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The Clinical Utility of Biochemical Biomarkers in Colorectal Cancer

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Abstract

Colorectal cancer (CRC) ranks as the third most prevalent cancer worldwide and is a leading cause of cancer-related mortality. Since many colon cancers present no significant clinical symptoms, identifying new biomarkers or a set of biological indicators significant for clinical trials is crucial for the early detection of CRC. This advancement also aids in establishing new objectives for interventional therapeutic strategies against the disease. Currently, research is exploring various proteins, glycoproteins, and cellular and humoral substances involved in cellular homeostasis mechanisms as potential cancer markers. This review examines the potential utility of fucosylation and sialylation processes, as well as sex hormones, as biomarkers in the diagnosis and prognosis of CRC. A comprehensive search was conducted in PUBMED, MEDLINE, and Google Scholar, supplemented by a manual search of relevant journals. The keywords were L-fucose, sialic acid, fucosyltransferase-4, galectin-3, and steroid hormones in CRCs.

Keywords: Glycoproteins, Fucosyltransferase, Galectin, L-fucose, Sialic acid

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Introduction

Colorectal cancer (CRC) results from the uncontrolled growth of epithelial cells within the colon and rectum layers of the gastrointestinal system. This uncontrolled cell proliferation, or neoplasia, stems from dysfunctional complications in cell homeostasis, including the regulation of cell cycle progression, differentiation, senescence, and apoptosis.[1-3] CRC is the third most

common cancer globally and is a significant cause of mortality.[4, 5] Diagnosis of CRC may arise from assessing symptoms presented by patients or through screening efforts. As most colon cancers start as benign or non-cancerous masses and later progress to more advanced stages without significant clinical symptoms, the identification of new biomarkers or a set of biological indicators critical for clinical trials is essential. These biomarkers serve as tools for the early detection of CRC and facilitate the development of promising new objectives in interventional therapeutic strategies for the disease.[6-9] Numerous studies have sought to distinguish the molecular differences between cancerous and healthy cells to identify biological markers that signal the presence of cancer at the systemic level. These investigations have unveiled several molecular characteristics of cancer, including signal transduction and cell senescence, contributing to identifying specific cancer cell markers. Recognizing these biological markers can significantly enhance early detection, prognosis, treatment response prediction, and recurrence risk.[10-12]

This review focuses on the currently available glycan biomarkers for the early diagnosis and prognosis of CRC. Glycans, complex carbohydrates, represent the most intricate molecules in living organisms, participating in critical biological cellular processes such as cell adhesion, molecular trafficking and release, receptor activation, signal transduction, and endocytosis. As glycoproteins, glycolipids, glycosaminoglycans, or other glycoconjugates, glycans act as functional molecules within biological systems. They are integral to molecular recognition activities, including cell migration and metastasis, host–pathogen interactions (e.g., bacterial and viral infections), and the initiation of immune responses.[13, 14] Glycosylation, the most frequent and structurally complex post-translational modification of cell surface and secreted proteins, undergoes alterations during malignant transformations, serving as a hallmark of cancer.[15, 16] Carcinogenesis, a multi-step process involving a variety of genetic or epigenetic changes, confers six functional cancer hallmarks:

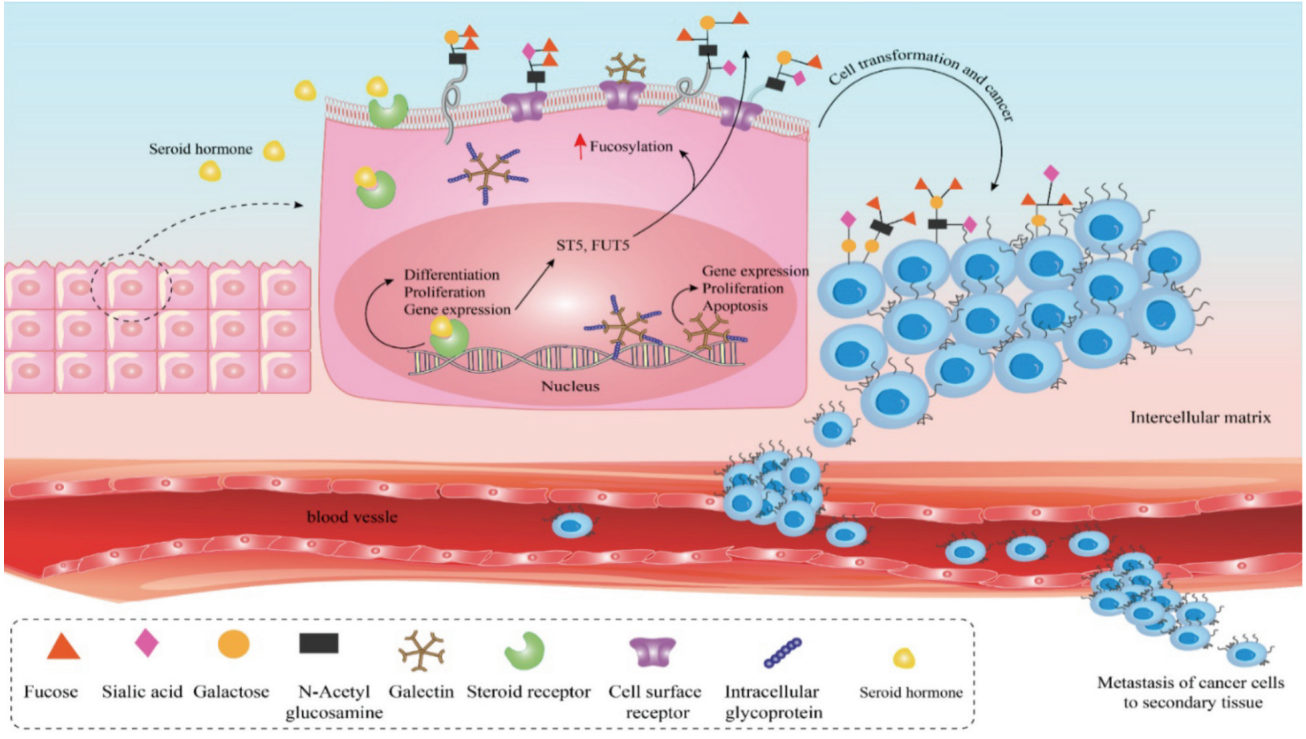

Figure 1. This figure illustrates the role of glycans and steroid hormones in the development and spread of colon and CRC, highlighting the complex interplay between biochemical markers and disease progression.
CRC: Colorectal cancer

(i) persistent proliferative signaling, (ii) evasion of apoptosis, (iii) resistance to anti-growth signals, (iv) unlimited replicative potential, (v) angiogenesis, and (vi) invasion and metastasis. Like normal cells during embryogenesis, tumor cells exhibit rapid growth and can adhere to and invade various cell types and tissues. Since protein glycosylation alterations occur during the early stages of embryonic development and cell activation in vertebrates, these changes indicate malignant transformation and tumor progression.[17]

Glycosyltransferases, enzymes that regulate glycosylation in humans, operate based on the availability of precursor monosaccharide molecules and other regulatory factors. Sialyltransferases (STs) and fucosyltransferases, responsible for adding sialic acid and fucose to glycan structures, are located in the endoplasmic reticulum, Golgi apparatus, cytosol, and nucleus. The natural glycosylation process becomes disrupted during cellular malignancy, leading to alterations in tumor cell surface glycans and affecting interactions with endogenous lectins, thereby influencing the metastatic potential of tumor cells.[18] Glycan compounds, capable of attaching to proteins and lipids at the cellular level, play a crucial role in these cells' phenotype and environmental interactions.[19] Alongside glycosylation changes, the expression and levels of carbohydrate-binding proteins also vary during malignancy, leading to shifts in the transfer of glycans and their receptors, lectins. Various glycosylation alterations have been observed in malignant cells, including changes in the number, linkages, and acetylation of sialic acids, as well as alterations in the branching of N-glycans mediated by glycosyltransferases.[20]

Glycoproteins, comprising glycans such as galactose, mannose, glucosamine, galactosamine, sialic acid, and fucose, can be structurally classified based on the bonding of glycans to the hydroxyl or amide groups of amino acids into two categories: O-glycans and N-glycans. These glycans on cell surface glycoproteins often conclude with sialic acid and play a pivotal role in intercellular interactions.[21] Any alterations in protein glycosylation can propel the progression of malignant features, including cell-cell adhesion, migration, and increased metastasis. Specifically, altered glycosylation is instrumental in activating oncogenic pathways and evading the immune system, leading to the proliferation of cancerous cells. The excessive expression and immature biosynthesis of Tn, sTn, and T antigens, resulting from abnormal O-glycosylation, promote tumor metastasis.[22] Since these structures are not found in standard cell glycoproteins, they offer the potential for identifying molecular differences between cancerous and healthy cells. Given that glycoproteins are secreted into the bloodstream or other body fluids, they present a viable option for non-invasive diagnostic methods (Figure 1).[23]

Fucosylation in Carcinogenesis

Fucosylation is a pivotal glycosylation process in carcinogenesis, catalyzed by fucosyltransferases, guanosine 5'-diphosphate (GDP)-fucose synthetic enzymes, and GDP-fucose transporters. GDP-fucose, a universal donor substrate for all fucosyltransferases, is synthesized in the cytosol.[24] 13 types of fucosyltransferase enzymes (FUT1-FUT13) expressed in cells are known to facilitate various glycosylated bonds crucial for the synthesis of Lewis group antigens and the transfer of fucose residues to glycoprotein cells.[25] Monosaccharides such as galactose, fucose, N-acetyl glucosamine, and sialic acid form different glycosylated bonds that constitute part of Lewis antigens, including H1, H2, Lewis a (Lea), Lewis b (Leb), Lewis x (Lex), and Lewis y (Ley) antigens. These Lewis antigens, playing critical roles in cell recognition and adhesion during embryogenesis and subsequent development, are moderately expressed in tissues like the gastrointestinal mucosal epithelium, brain, and some immune cells. However, their overexpression has been observed in various cancers, including CRC.[26, 27]

FUT4, a key enzyme catalyzing α1,3-fucosylation of the tumor-associated sugar antigen Lewis Y (LeY), has been highlighted for its specific role in cancer.[28] Sialyl Lewis x (SLex) expression is regulated by fucosyltransferases such as FUT4 and FUT3 in CRC. Inhibition of

FUT3 inhibits selectin-mediated adhesion and metastasis, while FUT4 knockdown is associated with reduced SLex expression in CRC cell lines.[29] A negative correlation exists between the high expression of FUT4 in serum and tissue of patients and the recovery rate in those with metastatic CRC, underscoring the tumor suppressive function's regulation of FUT4.[30-32] Recent studies have shown that FUT4 levels are elevated in CRC patients compared to control subjects, indicating its potential as a reliable marker for detecting this cancer.[33]

L-fucose is critical in modifying human molecules, including determining blood groups, modulating immunological responses, and signal transduction pathways. Elevated serum and urine levels of fucose in patients with malignant tumors suggest increased fucosylation within cancer cells.[34] There is a positive correlation between the serum level of L-fucose and the metastatic stage of oral cancer, with serum L-fucose levels rising by the extent of metastasis.[35]

The carcinoembryonic antigen (CEA), while widely used as a primary marker for screening, diagnosing, and monitoring CRC, has faced limitations in clinical application due to its lack of sensitivity and specificity. CEA, a glycoprotein composed of approximately 60% carbohydrates, underscores the potential of measuring serum L-fucose levels alongside traditional clinical diagnostic methods as an effective marker for cancer detection.[36]

Sialylation in Cancer Progression

Sialic acids cap the terminal ends of glycans (sialoglycans), where they are enzymatically bonded to other monosaccharides, such as galactose, via glycosidic bonds. Over 20 sialyltransferases (STs), located within the Golgi apparatus, are tasked with attaching sialic acids to carbohydrates through an enzymatic process.[37] Sialoglycans, expressed in various cell types, play crucial roles in determining the structure, stability, mobility, and function of glycoproteins and glycolipids. These sialoglycans, present on the surfaces of receptors and adhesion molecules including growth factor receptors, integrins, laminin, and cadherins significantly influence cell–cell interactions and cellular adhesion to the extracellular matrix. Aberrant expression of STs has been documented across multiple cancer models. Specifically, overexpression of α2,6-linked sialoglycoconjugates in CRC tissues has been correlated with poorer patient outcomes.[38] Moreover, various cancer types have observed elevated serum concentrations of sialic acid.

To date, three primary mechanisms have been proposed to account for aberrant sialylation in cancer cells:

1. Overexpression and/or altered activity of STs leading to increased sialylation of glycans and the expression of specific tumor-associated carbohydrate antigens. Notably, in colon cancer cells, the expression of STs and the synthesis of specific tumor-associated carbohydrate antigens escalate under hypoxic conditions.
2. The amplification of the sialic acid synthesis pathway in cancer cells is driven either by an excess of raw materials or by the overexpression of genes responsible for sialic acid production.
3. Differentially expressed endogenous sialidases as a mechanism for increased tumor cell sialylation. The reduction in sialidase expression, which detaches sialic acid from glycans, has been noted as a factor in carcinogenesis.[39] Research indicates that both L-fucose and sialic acid exhibit sensitivity and specificity as prognostic biomarkers in CRC patients.[40]

Elevated levels of total sialylation, especially α2,6-sialylation, have been identified in CRC. Intriguingly, the upregulation of ST6GAL1, which is responsible for α2,6-sialylation, is linked to CRC progression, invasion, and metastasis. Additionally, the increased expression of specific sialylated glycan epitopes, such as sialyl Lewis antigen (SLe) and sialyl-Tn (STn), alongside the heightened expression of STs, is associated with patient prognosis in breast, colorectal, and stomach cancers. The upregulation of sialylated Lewis-type blood groups antigens, such as SLea and SLex, enhances cancer cell migration through binding to endothelial selectins. The

overexpression of SLea and SLex, common across several carcinoma types (e.g., lung, colorectal, gastric, and pancreatic), is linked with increased metastatic potential and poor patient survival.[41] Sialylation facilitates tumorigenesis and tumor progression at multiple levels, including evasion of apoptosis through effects on apoptosis-involved receptors, formation of metastases by its presence in cell adhesion glycoproteins, and resistance to therapy. As such, sialylation impacts various vital processes in cancer cells and can be considered a critical prognostic factor in cancer diagnosis.[42, 43]

Galectins in Cancer Dynamics

Galectins are a family of 15 immunoregulatory lectins that bind to galactose, either β1,3 or β1,4 linked to N-acetyl glucosamine. These soluble proteins possess intracellular and extracellular functions and are expressed by many cells, including epithelial and immune cells, bound to proteins via N-linked and O-linked glycosylation. Their functions span mediating cell–cell interactions, cell–matrix adhesion, and apoptosis regulation.[44] The galectin family is categorized into three groups based on their protein structure: the prototype galectins, containing one carbohydrate recognition domain (CRD); the tandem repeat galectins, also known as biCRD, which contain two CRDs; and the chimera-type galectin, consisting of a large N-terminal region linked to a CRD that can form a pentamer.[45] Gal-3 is the sole chimera-type member, pivotal in various physiological and pathological processes.

Galectin-3 (Gal-3) is primarily located in the cytoplasm but resides in the nucleus and the intercellular matrix. Nuclear Gal-3 can alter gene expression by interacting with transcription factors and has a role in pre-mRNA splicing.[46] Numerous studies have explored Galectins' role in regulating cancer cells' functional characteristics, such as adhesion, invasion, and metastasis, highlighting the specific function of Gal-3 and its controversial effects on survival, depending on the tumor and tissue involved.[47] Serum Gal-3 levels in CRC patients were slightly higher than in healthy controls, correlating with biochemical and clinical features in CRC patients.[48] A 2020 study found no significant difference in serum Gal-3 levels, suggesting that Gal-3 measurement may not serve as a prognostic biomarker for CRC early detection, calling for further research.[49] Gal-3, abundantly found in the human gastrointestinal tract, including the colon and rectum, shows strong nuclear expression in normal colonic mucosa. Its presence in interchromatin spaces and at compacted chromatin edges in the nucleoplasm where mRNA synthesis and initial pre-mRNA splicing stages occur highlights its significance. During CRC progression, Gal-3 transitions from the nucleus to the cytoplasm, a shift likely crucial for cancer cell survival.[50]

The cytoplasmic Gal-3's inhibitory role in apoptosis is well-documented, suggesting its contribution to cancer cell survival. Gal-3 influences tumor angiogenesis by interacting with various endothelial cell surface receptors. High expression levels Gal-3 in cancer cells enhance intercellular and environmental interactions, promoting metastasis. Gal-3's association with matrix glycoproteins like laminin, fibronectin, CEAs, and lysosomal surface glycoproteins underscores its role in cell adhesion. It interacts with mucin-1 on the surface of cancerous cells within veins, aiding cancer cell survival in the circulatory system and facilitating their attachment to capillary epithelial cells.[51] Simultaneously measuring Fucosyltransferase-4 and Gal-3 could serve as a non-invasive method for early-stage CRC detection. Given its unique structural features and multifaceted role in cancer regulation, progression, and metastasis, this molecule holds potential for diagnostic and therapeutic applications.[52]

Hormones and CRC

Although CRC is not typically classified as hormone-dependent, emerging evidence suggests a connection between sex hormones and CRC risk. Specifically, the role of testosterone has been implicated in elevating the risk of various cancers, including lung, prostate, and CRC.[53] Epidemiological studies conducted over the past decade have revealed that increased levels of female sex hormones, such as estrogen and progesterone,

are associated with a reduced risk of developing colon cancer. This finding suggests that women may have a lower incidence of CRC compared with men, potentially due to the protective effects of hormonal estrogens.[54] Conversely, research indicates that testosterone exerts a more substantial impact on the development of colon cancer than the protective effect of estrogen. Moreover, the incidence of colon cancer decreases following the removal of testosterone.[55] The synthesis and transcriptional activation of sex hormones in target tissues, regulated by biosynthetic enzymes, metabolizing enzymes, and steroid receptors, can be influenced by genetic and epigenetic modifications of these proteins' genes, thereby affecting the risk of sex hormone-related cancers.[56]

A 2021 study found significant differences in hormone levels between female CRC patients and healthy controls: females with CRC exhibited elevated levels of FSH, LH, DHEA, and testosterone, while their estradiol levels were lower. Conversely, male CRC patients showed significant increases in FSH, LH, and estradiol levels, but unlike healthy controls, their levels of DHEA and testosterone were decreased. Receiver operating characteristic curve analysis confirmed that serum testosterone, LH, and FSH act as discriminatory factors to differentiate CRC patients from healthy individuals. Thus, these hormones have the potential to serve as diagnostic and monitoring markers for CRC, offering promising results for treatment.[57] Testosterone, through its interaction with the androgen receptor, plays a crucial role in regulating gene expression and protein synthesis, impacting intracellular protein levels by interacting with DNA-binding transcription factors.

Steroids and other ligands of nuclear receptors influence the production and function of various glycoproteins by affecting the synthesis, glycosylation, and storage of target proteins. Among small lipophilic hormone compounds, steroids, particularly testosterone, significantly regulate protein glycosylation. Testosterone has been shown to affect the activity of glycosyltransferases responsible for the transmission of galactose and xylose from UDP-GLU and UDP-GAL. Furthermore, the presence of galactosyltransferases in the hypophysectomized prostate notably increases with testosterone administration.[58] Estrogens exert an antitumor effect within the large intestine mucosa by activating anti-apoptotic cellular mediators, inhibiting cellular anti-inflammatory messages, mediating the tumor cell environment, and through various immune system mechanisms.[59-61]

Conclusion

The identification and application of novel biomarkers for the diagnosis and prognosis of colon cancer remain pivotal in the clinical landscape. Despite the extensive research, much remains to be elucidated about the principles and structures underlying glycosylation processes. A critical endeavor in this domain is to pinpoint a glycan biomarker characterized by high sensitivity and accuracy for clinical diagnostics. Notably, a negative correlation exists between the elevated expression of FUT4 in the serum and tissues of patients and the recovery rates in individuals with metastatic CRC. Moreover, increased levels of total sialylation, especially α2,6-sialylation, have been documented in CRC cases.

Gal-3, known for its widespread expression in the human gastrointestinal tract, including the colon and rectum, plays a significant role in the disease's pathology. Additionally, the influence of testosterone on increasing CRC risk contrasts with the protective association of estrogen and progesterone, suggesting a potential hormonal defense mechanism against colon cancer development.

Simultaneously measuring various biochemical biomarkers, including glycan markers, offers promising prospects for predicting CRC patient prognoses. Therefore, it is imperative to conduct large-scale clinical trials to detect these biomarkers and develop therapeutic strategies. Such efforts are essential for advancing the diagnosis, prognosis, and treatment of CRC, ultimately contributing to improved patient outcomes.

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Authors' Contribution

The authors confirm contribution to the paper as follows: study conception and design: Durdi Qujeq, Roya Abbasi Natajomrani; Data collection: Roya Abbasi Natajomrani, Khadijeh Hoznian, Arash Kazemi Veisari; Analysis and interpretation of results: Durdi Qujeq, Roya Abbasi Natajomrani, Reza Hajihosseini, Vahid Hosseini; Draft and manuscript preparation: Durdi Qujeq, Roya Abbasi Natajomrani.

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Conflict of Interest

None declared.

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