Am J Cancer Res 2025;15(4):1347-1383
www.ajcr.us /ISSN:2156-6976/ajcr0161435

Review Article

The role of glycan-lectin interactions in the tumor microenvironment: immunosuppression regulators of colorectal cancer

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Received October 24, 2024; Accepted March 17, 2025; Epub April 15, 2025; Published April 30, 2025

Abstract: Colorectal cancer (CRC) is a common malignant tumour and a serious global health issue. Glycosylation, a type of posttranslational modification, has been extensively studied in relation to cancer growth and metastasis. Aberrant glycosylation alters how the immune system in the microenvironment perceives the tumour and drives immune suppression through glycan-binding receptors. Interestingly, specific glycan signatures can be regarded as a new pattern of immune checkpoints. Lectins are a group of proteins that exhibit high affinity for glycosylation structures. Lectins and their ligands are found on endothelial cells (ECs), immune cells and tumour cells and play important roles in the tumour microenvironment (TME). In CRC, glycan-lectin interactions can accelerate immune evasion promoting the differentiation of tumour-associated M2 macrophages, altering T cell, dendritic cell (DC), natural killer (NK) cell, and regulatory T (Treg) cell activity to modify the functions of antigen-presenting cells functions. Here, we review our current knowledge on how glycan-lectin interactions affect immune-suppressive circuits in the TME and discuss their roles in the development of more effective immunotherapies for CRC.

Keywords: Colorectal cancer glycosylation, tumour microenvironment, glycan-lectin interactions, immunotherapy

Introduction

Cancer is the second most common disease worldwide. In 2024, an estimated 2,001,140 new cancer cases and 611,720 cancer deaths are expected in the United States [1]. CRC was the fourth most common cause of cancer death in both men and women younger than 50 years in the late 1990s but is now the second most common cause of cancer death in men and women [2]. Currently, the treatment methods for CRC include surgery in combination with multiple targeted therapies, such as those that target K-ras, EGFR, and VEGF [3]. Although overall CRC mortality continues to decline, the epidemiology of CRC is rapidly shifting; it is being diagnosed at a younger age, at a more advanced stage, and in the left colon/rectum [2]. Recently, immunotherapy has emerged as a promising option for CRC treatment [4, 5]. Compared with traditional standard treatments, immunotherapy utilizes and attacks cancer cells more effectively by interfering with the immune system of patients. Current immunotherapeutic treatments for CRC include immune checkpoint inhibitors, monoclonal antibodies, adoptive cell therapy, oncolytic viruses, anticancer vaccines, and cytokines [6]. To date, many immune checkpoint inhibitors, such as PD-1, PD-L1, LAG-3, CTLA-4, and TIM-3, have been used to treat CRC [7]. Inhibiting immune checkpoints can prolong the efficacy of antitumour therapy, improve the host's immunity against cancer by enhancing T-cell activation, and potentiate the cytotoxic killing of tumour cells [8]. Therefore, more immune checkpoints may need to be explored to offer promising solutions for the treatment of CRC with immune therapy.

Glycosylation is a common posttranslational modification whereby glycans connect with a

https://doi.org/10.62347/WBJL4045

protein for glycoconjugate synthesis. It generally occurs on the cellular membrane and may play a role in various biological processes, including signal transduction [9], cell apoptosis [10], transcriptional regulation [11], the immune response [12], inflammation [13], and the development of tumours [14]. Indeed, recent research has demonstrated that alterations in glycosylation, which are a hallmark of cancer, modulate the immune microenvironment [15-17]. Immune cells recognize abnormal glycosylation on cancer cells, and this recognition contributes to the modulation of immune processes. For example, some immune checkpoint molecules, such as B7 family members (PD-L1, PD-L2, B7-H3, and B7-H4), are known to be highly glycosylated, which prevents cytotoxic activity in infiltrated T cells [18]. Targeting cancer glycosylation repolarizes tumour-associated macrophages and enhances the efficacy of immune checkpoint blockade [19]. Combining anchoring DCs with recombinant prosaposin protects patients from tumours and improves the efficacy of immune checkpoint therapy [20]. The majority of proteins involved in glycan recognition are glycan-binding receptors expressed on the immune cell surface, which are generally referred to as lectins. Lectins are a large family of proteins that contain a representative carbohydrate recognition domain (CRD) that binds to specific glycosylation structures [21]. Recent studies have validated that glycan-lectin interactions can be utilized to improve cancer immunotherapy [22-24].

Here, we review the current state of research based on the microenvironment in CRC. We investigate the glycosylation changes in CRC and the impacts of lectin-glycan interactions on CRC cells and stromal or immune cells. Finally, we discuss the glycan-lectin axis as an immune checkpoint, which is expected to be a potential target for CRC treatment.

Tumour microenvironment in colorectal cancer

Tumour development and malignant progression are correlated not only with cancer cells but also with interactions with the surrounding microenvironment. The TME is the environment surrounding tumour cells and consists of a synthetic array of immune cells, fibroblasts, endothelial cells, etc. [25]. Cancer cells rely on pro-survival and proliferative signals from the abnormal environment that they create and reside in. The interactions between tumour cells and TME are important in tumour development and progression. Below, we summarize the functions of the main cell components of the CRC microenvironment (**Figure 1**).

Extracellular matrix and stromal cells in colorectal cancer

Extracellular matrix in colorectal cancer: The extracellular matrix (ECM), which consists of a sophisticated network of molecules, is commonly defined as the noncellular component of tissue. The ECM in mammals consists of many proteins, such as laminin, collagen, fibronectin, and proteoglycans. Thus, the majority of extracellular and transmembrane proteins are glycosylated [26]. It provides necessary biochemical and structural support for its cellular constituents. In cancer, a crucial feature of cancer cells is their ability to migrate through surrounding tissues and penetrate the adjacent basement membrane. Elevated deposition of ECM proteins in the TME increases the stiffness of the ECM, which affects cellular functions, such as proliferation, adhesion, migration, invasion and metastasis. Laminins are significantly more abundant in the serum of CRC patients than in that of healthy individuals [27]. The deposition of collagen is a common feature of CRC, and Type I, VI, VII, VIII, X, XI, and XVIII collagen accumulate in CRC. Recently, collagen has been associated with the immunoscore in the TME [28]. Fibronectin promotes the proliferation of CRC cells and drug resistance via a CDC42-YAS-dependent signalling pathway [29]. The heparin sulfate proteoglycan syndecan-2 (Sdc-2) plays an oncogenic role via epithelial-mesenchymal transition (EMT) and the MAPK pathway in CRC [30]. Nevertheless, a loss of Sdc-1 enhances colon cancer stem cell function via the activation of β-integrins and focal adhesion kinase [31]. Moreover, ECM remodelling interferes with pathological processes as a key determinant in CRC. Remodelling enzymes, including matrix metalloproteinases (MMP-1, MMP-2, MMP-7, MMP-9, MMP-13, and MMP-14) and LOX family oxidases, are correlated with both CRC development and progression. Thus, studies have demonstrated that these ECM components act as vital indicators of the tumorigenesis of CRC.

Endothelial cells in colorectal cancer: Endothelial cells (ECs) are a type of stromal cell present in the TME. They are involved in many processes, including angiogenesis, vascular per-

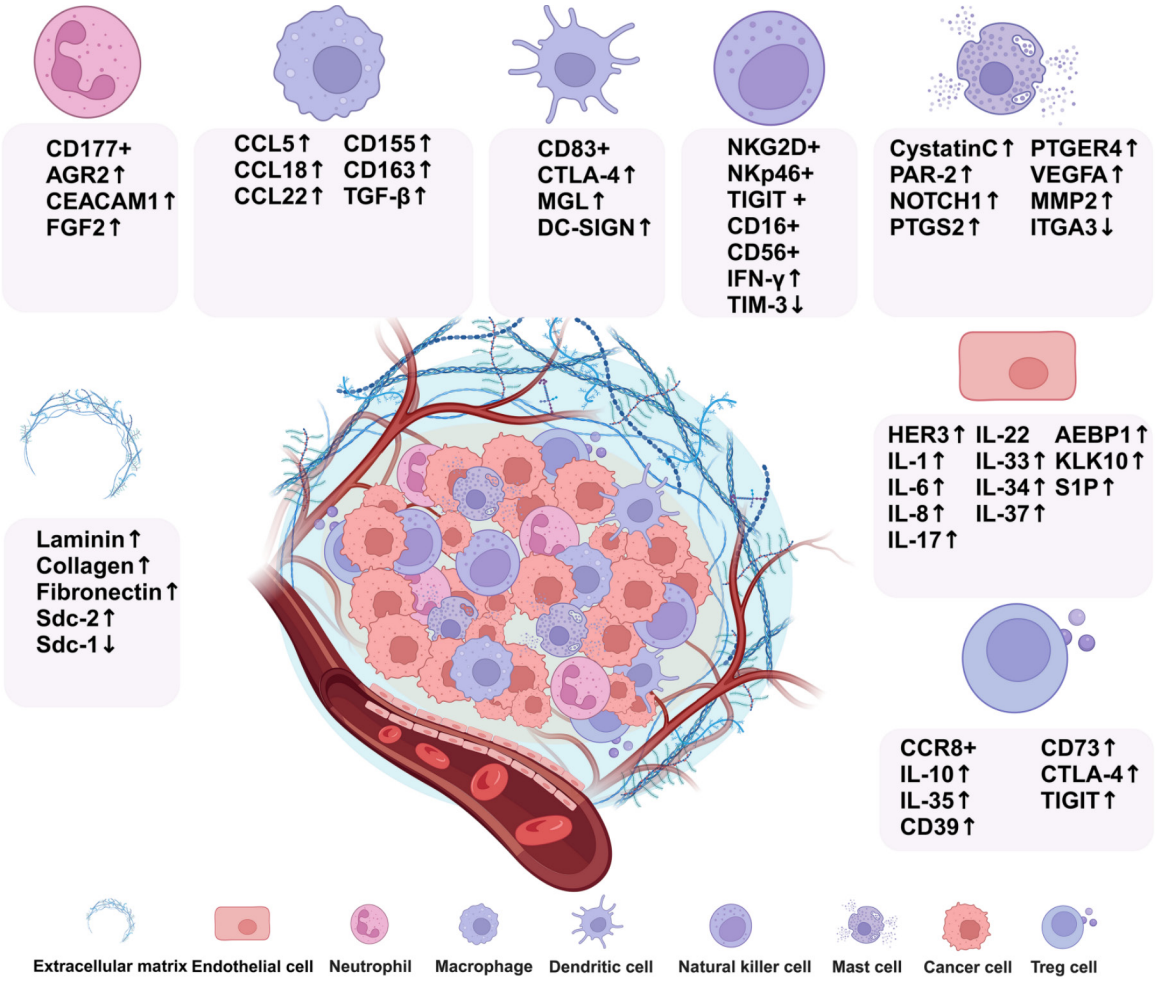

Figure 1. Schematic representation of CRC microenvironment. The TME is composed of various components, including ECM, endothelial cells and immune cells (neutrophil, macrophage, dendritic cell, NK cell, mast cell, regulatory T cell). Those components secrete soluble and insoluble factors, facilitate communication between tumor cells and their surroundings, regulate the development and progression of CRC. Created with BioRender.com.

meability, cancer cell migration, and invasion [32]. They are crucial components of the vascular wall required for angiogenesis via interactions with tumour cells [33]. In the TME, ECs exhibit increased permeability, which increases vascular leakage. Tumour cells infiltrate the normal epithelium and interact with surrounding ECs to produce various cytokines and growth factors that impact the function of cells in the TME. Liver ECs promote CRC cell growth and chemoresistance by acting on human epidermal growth factor receptor 3 (HER3)-AKT in a paracrine fashion [34]. Vascular ECs release many proangiogenic interleukins (ILs), such as IL-1, IL-6, IL-8, IL-17, IL-22, IL-33, IL-34, and IL-37. These upregulated ILs are potential drivers of the CRC angiogenesis process [35]. Adipocyte enhancer-binding protein 1 (AEBP1) expressed in human umbilical vein ECs contributes to tumour angiogenesis by regulating aquaporin 1 and periostin in CRC [36]. Kallikrein-related peptide 10 (KLK10) produced by ECs facilitates colon cancer cell proliferation and haematogenous liver metastasis formation [37]. EC-derived sphingosine-1-phosphate (S1P) facilitates GPR63 binding to Src to stimulate the JAK2/STAT3 pathway and therefore promotes the migration and metastasis of CRC cells [38]. These findings suggest that ECs are potential biomarkers of angiogenesis in CRC.

Immune cells in colorectal cancer

Neutrophils in colorectal cancer: Neutrophils were originally considered the first responders to acute infection or inflammation. Neutrophils

are involved in the regulation of the innate and adaptive immune systems and can be polarized towards different phenotypes in response to environmental signals [39]. Tumour-associated neutrophils exhibit considerable plasticity and affect the TME as either an antitumourigenic "N1" phenotype or a protumourigenic "N2" phenotype. They can facilitate tumour cell growth and metastatic progression via the secretion of protumour cytokines [40], modulation of the extracellular matrix [41], and enhancement of tumour angiogenesis [42]. Neutrophils can also form neutrophil extracellular traps (NETs), which promote the invasion and metastasis of tumour cells. In CRC, neutrophils may also play dual roles in cancer progression. CD177+ neutrophils suppress epithelial cell tumourigenesis and may act as therapeutic targets in the prognosis of colitis-associated cancer and CRC [43]. In contrast, neutrophils promote CRC cell proliferation, migration, angiogenesis and metastasis. An increase in the number of neutrophils in the peripheral blood has been identified as a poor prognostic factor for advanced cancer, especially left-sided colon cancer [44]. Li et al. revealed a strong relationship between dynamic changes in the neutrophil-to-lymphocyte ratio (delata-NLR) and overall survival in patients with colon cancer [45]. Tumour-associated neutrophils release anterior gradient-2 (AGR2) to promote CRC cell migration and metastasis through its receptor, CD98hc-xCT [46]. Neutrophil extracellular trap-associated carcinoembryonic Ag cell adhesion molecule 1 (CEACAM1) is important for CRC cell adhesion, migration, and metastasis [47]. Neutrophils promote CRC liver metastasis through fibroblast growth factor 2 (FGF2)-dependent angiogenesis in mice [48]. Indeed, many studies support that high neutrophil infiltration may be a hallmark of poor prognosis in CRC patients.

Macrophages in colorectal cancer: Macrophages are versatile immunocytes that perform a broad spectrum of functions in immune and inflammatory processes, including defending against pathogens, governing tissue haemostasis and facilitating wound healing. Furthermore, the roles of macrophages in the TME are more widely recognized. They participate in ECM transformation, angiogenesis, proliferation, immunosuppression, chemotherapeutic resistance, and metastasis in cancer [49]. They constitute the most abundant immune population of the TME and are a double-edged sword with both antitumourigenic (M1-like macrophages) and protumourigenic (M2-like macrophages) functions. Tumour-associated macrophages (TAMs), which have a phenotype similar to that of M2-like macrophages, have been reported to be crucial contributors to CRC. Vayrynen et al. reported that a high tumour stromal density of M2-like macrophages was correlated with worse colorectal cancer-specific survival, whereas the tumour stromal density of M1-like macrophages was not statistically associated with better survival in patients with colorectal cancer [50]. TAMs exhibit immunosuppressive features by generating the chemokines CCL5, CCL18, and CCL22 [51, 52] in CRC. TAM-specific CD155 contributes to M2 phenotype transition and promotes migration and invasion in CRC [53]. CD163+ TAMs accelerate the EMT program to promote CRC cell migration, invasion and metastasis via the JAK2/STAT3/miR-506-3p/FoxQ1 axis [54]. Transforming growth factor-β (TGF-β) derived from TAMs increases CRC progression in a hypoxia-inducible factor 1α (HIF1α)/Tribbles pseudokinase 3 (TRIB8)-dependent manner [55]. These studies support the idea that macrophages usually play tumour-promoting roles in the CRC microenvironment.

Dendritic cells in colorectal cancer: Dendritic cells (DCs) serve as the key sentinels of the immune response in innate and adaptive immunity, playing significant roles in the TME through their ability to recognize, present, and activate antigens, as well as coordinate and regulate immune responses [56]. The receptors expressed on the surface of DCs enable them to recognize and bind antigens released by tumour cells or their degradation products. The processed antigens are transferred by DCs to their organelles for "antigen presentation". Additionally, DCs promote immune responses by secreting a variety of immunomodulators, such as chemokines and cytokines. In CRC, the prognostic value of DCs is still unclear, perhaps due to the interchangeable expression of immunostimulatory and immunoinhibitory molecules by DCs. A greater number of tumour-infiltrating plasmacytoid DCs significantly correlates with increased progression-free survival and overall survival in colon cancer patients [57]. Colon cancer patients with a lower density of CD83+ DCs in the stroma and invasive margins had a worse prognosis than those with greater CD83+ DC infiltration [58]. Conversely, interactions between tumour-associated DCs and CRC cells

promote tumour progression via CXCL1 [59]. Suppressing cytotoxic T lymphocyte-associated protein (CTLA-4) expression on DCs along with loading CRC cell lysate increased antitumoral-specific T-cell responses, resulting in the production of IFN-γ and IL-4 [60]. MGLs are expressed by dendritic cells, and glycan changes in MUC1 are detected in colon carcinoma, which is correlated with poor prognosis in CRC patients [61]. Dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN) recognizes Mac-2-binding protein and carcinoembryonic antigen (CEA) on CRC cells [62, 63]. These interactions significantly inhibited DC functional maturation and suppressed DC functions. These data suggest that DCs are multifaceted immune cells that play a role in CRC progression.

Natural killer cells in colorectal cancer: Natural killer (NK) cells, an essential component of the immune system, play a pivotal role in the regulation of infection resistance and cancer [64]. In terms of infection resistance, NK cells can kill susceptible target cells, secrete cytokines to recruit DCs, promote the maturation of DCs and enhance adaptive immune responses. In cancer, NK cells interact with DCs through TRAIL binding to TRAIL-R2, which not only induces the expression of immunomodulatory molecules such as IL-10, iNOS and arginase-1 in DCs but also directly affects the activation and function of T cells. The mechanism by which NK cells contribute to antitumour immunity is closely related to the characteristics of their surface receptors, namely, activating receptors, inhibitory receptors, and some auxiliary receptors [65]. Activating receptors are crucial for the ability of NK cells to identify damaged or abnormal cells. NK cells recognize stress ligands expressed by tumour cells, such as MICA and ULBPs, through their surface receptors, thereby activating the cytotoxic mechanism of NK cells [66]. NKG2D is a C-type lectin receptor, and the interaction of NKG2D and MICA enhances NK cell sensitivity and NKG2D-mediated immunosurveillance in CRC [67]. Many NKp46+ NK cells are detected in the normal mucosa, but their numbers are reduced in CRC tissue and liver metastases [68]. Conversely, inhibitory receptors serve to prevent NK cells from targeting normal cells. TIGIT correlates with NK cell exhaustion in tumour-bearing mice and colon cancer patients. Blocking TIGIT inhibits the exhaustion of NK cells and promotes antitumour immunity [69]. Auxiliary receptors, including CD16 and CD56, are integral to NK cell functionality. The percentage of circulating CD16+CD56+ NK cells is negatively related to CRC occurrence and stage [70]. In addition, NK cells directly kill tumour cells by releasing cytotoxic granules, secrete IFN-γ, inhibit the proliferation of tumour cells and promote their apoptosis [71]. T-cell immunoglobulin and mucin domain 3 (TIM-3) are downregulated on peripheral NK cells in CRC patients and are significantly associated with the TNM stage [72]. These studies demonstrate the importance of NK cells in modulating the immune response against CRC.

Mast cells in colorectal cancer: Mast cells (MCs) are innate immune cells that originate from bone marrow stem cells [73]. These cells play crucial roles not only in allergic reactions by releasing cytokines, chemokines, proteases, leukotrienes, and bioactive polyamines but also in innate immune functions, participating in the host's defence mechanisms [74]. MCs are crucial for adaptive immune responses; they influence the functions of dendritic cells, T cells, and B cells, thereby triggering the immune response [75]. In addition, MCs are involved in the establishment of immune tolerance by preventing the occurrence of excessive or inappropriate immune responses [74]. Moreover, MCs play dual roles in tumour development. On the one hand, they recruit immune cells, release cytokines, promote inflammatory responses and potentially inhibit tumour growth or induce apoptosis. On the other hand, MCs act as potent protumourigenic factors in tumours via the production of VEGF, FGF, and matrix metalloproteinases [76, 77]. They may also inhibit T cells and NK cells by releasing adenosine into the microenvironment [78]. In CRC, the role of MCs is complex and remains controversial [79]. A high density of mast cells is associated with a better prognosis, and the density of mast cells is negatively correlated with the level of CysLTR1 [80]. MCs induce endoplasmic reticulum stress by secreting cystatin C, thereby inhibiting the development of colorectal cancer [81]. Nonetheless, additional studies have suggested that mast cells are correlated with a poor prognosis in CRC patients [82-84]. Depending on the interaction between regulatory T cells (Tregs) and MCs in CRC, MCs may lead to immune suppression or a reduction in Treg function [85]. MCs can activate protease-activated receptor-2 (PAR-2) and promote the invasion and metastasis of tumour cells [86]. TLR2 stim-

ulation of MCs promotes colon cancer spheroid growth. Compared with MCs cultured only in the ECM, MCs cocultured with colon cancer HT29 spheroids presented increased expression of five genes (NOTCH1, PTGS2, PTGER4, VEGFA, and MMP2) and decreased expression of one gene (ITGA3) [87]. These data imply that MCs have contradictory effects throughout CRC development.

Regulatory T cells in colorectal cancer: Regulatory T cells (Treg) play a pivotal role in the immunomodulation of CRC, predominantly facilitating tumour progression and immune evasion [88-90]. The degree of Treg cells infiltration within tumour tissues is significantly correlated with poor prognosis. An increase in tumour-infiltrating CD4+ Treg cells predicts tumour development, immunotherapy inefficacy, and adverse outcomes [88, 91, 92]. These Treg cells can robustly suppress the activation and proliferation of effector T cells in the CRC TME [93]. Cytokines such as TGF-β and metabolic byproducts secreted by CRC cells can induce the differentiation and proliferation of Treg cells [94, 95]. CRC organoids are capable of inducing the differentiation of CD4+ T cells into Treg cells with enhanced immunosuppressive capabilities [96]. Specifically, CCR8+ Treg cells exhibit a high degree of infiltration in the TME and are associated with unfavorable prognoses [93, 96]. Moreover, Treg cells mediate tumour immunosuppression through multiple mechanisms, including the secretion of immunosuppressive cytokines like IL-10 and IL-35, the expression of metabolic enzymes such as CD39 and CD73 to deplete local adenosine nucleotides, and the upregulation of co-inhibitory molecules like CTLA-4 and TIGIT, thereby inhibiting the functionality of antigen-presenting cells (APCs) and reducing the activation of effector T cells [92, 97-99]. Collectively, these findings suggest that Treg cells play a critical role in tumour immune escape in CRC.

Glycosylation pathways in colorectal cancer

Glycosylation is a common type of microenvironment posttranslational modification (PTM) of proteins and lipids. It is a process regulated by complex mechanisms, including glycosyltransferase expression, localization and the ratio of activity to donor substrate availability. Some specific glycosyltransferases, such as fucosyltransferases, sialytransferases and N-acetylglucosaminyltransferases, coordinate the addition of glycan structures to proteins and lipids. They participate in certain phases of the glycosylation process, carbohydrate chain core extension, elongation, branching and capping [22]. Furthermore, aberrant expression of glycosyltransferases, altered subcellular localization of glycosyltransferases and mutations in genes that encode glycosyltransferases may be associated with CRC occurrence and development (**Table 1**) [100-117]. For example, N-acetylgalactosamine transferase 2 (GALNT2) is overexpressed in colorectal tumours and promotes CRC cell migration and invasion through AXL [106]. Fucosyltransferase 3 (FUT3) overexpression mediates the fucosylation of TGFβR-I and drives the EMT that occurs during CRC progression [109]. ST6GALNAC1 upregulation results in MUC1-sTn glycoform production and is related to ulcerative colitis and colitis-associated colon cancer [113]. In contrast, high B4GALNT2 expression is considered a potential predictor of good prognosis in CRC, suggesting its relationship with a low-malignancy molecular signature, including bone marrow stromal cell antigen 2 (BST2), intelectin-1 (ITLN1) and so on [105]. FUT2 is found to be downregulated in CRC tissues and correlated with CRC patient survival [110]. Sialytransferase ST6GAL1 knockdown leads to increased rectal cancer cell apoptosis and decreased survival after chemoradiation treatment [116]. Thus, altered glycosyltransferases contribute to the progression and prognosis of CRC.

In addition, approximately 50% of human proteins are glycosylated for maturation [118]. Protein glycosylation contributes to a multitude of biological processes, such as protein stability, protein folding, protein clearance, cell-cell homotypic interactions and cell-matrix adhesion [119]. Glycosylation greatly expands the proteome by generating various protein isoforms that exhibit diverse characteristics and functions [120]. Recently, aberrant glycosylation has been identified as a hallmark of cancer. Generally, aberrant glycosylation consists of increased N-glycan branching, increased O-glycan density, incomplete synthesis of glycans, glycan neosynthesis, and increased fucosylation and sialylation (**Figure 2**). In CRC, altered glycosylation is a universal feature of tumorigenesis, metastasis, immunity modulation and therapy. For example, altered glycosylation of serum IgG is considered an early diagnostic biomarker in CRC [121]. N-glycosylation

Table 1. Dysregulated glycosyltransferase genes in CRC

Glycosyltransferase	Genes	Ref.
β 3-glycosyltransferases	B3GNT8↑, B3GNT6↓	[101-103]
β 4-glycosyltransferases	B4GALNT3↑, B4GALNT2↓	[104, 105]
Polypeptide N-acetylgalactosaminyl transferases	GALNT2↑, GALNT6↓	[106, 107]
Fucosyltransferases	FUT1↑, FUT3↑, FUT4↑, FUT5↑, FUT6↑, FUT8↑, FUT2↓	[108-112]
Sialyltransferases	ST6GALNAC1↑, ST6GALNAC6↓, ST6GAL1↓ ST6GAL3↓	[113-117]

of CD82 at Asn157 may inhibit CRC cell adhesion and lung metastasis [122]. Aberrant O-glycosylation contributes to CRC development by directly inducing oncogenic properties [123]. Furthermore, modifying the fucosylation of melanoma cell adhesion molecule (MCAM) might be an underlying therapeutic target for CRC patients, especially those with FUT2 gene defects [124]. Terminal α2,6-sialylation of EGFR plays an important role in regulating the susceptibility of CRC cells to antibody therapy [125].

Furthermore, aberrant glycosylation can affect the interactions between cancer cells and components of the TME, such as the extracellular matrix, stromal cells and immune cells. β1,3-galactosyltransferase alters the O-glycosylation profile of some cellular proteins and thus reciprocally affects tumour cell-cell and tumour-macrophage interactions regulated by galectin-3 and MGL in the context of colon cancer development and progression [126]. Galectin-2, -4 and -8 increase colon cancer cell adhesion to monolayers of macro- and microvascular endothelial cells [127]. The interactions of DC-SIGN and colorectal tumour-associated Lewis glycans mediate the function and differentiation of DC cells, which cause a series of effective antitumour responses [128]. Furthermore, Lewis-type antigens are another type of non-specific glycosylation in CRC. Lewis (X) and sialyl Lewis (X) were detected in 65.4% and 73.3% of CRC patients, respectively, and sialyl Lewis (X)-expressing patients had more advanced cancer [129].

These findings demonstrate that interactions with glycan-binding proteins can be affected and participate in various biological processes in CRC.

Overall, the current data highlight the importance of aberrant glycosylation in CRC, which involves many cellular substrates, thus contributing to CRC progression and immune escape.

Glycan-lectin interactions in colorectal cancer

Lectins are a family of proteins with specific affinities towards particular glycan structures. They are classified into C-type lectins, I-type lectins (including siglecs), S-type lectins (known as galectins) and so on. Glycan-lectin interactions play crucial roles in different cellular processes. Lectins participate in the immune response to pathogens or inflammation [130]. By recognizing specific glycosylation structures, they serve as ligands of glycan-binding proteins and impact glycoprotein function by enabling glycan-dependent signalling in the TME [21, 131, 132]. Currently, growing evidence supports the role of aberrant tumour glycosylation in dismantling antitumour defences through interactions with lectins on endothelial cells or immune cells (**Figure 3** and **Tables 2**-**5**).

It has been extensively elucidated how glycan structures can influence immune responses in cancer. One key mechanism is the alteration of interactions with lectins expressed in TME. Stromal and immune cells are equipped with various lectins that sense and decode the multiplicity of the cellular glycome. ECs, as a type of stromal cell, express several lectins, highlighting a strong correlation among TME, immunity and vascularization in CRC. C-type lectins E-selectin and P-selectin, expressed on ECs, bind to specific glycan ligands on the surface of tumour cells. This binding promotes the adhesion between tumour cells and ECs, thereby influencing the migration and invasion processes of tumour cells [133-135]. Additionally, increased expression of galectin-8 on ECs enhances adhesion to CRC cells, an effect that is dependent on the presence of lactose [127].

In CRC, the immune microenvironment is primarily composed of neutrophils, macrophages, DCs, NK cells, MCs and Treg cells. Neutro-

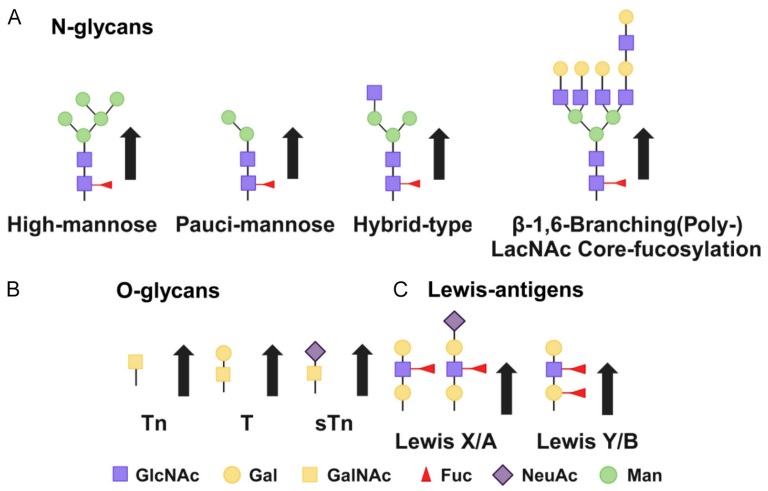

Figure 2. Aberrant glycosylation patterns in CRC. A. Four types of N-glycans frequently altered in CRC are shown as high-mannose, pauci-mannose, hybrid-type and β-1,6-branching(poly-)LacNAc core-fucosylation. B. O-glycan structures in CRC frequently exhibit the truncated Tn, T and sialylated Tn antigen (sTn). C. The Lewis antigens encompass Lewis X/A and Lewis Y/B structures. Created with BioRender.com.

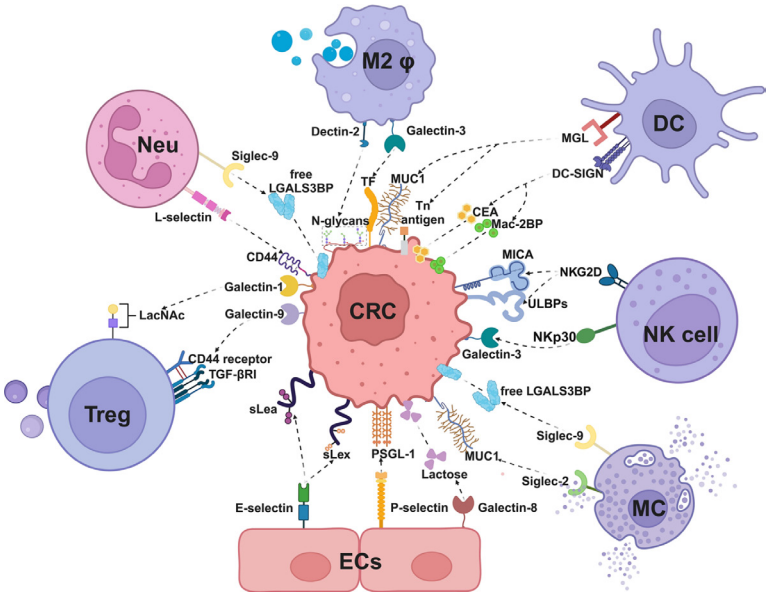

Figure 3. The diagram of lectin-mediated networks in CRC. Glycan-lectin mediated interactions take place between CRC cells and endothelial cells or immune cells in TME. The diverse molecular interactions highlight the intricate network that influences the progression and immune response of CRC. Created with BioRender.com.

phil lectins mainly include selectins/selectins ligands and Siglec-9. L-selectin, expressed on leukocytes, binds to CD44v isoforms and mediates tumour cell adhesion to leukocytes. P-selectin glycoprotein ligand (PSGL-1), a mucin-like protein located on the leukocyte surface, serves as the ligand of P-selectin and E-selectin on ECs [136]. The Siglec-9 ligand, Lectin Galactoside-binding Soluble 3 Binding Protein (LGALS3BP), may exert immunomodulatory effects on neutrophils through Siglec-9 engagement. Macrophages express various lectins on their surface, including C-type lectins such as dectin-2, dectin-3, Siglecs (Siglec-1, Siglec-7, Siglec-9, Siglec-15) and galectins (galectin-3, galectin-9). Members of the galectin family and dectin-2 can bind to glycans on the surface of tumour cells or other cells, thereby influencing the polarization state and functions of macrophages. Once the lectins on the surface of M2-like macrophages bind to specific glycans, they promote the formation of an immunosuppressive microenvironment [137, 138]. In addition, Siglecs typically transmit signaling through the immunoreceptor tyrosine-based inhibition motif (ITIM), leading to the TAM phenotype polarisation [139]. DCs play a crucial role in initiating and mediating immune responses. Immature DCs express various C-type lectin receptors, such as MGL and DC-SIGN [140]. DCs interact with CRC cells in a DC-SIGN-specific manner by recognizing glycan changes, which influences their antigen-presenting function [61, 128]. Concurrently, these glycostructural alterations also serve as specific recognition markers for MGL, enhancing DC-mediated tumour antigen uptake by targeting overexpressed α/β-linked N-acetylgalactosamine (GalNAc) terminal residues on CRC cell surfaces [141]. Furthermore, galectin-3 participates in DC activation, contributing to tumour immune escape [142]. The cytotoxic potentical of NK cells against CRC is regulated by receptors NK group 2, member D (NKG2D) and NKp30 [143].

Table 2. The characteristic and role of C-type lectins in CRC

C-type lectin	Expression	Recognized Carbohydrate Motif	Glycosylated Ligand	Molecular Mechanism	Role in CRC	Ref.
MGL	DCs Macrophages	Tn-antigen	MUC1 MET PTK7 SORL1 PTPRF ITGB1 ITGA3	glycosylation pathway CDX-2 regulation	Immunosuppression Poor prognosis	[61, 141]
DC-SIGN	DCs	Lewis^a/Lewis^b	Mac-2BP CEA CEACAM1	Increases PI3K/Akt/β-catenin signaling Induces TCF1/LEF1-mediated suppression of miR-185	Cell invasion Metastasis	[62, 128, 154]
Dectin-2	Kupffer cell	High-mannose N-glycan	Mucin Galectin-3	Mediates phagocytosis of cancer cells by Kupffer cells	Suppression of liver metastasis	[155, 156]
MBP	CRC cells	Lewis^a Lewis^b	CD26 CD98hc CA199	MBL/MASP complement activation pathway	Recurrence Poor survival	[157-159]
Dectin-1	MDSCs	N-glycan	Galectin-3	Promotes PGE2 production and suppresses IL-22BP	Tumor development	[156, 165]
Dectin-3	DCs Neutrophils Macrophages	α - mannan	TDM Dectin-2	Promotes Kupffer cells to phagocytize cancer cells	Inhibits metastasis	[271, 275]
CLEC-2	Activated platelets Megakaryocytes	sialylated O-glycans	Podoplanin	Promotes platelet - tumor cell aggregation	Cell motility Cell invasion	[167]
NKp30	NK cells	N-glycan	Galectin-3	Modulates the phenotype of circulating NK- and NKT cells	MDSCs mediated immunosuppression	[144]
NKG2D	NK cells T cells	Sialyl Lewis^X	rG7S-MICA MICB	Activates NK cell cytotoxicity	Enhances NK cell sensitivity and immunosurveillance	[67, 169]
L-Selectin	Leukocytes	Sialylated carbohydrates	CD44 Podocalyxin-like protein	Local induction of endogenous ligands via fucosyltransferase-7	Adhesion of cancer cells to vascular endothelium Angiogenesis Metastasis	[170, 171, 175-178, 180]
E-Selectin	Endothelial cells	Sialyl Lewis^X Sialyl Lewis^a	LAMP-1 LAMP-2 Mucin-1Podocalyxin- like protein PSGL-1	Activation of the p38/Hsp27/actin reorganization pathway	Cell motility Adhesion of cancer cells to vascular endothelium Angiogenesis Metastasis	[136, 170-172, 174, 175, 177, 178, 181]
P-Selectin	Activated platelets Endothelial cells	Sialyl Lewis^X Sialyl Lewis^a	CD44 Mucin PSGL-1	Activation of p38 and PI3K signaling	Adhesion of cancer cells to vascular endothelium Angiogenesis Metastasis	[136, 170, 171, 173, 175, 176, 178, 179]

Lewis^a: Fuc α1-4(Gal β1-3)GlcNAc-R structure. Lewis^b: Fucα1-2Galβ1-3(Fucα1-4)GlcNAc structure. Lewis^X: Gal(β1-4)[Fuc(α1-3)]GlcNAc structure.

Table 3. The characteristic and role of Siglecs in CRC

Siglec	Expression	Recognized Carbohydrate Motif	Glycosylated Ligand	Molecular Mechanism	Role in CRC	Ref.
Siglec-1 (CD169)	Macrophages	α2,3-linked sialic acid	CD43	Promote CD8(+) T-cell-mediated antitumor immunity	Antitumor immunity	[184]
Siglec-2 (CD22)	Mast cells B cells	α2,3-linked sialic acid	Mucin	SHP-1 recruitment Phosphorylation of ERK-1/2	Downr-egulates signal transduction	[189, 298]
Siglec-5	Mast cells Neutrophils Eosinophils	α2,3-linked sialic acid	LGALS3BP	Tumor immune evasion	Metastasis	[195, 299]
Siglec-7	Mast cells Macrophages CD8+ T cell	α2,3-linked sialic acid α2,8-linked disialic acids Disialyl Lewis^{a} Sialyl 6-sulfo Lewis^{x}	GD3 SIA- IgG	Exerts a suppressive effect on COX expression Suppresses BGN/TLR4/NF-κB pathway	Immunosuppression	[115, 139, 191-194, 300]
Siglec-9	Mast cells Macrophages Neutrophils	α2,3-linked sialic acid α2,6-linked sialic acid α2,8-linked disialic acids Disialyl Lewis^{a} Sialyl 6-sulfo Lewis^{x}	MUC1 LGALS3BP	Inhibits neutrophil-mediated tumor cell killing Induces the recruitment of β-catenin	Cell growth	[139, 192, 195, 196, 300, 301]
Siglec-10	Mast cells	α2,3-linked sialic acid	LGALS3BP CD24	Increases in KRAS/TP53 dual mutant tumors	Immunosuppressive signaling	[195, 197, 298]
Siglec-15	Mast cells Macrophages	α2,3-linked sialic acid α2,6-linked sialic acid Sialyl-Tn	PD-L1	Secrets some inhibitory cytokines N-glycosylation pathway	Inhibits T-cell proliferation Correlates with the microsatellite instability status Decreases its lysosome-dependent degradation Metastasis	[185-188]

Lewis^{a}: Fuc α1-4(Gal β1-3)GlcNAc-R structure. Lewis^{X}: Gal(β1-4)[Fuc(α1-3)]GlcNAc structure.

Table 4. The characteristic and role of galectins in CRC

Galectin	Expression	Recognized Carbohydrate Motif	Glycosylated Ligand	Molecular Mechanism	Role in CRC	Ref.
Galectin-1	CRC cells	β-galactosides	CEA Lamp-1 Lamp-2→ CD44 CD326 90K/Mac-2BP	Recalibrate CD8+ Tregs	Immunosuppression Lung metastasis	[148, 212, 218, 223]
Galectin-2	Gastrointestinal epithelial cells	N-acetyl-lactosamine	ASF	STAT3 phosphorylation	Cell proliferation Adhesion of cancer cells to blood vascular endothelium Metastasis→	[127, 206]
Galectin-3	CRC cells Macrophages DCs T cells	β-galactoside	TF LAG3 CEA Laminin Lysosome-associated membrane glycoproteins Haptoglobin-related glycoprotein	EGFR activation, ERK1/2 signaling STAT3/Galectin-3/LAG3 pathway	Adhesion cancer cells to endothelium Cell proliferation	[208, 213, 214, 219, 220, 224]
Galectin-4	CRC cells	Galβ1→4(3) GlcNAc Fucα1→2Galβ 1→3(4)-GlcNAc	CEA ABM	Downregulation the function of Wnt signaling pathway	Tumor suppressor Cell motility Cell proliferation Cell migration Cell cycle	[204, 215]
Galectin-8	Vascular endothelial cells Lymphatic endothelial cells	α-galactoside β-galactoside α-glucose lactose residues	LILRB4	STAT3 activation and NF-κB inhibition	Cell migration MDSCs mediated immunosuppression	[205, 209, 216]
Galectin-9	CRC cells Macrophages	β-galactosides	CD44 Tim-3 E-selectin	Mature DCs infiltration T cell immune response	Tumor suppressor Cell proliferation Cell apoptosis Inhibits the binding of tumor cells to ECM components Metastasis	[207, 221, 222, 225]
Galectin-12	CRC cells	β-galactoside lactose	SLC3A2 SLC1A5	Promoter hypermethylation	Tumor suppressor	[203, 217]

Table 5. The characteristic and role of other lectins in CRC

Other lectins	Expression	Recognized Carbohydrate Motif	Glycosylated Ligand	Molecular Mechanism	Role in CRC	Ref.
HPA	CRC cells	O-linked N-acetylgalactosamine N-acetylglucosamine	Integrin av Integrin a6 Annexin 2 Annexin 4 Annexin 5 CLCA1	Recognize antiapoptotic pathway	Cell migration Metastasis	[226-228]
ZG16p	CRC cells	Mannose	PD-L1	Promote T-cell mediated immunity	Inhibits Proliferation and cell cycle	[229-231]
PNA	Colon epithelial cells CRC cells	Galactose beta1-3N-acetylgalactosamine alpha	CD44	Activate c-Met and MAPK	Cell proliferation	[232, 233]

NKG2D activates NK cell-mediated immunosurveillance by binding to its ligand, major histocompatibility complex (MHC) class I-related chain A (MICA), which is expressed on CRC cells [67]. NKp30 specifically interacts with soluble galectin-3 present on antitumour T cells [144]. MCs predominantly express lectins from the Siglecs family, including Siglec-2, Siglec-5, Siglec-7, Siglec-9 and Siglec-10. Siglecs are a family of immunoglobulin-like receptors that bind to sialic acids and modulate the immune response against cancer cells. In CRC, cancer cells secrete sialylated glycans such as sialyl-Tn and sialyl-Lewis X, which serve as "camouflage signals" [145]. These glycan signals facilitate MCs interaction with cancer cells through Siglecs expression. For instance, Siglec-2 binds to α2,6-sialic acid, while Siglec-7 binds to α2,8-sialic acid [146]. Different Siglecs can collaboratively recognize distinct glycosyl epitopes. Moreover, CRC cells promote the infiltration of MCs and establish a multi-layer immune suppression network. Specifically, Siglec-5 and Siglec-9 inhibit antigen presentation, while Siglec-7 and Siglec-10 block the cytotoxicity of NK cells [147]. Treg cells gain prominence through the expression of cell surface markers and their immunosuppressive profiles. The galectin family significantly influences the functionality and distribution of Treg cells. Galectin-1 recognizes the LacNAc structure on the surface of Treg cells and selectively expands CD8+CD-122+PD-1+ Treg cells, thereby facilitating tumour immune evasion [148]. Galectin-9 binds directly to CD44 situated on the surface of Treg cells, forming a complex with TGF-β receptor I (TGF-βRI), which activates the Smad3 signaling pathway. This interaction markedly enhances the stability and functionality of Treg cells. Furthermore, the galectin-9 signaling pathway regulates the induction of induced Treg (iTreg) cells by specifically targeting the CNS1 region of the Foxp3 locus [91, 149]. Consequently, the glycan signatures of CRC can be recognized by various lectins expressed on stromal cells or immune cells within the TME.

In CRC, a variety of lectins have been characterized, and their potential roles have been investigated. The primary glycan-lectin interactions in CRC are outlined as follows.

C-type lectins in colorectal cancer

C-type lectins are a superfamily of proteins that contain conserved C-type lectin-like domains (CTLDs) that recognize a broad range of carbohydrate motifs. These genes have been subdivided into 17 subgroups based on their phylogeny and domain organization [150]. C-type lectins act as secreted molecules or transmembrane proteins in mammals. They mediate immune responses and participate in the immune escape of pathogens and tumours [151]. In CRC, much attention has been given to the expression of C-type lectins and their interactions with the TME via the glycan-lectin pattern. Type II, III, IV and V C-type lectins are known for their roles in the stabilization of immune networks in CRC.

The type II C-type lectins in CRC are mainly MGL, DC-SIGN and dectin-2. MGL on DCs specifically binds to MUC1 derived from primary colon carcinoma via the Tn antigen [61]. N-acetylgalactosamine-transferase 3 (GALNT3) affects BRAFV600E mutations, resulting in aberrant glycosylation and increasing the number of MGL ligands in CRC [152]. In CRC cell lines, HCT116 and HT29 cells are high MGL-binding cells, and the cell surfaces contain MGL ligands, such as MET, PTK7, SORL1, PTPRF, ITGB1, and ITGA3 [141]. N-glycans play a major role in MGL binding to CRC cell lines [153]. DC-SIGN is restricted to the most potent antigen-presenting cells, namely, DCs. DC-SIGN promotes CRC cell invasion and metastasis by increasing PI3K/Akt/β-catenin signalling and inducing TCF1/LEF1-mediated suppression of miR-185 [154]. Moreover, DC-SIGN is involved in the correlation between DCs and CRC cells in situ by recognizing the cancer-related Lea/Leb glycans CEA and CEA-related cell adhesion molecule 1 (CEACAM1) [128]. The α1-3,4-fucose moieties of Le glycans expressed on Mac-2-binding protein (Mac-2BP) are binding sites for DC-SIGN recognition [62]. Dectin-2 is expressed on Kupffer cells and enhances the phagocytosis of cancer cells by Kupffer cells to suppress liver metastasis [155]. Furthermore, Leclaire et al. reported interactions between galectins and C-type lectins in mice. Galectin-3 can bind to three C-type lectins, namely, mDectin-1, mDectin-2 and SIGNR1. These C-type lectins are decorated with N-glycan structures that can be recognized by galectin-3 [156].

Mannose-binding protein (MBP) belongs to the type III group of C-type serum lectins. MBP is upregulated in CRC patients compared with healthy individuals [157]. CD26 and CD98hc have been identified as MBP ligands, which in-

clude high-mannose-type or hybrid-type oligosaccharides [158]. The MBP staining pattern in CRC mucosae significantly overlaps with that of Lewis b [Fucα1-2Galβ1-3(Fucα1-4)GlcNAc] staining and carbohydrate antigen (CA199) Lewis b [Fucα1-2Galβ1-3(Fucα1-4)GlcNAc] staining [159].

The C-type lectin genes in the NK cell receptor gene complex belong to the II and V groups of the C-type lectin superfamily [160]. In CRC, the main NK cell receptor gene complex includes members of the immunoglobulin superfamily, such as KIRs (killer-cell immunoglobulin-like receptors), which can recognize MHC Class I molecules and regulate the activation and inhibition of NK cells [161, 162]; natural cytotoxicity receptors (NCRs), such as NKp30, NKp44, and NKp46, which are involved in the direct cytotoxic effect of NK cells [162, 163]; and non-NK cell receptors, such as LOX-1, Dectin-1, CD69 and CLEC2, which can recognize a variety of stress-induced ligands [164-167]. According to research findings, the number of KIR3DL1-positive NK cells is significantly greater in CRC patients than in healthy controls [162]. The Dectin-1 signalling pathway might promote the development of colorectal tumours by increasing the production of prostaglandin E2 (PGE2) in myeloid-derived suppressor cells (MDSCs) and inhibiting the expression of antitumour IL-22 binding protein (IL-22BP) [165]. In contrast, Vδ1 CD69+ tumour-infiltrating lymphocytes have strong antitumour effects and are related to better clinical outcomes in patients, as indicated by fewer liver metastatic lesions and longer overall survival [166]. The NKp46+ Vδ1 T-cell subset exhibited high antitumour activity against colorectal cancer in the human intestine [163]. Furthermore, glycosylation is an important modification of NK cell receptors in the CRC microenvironment. First, these glycan-binding proteins can interact with the glycosylation structures of NK cell receptors, thereby affecting the function of NK cells. For example, the interaction of oat beta-glucans with the Dectin-1 receptor and the pattern recognition Toll-like receptors impacts the apoptosis and autophagy of colonocytes [168]. Second, NK cell receptors can recognize certain glycoproteins that are expressed on CRC cells. In primary CRC tissues, high expression of the NKp30 ligand galectin-3 correlated with low NKp30 expression on circulating natural killer T cells [144]. Third, the ligands of the NK cell receptor may interact with glycoproteins and affect the functions of NK cells in the TME. Wang et al. demonstrated that the ligand of the NK cell receptor NKG2D immunoligand rG7S-MICA binds to both CD24 and NKG2D, which promoted NK cell sensitivity and NKG2D-mediated immunosurveillance in CRC [67]. Morimoto et al. reported that MUC1-C, a regulator of the NKG2D ligand MICA/B, promoted NK cell-mediated killing [169].

Selectins are Group IV C-type lectin. The selectin family includes L-selectin (leukocyte selectin), E-selectin (endothelial selectin) and P-selectin (platelet selectin). Studies have shown that the expression of selectins is significantly increased in CRC tissues and closely related to the metastatic and invasive capabilities of tumour cells [170-172]. Selectins interact with various cellular components in the microenvironment of CRC, jointly regulating the growth and metastatic processes of the tumour [173]. Furthermore, selectins may be involved in the occurrence and development of CRC via glycosylation. Selectins can recognize many glycoproteins or glycans as ligands on colon cancer cells [174-179]. The interactions between E-selectin and its glycoprotein ligands could be conducive to the communication between colon tumour cells and endothelial cells. Selectin-binding effects are thought to be associated with CRC metastasis and angiogenesis. L-selectin facilitates metastasis via leukocyte-endothelial interactions, which are facilitated by FUT-7-mediated ligands [180]. Moreover, considerable knowledge has been gained regarding the therapeutic implications of targeting this cell adhesion system. 5-Substituted UDP-Gal analogues inhibit the activity of the β-1,4-galactosyltransferase-1 enzyme toeffectively prevent the synthesis of the core 2 structural domain of selectin ligands, such as sLex and sLea. This process markedly reduces the adhesive interactions between colon cancer cells and vascular endothelial cells [170]. NEU4, the sole neuraminidase capable of effectively targeting sialyl Lewis ligand mucins, substantially reduces the adhesion, migration, and proliferation of cancer cells bearing sialylated Lewis structures to E-selectin [181].

In summary, C-type lectins play pivotal roles in CRC progression. The interactions between C-type lectins and their ligands are junctions that enhance the communication between can-

cer cells and immune cells. By precisely regulating the aberrant glycosylation process, new methods for the treatment of CRC could be developed.

Siglecs in colorectal cancer

Sialic acid-binding immunoglobin-like lectins (Siglecs) are animal cell surface glycan-binding proteins. They either are secreted into the extracellular environment or interact with sialic acid on glycan structures. In humans, 14 genes are expressed on overlapping subsets of immune system cells, which serve as important regulators of inflammatory responses, leukocyte proliferation, and host-microbe interactions [182]. Moreover, single genes are also expected to be novel targets for cancer immunity [183].

In CRC, Siglec-1 (CD169) is expressed in macrophages in regional lymph nodes and is associated with overall survival in CRC patients [184]. Siglec-15 is closely related to the aggressiveness of the tumour poor prognosis, which may further promote tumour progression by suppressing the activity of immune cells in CRC [185, 186].

Siglecs function as immunomodulatory receptors and play important roles in the regulation of immune homeostasis. Siglec-15, which is highly structurally homologous to PD-L1, is glycosylated at the N172 residue (N173 in mice). Targeting the N-glycosylation of Siglec-15 might be a promising target for cancer immunotherapy [187, 188]. In CRC, glycan-siglec interactions may trigger inhibitory signals in immune cells, such as macrophages, CD8+ T cells, and MCs. The sialyltransferase ST8Sia6, which generates α2,8-linked disialic acids, binds to murine Siglec-E and human Siglec-7 and Siglec-9. ST8Sia6 promotes cancer cell growth, and the altered polarization of macrophages depends on host Siglec-E expression [139]. Most Siglec-1-positive macrophages in regional lymph nodes, which express the Siglec-1 ligand CD43, are in direct contact with infiltrating CD8+ T cells in CRC tissues [184]. Mucins isolated from colon cancer cells can bind to Siglec-2 expressed on splenic B cells, thus leading to decreased signal transduction [189]. Siglec-6 was upregulated on MCs in coculture with colon cancer cells, negatively regulated the activation of MCs and suppressed the degranulation of MCs, thus exerting an inhibitory effect on tumour growth and metastasis. Moreover, ligands of Siglec-6 are present in CRC tissues [190]. Disialyl Lewisa and sialyl 6-sulfo Lewisx are expressed in nonmalignant colonic epithelial cells and act as ligands for Siglec-7 and Siglec-9. The interactions between glycan and siglec suppress COX expression in colonic mucosal macrophages [191, 192]. Siglec-7 can recognize glycosphingolipid structures and bind to the ganglioside GD3 expressed on colon cancer cells [193]. Additionally, SIA-IgG, which exhibits an extremely high degree of sialylation, was recently investigated as a ligand of Siglec-7 in the TME [194]. The interaction of Siglec-7 with glycans may be mediated by the BGN/TLR4/NF-κB pathway in the early stage of colon cancer carcinogenesis [115]. LGALS3BP, a tumour-associated immunomodulatory ligand for CD33-related Siglecs (Siglec-5, Siglec-9 and Siglec-10), inhibits neutrophil-mediated tumour cell killing via Siglec-9 engagement [195]. Siglec-9 also binds to MUC1 expressed on colon cancer cells, and the ligation induced the recruitment of β-catenin, leading to cell growth [196]. The protumoural interaction of CD24-Siglec-10 induces immunosuppressive signalling, which is dramatically increased in KRAS/TP53 dual-mutant tumours and highly consistent with the poor prognosis of CRC [197].

Overall, Siglecs can function as immunomodulatory molecules via glycan-Siglec interactions in CRC. These findings shed new light on Siglecs as a new generation of immune checkpoints.

Galectins in colorectal cancer

Galectins, a superfamily of lectins that recognize β-galactosides, participate in the regulation of cellular biological processes by binding to glycan structures through their CRDs. Galectins are located in the nucleus, cytoplasm, and extracellular space. Twelve galectin members are expressed in humans, including galectin-1, galectin-2, galectin-7, galectin-10, galectin-13, galectin-14, and galectin-16 (prototypic), galectin-3 (chimeric type), galectin-4, galectin-8, galectin-9, and galectin-12 (tandem repeats). Galectins are generally recognized as crucial regulators of innate and adaptive immune responses [198], inflammation [199], and autoimmune diseases [200]. Moreover, increasing data are available concerning the role of galectins in cancer progression, especially in CRC [201-

203]. Galectins participate in many steps of cancer development by recruiting immune cells, such as neutrophils, monocytes, and lymphocytes, to inflammatory sites. Notably, both tumour cell- and stromal cell-derived galectin-1 affect the immunosuppressive capacity of CD8+ Tregs in CRC [148]. Galectin-2, galectin-3, galectin-4, and galectin-8 are significantly upregulated in colon cancer patients compared with healthy individuals and promote cancer cell adhesion to the blood vascular endothelium [127, 204-206]. Galectin-8 is an important component of the angiogenesis network [205]. Galectin-9 expression is correlated with mature DC infiltration and the CD8+ T-cell immune response in CRC [207].

In recent years, galectins have been shown to engage many glycan determinants to affect various processes of CRC. β-Galactosides produced by papaya chelate-soluble pectin bind to galectin-3, which suppresses the proliferation of colon cancer cells [208]. Galectin-8 was downregulated in vivo compared with in vitro human colon cancer models, and this feature was not only specific to galectin-8 but also occurred with α- and β-galactoside, α-glucose, and lactose residues [209]. Glycosyltransferases, such as β-1,3-N-acetylglucosaminyltransfera se (β3GnT8) and β1,3-galactosyltransferase (C1GalT1), also play key roles in the glycan-galectin axis. β3GnT8 indirectly promotes the invasiveness of colon cancer cells by increasing the expression of galectin-3 [210]. Suppression of C1GalT1 expression not only led to substantial changes in the glycosylation of galectin-3 ligands but also decreased galectin-3-mediated tumour cell-cell interactions and activities in CRC [126]. Galectin-1 and β1,6-N-acetylglucosaminyltransferase V (GnTV) may have coordinated effects on CRC progression [211].

Furthermore, evidence suggests that galectins recognize many glycoproteins in CRC. Circulating galectin-1 and its ligand 90K/Mac-2BP are related to tumour stage in patients with CRC [212]. CEA, laminin and lysosome-associated membrane glycoproteins act as ligands for galectin-3 in human colon carcinoma KM12 cells [213]. The levels of the circulating ligand galectin-3 haptoglobin-related glycoprotein were significantly elevated in patients with colon cancer [214]. Galectin-4 bound to CEA on the cell surface of human colon adenocarcinoma CCK-81 and LS174T cells [215]. Galectin-8, an LILRB4 ligand, induces MDSCs by activating STAT3 and inhibiting NF-κB [216]. ISLC3A2 and SLC1A5 interact in the glycosylation-dependent binding of galectin-12 in CRC [217]. Galectins and their glycoproteins act as physiological modulators of cell adhesion. CEA, lamp-1, and lamp-2 have emerged as endogenous galectin-1 ligands and have been shown to be crucial for colon cancer cell adhesion and metastasis [218]. Terminal Thomsen-Friedenreich (TF) disaccharides on cancer-associated MUC1 are involved in galectin-2-, galectin-3- and galectin-4-mediated cancer cell adhesion to the endothelium. The TF-expressing glycoprotein asialofetuin (ASF) is the strongest ligand for galectin-2, whereas asialo bovine mucin (ABM) is the strongest ligand for galectin-4 [127]. The interaction between galectin-3 and TF promotes colon cancer cell adhesion to the endothelium, facilitates EGFR activation, and induces ERK1/2 signalling in colon cancer [219, 220]. Galectin-9 can interact with CD44 on the surface of Colon26 colon cancer cells and lead to the suppression of tumour cell adhesion to the vascular endothelium and ECM [221]. Galectin-9 isoforms modulate the adhesion of colon cancer cells to human umbilical vein endothelial cells by influencing the expression of E-selectin [222]. Galectins have also been implicated in the suppression of T-cell-mediated immune responses. Inhibiting the interactions between galectin-1 and its ligands CD44 and CD-326 reduces cell adherence, increases T-cell responses and suppresses murine lung metastasis [223]. APS promotes CD8+ T-cell function and inhibits CRC development via the STAT3/galectin-3/LAG3 pathway [224]. The interaction between galectin-9 derived from colon cancer cells and TIM-3 on CD8+ T cells increases the apoptosis of tumour-infiltrating TIM-3+CD8+ T cells in a CT26 mouse colon tumour model [225].

In conclusion, galectin-glycan interactions have emerged as reliable predictors of cell adhesion, cell proliferation, cell invasion, metastasis and the regulation of T-cell responses in CRC. These findings will contribute to the design of novel therapeutic strategies aimed at regulating their function via immunotherapeutic treatment in CRC.

Other lectins in colorectal cancer

Lectin from Roman snail Helix pomatia agglutinin (HPA) recognizes O-linked glycan structures and has been shown to be related to metastatic breast cancer [226]. Recent studies have demonstrated its utility in identifying other metastatic solid tumours, such as CRC, gastric cancer. In CRC, HPA exhibits minimal binding to nonmetastatic SW480 cell but shows conversely intense binding to metastatic HT29 cell. Proteome analysis reveals HPA recognizes metastatic CRC cells membrane proteins, such as integrin av/a6 and annexin A2/A4 [227]. Furthermore, pooled proteins from metastatic CRC tissues are fractionated using HPA affinity chromatography and identify O-linked glycoproteins annexin 5 and calcium activated chloride channel protein 1(CLCA1) [228]. Zymogen granule protein 16 (ZG16), a soluble lectin highly expressed in mucus-secreting cells, binds to mannose [229]. Overexpression of ZG16 interacts with Caco-2 cell surface and inhibits cell proliferation via Asp151 [230]. ZG16 promotes T-cell mediated immunity and may directly bind to glycosylated PD-L1 via its lectin domain [231]. Plant lectin peanut agglutinin lectin (PNA) is a galactose-binding lectin and overexpressed by ~90% cancers in human. PNA exhibits mitogenic activity in colon epithelial cellls and CRC cells [232]. It binds to the TF antigen and the interaction stimulates CRC cells proliferation by activating c-Met and MAPK signaling pathways [233]. Overall, it is outlined the critical relationship between non-typical lectins, such as PNA and aberrant glycan expression profiles in CRC. These data highlight that these lectins can modulate glycan profiles and contribute to CRC progression. Overall, the processes of glycan-lectin interactions are complex and multifaceted, playing pivotal roles in the development and progression of various cancers. These interactions can promote tumour growth, immune evasion, and metastasis. Multiple types of cancer cells exhibit different glycan profiles on their surfaces, which is a feature related to malignancy. Glycan-lectin interactions are observed not only in CRC, but also in other cancer types, including breast cancer [199, 234-251], ovarian cancer [146, 242, 252-262], and glioblastoma [22, 199, 263-269]. In **Table 6**, we will highlight the different aspects of glycan-lectin interactions in various cancer types compared to CRC, focusing on expression, regulation, target glycan/ligand, and effect.

The glycan-lectin interactions in intestinal microbiota-inflammation-colorectal cancer axis

In human bodies, the intestinal environment provides a shelter for a large number of microorganisms. Once the balance in the crosstalk between the host and gut micobiota is disrupted and affects the function of intestinal barrier, it will lead to inflammatory diseases and CRC. Pathogenic bacteria reach intestinal epithelial cells and they adhere to the abundant layers in the intestinal epithelial cells via glycan-lectin interactions [270]. Then, intestinal epithelial cells glycosylation promotes malignant transformation.

C-type lectins, as a subset of pattern recognition receptors (PRRs), contribute to the pathogenesis of intestinal inflammation, thereby becoming a significant risk factor for CRC. These lectins function as a critical link between microbiota, intestinal epithelial barrier, and immune system [271]. Specifically, C-type lectins play a key role in mediating immunity against fungal pathogens in the gut microbiota by binding to glycans expressed on the surface of pathogenic fungi cell wall in the gastrointestinal tract [272]. For example, myeloid DCs can recognize β-1, 3-glucan from Aspergillus fumigatus via dectin-1 [273]. Dectin-3, which is expressed on macrophages, recognizes α-mannan from Candida albicans and plays an important role involved in the pathogenesis of colitis [274].

Moreover, fungal dysbiosis and its associated immune responses may play a significant role in CRC pathogenesis. The mycobiota/dectin-3/IL-22 axis is involved in the progression of colitis-associated colon cancer (CAC) progression. Compared to wild type mice, dectin-3-deficient mice display significantly more severe colitis, more tumour lesions and increase IL-22 expression [275]. In the immune response induced by dectin-1 and dectin-2, caspase recruitment domain 9 (CARD9) acts as a central adaptor for signal transduction [276]. These C-type lectins are coupled with Syk kinase and activate the NF-κB pathway via CARD9. The Syk-CARD9 signaling pathway plays a protective role in the interaction between fungal microbiota and CAC [277]. CARD9-deficient mice exhibit an increased incidence of CAC, attributed to the differentiation of myeloid cells into myeloid-derived suppressor cells, accompanied with in-

creased Candida tropicalis [278]. Therefore, the glycan-lectin interactions appear to be crucial in the molecular mechanism underlying intestinal microbiota-inflammation-colorectal cancer axis.

The glycan-lectin axis in colorectal cancer immunotherapy

Tumour growth is followed by tumour cell evasion of the immune system. Aberrant tumour glycosylation has not only been investigated in relation to tumour growth and metastasis but also enables tumour cells to escape immunosurveillance mechanisms via glycan-lectin interactions [279]. Our understanding of the roles of glycan-lectin interactions in immunity has expanded substantially to include the regulation of every stage of immune responses in the TME.

Microsatellite instability (MSI) is a molecular phenotype resulting from mismatch repair deficiency (dMMR). In CRC, dMMR/MSI is observed in about 5% of metastatic CRC and considered as an essential biomarker for the efficacy of immune checkpoint inhibitors. Therefore, glycan-lectin interactions may be correlated with dMMR/MSI status in CRC. Specifically, Tn antigen on CRC cells interacts with MGL on antigen-presenting cells, leading to an immune inhibitory signaling through IL-10 production and affecting T cell apoptosis. Clinical trials have shown that tumours exhibiting Tn-negative/weak are predominantly mismatch repair proficient (pMMR). And dMMR colorectal cancers are divided into Tn-strong dMMR (40%) and Tn-negative/weak dMMR tumours (60%). Patients with Tn-strong dMMR CRC may benefit significantly from immune checkpoint inhibitors targeting Tn antigen [280]. Galectin-9 levels are upregulated in dMMR tumours and the right colon, which is strongly related to immune cell infiltration and immunomodulators. Additionally, higher densities of CD208+ DCs are more frequently observed in dMMR tumours compared to pMMR tumours [207]. C-type lectin-like receptor 2 (CLEC-2) belongs to the C-type lectin superfamily. The expression of CLEC-2 is signi ficantly higher among CRC patients with MSI status. The mechanism by which CLEC-2 contributes to MSI CRC may be correlated with platelet activation. While, CLEC-2 and its ligand podoplanin may co-activate platelets, thereby promoting thrombosis and metastasis CRC [167]. Peanut agglutinin is a galactose-binding lectin and binds to the TF antigen. TF antigen is indicated as a biomarker of better prognosis in MSI CRCs [281]. Thus, glycan-lectin interactions are likely to be pronounced in dMMR & MSI compared to lower CRC.

Currently, emerging research has explored how glycan-lectin modifies immunity and is considered a novel immune checkpoint for cancer. Below, we discuss how glycan-lectin interactions can be utilized for CRC therapy (**Figures 4**, **5**).

Removal of branched N-glycans

The aberrant expression of N-glycans is correlated with a protumoural role in immune evasion. N-glycan expression hinders the immune recognition of tumour cells. Glycan-targeting strategies serve as efficient methods for enhancing the antitumour immune response. The removal of N-glycans contributes to accelerating immune recognition and improving cancer immunotherapy. Madureira et al. reported that the N-glycan biosynthesis inhibitors swainsonine and tunicamycin induced anticancer activity and appeared to be a potential therapeutic tool for CRC treatment [282]. Owing to the immunosuppressive activity of Siglec-15, removal of N-glycosylation with PNGase-F (PNG-F) facilitated the detection of Sigle15, which bound to the sugar recognition domain of Siglec-15, blocked its binding to sugar molecules on the surface of tumour cells, released the inhibitory signals of immune cells, and led to an effective antitumour response [187]. Removing branching N-glycosylation on CRC cancer cells via kifunensine (KF) exposes the relevant glycoepitopes and promotes immune recognition by DC-SIGN-expressing immune cells [283]. These data confirm that the removal of a “glycan mask” may be a tool for immune diagnostic purposes.

Cellular immunotherapy

Recent research has demonstrated that specific surface molecules on CAR-T cells undergo glycosylation modifications. These glycosylation modifications can influence the interactions between CAR-T cells and lectins on tumour cell surfaces. For instance, alterations in the glycan structures on CAR-T cells may affect their binding affinity to lectins within the TME, thereby affecting the infiltration, activation, and

Table 6. The list of lectins along with their sugar specificity in different cancer types versus CRC

Lectin	Cancer	Expression	Regulation (up: ↑; down: ↓)	Target Glycan/Ligand	Effect	Ref.
MGL	Colorectal cancer	DCs Macrophages	↑	Tn antigen MUC1, MET PTK7, SORL1 PTPRF, ITGB1 ITGA3	Immunosuppression	[61, 141]
	Breast cancer	DCs Macrophages	↓	Sialyl-Tn antigen MUC1	Antiproliferative	[234, 235]
	Ovarian cancer	DCs Macrophages	↑	Tn antigen MUC1, MUC16 MUC24, ERP44	Enhances metastasis	[252-254]
	Glioblastoma	DC and cDC2 Macrophages CD163+ cells Activated MG	↑	Sialyl-Tn antigen CD45RA, VCAN SDC3, PODXL NID-2, FN1, DAG1, APP, AGRN, ERP44, LAMP1/2, QSOX1, SEL1L, LRR8CD MUC1, MUC16 MUC24	Promotes invasion Immunosuppression	[199, 263-265]
Siglec-9	Colorectal cancer	Mast cells Macrophages NK cells Neutrophils	↑	α2,3-linked sialic acid α2,6-linked sialic acid α2,8-linked disialic acids Disialyl Lewis^{a} Sialyl 6-sulfo Lewis^{x} MUC1 LGALS3BP	Proliferation	[139, 192, 195, 196, 300, 301]
	Breast cancer	MacrophagesMyeloid cells	↑ (triple - negative) ↓ (estrogen receptor - positive)	Sialic acid MUC1-ST	Enhances immune evasion Immunosuppression	[236-241]
	Ovarian cancer	Leukocytes NK cells T cells	↑	Sialic acid MUC16	Inhibits antitumour	[255]
	Glioblastoma	NK cells DCs T cells Neutrophils Macrophages Monocytes	↑	α-(2-3)-Sialic acid α-(2-6)-Sialic acid α-(2-8)-Sialic acid Glycophorin Hyaluronic acid MUC1/5	Immunosuppression	[22, 266]

Galectin-1	Colorectal cancer	CRC cells	↑	β-galactosides CEA Lamp-1 Lamp-2 CD44 CD326 90K/Mac-2BP	Immunosuppression	[148, 212, 218, 223]
	Breast cancer	Macrophages T cells	↑	β-galactosides Selectin FOXP3 α-2-macroglobulin, Haptoglobin	Immunosuppression	[199, 242-246]
	Ovarian cancer	Ovarian cancer cells	↑	β-galactosides MUC16	Enhances tumour progression Immunosuppression	[242, 256-260]
	Glioblastoma	Endothelial cells Astrocytes APCs Treg	↑	Lactose poly-N-acetyllactosamine CD3, CD4, CD7, CD43, CD45, CD69	Activates tumour progression Angiogenesis	[22, 267]
Galectin-3	Colorectal cancer	CRC cells Macrophages DCs T cells	↑	β-galactosides TF LAG3 CEA Laminin Lysosome-associated membrane glycoproteins Haptoglobin-related glycoprotein	Promotes tumour immune escape	[208, 213, 214, 219, 220, 224]
	Breast cancer	Breast cancer cells Macrophages	↑	β-galactosides GPVI AnxA2	Enhances tumour progression	[247-250]
	Ovarian cancer	Ovarian cancer cells	↑	β-galactosides GPVI	Immunosuppression	[146, 261]
	Glioblastoma	ECs Activated microglia Activated astrocytes Myeloid cells Fibroblasts	↑	Lactose Acetyllactosamine Laminin, Vitronectin, Collagen I/IV, MCAM TCR complex, CD7, CD29, CD45, CD71, LFA-1, TLR-4, LAG-3, CTLA-4 VEGF-R2	Proliferation	[22, 268]
Galectin-9	Colorectal cancer	CRC cells Macrophages	↓	β-galactosides TIM-3 PD-1 CD44 DR3	Enhances antitumour	[207, 221, 222, 225]
	Breast cancer	Breast cancer cells	↑	β-galactosides TIM-3	Promotes tumour immune escape	[251]
	Ovarian cancer	Ovarian cancer cells	↓	β-galactosides TIM-3	Antiproliferative Induces apoptosis	[255, 262]
	Glioblastoma	Activated astrocytes Microglia ECs	↑	Lactose N-acetyllactosamine Forssman pentasaccharide TIM3, DECTIN-1, CD44, VISTA, CD274, PD-L1, IDO1, LAG3 β3-interini Glut-2	Enhances immune response	[22, 269]

Lewis^a: Fuc α1-4(Gal β1-3)GlcNAc-R structure. Lewis^x: Gal(β1-4)[Fuc(α1-3)]GlcNAc structure.

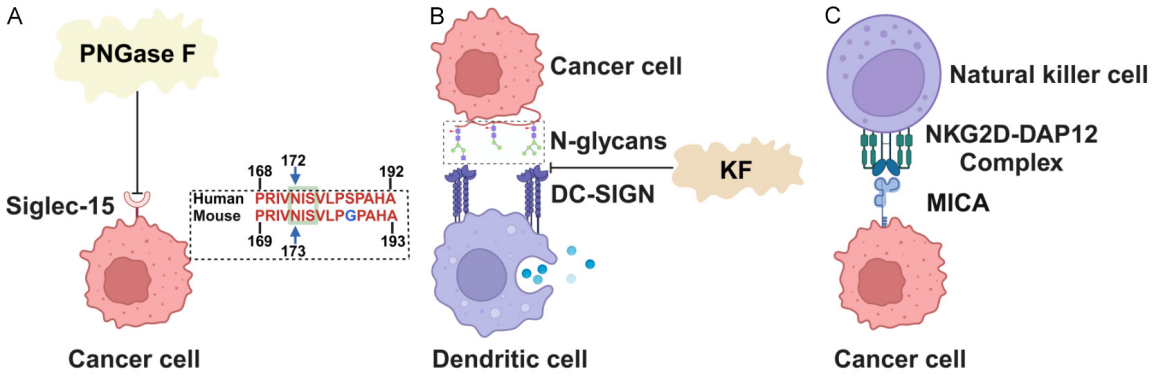

Figure 4. The glycan-lectin axis in CRC immunotherapy via N-glycan removal and cellular immunotherapy. A. Removal N-glycan of Siglec-15 by PNGase-F contributes to an effective antitumour response. B. Removing N-glycosylation via KF facilitates immune recognition by DC-SIGN-expressing immune cells. C. The NKG2D-DAP12 complex recognizes the ligand on CRC cells, activates NK cells and promotes the antitumour process.

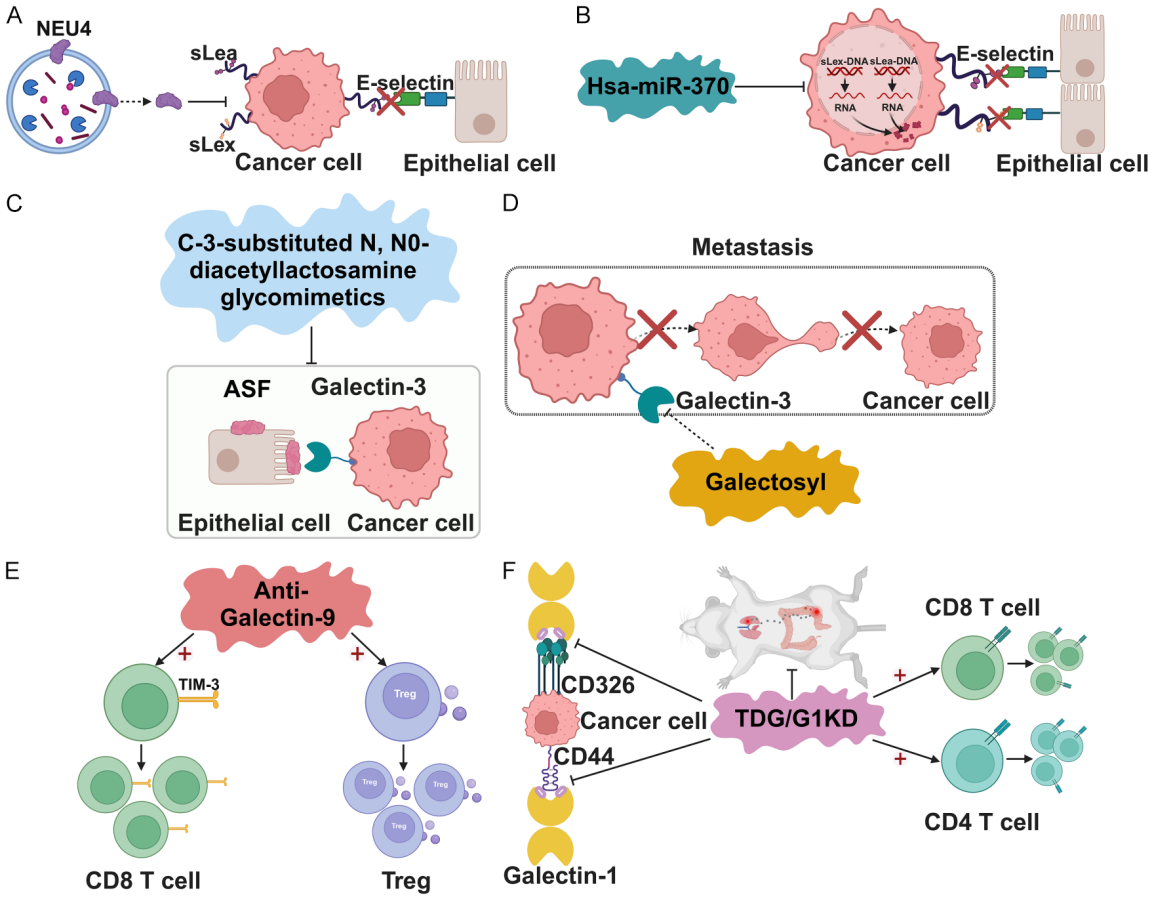

Figure 5. The glycan-lectin axis in CRC immunotherapy via blocking tumour-associated glycan-lectin interactions. A, B. NEU4 and hsa-miR-370 inhibit the attachment of sLea and sLex to E-selectin. C. C-3-substituted N,N0-diacetyllactosamine glycomimetics hinder the binding of cancer cells and epithelial cells via galectin-3-ASF interaction. D. Galectosyl prevents the growth and metastasis of CRC cells by inhibiting galectin-3. E. Anti-galectin-9 leads to an increased frequency of CD8 T cells and Treg cells. F. TDG or G1KD blocks the binding of galectin-1 with CD44 and CD306, increases the expression of CD4+ and CD8+ cells and prevents CRC lung metastasis.

cytotoxicity of CAR-T cells on tumour cells [284, 285]. Simultaneously, the glycan-lectin interactions on tumour cells may also interfere with the recognition of tumour cells by CAR-T cells.

For example, when certain lectins bind to the glycans on tumour cells, they can mask tumour antigens, hindering CAR-T cells recognition. It is shown that optimizing the glycosylation patterns on CAR-T cells to facilitate their interaction with the lectins on tumour cells holds promise for improving the efficacy of CAR-T cell therapy in CRC treatment [284, 286, 287]. Hence, understanding glycan-lectin interactions provides valuable insights into the mechanisms and therapeutic potential of CAR-T cell therapy in CRC.

To improve the efficiency of NK cell therapy in cancer, chimeric antigen receptors (CARs) have been introduced to modify immune cells via gene transfer. NKG2D is an activating immunoreceptor and plays an antitumour role in CRC. NKG2D ligands are typically expressed on tumour cells or stressed cells and are absent in healthy tissues, suggesting that they are promising CAR candidates. Xiao et al. constructed a CAR that contained the extracellular domain of NKG2D with the cytoplasmic domain of DAP12. The CAR identified NKG2D ligands on cancer cells and activated NK cells, thus boosting the antitumour immunity of the cells [143]. Zarein et al. combined a second-generation NKG2D-CAR construct with lenalidomide, resulting in high potential for removing CRC cells in vitro [288]. Indeed, a number of clinical trials that are based on NKG2D CAR-T cells are underway [289]. Therefore, NKG2D CAR therapy has shown excellent antitumour effects and represents a rapidly growing area of tumour therapy.

Blocking tumour-associated glycan-lectin interactions

Strategies that prevent the interaction between lectins and glycans with inhibitory immune receptors may be considered therapeutic interventions for cancer. A broad spectrum of inhibitors, such as glycosidases, metabolic mimetics and blocking antibodies specific for lectin receptors or for glycans, have been generated. The suppressive effect of these inhibitors is due to inhibited endothelial cell adhesion, promoted T-cell-mediated antitumour responses, and enhanced NK cell activity. NEU4 is a unique sialidase, and its validated substrates are sLea and sLex. NEU4 can downregulate tumour cell surface sLea and sLex and inhibit the attachment of these glycans to the endothelium via E-selectin [181]. Hsa-miR-370 blocks selectin-induced cell adhesion by inhibiting the expression of the sLea and sLex gene, providing a new approach for colorectal cancer treatment [290].

In addition, galectin inhibitors include small-molecule carbohydrate inhibitors, natural polysaccharides and their derivatives, peptides, peptidomimetics, and biological agents. These inhibitors affect the CRD of galectin via competitive or allosteric inhibition to block the binding of galectin to glycans [291-294]. For example, C-3-substituted N,N0-diacetyllactosamine glycomimetics inhibit galectin-3 binding to their glycoprotein ligand ASF on DLD-1 cells [295]. Galectosyl, a main component of modified citrus pectin, significantly inhibits the growth and metastasis of colon cancer cells in nude mice by inhibiting the activity of galectin-3 [296]. Anti-galectin-9 therapy selectively increases intratumoral TIM-3+ cytotoxic CD8+ T cells and Treg cells [297]. Synthetic disaccharide thiodigalactoside (TDG) or shRNA galectin-1 knockdown (G1KD) might block galectin-1 binding to CD44 and CD326, upregulate the expression of CD4+ and CD8+ cells and reduce murine colon cancer lung metastasis [223].

Thus, the data imply that glycan-lectin interactions are immune checkpoints, and these interactions may result in the design of improved immunotherapies for antitumour treatment.

Conclusions

In summary, characterizing changes in the TME and glycan components in CRC may help elucidate the mechanisms of tumour progression. Exploring the relationship between tumour cells and the immune system is crucial for identifying novel therapeutic strategies in CRC. Accordingly, several inhibitory glycan-lectin interactions have emerged and are considered immune checkpoints for tumour immunotherapy. More investigations and experiments are needed to explore new strategies that target glycan-lectin interactions, which are significantly beneficial for patients who do not respond to current immunotherapy regimens.

Acknowledgements

This work was supported by grants from the Chinese National Science Foundation Project (82002231) and the Science and Technology

Planning Project of Liaoning province, China (2023-MS-052).

Disclosure of conflict of interest

None.

Abbreviations

AEBP1, Adipocyte Enhancer-Binding Protein 1; AGR2, Anterior Gradient-2; B3GNT, β-3-N-Acetylgluco-Saminyltransferase; B4GALNT, β1,4-N-Acetylgalactosaminyltransferase; BST2, Bone Marrow Stromal Cell Antigen 2; CAC, Colitis-associated Colon Cancer; CARD9, Caspase Recruitment Domain 9; CCL, Cysteine-cysteine Motif Chemokine Ligand; CD, Cluster of Differentiation; CEA, Carcinoembryonic Antigen; CEACAM1, Carcinoembryonic Antigen-Related Cell Adhesion Molecule 1; CLCA1, Calcium Activated Chloride Channel Protein 1; CRD, Carbohydrate Recognition Domain; CTLA-4, Cytotoxic T-Lymphocyte-Associated Protein 4; DC, Dendritic Cell; DC-SIGN, Dendritic Cell-Specific Intercellular Adhesion Molecule-3 Grabbing Nonintegrin; DCs, Dendritic Cells; dMMR, Mismatch Repair Deficiency; ECM, Extracellular Matrix; ECs, Endothelial Cells; EGFR, Epidermal Growth Factor Receptor; EMT, Epithelial-Mesenchymal Transition; ERP44, Endoplamic Reticulum Resident Protein 44; FGF2, Fibroblast Growth Factor 2; FUT, Fucosyltransferase; GalNAc, N-acetyl Galactosamine; GALNT, N-Acetylgalactosaminyltransferase; GPR63, G Protein-Coupled Receptor 63; GPVI, Glycoprotein VI; HER3, Human Epidermal Growth Factor Receptor 3; HIF1α, Hypoxia-Inducible Factor 1α; HPA, Helix Pomatia Agglutinin; IBD, Inflammatory Boweel Disease; IFN-γ, Interferon Gamma; IL, Interleukin; ITGA3, Integrin Subunit α3; ITLN1, Intelectin-1; JAK2, Janus Kinase 2; KLK10, Kallikrein-Related Peptide 10; LAG-3, Lymphocyte-Activation Gene 3; LGALS3BP, Lectin Galactoside-binding Soluble 3 Binding Protein; LOX, Lysyl Oxidase; M1-like macrophages, Antitumourigenic Macrophages; M2-like macrophages, Protumourigenic Macrophages; MCs, Mast Cells; MGL, Macrophage Galactose-type Lectin; MICA, MHC Class I Chain-Related A; MMP, Matrix Metalloproteinases; MUC, Mucin; MSI, Microsatellite Instability; NK, Natural Killer; NKG2D, Natural Killer Group 2D; NLR, Neutrophil-to-Lymphocyte Ratio; NOTCH1, Neurogenic Locomotion-Related Protein 1; PAR-2, Protease-Activated Receptor-2; PRRs, Pattern Recognition Receptors; PD-1, Programmed Death-1; PD-L1, Programmed Death-Ligand 1; pMMR, Mismatch Repair Proficient; PSGL-1, P-selectin Glycoprotein Ligand; PTGS2, Prostaglandin-Endoperoxide Synthase 2; PTGER4, Prostaglandin E Receptor 4; Sdc, Syndecan; S1P, Sphingosine-1-Phosphate; ST6GALNAC, ST6 N-Acetylgalactosaminide α-2,6-Sialyltransferase; ST6GAL1, ST6 β-galactoside α-2, 6-Sialyltransferase; TF, Thomsen-Friedenreich; TGF-β, Transforming Growth Factor Beta; TIM-3, T-Cell Immunoglobulin and Mucin Domain 3; TLR2, Toll-Like Receptor 2; TME, Tumour Microenvironment; TNM, Tumour Node Metastasis; Tregs, Regulatory T Cells; TRIB8, Tribbles Pseudokinase 3; TRAIL, Tumour Necrosis Factor-Related Apoptosis-Inducing Ligand; TRAIL-R2, Tumour Necrosis Factor-Related Apoptosis-Inducing Ligand Receptor 2; TIGIT, T Cell Immunoreceptor with Ig and ITIM Domains; VEGF, Vascular Endothelial Growth Factor; VEGFA, Vascular Endothelial Growth Factor A; YAS, Yes1 Associated Transcriptional Regulator; ZG16, Zymogen Granule Protein 16.

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