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REVIEW

The Roles of Transmembrane Mucins Located on Chromosome 7q22.1 in Colorectal Cancer

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Abstract: Colorectal cancer (CRC) is one of the most common types of cancers. It is associated with a poor prognosis and high mortality. The role of mucins (MUCs) in colon tumorigenesis is unclear, but it might be significant in the progression of malignancy. Some mucins, such as MUC1 and MUC13, act as oncogenes, whereas others, such as MUC2 and MUC6, are tumor suppressors. However, there are still mucins with unidentified roles in CRC. In this review, we discuss the reported roles of mucins in CRC. Moreover, we review the capability of the mucin family to serve as a sensitive and specific histopathological marker for the early diagnosis of CRC. Lastly, the role of mucin genes clustered on chromosome 7q22 in CRC and other cancers is also discussed.

Keywords: colorectal cancer, mucins, MUC3, MUC12, MUC17, chromosome 7q22.1

Introduction

Colorectal cancer (CRC) has an annual incidence of 1.9 million cases and is the second leading cause of cancer-related death globally (935,000 deaths per year).[1] The incidence of CRC is low in patients younger than 50 years old, but the rates increase thereafter, with a median age of 70 years.[2,3] The lowest incidence was reported in central and southern Asia, as well as Africa. The highest incidence was reported in Europe and North America.[1,4] In developed countries, the CRC incidence has stabilized or has started to decrease. This might be linked to the use of sigmoidoscopy and colonoscopy with polypectomy.[5]

In the Kingdom of Saudi Arabia (KSA), colorectal cancer is the most common cancer in men and the third most common in women.[5] For both sexes, CRC is the most common cancer in this region, with an estimated age-standardized incidence of 88.7 cases for every 100,000 people.[6] Additionally, the median ages of reported colon neoplasia among Saudi men and women are 60 and 55 years, respectively.[7] These are lower than those reported (70 years old) around the world.[2] The high incidence among the younger age population might be due to the relatively younger median age in this region since 71% of the population are younger than 45 years of age. Consequently, a national committee was formed by the Saudi Ministry of Health, and the panel of experts recommended that screening for CRC in KSA should be done at the age of 45 years due to the high prevalence.[8,9]

The treatment strategy for CRC depends on the tumor stage. For surgical intervention, polypectomy or colectomy is the first treatment option in the early stages of the disease. For advanced cases, adjuvant and neoadjuvant CRC therapies are used depending on the disease stage.[10,11] Fluorouracil (5–FU) treatment is the primary therapy for

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CRC and some patients are resistance to this therapy and even to new chemotherapies or targeted therapies.[11–15] The mechanistic basis behind the anti-cancer drug resistance in CRC might include defective drug delivery within tumor cells, impaired cellular homeostasis, and the deterioration of drug sensitivity at the molecular level. Moreover, additional mechanisms might include dysregulated programmed cell death, diminished DNA damage repair systems, and defective cell cycle checkpoints.[16] This drug resistance leads to a poor prognosis and relatively lower survival rate. Half of CRC patients have a 5-year survival and this reduces with age.[14,15,17] Approximately 40% of the 5-year-relative survival rate of patients with CRC.[9] These rates emphasize the urgent need to develop new diagnostic approaches that are more sensitive and specific for the detection of pre-neoplastic lesions in high-risk populations to maintain better prognosis and decrease CRC-associated morbidity.

Neoplastic colon lesions develop from the stem cell niche located at the base of the colonic crypts. Colon adenoma and subsequent adenocarcinoma originate from abnormal colonic stem cell proliferation. Clinically, the diagnosis of CRC relies on the visualization of the tumor by colonoscopy or sigmoidoscopy, followed by histopathological examination of the collected tissue biopsies for confirmation.[18] For earlier diagnosis of neoplastic transformation during the early stages of colonic malignancy, the detection of premalignant lesions is recommended. Aberrant crypt foci (ACF) and mucin-depleted foci (MDF) are pre-neoplastic lesions. ACF are detected via high-magnification chronoscopic colonoscopy, which enhances the detectability of ACF and flat adenomas after methylene blue staining in vivo.[19,20]

Only 5% of ACF were found to be premalignant, and the absence of mucin secretion by these aberrant foci suggested that there was a more specific marker for pre-neoplastic transformation of the colonic mucosa. Hence, the latter was named MDF, and they were found to be highly correlated with CRC development.[21] MDF were also observed in both hereditary and sporadic CRC forms.[22] Therefore, it was suggested that these pre-neoplastic lesions can be used as additional biomarkers of colon cancer.[23]

PubMed search engine was used to retrieve the most relevant articles in this topic[24–34] and.[25,35–39] The key words used to obtain the search results and the main relevant articles are summarized in flowchart (Figure 1). The related studies that mentioned in the bibliography these relevant articles were cited in this review article.

Colorectal Cancer Molecular Pathways

The sporadic of subtype of colorectal cancer accounts for ~85% and the rest include the family subtype (hereditary). CRC is traditionally classified either by chromosomal instability (CIN) or microsatellite instability (MSI). The chromosomal instability pathway accounts for approximately 80% of sporadic CRC patients.[40] The first adenoma-carcinoma sequence in CRC was introduced by Fearon and Vogelstein in 1990.[41] The mutation and loss of heterozygosity of several oncogenes and suppressor genes results in CIN tumors. One of the early events in the adenoma-carcinoma sequence is a mutation in the tumor suppressor gene adenomatous polyposis coli (*APC*). The mutation in *APC* leads to hyperactivation of the WNT signaling pathway in 80% of CRC patients, and

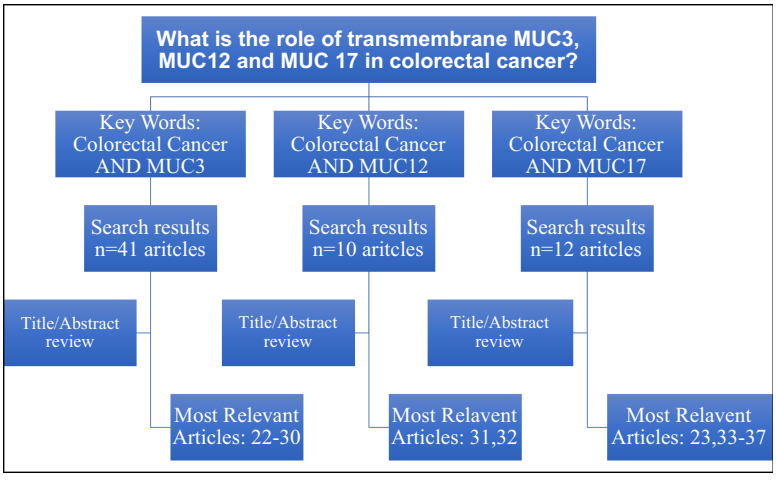

Figure 1 Flowchart illustrating the search strategy in PubMed database.

other mutations in WNT components account for approximately 10%[42,43] The CpG island methylator phenotype (CIMP) comprises highly frequent abnormal methylation in the CpG islands, which is reported in female and older CRC patients, and it is associated with *BRAF* mutations and deficiencies in mismatch repair genes.[44,45]

KRAS is an important member of several growth pathways, including the epidermal growth factor pathway. Constant activation of KRAS due to mutation leads to the upregulation of RAF-MEK-ERK, PI3K, and NF-KB.[46] The activating mutations in the *KRAS* gene occur in 40% of CRC patients and is usually reported after *APC* mutation.[47,48] Concordant mutations in *KRAS* and *PIK3CA* genes have been reported in CRC.[49] Further, overactivation of the PI3K pathway inhibits the apoptosis of CRC cells.[50]

A late event in adenoma transition to carcinoma is the loss of heterozygosity (LOH) of chromosome 17p, which harbors the *TP53* gene. Inactivation of this suppressor gene accounts for 70% of the CIN subtype of CRC patients.[51] Furthermore, LOH occurs in chromosome 18, which contains the tumor suppressor genes *DCC, SMAD2*, and *SMAD4*. The latter two genes regulate the transforming growth factor (TGFB) pathway.

It is also important to highlight the molecular importance of differences between right and left colon carcinoma. In right-side colon cancer, there tends to be a high prevalence of MSI, *BRAF* mutations, and a high CIMP+ phenotype, and this is associated with poorer prognosis.[52] For left–sided CRC, the carcinomas tend to have a high prevalence of CIN, *KRAS, APC*, and *P53* mutations, as well as high expression of EGFR.[52–54] Furthermore, chromosomal amplification has been identified in chromosomes 1q, 7, 8q, 13q, and 20q. Deletions of 1p, 4, 5q, 8p, 14q, 15q, 17p, and 18q have also been noted.[55]

Chromosome 7 Amplification in CRC

Chromosome 7 amplification has been reported in several studies.[56–58] Several genes located on chromosome 7 have been reported to drive CRC carcinogenesis. Phosphoserine phosphatase (*PSPH*),[59] *GTF2IRD1*,[60] and *TSA* have specifically been reported to drive pathogenesis.[61] Given the role of chromosome 7 amplification and its genes in CRC carcinogenesis, MUC3, MUC12, and MUC17 mucins, encoded by the same chromosome, have been implicated in CRC pathogenesis.

Mucins

Mucins are glycosylated proteins that are synthesized and expressed by a variety of tissues, including the colon.[62] Mucins can be categorized into three categories as follows: (i) membrane-bound/transmembrane mucins, (ii) secreted (gel-forming), and (iii) soluble (non-gel-forming) mucins.[62] Mucins have a surface protective role for epithelial cells via the entrapment of pathogens.[63] They are also involved in cell signaling pathways.[63] Therefore, they have a fundamental role in cellular functions, mainly at the surface of epithelial cells (Table 1). The molecular identification of mucins has revealed more than 20 mucinous proteins (MUC). These include membrane mucins, such as MUC1, MUC3A, MUC3B, MUC4, MUC12,

Table 1 Mucin Genes and Cytogenetic Localization

Gene Symbol	Cytogenetic Band	Entrez Gene ID (Gene)	Mucin Form
MUC1	1q22	4582	Membrane-bound mucin
MUC2	11p15.5	4583	Secreted
MUC3A	7q22.1	4584	Membrane-bound mucin
MUC3B	7q22	57876	Membrane-bound mucin
MUC4	3q29	4585	Membrane bound mucin
MUC5AC	11p15.5	4583	Secreted
MUC5B	11p15.5	727897	Secreted
MUC6	11p15.5	4588	Secreted
MUC7	4q13.3	4589	Secreted
MUC8	12q24.33	100129528	Secreted
MUC9	1p13.2	5016	Secreted
MUC12	7q22.1	10071	Membrane-bound mucin
MUC13	3q21.2	56667	Membrane-bound mucin
MUC14	4q24	51705	Membrane-bound mucin
MUC15	11p14.3	143662	Membrane-bound mucin
MUC16	19p13.2	94025	Membrane-bound mucin
MUC17	7q22.1	140453	Membrane-bound mucin
MUC19	12q12	283463	Secreted
MUC20	3q29	200958	Membrane-bound mucin
MUC21	6p21.33	394263	Membrane-bound mucin
MUC22	6p21.33	100507679	Membrane-bound mucin

MUC13, MUC15, MUC16, MUC17, and MUC2, and secreted mucins, such as MUC2, MUC5AC, MUC5B, MUC6, and MUC19. Further, MUC7, MUC8, MUC9, and MUC20 are soluble mucins.[62]

The primary function of mucins is to protect the surface of epithelial tissues. However, several mucins have been found to be pathologically expressed and involved in the tumorigenesis of various solid tumors. Additionally, published studies on MUCs in CRC are limited and only include certain members of the mucin family. MUC1 is expressed by both neoplastic and normal colonic tissues. Its expression is significantly higher in malignant lesions and is associated with a worse prognosis.[64] However, no correlation was observed between MUC1 expression and MSI CRC cases.[65] Additionally, the upregulation of MUC1 with β-catenin in gastric and colon neoplasia is considered a predictor of worse prognosis.[66,67] However, the proposed underlying pathogenic mechanisms associated with MUC1 are conflicting. Several studies have suggested that MUC1 induces cell proliferation and invasion by binding to β-catenin, thus inducing nuclear translocation of the latter.[68] Other studies have proposed that MUC1 suppresses cellular proliferation by preventing β-catenin nuclear localization.[69] More studies are needed to illustrate the precise role of MUC1 in CRC.

Similarly, contradictory results related to the role of MUC4 in colon tumorigenesis have been reported. Overexpression of MUC4 has been reported in tissues obtained from colon malignancies and is associated with worse prognosis.[70] However, others also reported the loss of MUC4 in tissue samples obtained from CRC.[71] Another membrane mucin, MUC13, was also found to be upregulated in primary and metastatic CRC.[72,73] Its overexpression has recently been linked to the development of resistance to chemotherapy in patients diagnosed with CRC.[74]

The oncogenic role of MUC15 in CRC has been reported, in which overexpression was reported in CRC tissues compared to levels in the non-tumor tissue of the same cases.[75] The effects of MUC15 in vitro in CRC cell lines have been studied, in which MUC15 was determined to increase proliferation and cell motility.[75] MUC16 (known as CA125) is the best biomarker for monitoring the progression of ovarian cancer and also can be used to monitor progression and predict lymph node metastasis in CRC cases.[76,77]

Alternatively, the overexpression of other mucins has been shown to be favorable for the prognosis of CRC. MUC2 is the most commonly secreted mucin in the intestines,[71] and mice deficient in the *MUC2* gene (Muc2 −/−) spontaneously develop colon cancer.[78,79] Furthermore, MUC2 is downregulated in CRC tissues obtained from humans, which suggests its tumor suppressor role.[80,81] Therefore, an increase in MUC2 can protected and/or enhance the outcome of CRC. Correspondingly, an increase in the expression of both MUC5AC and MUC6 also contribute to a better outcome for CRC.[34,49,71,82]

Regarding soluble forms, aberrant glycopeptides of MUC7 were not detected in CRC cases.[83] Nevertheless, MUC7 expression is related to the recurrence of bladder cancer.[84] However, other mucins like MUC8, MUC9, and MUC20 have not been studied in CRC. The serum level of MUC9 (known as OVGP1) increases with ovarian cancer stages.[85] In addition, the overexpression of MUC20 was reported in endometrial cancer, and it is associated with tumorigenesis and poor survival.[86]

Notably, genes encoding secreted mucins (MUC2, MUC5AC, MUC5B, MUC6, and MUC19) are all clustered-on chromosome 11 and are reportedly co-expressed.[87] Furthermore, recent studies have also explored the expression of secreted mucins located on chromosome 11 in a large series of CRC,[87] demonstrating that the overexpression of MUC5AC, MUC5B, and MUC6 is associated with serrated types of colonic glandular neoplasia. Serrated CRC is associated with DNA hypermethylation, MSI, and *BRAF* somatic mutations.[87] Additionally, mucin genes contain numerous transcription factor sites, such as those for Sp1, SP3, AP-1, NFκ-B, and CDX2.[68] The loss of CDX2 expression has been reported in several studies, due to mutation or microsatellite repeats within *CDX2* or through epigenetic silencing.[88,89] CDX2 expression was found in only 5% of CRC patients, and in another study, it was determined to be completely lost.[87,90] Downregulation of this transcription factor upregulates the expression of MUC2, MUC5AC, and MUC6. Furthermore, epigenetic regulation of genes expressing mucins in chromosome 11p15 has been explored by Vincent et al in several epithelial cancer cell lines, which include esophageal, pancreatic, gastric, and colon.[91] They showed that *MUC2* and *MUCB* genes are mainly affected by epigenetic changes in which *MUC2* expression is controlled by the repressive histone code and *MUC5B* methylation at CpG sites controls expression. However, one study has reported that *MUC6* expression is not affected by epigenetic changes, and the *MUC5AC* epigenetic mechanism has not been fully understood.[91] Regarding MUC5AC expression, hypomethylation was reported in MSI CRC cases and it is associated with poor differentiation and *BRAF* mutations.[92] Furthermore, expression of MUC2 was reported

to be associated with poorly differentiated cases and mucinous carcinoma.[92]

There are several therapeutical approaches for CRC treatment have been significantly improved the last decades. Drug combination has been used to enhance the effect of chemotherapy such as FOLFOX (5-FU +Oxaliplatin), however most of these approaches are failed to prevent the progression of CRC.[93] Therefore, the novel therapeutical approaches are urgent required. Mucins are the essential targets for prevent progression and metastasis of various type of cancers include CRC. Table 2 summarized some of clinical trial and anticancer therapeuticaltargeted mucins by using either vaccine or immunotherapy.[94–96]

Transmembrane Mucins Located on Chromosome 7q22.1

The transmembrane mucins MUC3A/B, MUC12, and MUC17 have short amino-terminal domains in the extracellular region, followed by long (> 4000 amino acids) heavily O-glycosylated tandem repeat domains. This structure is followed by two Cys-rich motifs (CRD1 and CRD2), proximal to the membrane, and both have a similar structure to the epidermal growth factor (EGF) domain.[38] In addition, these two Cys-rich motifs are separated by a Linker-SEA (L) domain, which contains a sea urchin sperm protein, enterokinase, and agrin.[25] Furthermore, these two Cys-rich motifs are followed by a small cytoplasmic domain. Notably, the transmembrane mucin genes *MUC3A, MUC3B, MUC12*, and *MUC17* are clustered on chromosome 7q22.

MUC3

The expression of MUC3 has been observed in normal colon and colon malignancies.[26,32] Several clinical studies have suggested an association between poor prognosis and MUC3 expression. Increased expression of MUC3 in pancreatic intraepithelial neoplasia is associated with the progression of neoplasia and is negatively correlated with

Table 2 Therapeutic Targets of Mucins in Several Cancer Types

Mucins	Cancer Type	Therapy	Ref
Muc1	Various cancer types	Vaccines: L-BLP25 (Phase III, NSCLC), TG4010 (Phase III, NSCLC) and PANVAC, (Phase II for various cancers)	[102]
MUC1	Various cancer types	Antibodies: DMC209 (against both MUC1-N and MUC1-C)	[103]
MUC1	Breast	Drugs: GO-201 (a direct inhibitor of MUC1-C function)	[104]
MUC1	Lung Cancer	TG4010 plus chemotherapy seems to improve progression-free survival	[105]
	Lung and prostate	Tecemotide Liposome Vaccine (L-BLP25) in Non-Small Cell Lung Cancer NSCLC Patients with Unresectable Stage III Disease	[106,107]
MUC1	Cholangiocarcinoma and colorectal cancer	ETBX-051+ ETBX-061+ ETBX-011 Multi-Targeted Recombinant Adeno Multitargeted Recombinant Adenovirus 5 (CEA/MUC1/Brachyury)	[108]
MUC1	Lung	Anti-MUC1 CAR T cells A Clinical Study of Anti-MUC1 CAR T Cells and PD-1 Knockout Engineered T Cells.	[109]
MUC1	Breast and ovary	^{131}I-mAb2G3E1 anti-mucin monoclonal antibody (mAb) 2G3 labeled with 1311 uptake of mAb by tumor nodules was small and variable	[110]
MUC1	Head and neck squamous cell carcinoma	^{90}Y-HMFG/1311-HMFG IgG1 radiolabeled anti-mucin mAb (HMFG1) improved in patients with head and neck cancer.	[111]
MUC7	Urothelial cancer cells	Conjugated MUC7 antibody with gold nanoparticles and a green light laser has kill cancer cell and do not affect the normal cell.	[95]
MUC13	Adenocarcinoma cells	Antibody-drug conjugate mAb TCC56, MUC13	[112]
MUC16	Various cancer types	Congregated MUC16 antibody has been exhibited preliminary effectiveness in ovarian cancer patients.	[113]
MUC18	Breast cancer cell	Anti-MUC18 scFv Ab has suppress invasion and migration in breast cancer cells.	[96]

differentiation.[30] In pancreatic ductal cell adenocarcinoma, the protein expression of MUC3 distinguishes the malignant tissue from normal tissue.[24] Furthermore, among 1447 cases of invasive breast carcinoma, the overexpression of MUC3 was found to be correlated with local recurrence and the lymph node stage, and this suggested the role of MUC3 as a prognostic marker.[28] Moreover, MUC3 is associated with gastric cancer progression.[29] The upregulation of MUC3 was also noted in clinical CRC samples in 84% of the cases. Among these, cytoplasmic localization and membrane localization were found in 91% and 38% of the cases, respectively.[26] Others, however, have shown the opposite findings wherein decreased MUC3 protein expression was reported in CRC.[31,32,97]

MUC12

MUC12 has a structure similar to MUC3 and MUC17.[98] Few studies have evaluated MUC12 in CRC and other cancer types. Matsuyama et al studied the expression of *MUC12* mRNA in CRC. The expression of *MUC12* was lower in cancer than in normal colonic tissue, and low expression was found to be associated with a poorer survival rate.[34] Furthermore, CRC tissues have lower expression of MUC12 than non-tumor tissues.[99] MUC12 was also determined to be expressed more in renal cell carcinoma than in the normal kidney and when knocked down. Growth and migration are decreased.[33]

MUC17

MUC17 harbors two EGF-like domains and is genetically similar to rodent MUC3[39] Several studies have examined the recombinant mouse Muc3-CRD1-L-CRD2.[25,27] This recombinant protein increases cell motility and migration, inhibits apoptosis in vitro, and promotes wound healing in vivo.[27] MUC17 showed a similar effect on a CRC cell line.[25] In addition, clinical studies on MUC17 expression have been conducted in several cancers. Aberrant expression of MUC17 protein in pancreatic ductal adenocarcinomas has been reported.[37,38] In addition, the downregulation of MUC17 protein in breast cancer is associated with a longer survival rate in patients treated with chemotherapy.[35] Furthermore, high expression of MUC17 in gastric carcinoma is associated with better prognosis.[100] The hypermethylation of *MUC17* in gastric cancer was determined to be associated with cancer development in *Helicobacter pylori* infection.[36] Moreover, sessile serrated adenoma/polyps (SSA/P) show the upregulation of MUC17.[101] The SSA/P pathways are associated with a high frequency of MSI and CIMP, as well as with *BRAF* mutations.[52] The overexpression of MUC17 protein in the CRC SSA/P pathway, with its distinct molecular features, suggest the possibility to further evaluate of MUC17 as a biomarker for the MSI and CIMP pathway.

Conclusion

The association among MUC17 in CRC, *BRAF* mutations, MSI, and CIMP needs further evaluation. The expression patterns of MUC3, MUC12, and MUC17, as well as their associations with histopathological features and clinical outcomes, have not been studied in CRC. These three mucins require further investigations involving larger clinical sample sizes. The biological activities of these three mucins in CRC also need to be explored in vitro and in vivo.

Abbreviations

ACF, aberrant crypt foci; AOM, azoxymethane; CIN, chromosomal instability; CRC, colorectal cancer; EGF, epidermal growth factor; KSA, Kingdom of Saudi Arabia; MSI, microsatellite instability; MDF, mucin-depleted foci; MUC, mucinous proteins; PSPH, phosphoserine phosphatase.

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Disclosure

The author reports no conflicts of interest in this work.

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