Multiple roles and mechanisms of MUC6 in cancer (Review)

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Abstract. Mucin 6 (MUC6), primarily expressed in the gastrointestinal (GI) epithelium, is a member of the mucin family characterized by a protein backbone with extensive glycosylation, playing a crucial role in preserving epithelial barrier integrity. Accumulating evidence indicates that MUC6 glycosylation contributes significantly to cancer development, diagnosis, therapy and prognosis-particularly in GI malignancies such as gastric, pancreatic and colorectal cancers. In the present review, current findings on the multifaceted roles of MUC6 across various cancers were comprehensively summarize. For instance, loss of MUC6 expression is frequently associated with gastric cancer risk, while its upregulation may serve as a valuable biomarker in prostate cancer biopsy, aiding in early detection. Additionally, the identification of MUC6-Tn glycoforms offers promising avenues for novel therapeutic strategies. The distinctive tandem repeat polymorphisms within the MUC6 gene further suggest its potential utility in assessing cancer susceptibility based on allele length variation. These insights underscore the relevance of MUC6 in both mechanistic research and clinical oncology. Although preliminary data are encouraging, large-scale, multicenter studies are necessary to fully validate the clinical application of MUC6 as a biomarker for cancer staging and prognosis. Finally, the present review outlines future directions for exploring MUC6 in the context of cancer therapy development.

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Abbreviations: PTS, proline, threonine and serine; VNTR, variable number tandem repeat region; TLR7, Toll-like receptor 7; vWF, von Willebrand factor; ppGalNAc-Ts, polypeptide N-acetylgalactosamine transferases; α-1,4-GlcNAc, α-1,4-linked N-acetylglucosamine; SSA/P, sessile serrated adenomas also termed sessile serrated polyps; SSA/PD, SSA/Ps with dysplasia; HPPs, hyperplastic polyps; TFF2, trefoil factor family 2; lncRNA, long non-coding RNA; CASC2, cancer susceptibility candidate 2

Key words: MUC6, gastrointestinal tumors, mucin, glycosylation, tumor biomarkers, immunotherapy

Contents

1. Introduction

Mucins, major components of mucus, are a family of high-molecular-weight proteins that are rich in proline, threonine and serine (PTS) residues and contain numerous O-glycosylation sites (1,2). Common mucins can be categorized into two types, secreted mucins and membrane-bound mucins, which form a selective protective barrier on epithelial surfaces and perform other physiological functions (3). In general, mucins consist of a core protein backbone and highly complex glycosylations (4). The glycan chains are linked to serine or threonine residues by O-glycosylation to form N-acetylgalactosamine (GalNAc) attached to the core polypeptide backbone (5). Additionally, mucins have numerous tandem repeats, especially around glycosylation sites, which allow mucins to carry massive glycan chains, resulting in their unique adhesive and protective functions (1,6,7). There are currently 22 known human genes encoding mucins, but there are likely additional mucin proteins waiting to be discovered (8-11).

Mucins are generally produced by epithelial cells to lubricate body cavities, where they serve as the first barrier against external attacks. Therefore, they are more abundant in the cavities of the respiratory tract, digestive system, eyes and lacrimal glands (12,13). Mucins also partly assume the role of maintaining the dynamic balance of mucus in terms of pH, oxygen concentration and hydration (14). Normally, mucin expression is relatively specific and restricted to specific tissues and organs at specific developmental stages. By contrast, aberrant expression of mucins is often considered to be associated with pathologic conditions such as inflammation and cancer (11,15,16).

The main challenges in treating cancer are its ability to invade surrounding tissues, metastasize remotely, and circumvent the surveillance of the host immune system through immune escape or suppression mechanisms (17-19).

Since mucin glycosylation is diverse and most of its functions depend on its glycosylation and dimerization, changes in tumor-related glycosylation can greatly enhance tumor immune evasion or immunosuppression (20-22). Therefore, the abnormal expression of these mucins may be related to cancer, and they can even be used as tumor markers, as well as to assess patient prognosis and guide treatment. For example, researchers have combined toll-like receptor 7 (TLR7) agonists with abnormally glycosylated MUC1, which can produce a non-specific immune response and can enhance the body's cellular and humoral immunity against MUC1, thereby exerting an antitumor effect, which is used clinically for the treatment of recurrent breast cancer (23,24). Among mucin family members, MUC1 and MUC2 have been extensively studied in various cancers; by contrast, MUC6 remains relatively under-investigated despite its unique structural features, highly tissue-specific expression, and reported associations with several gastrointestinal (GI) and gynecologic tumors. Importantly, recent findings suggest that MUC6 polymorphisms and aberrant glycosylation patterns may affect tumor risk, immune interactions and prognosis. These characteristics point to MUC6 as a biologically and clinically relevant but underappreciated mucin, warranting a comprehensive review of its mechanisms, expression dynamics and translational potential.

The research prospects of the relationship between MUC and cancer are very broad. MUC1 is the most widely studied mucin in breast cancer, and the role of Mucin 6 (MUC6) has also emerged in recent studies (25,26). MUC6 belongs to the gel-forming mucin family and is the main component of gastric mucus. It is also widely expressed in other tissues, mainly in the hollow organs of the digestive system (including the stomach, gallbladder, duodenum, pancreas, bronchi and endocervix) (27-29). A recent large-scale tissue microarray analysis further demonstrated the expression profile of MUC6 across 119 tumor types, involving 15,412 tumor samples, highlighting its variable yet widespread presence beyond the GI tract (30). Studies have shown that the pyloric glands of the gastric antrum and mucopeptic cells of the neck zone also express MUC6 to a certain extent (24,31,32). Numerous studies have reported that aberrant expression of MUC6 is generally associated with GI diseases and cancer. For example, Lee *et al* (33) showed that the number of tandem repeat sequences of MUC6 can be used to predict gastric cancer risk. In addition, MUC6-TN (highlighted below as a cancer-associated mucin that has been considered a potential target for immunotherapy) can be used as a target for tumor vaccines, which may constitute a new direction for cancer therapy (34-37). However, the specific mechanisms of MUC6 in the tumor microenvironment (TME), for example, how MUC6 is involved in cancer development, invasion and metastasis, have not been fully elucidated. It remains unknown whether MUC6 acts synergistically or antagonistically with other mucins (for example, MUC1 and MUC5AC). These questions suggest that although the clinical promise of MUC6 is very high, numerous aspects still need to be explored. The clinical significance of MUC6 and its mechanism in human tumor development, especially in GI tumors, were reviewed with the aim of providing clinical diagnosis and targeted therapy for a variety of tumors.

2. Structure and basic functions of MUC6

The composition of mucins differs from that of most proteins in that their molecular weight is usually very large because of the presence of a variable number tandem repeat (VNTR) region, also known as minisatellite RNA (38). These repeats are rich in PTS; some are extremely similar, and some are identical (39-41). The repetitive sequences are arranged densely in an ordered array and are relatively concentrated (42). After translation, further folding and modification are needed, and glycosylation is the primary modification of mucins. Glycoproteins are transported to the Golgi apparatus via COP II to accomplish more complex biochemical reactions, such as N-glycosylation (43-46). Normal N-glycosylated proteins subsequently undergo further O-glycosylation and dimerization (43,47,48). O-glycosylation depends on the length and number of PTS repeats, and owing to gene polymorphisms, O-glycosylation is different for each mucin and even the same mucin in different contexts (43,49).

MUC6 belongs to the family of gel-forming secreted mucins (including MUC2, MUC5AC and MUC5B), which have high sequence similarity (50,51). These genes are concentrated at p15.5 in the recombination enrichment region of ~400 kb in the sub-telomeric region of chromosome 11, between H-ras and IGF2 (9). However, the transcription direction of MUC6 is opposite to that of other family members (52) (Fig. 1). Its gene is ~28 kb in length and includes 35 exons and 34 introns (41). A recent study using long-read sequencing confirmed that the exon 31 tandem repeat region of MUC6 encodes highly glycosylated PTS sequences, with significant copy number variation among individuals-explaining observed polymorphisms in gene length and protein isoforms (42). Furthermore, structural comparisons revealed that MUC6 lacks conserved domains (D4, B and C) found in other gel-forming mucins such as MUC2, causing it to adopt a distinct polymerization behavior (53). These genomic characteristics likely underpin MUC6's unique functional role in mucosal defense.

The core length of the tandem repeat sequence is ~169 amino acids, and the corresponding gene length is between 8 and 13.5 kb. The uncertainty of the tandem repeat sequence in exon 31 causes changes in the length of the MUC6 gene (54,55). The center of MUC6 is rich in serine and threonine residues, followed by the CK region, and the highly glycosylated central domain is encoded by tandem repeats. The N-terminal domain of MUC6 is similar to that of von Willebrand factor (vWF). Both have a D-like domain and high cysteine content. vWF is highly similar to MUC2, but unlike other homologous MUC genes, some exons encoding the D4, B and C regions were lost during the evolution of MUC6 (53,56-58). There is a cystine structural motif in its short C-segment region, and a class D domain or a cystine structural motif is very important for the dimerization of mucins (52,56,59).

Initially, MUC6 was discovered in a gastric cDNA library, and it is most abundantly expressed in the stomach (52,60). Together with MUC5AC, it participates in the formation of the mucus barrier on the gastric surface (31,61). Its side chain can interact with bicarbonate to resist external gastric acid and pepsin. It also helps protect the gallbladder and bile duct

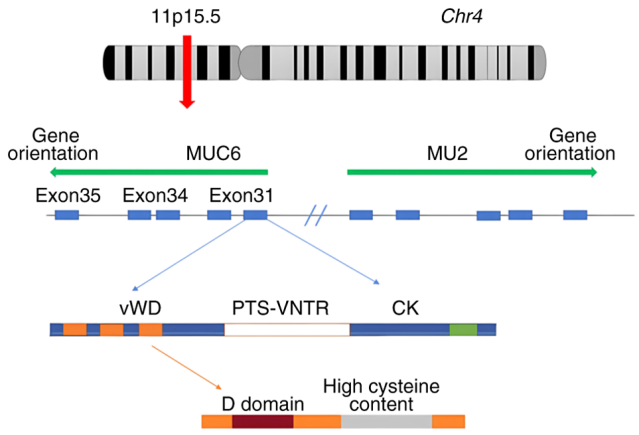

Figure 1. Gene location and structure of MUC6. MUC6, mucin 6; PTS, proline, threonine and serine; VNTR, variable number tandem repeat region; TLR7, vWF, von Willebrand factor.

from being corroded by hydrophobic bile acids. The pancreatic tubules need to resist the action of a variety of digestive enzymes and trypsin, and the seminal vesicles are also rich in pepsin (31). The side chain structures of MUC6 and other mucins in the cervical and endometrial glands can interact with certain bacterial structures to prevent infection (31). These findings indicate that under normal physiological conditions, the expression of MUC6 in epithelial cells can protect the human body from invasion and damage caused by digestive enzymes and bacteria (29,31).

Previous studies have quantified the structural and rheological contributions of MUC6 to the mucus barrier. In humans, the gastric mucus layer-composed primarily of MUC5AC and MUC6-reaches thicknesses of 0.2-0.6 mm, forming a bi-layered gel essential for buffering gastric acid and limiting pathogen access (62). Additionally, the lectin trefoil factor family 2 (TFF2), co-secreted with MUC6, cross-links MUC6 via GlcNAc-specific interactions, enhancing mucus viscosity and barrier stability *in vivo* and *in vitro* (63). Mechanically, enhanced mucus viscoelastic behavior under shear stress underscores the importance of mucin glycoprotein architecture in determining barrier resilience and microenvironment homeostasis.

3. MUC6 in common digestive tract tumors

The role of mucin in cancer is becoming clearer, where it generally indicates an improved outcome. Its expression in numerous cancers, including gallbladder, cholangiocarcinoma, lung, colorectal, prostate, breast, gastric, pancreatic and endometrial cancer, is different from that in normal tissues, potentially improving the prognosis and reducing metastasis. Although the relationships between MUC6 and various clinical indicators of patients with cancer, such as sex, age, stage and depth of invasion, are not clear, the positive role of MUC6 in cancer is obvious (Table I). It is known that most of the functions of mucin are inseparable from glycosylation, and some mucin structures in tumors are produced by obstructed O-glycosylation, such as TN, sialyl-TN or TF antigens (2,34). Among them, MUC6-TN, which has different antigenicity than other mucins, is expressed in the MCF7 breast cancer cell line. Further research revealed that the formation of MUC6-TN requires the participation of polypeptide N-acetyl galactosamine transferases (ppGalNAc-Ts). Although the prepared MUC6-TN partially eliminated the ability of MUC6 to promote the proliferation of specific T cells, MUC6-TN can stimulate T cells to preferentially produce IL-17. MUC6-TN can be recognized by specific antibodies against MUC6 and TN, thereby inducing the production of corresponding IgG antigens in the body, and the specific TN-induced IgGs can recognize the TN antigen of tumor cells to activate antitumor immunity (34,35,37). Researchers have also reported that the participation of multiple ppGalNAc-Ts (-T1, -T2 and -T7) may act together to produce MUC6-TN with a relatively high TN concentration, thereby improving the quality of antitumor vaccines (35).

In tissues that normally express MUC6, the loss of MUC6 is often accompanied by increased tumor invasiveness. In the early stages of pancreatic intraepithelial neoplasms (PanINs), the level of MUC6, especially in gastric PanIN, is elevated, but MUC6 expression is lost during progression to invasive ductal adenocarcinoma, especially in the final stage (28,64,65). It has been revealed that there is almost no difference between the levels of the MUC6 N-terminus (MUC6-N) and the MUC6 C-terminus (MUC6-C) in breast cancer cells, which are inherently weakly invasive (56). In pancreatic cancer and colon cancer cell lines, expression of the MUC6 domain can effectively inhibit their invasiveness; however, its effect on poorly differentiated pancreatic cancer is less pronounced than that on moderately differentiated colon cancer. This may also be due to the faster adhesion of pancreatic cancer and its weaker invasiveness. It has been identified that the expression of MUC6-N and MUC6-C can significantly reduce the adhesion of pancreatic cancer cells to type I and IV collagen, but there is no significant difference in their adhesion to fibronectin and laminin (56). In addition, in colon cancer cells, the expression of MUC6-N more significantly affects the adhesion of cancer cells to the four aforementioned proteins, but the expression of MUC6-C has a lesser effect on adhesion. In gallbladder cancer, the downregulation of MUC6 may be necessary for cancer metastasis. Shortly, the loss of MUC6 often indicates an increase in tumor aggressiveness and cancer metastasis. This may explain why the expression of MUC6 in most cancers predicts an improved outcome (36,56,66). In the following chapters, the results of research on the roles of MUC6 in various tumors are separately introduced (part of the mechanism is schematically shown in Fig. 2).

Gastric carcinoma. Although the incidence and mortality of gastric cancer have decreased in recent years, it is still among the leading causes of cancer-related death worldwide, with a mortality rate of ~75% and an estimated 5-year survival rate of only 20% (67). According to GLOBOCAN cancer statistics, there were >1 million new gastric cancer cases and 769,000 gastric cancer-related deaths in 2020. It is the fifth most common cancer and the fourth leading cause of cancer-related death worldwide (68). As a global health problem that threatens human safety, all aspects of gastric cancer should be studied to promote an early clinical diagnosis, early treatment and improved prognosis (69,70). *Helicobacter pylori* (*H. pylori*) infection is a recognized risk factor for gastric

Table I. Expression and roles of MUC6 in different types of human cancer.

Authors, year	Cancer type	Expression	Functional role (Inhibit)	Related signaling pathways	(Refs.)
Kwon *et al*, 2010; Jia *et al*, 2010; Khattab *et al*, 2011	Gastric carcinoma	Unclear[a]	Proliferation, migration, invasion		(54,76,77)
Bartley *et al*, 2010; Owens *et al*, 2008; Ahn *et al*, 2013	Colorectal cancer	Down	Migration, invasion		(95,97,98)
Park *et al*, 2009; Carrasco *et al*, 2021	Biliary tract carcinoma	Down	Migration, invasion	Co-expression of trefoil factor family 2	(102,107)
Leir and Harris, 2011; Xu *et al*, 2020	Pancreatic cancer	Down	Proliferation, invasion	Cancer susceptibility candidate 2-microRNA-24-MUC6; Pancreatic duodenum homeobox-1 induces transcription; nuclear factor kappa-B and Sp families of genes	(56,110)
Freire *et al*, 2012; Pereira *et al*, 2001	Breast cancer	Up[b]	Proliferation, invasion		(36,122)
Hamamoto *et al*, 2005; Kishikawa *et al*, 2021; Lee *et al*, 2019	Lung cancer	Up[b]	Proliferation, migration, invasion		(129-131)
Cozzi *et al*, 2005; Leroy *et al*, 2003;	Prostate cancer	Not express[c]			(60,135)
Hodgson *et al*, 2019; Alameda *et al*, 2007	Endometrial cancer	Up	Proliferation, migration, invasion		(142,144)

[a]The role of MUC6 in gastric cancer does not depend on its expression level, but on its genes; [b]MUC6 is not expressed in normal breast and lung, but its expression is elevated in breast cancer and lung cancer, but its expression usually reflects an improved prognosis; [c]MUC6 is not expressed in normal prostate and prostate cancer, but it has a unique clinical effect.

cancer, and it has also been identified as a human carcinogen by the IARC (71). Studies have shown that shorter VNTRs in MUC6 promote infection by *H. pylori*. This is due to the presence of α-1,4-linked N-acetylglucosamine (α-1,4-GlcNAc) in the variable region of MUC6, which has antibacterial effects against *H. pylori*. Accordingly, shorter VNTRs lead to less α-1,4-GlcNAc, and the antibacterial effect against *H. pylori* is weaker, increasing the risk of infection and subsequent development of gastric cancer (72,73). This theory is also consistent with the distribution of *H. pylori* (74,75).

The relationships between MUC6 and patient sex, tumor location, lymphatic invasion, clinical stage, metastasis and histological classification in gastric cancer remain unclear, and a consensus has not yet been reached. Certain studies indicate that MUC6 has no significant relationship with these clinicopathological characteristics (76-83). It has been also indicated that the loss of mucin predicts cell degeneration, especially intestinal metaplasia (precancerous lesions preceding gastric cancer) (84). Therefore, MUC6 is involved in the development of malignant lesions from gastric epithelial cells. The downregulation of MUC6 is correlated with the progression of gastric cancer and a poor prognosis, supporting the aforementioned theory (85). However, a study by Oosterlinck *et al* (86) revealed that MUC6 abundance was associated with a more favorable prognostic outcome in patients with gastric adenocarcinoma. In addition, MUC6 is a promising diagnostic marker for endocervical gastric-type adenocarcinoma (GAS) (87). Furthermore, a population-based histopathological analysis revealed notable regional differences in MUC6 expression between European and Latin American patients with gastric cancer, suggesting potential ethnicity-related biological variability (88). These data collectively underscore the diagnostic and prognostic potential of MUC6, though the precise associations with clinical indicators remain to be definitively established.

Notably, a new breakthrough in the study of MUC6 gene polymorphisms was previously reported (89). Studies of the relationship between MUC6 gene polymorphisms and gastric cancer have concluded that smaller alleles increase the risk of gastric cancer, irrespective of its histological classification (89).

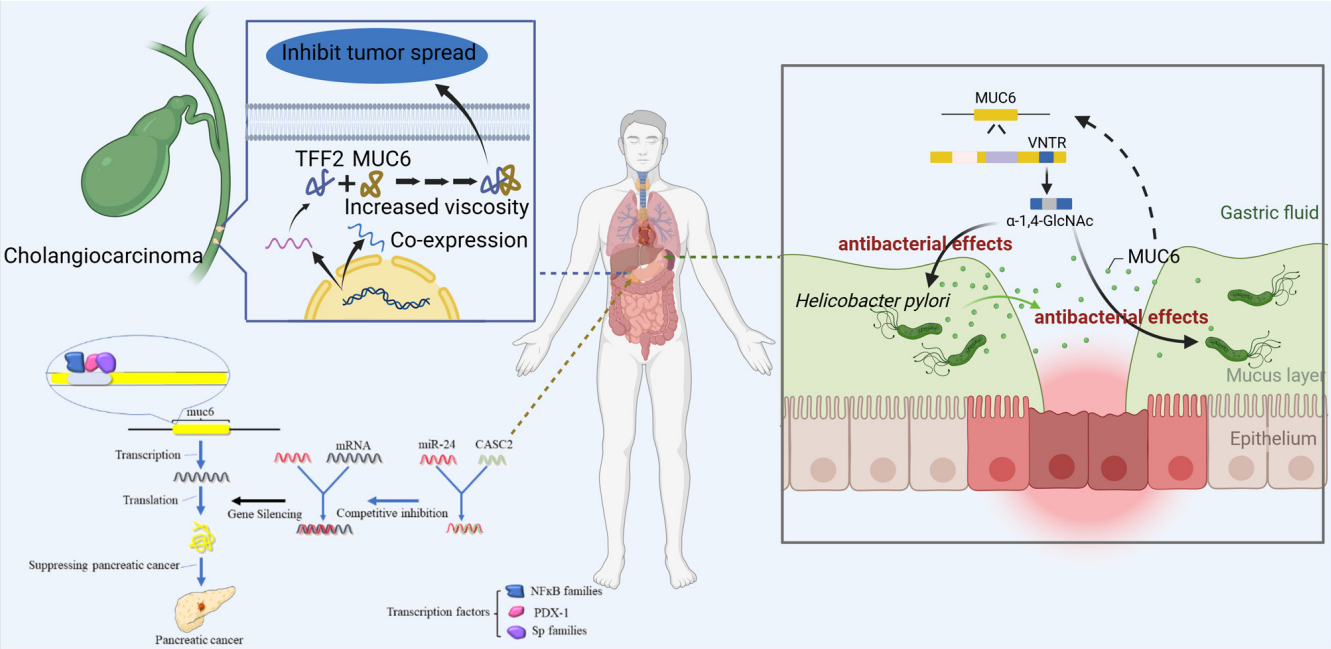

Figure 2. Patterns of the mechanism of MUC6 in common digestive tumors. MUC6, mucin 6; TFF2, trefoil factor 2; CASC2, cancer susceptibility candidate 2; NF-κB, nuclear factor kappa-B; Sp families, speckled protein families; PDX-1, pancreatic duodenum homeobox-1; VNTR, variable number of tandem repeats.

Subsequent research revealed that shorter tandem repeats may inhibit the expression of MUC6, which is ultimately associated with an increased risk of gastric cancer (54). Overall, the length and genetic polymorphism of MUC6 can be used to predict the risk of gastric cancer, but whether the expression level of MUC6 in gastric cancer is related to multiple clinical indicators remains uncertain. More data are needed to verify the relationship between MUC6 and gastric cancer, and the relationship between polymorphisms of other minisatellites of MUC6 and the risk of gastric cancer also needs further verification.

Colorectal cancer. Colorectal cancer is one of the most common cancers in the world, and its mortality is closely related to the failure of early screening (90,91). In 2020, a total of 1,931,590 cases of colorectal cancer were diagnosed worldwide, and 935,173 patients succumbed to the disease. The incidence of colon cancer varies greatly worldwide. Europe, Australia/New Zealand and North America have the highest incidences of colon cancer. The incidence of colon cancer in the most affected regions is 9-fold greater than that in the least affected regions (68,92).

MUC6 is generally not expressed in the colorectal mucosa, but some colorectal cancers are positive for MUC6 expression, and when most cancer cells in a colorectal tumor express MUC6, the prognosis of the patient tends to be improved. Therefore, MUC6 is recommended as a molecular marker for prospective risk assessment of patients with colorectal cancer (56). Studies have also shown that the expression of MUC6 is significantly correlated with a number of clinical indicators, such as whether the tumor is on the left or right, pathological type, tumor infiltrating lymphocytes, p53 expression, mismatch repair and MLH1 methylation, and other factors (93). In recent years, a new concept called the serrated pathway, which includes a series of molecular events, such as BRAF mutations, CpG island methylation, and microsatellite instability, has been proposed to explain the occurrence and development of colorectal cancer (10,14). This pathway starts with a variety of polyps, such as traditional serrated adenomas; sessile serrated adenomas, also termed sessile serrated polyps (SSAs/Ps); SSA/Ps with dysplasia (SSAs/PDs); and hyperplastic polyps (HPPs). Among them, HPPs are different from the other types and are considered benign. It has been noted that MUC6 may be involved in the serrated pathway of colorectal cancer (94). Compared with that of the HPPs, its level is significantly greater in SSA/P and SSA/PD. Although using this indicator to differentiate HPPs, SSA/P and SSA/PD is not ideal, it still supports the idea that HPPs may be a type of SSA. Although the relationship between MUC6 and various clinical indicators of colorectal cancer and polyps (including sex, age and size) is inconclusive (95,96), the results of these studies reached a consensus in some aspects. First, the expression of MUC6 is significantly increased in colon polyps, especially adenomatous polyps. Second, the physiological difference between the left colon and the right colon causes MUC6 expression in the serrated polyps of the right colon to be significantly greater than that in the serrated polyps of the left colon (95,97). As observed in gastric cancer, genetic polymorphisms of MUC6 may be associated with susceptibility to colon cancer (54). Similar to gastric cancer, having a shorter allele also indicates a higher probability of rectal cancer. However, unlike gastric cancer, MUC6 also has significant sex differences, whereby men generally have shorter alleles. However, that study was conducted in ethnic Asians, and this result is consistent with the fact that the prevalence of rectal cancer is higher in men than in women in Asians. Although the reason why the length of MUC6 is related to the incidence of cancer is not clear, there are more transcription factor-binding sites in the fifth tandem repeat of MUC6, and perhaps the underlying mechanism may be related

to the regulation of gene expression (54,98). In general, genetic polymorphisms of MUC6 are also related to susceptibility to colon cancer, and MUC6 expression is significantly increased in adenoma, but its relationship with other clinical indicators is not clear. Research on the genetic polymorphisms of colon cancer is promising, and global multi-center big data studies are needed to verify the established conclusions.

Biliary tract carcinoma. Biliary tract cancer, including gallbladder cancer and cholangiocarcinoma, is caused by the malignant transformation of biliary epithelial cells. Biliary tract cancer is characterized by a poor prognosis and early dissemination. Moreover, most patients are diagnosed with late-stage disease, which results in a dismal 5-year survival rate of <10% (99). Therefore, it is particularly important to correctly evaluate its prognosis and study the factors affecting its early dissemination.

Studies have shown that MUC6 expression is correlated with reduced lymph node metastasis in cholangiocarcinoma, which may be related to the co-expression of TFF2. When TFF2 is co-expressed and combines with MUC6, they form a complex, increase the viscosity of the mucin around the tumor mass, and ultimately prevent the tumor from spreading. It has been revealed that the downregulation of MUC6 is necessary for the metastasis of cholangiocarcinoma (100) (Fig. 2). The expression of MUC6 in cholangiocarcinoma is related to the histological type and extent of metastasis (101,102). MUC6 is more abundantly expressed in the pyloric glands (31), and pseudopyloric metaplasia is closely related to the occurrence of gallbladder cancer. Therefore, MUC6 may help us study the occurrence and classification of gallbladder cancer (103-106). In moderately and well-differentiated gallbladder cancers, the upregulation of MUC6 indicates an improved prognosis, and after the cancer progresses further, the dedifferentiation of the cancer cells results in the disappearance of the antimetastatic effect of MUC6 (107). The level of MUC6 may be used as a new indicator for the classification of biliary tract cancer and may even be necessary for its metastasis. The expression level of MUC6 may be an indicator of the prognosis of patients with biliary tract cancer, but the mechanism is not clear, and further research is needed.

Pancreatic cancer. As a common malignant tumor of the digestive tract with the worst prognosis, pancreatic cancer usually exhibits symptoms only in the late stage (108). In 2018, 458,918 new cases of pancreatic cancer were diagnosed worldwide, and 432,242 patients succumbed to the disease (109). Despite the continuous advancements in pancreatic cancer detection and treatment technology, the five-year survival rate is still only ~9% (68,109).

Under normal physiological conditions, MUC6 is most abundantly expressed in the intercalated ducts of the pancreas, followed by occasional detection in centroacinar cells and almost no expression in the interlobular ducts (56). Studies have suggested that MUC6 can inhibit the growth and development of pancreatic cancer. This is mainly because long non-coding RNA (lncRNA) cancer susceptibility candidate 2 (CASC2) indirectly regulates the expression of MUC6 by regulating microRNA (miR)-24, thereby exerting a tumor suppressor effect (110-112). It was also reported that the

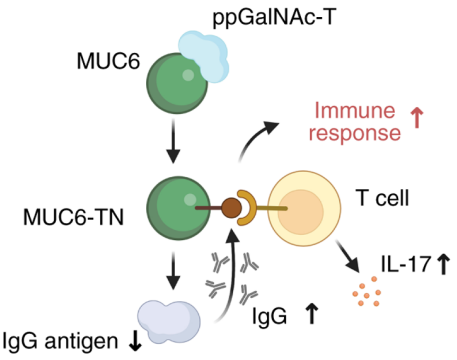

Figure 3. Diagram of MUC6-TN functioning pattern. ppGalNAc-T, polypeptide N-acetylgalactosamine transferase.

NF-κB and Sp families of genes, which are related to the occurrence of pancreatic cancer, may regulate the expression of MUC6 (113-117). In addition, it was proposed that PDX1 can induce MUC6 transcription as an important factor in the foregut endoderm cell lineage. Therefore, the role of MUC6 in the early development of pancreatic cancer also has a certain physiological basis (113,118) (Fig. 3). Given the poor prognosis of patients with pancreatic tumors, early diagnosis is the only means to effectively improve their outcomes. A study confirmed the feasibility of semiquantitative immunohistochemical (IHC) evaluation of three MUC genes (MUC3, MUC5AC and MUC6) as diagnostic markers for pancreatic cancer, which can effectively distinguish pancreatic cancer, chronic pancreatitis and normal pancreas. However, more data and multicenter studies are needed to verify the feasibility of this approach (119). Interestingly, there is no correlation between MUC6 and pancreatic invasive ductal carcinoma, possibly because MUC6 is related only to adenocarcinoma (120). MUC6 cannot only play a clinical role but also be used to study the development of tumors. It has been shown that MUUC6 is expressed mainly in central glandular secretions and that MUC6 expression may indicate the progression of a pancreatic cystic tumor to the central gland (121). The CASC2 (lncRNA)-miR-24 axis and PDX1 can both regulate MUC6 levels, thereby inhibiting the occurrence and development of pancreatic cancer. Accordingly, MUC6 may be an effective marker for early screening of pancreatic cancer together with other mucins and may help to distinguish different pathological types of pancreatic cancer. Nevertheless, more data and samples from multiple centers are needed to verify the existing conclusions.

4. In other cancers

Breast cancer. The incidence of breast cancer ranks first among female malignant tumors and has surpassed that of lung cancer to become the world's most common cancer, with 2,261,419 new cases of breast cancer diagnosed in 2020 (68).

MUC6 is not normally expressed in breast tissue but is expressed in non-cancerous tissues surrounding breast cancer (122). Some studies have shown that the expression of MUC6 is related to the grade and degree of lymphatic invasion of invasive breast cancer, which is related to prognosis (36,66,123-125), but other studies have reached different

conclusions. Notably, the standard used to judge positive MUC6 expression has improved (>30% of cancer cells expressing MUC6 are considered positive), and subsequent studies have confirmed this theory. Perhaps the formation of a mucin barrier by MUC6 requires a sufficient amount of MUC6, which may also exert other biological effects. Therefore, the functional relationship between MUC6 and cancer is more pronounced at higher expression levels (66,123). There are numerous examples of mucin expression being regulated by steroid hormones, and MUC6 is also upregulated by hormones *in vitro*. The abnormal expression of MUC6 in breast cancer may therefore be related to abnormal levels of steroid hormones during the development of breast cancer (126). TN (α-GalNAc-O-Ser/Thr) is a specific tumor antigen that is found mainly on mucins, and MUC6 was found to be a very favorable substrate for ppGalNAc-ts (the enzyme related to the synthesis of the TN antigen) in breast cancer and a relatively bad substrate for 1β3Gal-T (the enzyme that converts the MUC6-TN glycopeptide into MUC6-TF). This leads to the preferential enrichment of MUC6-TN rather than MUC1-TN in breast cancer cells (36,37). The TN antigen has numerous positive effects on cancer; thus, the relationship between MUC6 and breast cancer is very promising.

Lung cancer. Lung cancer is the cancer with the fastest increase in morbidity and mortality in recent years. As the second most common cancer in the world, there were 2,206,771 new cases of lung cancer in 2020, affecting twice as numerous men as women, and the number of deaths was 1,796,144 (68).

The expression of MUC6 has been increasingly recognized for its value in the classification and differential diagnosis of lung cancer subtypes. Specifically, subtype-specific expression patterns of MUC6 have been reported in lung adenocarcinoma, with immunoreactivity scores varying significantly between mucinous and non-mucinous forms (127). This aligns with earlier findings that MUC6 expression distinguishes bronchioloalveolar carcinoma from invasive mucinous adenocarcinoma and is often associated with a more favorable prognosis (119,128-131).

Moreover, MUC6 has shown diagnostic utility when combined with lineage-specific markers such as CDX2 and SATB2 in differentiating primary pulmonary mucinous adenocarcinoma from metastatic colorectal carcinoma (132). However, inconsistencies remain-some studies have found MUC6 expression to be positively correlated with lymph node metastasis, contradicting its previously reported protective role (133). These discrepancies underscore the need for larger, standardized studies to clarify the clinical relevance of MUC6 in lung cancer.

Prostate cancer. In 2020, there were 1,414,259 new cases of prostate cancer and 375,304 related deaths. It is the fourth most common cancer in the world and the second most common cancer in men, ranking fifth in terms of cancer-related deaths in men (68,134).

False-positive biopsy-based diagnosis of prostate cancer is often due to the presence of seminal vesicle-ejaculatory ducts. Studies have shown that MUC6 is not expressed in prostate cancer or normal prostate tissues but is strongly expressed in seminal vesicle-ejaculatory duct tissues. Therefore, MUC6 can provide strong evidence for distinguishing prostate cancer from seminal vesicles and ejaculatory ducts, greatly reducing the false-positive rate of prostate biopsy (60,135). Previous studies have indicated that MUC6 expression indicates an improved prognosis and is strongly correlated with the occurrence of prostate cancer (136,137). MUC6 expression may not directly lead to the occurrence of prostate cancer, but its presence may assist in increasing the detection rate of prostate cancer or have other indirect effects. More data are needed to verify the relationship between MUC6 and prostate cancer.

Endometrial cancer. Endometrial cancer is a group of epithelial malignant tumors that occur in the endometria of perimenopausal and post-menopausal women (138,139). Endometrial cancer causes ~76,000 deaths among women worldwide annually (140,141). Cervical GAS, also known as minimally offset mucinous adenocarcinoma or malignant adenoma, is characterized by HIK1083 and/or MUC6 immunopositivity and is more aggressive than ordinary endometrial cancer. The expression of MUC6 is focal, thus the absence of MUC6 on a sub-biopsy section does not rule out a diagnosis (88,142). A 2023 meta-analysis further supported this diagnostic approach, confirming that MUC6, in combination with HIK1083, provides high specificity in identifying GAS, reinforcing its utility as a reliable IHC marker (143). The aforementioned steroid hormone regulation of mucin has also been mentioned in endometrial cancer, but the data are not complete (144). More in-depth research on endometrial cancer is needed since the current data are insufficient for existing conclusions to be translated into clinical applications, but there are broad research prospects.

5. The role of MUC6 in tumor immunotherapy

Cancer immunotherapy focuses on the body's immune response to cancer cells without causing damage to normal cells. This requires cancer-specific antigens to induce a specific immune response (34), and only peptide modifications can be identified by the immune system (for example, mutations, glycosylation and phosphorylation) (145,146). MUC6, along with other mucins (for example, MUC1 and MUC5AC), all exhibit important biological functions, such as glycosylation, masking tumor antigens, and evading immune recognition (147-149). Glycosylations allow these mucins to form structural barriers that mask tumor antigens on the cell surface and reduce recognition by immune cells (for example, T cells and natural killer cells), thus facilitating tumor immune escape (20). MUC6, as a secreted mucin, impedes the penetration of immune cells, whereas MUC1, as a membrane-bound mucin, has a glycosylation that not only masks antigens but also participates in the process of immunosuppression through intracellular signaling (150,151). Moreover, the aberrant secretion of MUC5AC further aggravated the formation of the mucus barrier in the TME, limiting immune cell infiltration and antitumor activity (152). In terms of expression pattern, MUC6 is more commonly expressed in tissues such as the stomach and pancreas, whereas MUC1 and MUC5AC are more widely expressed and tend to be differentially expressed in different cancer types. Accordingly, highly glycosylated and relatively specific MUC6 is an attractive target. Abnormal mucin expression can expose core proteins (2). This makes MUC6 a

Table II. Characteristics and immunogenicity of MUC6 glycoforms.

Differential aspects	Glycosylation degree	Number of GalNAc	Molecular weight, Da	Immunogenicity	Antigenicity	T cell epitope immunodominance	Antibody induction ability
MUC6	None	0	12,120.3	High	High	Normal	High
MUC6: Tn(T1)	45%	24	15,993.1	Low	Low	Reduced	None
MUC6: Tn(T2)	38%	16	15,375.1	Moderate	Low	Reduced	Moderate
MUC6: Tn(T1+T2)	45%	24	15,982.6	Low	Low	Reduced	None
MUC6: Tn(T1+T7)	57%	24	16,994.5	High	Low	Normal	High
MUC6: Tn(T2+T7)	48%	20	16,196.2	Moderate	Low	Reduced	None
MUC6: Tn(T1+T2+T7)	67%	28	17,808.3	High	Low	Normal	High

GalNAc, N-acetylgalactosamine.

new cancer immunotherapy target, and TN-related vaccines, such as α-N-acetylgalactosamine-O-serine/threonine conjugate vaccines, have shown promise (153). The ppGalNAc-T enzyme is a glycosyltransferase that can transfer GalNAc to a specific MUC6 residue and connect it with a serine or threonine to form a -TN antigen. There are numerous isozymes in the ppGalNAc-T family and choosing the one with the highest glycosylation efficiency has become a research hotspot. It was aforementioned that MUC6 is a favorable substrate for ppGalNAc-Ts and has a low reactivity to 1β3Gal-T, which leads to its enrichment in MCF7 breast cancer cells (36,153). The latter can also induce immune responses in mice, leading to the production of IgGs that can recognize TN antigens to attack tumor cells (36,153).

On this basis, Freire *et al* (35) glycosylated MUC6 with different combinations of ppGalNAc-Ts to obtain various MUC6: Tn glycoproteins and injected them into mice. Only MUC6: Tn(T2) and MUC6: Tn (T1 + T2 + T7) were found to induce specific antibodies capable of recognizing tumor cells, suggesting that the linkage of GalNAc to the MUC6 protein alters its immunogenicity and that there is no significant correlation between the number of GalNAc residues and the antigenicity of MUC6 or TN (35). Glycosylation may mask dominant T-cell epitopes, thereby reducing recognition, which may explain why MUC6 occasionally stimulates IL-2 to greater effect (35). In conclusion, the TN antigen of MUC6-TN affects its immunogenicity against B and T cells; thus, adjusting the combination of ppGalNAc-T is necessary when designing a vaccine to ensure its antigenicity (Table II).

Supporting this immunomodulatory role of MUC6 *in vivo*, it has been recently demonstrated that Muc6 upregulation in the mouse intestine after low-dose radiation exposure leads to mucosal immune alterations resembling inflammatory bowel disease (IBD) pathogenesis (154). Furthermore, MUC6 IHC staining has been proposed as a useful adjunct for histologic assessment in Crohn's disease, potentially identifying gastric-type metaplasia and related immune phenotypes (155). These observations collectively reinforce the concept that MUC6 is not only a structural mucin but also an active participant in regulating mucosal immunity-implications that extend to both autoimmunity and cancer immunotherapy.

Clinical considerations for MUC6 detection. In clinical oncology, MUC6 has emerged as a tissue-restricted marker with increasing relevance for both tumor classification and differential diagnosis, particularly in the GI tract (156,157). IHC detection remains the most widely used and practical method for assessing MUC6 expression in formalin-fixed tissues (158). Multiple tissue-based studies, including large-scale tumor microarray profiling, have validated MUC6 IHC in various cancers ranging from gastric and pancreatic to endometrial and breast carcinomas (159-161).

Recent experimental evidence suggests that altered glycosylation patterns of MUC6, particularly truncated Tn antigens, may offer enhanced specificity for identifying neoplastic transformation. A 2024 murine study demonstrated that loss of MUC6 leads to impaired O-glycosylation, enrichment of mannose-rich glycans, and subsequent tumor-promoting changes via MAPK signaling. These modifications were effectively detected by lectin-based assays and glycoform-sensitive IHC, providing a novel diagnostic approach (5).

Selection of wild-type vs. glycoform-specific MUC6 detection should be guided by tumor type and diagnostic goal. In pancreatic and biliary neoplasms, wild-type MUC6 is a useful surrogate marker for pyloric-type differentiation (63,162). By contrast, in breast, lung, or serrated colorectal lesions, MUC6 expression is ectopic and often associated with glycan alterations (163,164). In such settings, detection of Tn-modified MUC6 may better reflect tumor phenotype and immunogenicity (165).

Of particular interest is the potential co-expression of MUC6 with Claudin 18.2, a tight junction protein that has recently emerged as a promising therapeutic target across multiple GI cancers. A recent immunopathological study reported that over 57% of IBD-associated small bowel adenocarcinomas co-express MUC6 and Claudin 18.2,

suggesting a shared gastric lineage phenotype (166). Similarly, Yang *et al* (87) demonstrated in GAS that dual staining for MUC6 and Claudin 18.2 significantly improves diagnostic sensitivity and subclassification.

Despite these advances, standardization of antibody clones, scoring criteria, and threshold definitions remains lacking. Furthermore, few large-scale prospective studies have evaluated MUC6 performance in clinical cohorts or in comparison with other epithelial markers such as MUC5AC, MUC1, or CDX2 (30). Integration of glycoform-specific detection tools-such as lectins or monoclonal antibodies targeting the Tn epitope-remains in early translational stages and requires further validation (167,168).

Nonetheless, the spatially restricted, differentiation-dependent nature of MUC6, combined with its potential to reflect glycosylation-linked immune signatures, positions it as a promising companion marker for tumor profiling. In selected cancers, especially those with gastric or pyloric features, MUC6 may also contribute to personalized immunotherapy or stratification for Claudin 18.2-targeted treatment.

6. Conclusions

The present study reviewed the current research status of MUC6, focusing on its biological roles in cancer, especially GI tumors, and the possibility of its clinical application. The expression of MUC6 has strong specificity. Under normal physiological conditions, it is expressed only in specific tissues and organs during a specific developmental stage. Therefore, abnormal MUC6 expression usually indicates disease (11,15,16). In most studies, the presence of MUC6 indicates an improved outcome. MUC6 can enhance the adhesion of tissues, therefore the erosion and spread of tumor cells become more difficult, thereby improving the prognosis (56,66). MUC6 can protect the cavities of the digestive system and other organs and tissues from attack by digestive enzymes and bacteria. Tumorigenesis can also be induced by repeated stimulation and inflammation due to damage to tissues and organs. Therefore, the correct expression of MUC6 is essential for preventing the occurrence of cancer. However, while the expression level of MUC6 does not appear to be a suitable choice for evaluating various clinical indicators of cancer, its genetic polymorphisms can be used as important factors in cancer risk assessment. The length of the tandem repeats in MUC6 is significantly related to susceptibility to gastric and colorectal cancer. Accordingly, the possible relationship between MUC6 gene polymorphisms and susceptibility to other cancers merits further investigation (54,98). MUC6 is also used to distinguish false positives in prostate cancer biopsies (60,135). Moreover, MUC6-TN may provide a new direction for cancer treatment, and its practicality may surpass that of the widely recognized MUC1 to become a new target for cancer vaccines (34,35,37).

In the future, genetic polymorphisms of MUC6, duplication of VNRT in small satellites and susceptibility to cancer have broad research prospects, and they may become important indicators for early cancer prevention (96,98). The relationship between colorectal serrated polyps and MUC6 also appears to be a direction worthy of further research. MUC6 is not expressed by colon tissue under normal physiological conditions, and its appearance is often accompanied by increased cancer risk or activation of the serrated pathway, which may serve as an effective indicator for colorectal cancer risk assessment (54,56). Because pancreatic disease itself is difficult to diagnose and distinguish, while pancreatic cancer has almost no symptoms in the early stage, effective indicators that can be used for early screening and differential diagnosis are urgently needed, and MUC6 has significant potential in this regard (119). The promising performance of MUC6 in cancer immunotherapy suggests that it has broad development prospects. Overall, the roles of MUC6 in all aspects of cancer biology and therapy require more in-depth research.

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PX contributed to the conception and design of the work, reviewed and revised the manuscript critically for important intellectual content, and approved the final version. XL drafted the initial version of the manuscript and participated in its revision. XF contributed to the interpretation of content and manuscript editing. YX and PX jointly reviewed and revised the manuscript for intellectual content. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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