8 gene has been observed in most cancers.[37] Importantly, in most of cancers the presence of core fucosylated glycans on the cell surface is largely mirrored by their presence, thereby demonstrating the potential for further use of specific protein glycoforms for early cancer detection.[38]

Terminal Fucosylation: 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

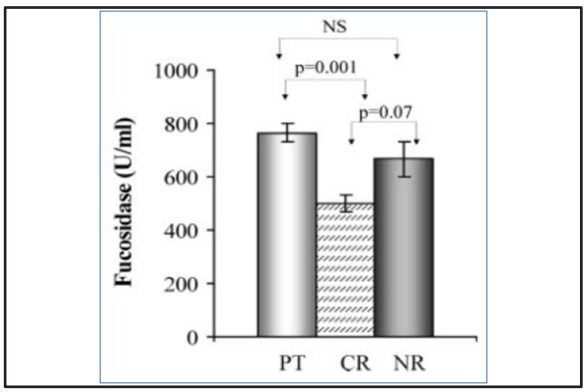

Figure 3: α-L-fucosidase between the untreated/pretreatment (PT) patients with OC and patients who achieved a CR or who had an NR[41]

Lewis blood group antigens, such as $Le^{x/y}$ and $Le^{a/b}$. Several FUTs are involved in the formation of Lewis antigens including those coded by FUT 1-7 and FUT 9[39] with FUT 3-7 and FUT 9 gene products known to produce the Lex structure. FUT 1-2 genes, on the other hand are involved in creating the precursor of H-antigen.[38]

Although fucosylation is essential for normal biological functions, alterations in fucosylation are strongly implicated in cancer and increasing metastatic potential. Alterations in fucosidase and fucosyltransferase expression have been reported in various cancers.

α-L-fucosidase (EC: 3.2.1.51) is a lysosomal enzyme that catalyzes the hydrolytic cleavage of terminal fucose residue that is involved in maintaining the homeostasis of fucose metabolism. The presence of fucosidases (FUCAs) is necessary for rapid turnover of N-glycans (including fucose) followed by reglycosylation and reinsertion of the proteins in plasma membrane.[40] Our earlier studies have documented serum a-L-fucosidase as a useful marker for close monitoring of patients during post–treatment follow-up. (Figure: 3) [41] Our pervious study has also reported significantly higher serum and salivary α-L-fucosidase activity in oral cancer patients as compared to controls.[42]

It has been observed that 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.[43] So, the tumor cells expressing lower FUCA protein levels exhibit increased cell surface fucosylation, which enhances the malignant potential of the tumor cells in triple-negative breast cancer.[43] A study has reported that over expression of α-L-fucosidase 1 (FUCA1) suppressed the growth of cancer cells and induced cell death by protein defucosylation which is further involved in tumor suppression in several cancers.[44] In HNSCC, primary tumors exhibiting higher FUCA1 expression were found to be associated with significantly worse patient survival.[45] In adition, down-regulation of FUCA1 was also found to be correlated with increased aggressiveness of thyroid cancer.[46]

It has been demonstrated that altered expression of various FTs such as FUT3,[47] FUT4, 48 FUT6 ,[49, 50] FUT7, [51, 52] FUT8 [53, 54] mediate cancer cell migration and thereby metastasis, suggesting that altered fucosylation may play an important role in disease progression. Our laboratory has reported a significant decrease in FUT3 and FUT5 mRNA expressions in oral cancer patients.[22] Increased fucosylation has been established as a crucial character in invasive and metastatic properties of head and neck cancer stem cells.[55] In breast cancer high FUT8 protein expression was found to be correlated with lymphatic metastasis and stage status.[56] High expression of FUT8 was also found to be associated with poor survival which can be a significant and independent unfavorable prognostic factor in patients with potentially curatively resected non-small cell Lung Cancer.[57] Further, over expression of FUT8 was found to be associated with aggressive prostate cancer which can serve as a promising target to differentiate between aggressive and non-aggressive prostate tumors.[58] Moreover, altered levels of FUT8 were also significantly linked to the malignant behavior of proliferation and invasion in human hepatocarcinoma cell lines.[59] In addition, FUT4 was found to be associated with the proliferation and metastasis of breast cancer and which can serve as novel biomarker in the diagnosis and prognosis of breast cancer.[48] FUT3 mRNA over expression was found to be responsible for increased SLe^X biosynthesis leading to metastasis in colon carcinoma cell line whereas increased FUT7 levels were observed to be a significant indicator of poor prognosis.[60] The results documented here reveal the importance of monitoring fucosylation changes during various stages of cancer progression which can be helpful for early detection and management of cancer patients.

Our laboratory has long been keenly involved in studying clinical significance of glycosylation changes in various cancers. Our recent review has also summarized the correlation of altered glycosylation with other hallmarks of cancer.[5] Furthermore various studies which have documented alterations in sialylationa and fucosylation and its association with tumour burden, invasion and metastasis in a variety of cancers has strengthen our concept that glycosylation is a new hallmark of cancer progression.

Conclusion

Glycosylation is a posttranslational modification of proteins playing a major role in cell

signalling, immune recognition and cell-cell interactions. Aberrant glycosylation has been identified in almost every type of cancer due to significant modification/ alterations in sialylation and fucosyltion by altered expression of various enzymes involved in it. The current review summarizes various literatures including our data documenting clinical utility of altered expression of STs, sialidase, FUTs and fucosidase in various cancers. In nut shell, distinctive alterations in tumor-associated glycosylation may provide us a unique feature of cancer cells and therefore grant novel diagnostic and even therapeutic targets. This suggests that altered glycosylation has an important translational value in clinical setting. More interestingly, the development and progression of cancer results in the fundamental changes to the glycome; so, changes in glycosylation can be believed as a brand new hallmark of malignant transformation and a hallmark of translational value in cancer.

References

1. Hanahan D, Weinberg RA: The hallmarks of cancer. Cell 2000; 100: 57-70
2. Hanahan D, Weinberg RA: Hallmarks of cancer: the next generation. Cell 2011; 144: 646-674
3. Varki A, Freeze HH, Vacquier VD: Glycans in Development and Systemic Physiology. In: Varki A, Cummings RD, Esko JD, Freeze HH, Stanley P, Bertozzi CR, Hart GW, Etzler ME, eds. Essentials of Glycobiology: Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; 2009. Chapter 38
4. Varki A, Kannagi R, Toole B, Stanley P: Glycosylation Changes in Cancer 2017. In: Varki A, Cummings RD, Esko JD, Stanley P, Hart GW, Aebi M, Darvill AG, Kinoshita T, Packer NH, Prestegard JH, Schnaar RL, Seeberger PH, eds. Essentials of Glycobiology [Internet]. 3rd edition. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; 2015-2017. Chapter 47.
5. Vajaria BN, Patel PS: Glycosylation: a hallmark of cancer? Glycoconjugate Journal 2017; 34:147-156
6. Munkley J, Elliott DJ: Hallmarks of glycosylation in cancer. Oncotarget 2016; 7:35478-35489
7. Pinho SS, Reis CA: Glycosylation in cancer: mechanisms and clinical implications. Nature Reviews Cancer 2015; 15: 540-555
8. Tuccillo FM, de Laurentiis A, Palmieri C et al: Aberrant glycosylation as biomarker for cancer: focus on CD43 Bio Med research international 2014; 2014: 742831
9. Stowell SR, Ju T, Cummings RD: Protein glycosylation in cancer. Annual Reviews Pathology 2015; 10: 473-510
10. Shah MH, Telang SD, Shah PM, Patel PS: Tissue and serum alpha 2-3- and alpha 2-6-linkage specific sialylation changes in oral carcinogenesis. Glycoconjugate Journal 2008; 25: 279-290
11. Mattox S, Walrath K, Ceiler D, Smith DF, Cummings RD: A solid-phase assay for the activity of CMP NeuAc:Gal beta 1-4GlcNAc-R alpha-2,6-sialyltransferase. Analytical Biochemistry 1992; 206: 430-436
12. Harduin-Lepers A, Vallejo-Ruiz V, Krzewinski-Recchi MA et al: The human sialyltransferase family. Biochimie 2001; 83: 727-737
13. Carvalho AS, Harduin-Lepers A, Magalhães A et al: Differential expression of alpha-2,3-sialyltransferases and alpha-1,3/4-fucosyltransferases regulates the levels of sialyl Lewis a and sialyl Lewis x in gastrointestinal carcinoma cells. The International Journal of Biochemistry and Cell Biology 2010; 42: 80-89
14. Harduin-Lepers A, Mollicone R, Delannoy P, Oriol R: The animal sialyltransferases and sialyltransferase-related genes: a phylogenetic approach. Glycobiology 2005; 15: 805-817
15. Miyagi T, Yamaguchi K: Mammalian sialidases: physiological and pathological roles in cellular functions. Glycobiology 2012; 22: 880-896
16. Vajaria BN, Patel KR, Begum R et al: Expression of glycosyltransferases; ST3GAL1, FUT3, FUT5, and FUT6 transcripts in oral cancer. Glycobiology Insights 2014; 2014: 7-14
17. Kawamura S, Sato I, Wada T et al: Plasma membrane-associated sialidase (NEU3) regulates progression of prostate cancer to androgen-independent growth through modulation of androgen receptor signaling. Cell Death and Differentiation 2012; 19: 170-179
18. Kakugawa Y, Wada T, Yamaguchi K et al: Up-regulation of plasma membrane-associated ganglioside sialidase (Neu3) in human colon cancer and its involvement in apoptosis suppression. Proceedings of the National Academy of Sciences U S A 2002; 99: 10718-10723
19. Takahashi K, Hosono M, Sato I et al: Sialidase NEU3 contributes neoplastic potential on colon cancer cells as a key modulator of gangliosides by regulating Wnt signaling. International Journal of Cancer 2015; 137: 1560-1573
20. Shiga K, Hara M, Nagasaki T et al: Cancer-Associated Fibroblasts: Their Characteristics and Their Roles in Tumor Growth. Cancers International Journal of Cancer 2015; 7: 2443-2458
21. Shiozaki K, Yamaguchi K, Takahashi K, Moriya S, Miyagi T: Regulation of sialyl Lewis antigen

expression in colon cancer cells by sialidase NEU4. Journal of Biological Chemistry 2011; 286: 21052-21061
22. Vajaria BN, Patel KR, Begum R et al: Salivary glyco-sialylation changes monitors oral carcinogenesis. Glycoconjugate Journal 2014; 31: 649-659
23. Harduin-Lepers A, Krzewinski-Recchi MA, Colomb F et al: Sialyltransferases functions in cancers. Frontiers in Bioscience (Elite edition) 2012; 4:499-515
24. Häuselmann I, Borsig L: Altered tumor-cell glycosylation promotes metastasis. Frontiers in Oncology 2014; 4:28
25. Bai Q, Liu L, Xia Y et al: Prognostic significance of ST3GAL-1 expression in patients with clear cell renal cell carcinoma. BMC Cancer 2015 Nov 9;15:880
26. Videira PA, Correia M, Malagolini N et al: ST3Gal.I sialyltransferase relevance in bladder cancer tissues and cell lines. BMC Cancer 2009; 9:357
27. Zhang X, Pan C, Zhou L et al: Knockdown of ST6Gal-I increases cisplatin sensitivity in cervical cancer cells. BMC Cancer 2016; 16:949
28. Park JJ, Lee M: Increasing the α 2, 6 sialylation of glycoproteins may contribute to metastatic spread and therapeutic resistance in colorectal cancer. Gut and Liver 2013; 7:629-641
29. Zhao Y, Li Y, Ma H et al: Modification of sialylation mediates the invasive properties and chemosensitivity of human hepatocellular carcinoma. Molecular and Cellular Proteomics 2014; 13:520-536
30. Jun L, Yuanshu W, Yanying X et al: Altered mRNA expressions of sialyltransferases in human gastric cancer tissues. Medical Oncology 2012; 29: 84-90
31. Gomes C, Osório H, Pinto MT et al: Expression of ST3GAL4 leads to SLe(x) expression and induces c-Met activation and an invasive phenotype in gastric carcinoma cells. PLoS One 2013; 8:e66737
32. Ma H, Zhou H, Li P et al: Effect of ST3GAL 4 and FUT 7 on sialyl Lewis X synthesis and multidrug resistance in human acute myeloid leukemia. Biochim Biophys Acta 2014; 1842: 1681-1692
33. Mondal S, Chandra S, Mandal C: Elevated mRNA level of hST6Gal I and hST3Gal V positively correlates with the high risk of pediatric acute leukemia. Leukemia Research 2010; 34: 463-470
34. Becker DJ, Lowe JB: Fucose biosynthesis and biological function in mammals. Glycobiology 2003; 13: 41R-53R
35. Ma B, Simala-Grant JL, Taylor DE: Fucosylation in prokaryotes and eukaryotes. Glycobiology 2006; 16: 158R-184R
36. Mollicone R, Moore SE, Bovin N et al: Activity, splice variants, conserved peptide motifs, and phylogeny of two new alpha1,3-fucosyltransferase families (FUT10 and FUT11). Journal of Biological Chemistry 2009; 284: 4723-4738
37. Zhao YY, Takahashi M, Gu JG et al: Functional roles of N-glycans in cell signaling and cell adhesion in cancer. Cancer Science 2008; 99:1304-1310
38. Christiansen MN, Chik J, Lee L et al: Cell surface protein glycosylation in cancer. Proteomics 2014; 14:525-546
39. Miyoshi E, Moriwaki K, Nakagawa T: Biological function of fucosylation in cancer biology. Journal of biochemistry 2008; 143:725-729
40. Horstkorte R, Fan H, Reutter W: Rapid isolation of endosomes from BHK cells: identification of DPP IV (CD26) in endosomes. Experimental Cell Research 1996; 226:398-401
41. Shah M, Telang S, Raval G, Shah P, Patel PS: Serum fucosylation changes in oral cancer and oral precancerous conditions: alpha-L-fucosidase as a marker. Cancer 2008; 113:336-346
42. Vajaria BN, Patel KR, Begum R et al: Evaluation of serum and salivary total sialic acid and α-l-fucosidase in patients with oral precancerous conditions and oral cancer. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 2013; 115: 764-771
43. Cheng TC, Tu SH, Chen LC et al: Down-regulation of α-L-fucosidase 1 expression confers inferior survival for triple-negative breast cancer patients by modulating the glycosylation status of the tumor cell surface. Oncotarget 2015; 6: 21283-21300
44. Ezawa I, Sawai Y, Kawase T et al: Novel p53 target gene FUCA1 encodes a fucosidase and regulates growth and survival of cancer cells. Cancer Science 2016; 107:734-745
45. Liu CJ, Liu TY, Kuo LT et al: Differential gene expression signature between primary and metastatic head and neck squamous cell carcinoma. The Journal of Pathology 2008; 214:489-497
46. Vecchio G, Parascandolo A, Allocca C et al: Human a-L-fucosidase-1 attenuates the invasive properties of thyroid cancer. Oncotarget 2017; 8:27075-27092
47. Osuga T, Takimoto R, Ono M et al: Relationship Between Increased Fucosylation and Metastatic Potential in Colorectal Cancer. JNCI: Journal of the National Cancer Institute 2016; 108(8)
48. Yan X, Lin Y, Liu S, Aziz F, Yan Q:

Fucosyltransferase IV (FUT4) as an effective biomarker for the diagnosis of breast cancer. Biomedicine and Pharmacotherapy 2015 ; 70: 299-304
49. Muinelo-Romay L, Vázquez-Martín C, Villar-Portela S et al: Expression and enzyme activity of alpha(1,6)fucosyltransferase in human colorectal cancer. International Journal of Cancer 2008; 123:641-646
50. Li J, Guillebon AD, Hsu JW et al: Human fucosyltransferase 6 enables prostate cancer metastasis to bone. British Journal of Cancer 2013; 109:3014-3022
51. Liu F, Qi HL, Chen HL: Regulation of differentiation- and proliferation-inducers on Lewis antigens, alpha-fucosyltransferase and metastatic potential in hepatocarcinoma cells. British Journal of Cancer 2001; 84:1556-1563
52. Koike T, Kimura N, Miyazaki K et al: Hypoxia induces adhesion molecules on cancer cells: A missing link between Warburg effect and induction of selectin-ligand carbohydrates. Proceedings of the National Academy of Sciences of the United States of America 2004; 101(21):8132-8137
53. Matsumoto K, Yokote H, Arao T et al: N-Glycan fucosylation of epidermal growth factor receptor modulates receptor activity and sensitivity to epidermal growth factor receptor tyrosine kinase inhibitor. Cancer Science 2008; 99:1611-1617
54. Chen CY, Jan YH, Juan YH et al: Fucosyltransferase 8 as a functional regulator of nonsmall cell lung cancer. Proceedings of the National Academy of Sciences 2013; 110:630-635
55. Desiderio V, Papagerakis P, Tirino V et al: Increased fucosylation has a pivotal role in invasive and metastatic properties of head and neck cancer stem cells. Oncotarget 2015; 6:71-84
56. Yue L, Han C, Li Z et al: Fucosyltransferase 8 expression in breast cancer patients: A high throughput tissue microarray analysis. Histol Histopathol 2016; 31:547-555
57. Honma R, Kinoshita I, Miyoshi E et al: Expression of fucosyltransferase 8 is associated with an unfavorable clinical outcome in non-small cell lung cancers. Oncology 2015; 88:298-308
58. Wang X, Chen J, Li QK et al: Overexpression of α (1,6) fucosyltransferase associated with aggressive prostate cancer. Glycobiology 2014; 24:935-944
59. Cheng L, Gao S, Song X et al: Comprehensive N-glycan profiles of hepatocellular carcinoma reveal association of fucosylation with tumor progression and regulation of FUT8 by microRNAs. Oncotarget 2016; 7: 61199-61214
60. Trinchera M, Malagolini N, Chiricolo M et al: The biosynthesis of the selectin-ligand sialyl Lewis x in colorectal cancer tissues is regulated by fucosyltransferase VI and can be inhibited by an RNA interference-based approach. The International Journal of Biochemist and Cell Biology 2011; 43:130-139