Expression of MUC1 in different tumours and its clinical significance (Review)

YUE LAN, WEIHUA NI and GUIXIANG TAI

Department of Immunology, College of Basic Medical Science, Jilin University, Changchun, Jilin 130021, P.R. China

Abstract. Mucin 1 (MUC1) was the first discovered transmembrane protein of the mucin family; it normally covers epithelial cells of the mucous membrane, providing lubrication and protection. However, aberrant expression of MUC1 is involved in cancer development, invasion and metastasis. It has been reported that MUC1 upregulation is highly associated with the progression of different epithelial cancer types, such as lung, liver, pancreatic and breast cancer. Therefore, MUC1 can be used as a specific marker and a target for immunotherapy in clinical applications, and the detection of MUC1 expression levels can be used to diagnose the occurrence, metastasis, prognosis and recurrence of cancer. The present review summarizes the abnormal expression of MUC1 in different tumours and discusses its clinical significance, thereby highlighting the potential diagnostic and therapeutic significance of MUC1 in cancer.

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Correspondence to: Professor Guixiang Tai, Department of Immunology, College of Basic Medical Science, Jilin University, 125 Xinjiang Street, Changchun, Jilin 130021, P.R. China
E-mail: taiguixiang@163.com

1. Introduction

Mucins are a family of high-molecular weight glycoproteins. In recent years, accumulating evidence has demonstrated that mucins play an important role in the initiation and progression of tumours (1). Therefore, research on the members of the mucin family has become a hot spot in the field of tumour immunotherapy. Among them, Mucin 1 (MUC1) is widely studied for its role in the pathogenesis of various cancer types, and it is the most intensively studied transmembrane protein of the mucin family. In general, abnormal expression of the MUC1 oncogene is associated with the progression of malignant tumours. For example, studies have found that the high expression of MUC1 is associated with the survival and prognosis of patients with lung, gastric, colorectal and pancreatic cancer (2-4). Thus, MUC1 is potentially a valid marker for the clinical diagnosis of tumours and an important antigen for targeted therapy (5).

2. Distribution, structure and biological characteristics of MUC1

In healthy tissues, MUC1 is expressed on the proximal luminal surface or proximal glandular surface of glandular epithelial cells, and its expression is characterized by apical expression, polar distribution and complete glycosylation. In diseased tissues, the upregulation of MUC1 together with loss of polarization and exposure of sites originally covered by glycan chains leads to the recognition of MUC1 as a tumour-associated antigen (TAA) by the immune system, indicating that it is a target for immunotherapy (6,7).

MUC1 is a high-molecular weight transmembrane glycoprotein, with a molecular weight of 300-600 kD, that is composed of two subunits, including the extracellular amino-terminal subunit (MUC1-N) and the transmembrane carboxy-terminal subunit (MUC1-C) (8). These two subunits are linked by non-covalent bonds to form a heterodimeric complex in the cell membrane and can also be spontaneously hydrolysed into two subunits. MUC1-N consists of 20-amino acid variable number tandem repeats, which are rich in amino acid residues and can be highly glycosylated. MUC1-C is a transmembrane subunit containing extracellular, transmembrane and intracellular domains (9). The cytoplasmic tail of MUC1 (MUC1-CT) consists of an extracellular domain of 58 amino acids, a transmembrane domain of 28 amino acids

and an intracellular domain of 72 amino acids. MUC1-CT is highly conserved among different species and plays an important role in numerous processes, such as signal transduction and intercellular interactions (10).

MUC1 has a lubricating and protective function in normal mucosal epithelial cells. However, upregulation of MUC1 promotes tumour progression by affecting multiple signalling pathways, as well as by regulating the proliferation and epithelial mesenchymal transition of tumourcells. Therefore, MUC1 is considered a vital oncogene that regulates the developmental processes of cancer. It has been shown that MUC1 promotes cell growth and the proliferation of cancer by regulating PI3K/AKT, MEK/ERK, p53, nuclear factor-κB, epidermal growth factor receptor, WNT/β-catenin and JNK/TGF-β (3,11,12). MUC1 also regulates tumour cell invasion and metastasis by interacting with E-calmodulin and intercellular adhesion molecules (13,14). In addition, MUC1 promotes tumour angiogenesis and accelerates the invasion and metastasis of tumours by stimulating the expression of proangiogenic factors, such as vascular endothelial growth factor (4,15). Taken together, these results show that the MUC1 oncogene plays an important role in cancer development (Fig. 1).

3. MUC1 expression in different tumours and its clinical significance

It has been reported that the MUC1 oncogene is commonly overexpressed in various epithelial adenocarcinomas, such as lung, liver, pancreatic, breast and ovarian cancer (10). The expression level of MUC1 in different cancer types is a key factor for the application of MUC1 in clinical diagnosis and treatment. The present review assesses the clinical significance of MUC1 by assembling cutting-edge data about the expression of MUC1 in different tumours.

Expression of MUC1 in lung cancer. Lung cancer has become the most common cause of cancer death worldwide. It has been reported that the mucin family, especially MUC1, plays an important role in the progression of lung cancer, and various vaccines for lung cancer targeting MUC1 are in clinical trials (16,17).

Approximately 85% of patients with lung cancer have the same histological subtype, namely, non-small cell lung cancer (NSCLC) (18). MUC1 is apically expressed and polar in normal tissues. However, in malignant tumours, the distribution of MUC1 loses its polarity and shows abnormal depolarization expression on the surface of the entire tumour cell, which is often associated with a poor prognosis (6,19). A clinical study reported that among 126 patients with non-small cell lung cancer, the 5-year survival rates of patients in the MUC1 depolarized expression group (percentage of tumour cells with depolarized MUC1 expression >10%), the low-grade polarized expression group (polarized MUC1 expression <50% and depolarized MUC1 expression <10%) and the high-grade polarized expression group (polarized MUC1 expression >50% and depolarized MUC1 expression <10%) were 43.9, 61.5 and 79.4%, respectively (19). These findings suggest that the depolarized expression of MUC1 in tumour cells is significantly associated with poor outcome in patients with lung cancer.

Lung adenocarcinoma and lung squamous cell carcinoma are the most common types of NSCLC. In a previous study that included 178 patients with stage IB NSCLC, the percentages of high MUC1 expression in patients with lung adenocarcinoma and lung squamous carcinoma were 86.3 and 39.1%, respectively (20). These findings suggest that MUC1 plays an important role in the progression of lung adenocarcinoma. MUC1-Tn antigen is an oversimplified mucin-1 O-glycan that is overexpressed in different cancer types. For example, the study found that MUC1-Tn was abnormally expressed in breast, lung and gastric cancer, among others, and may therefore be a target for cancer diagnosis (21). Therefore, the expression of MUC1-Tn in cancer tissues should be screened. In a previous study, the results of immunohistochemical analysis of 175 lung adenocarcinoma tissues showed that high MUC1-Tn (MUC1 glycoconjugate antigen) expression was observed in 44 (25.1%) specimens and was associated with patient sex (male patients, 33.3%; female patients, 17.6%), smoking history (ex-smoker, 31.8%; non-smoker, 12.5%), tumour stage (T1a-c stage, 16.2%; T2a-b+T3+T4 stage, 40.6%) and pleural invasion (positive, 40%; negative, 20%) (22). Another study suggested that the abnormal expression of MUC1 was correlated with the poor prognosis of patients with lung adenocarcinoma (23). Results indicate the potential utility of MUC1 as a clinical diagnostic marker and therapeutic target for lung adenocarcinoma through the contributing role in pathological features, such as development and invasive metastasis (24).

As it is difficult to obtain tumour tissues for clinical analysis from patients with lung cancer who have contraindications to surgery, blood markers are needed to predict the degree of cancer disease progression and chemotherapy efficacy in patients with advanced disease. It has been suggested that MUC1 can be used as a marker of circulating tumour cells (CTCs) in the peripheral blood of patients with NSCLC (25). A previous study on 66 patients with advanced NSCLC showed that MUC1 mRNA expression in the peripheral blood of patients treated for 4 weeks (relative expression, 4.46) was significantly lower than that in the patients before treatment (relative expression, 5.95) (26). In this previous study, the researchers also set 4.2 as the threshold of positivity for MUC1 mRNA in the peripheral blood of patients with NSCLC on the basis of the association between the level of MUC1 mRNA and pathological features. According to this, the positive expression of MUC1 in patients before and after 4 weeks of gefitinib treatment was 75.8% (50/66) and 45.5% (30/66), respectively, and the follow-up revealed that the survival time of MUC1-positive patients was significantly shorter than that of MUC1-negative patients. These findings suggest that peripheral blood MUC1 mRNA can be used to assess the therapeutic efficacy of gefitinib for patients with NSCLC. Another study also found that MUC1 could be used as a marker of CTCs in patients with NSCLC (27). Therefore, MUC1 mRNA in peripheral blood is expected to provide significant guidance for adjusting treatment regimens for patients with advanced disease.

Expression of MUC1 in breast cancer. Breast cancer is the most common cancer in women. The early diagnosis and treatment of patients with breast cancer is often poor, as the pathogenesis of the disease is still not clear.
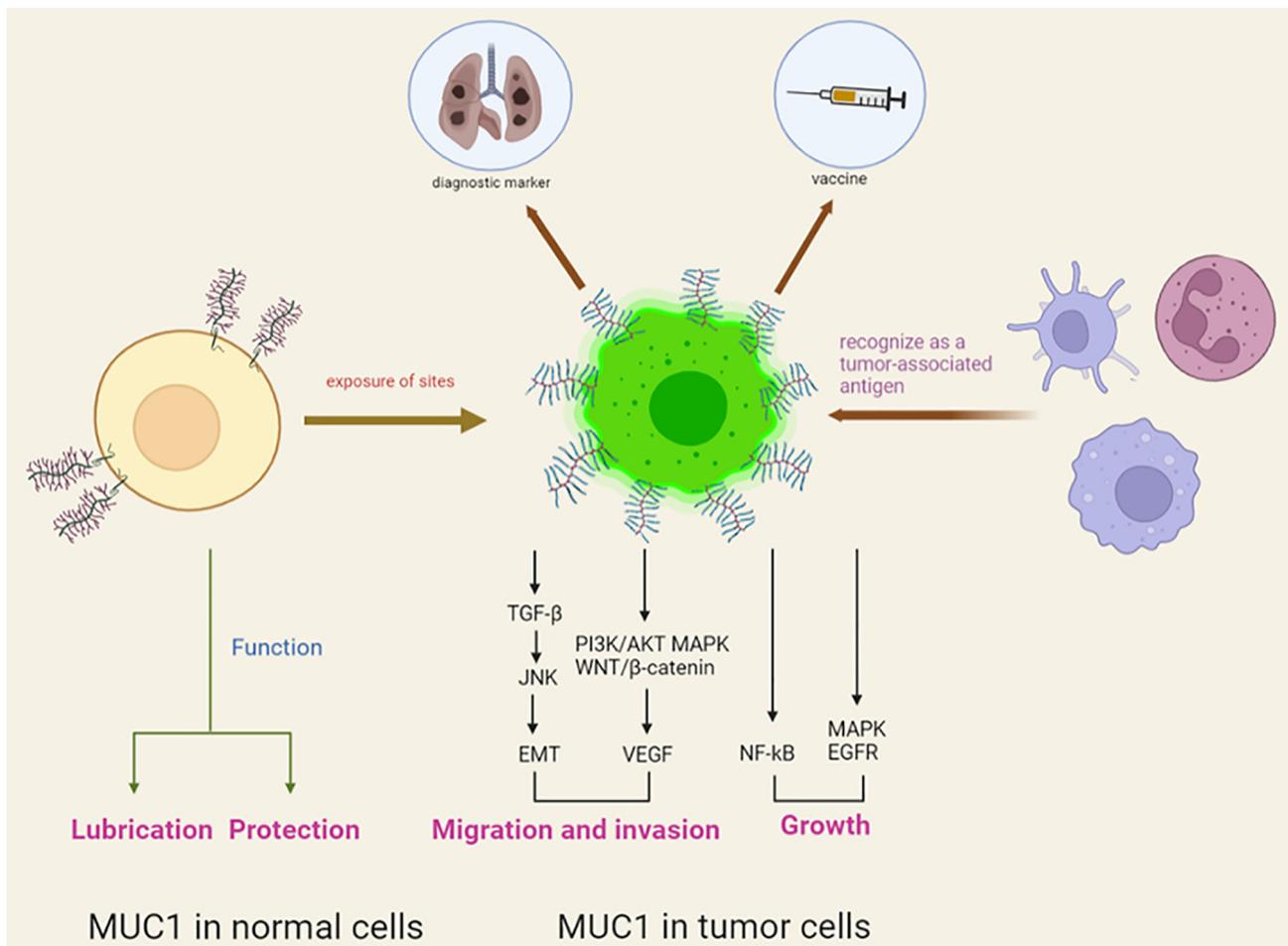
Figure 1. Different functions of MUC1 in normal or tumour cells. MUC1, mucin 1; NF-κB, nuclear factor κB; EMT, epithelial-mesenchymal transition; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

Triple-negative breast cancer (TNBC) is a subtype of breast tumour lacking oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 expression. TNBC is difficult to treat and has a high mortality rate due to a lack of therapeutic target molecules (28). A previous clinical study showed that 49 out of 52 (94.2%) cancer tissues of patients with TNBC were positive for MUC1 expression (29). These findings suggest that MUC1 is an ideal target of tumour immunotherapy for TNBC. MUC1 promotes the expression of programmed death ligand 1 in TNBC cells, resulting in increased immune escape function and invasiveness of tumour cells (30). MUC1 has been suggested to be a potential target to inhibit the development and progression of TNBC (31).

In addition, MUC1 has great potential for the rapid diagnosis of breast cancer. A previous clinical study showed that the expression levels of serum and salivary IgG anti-MUC1 in patients with breast cancer were higher than those in healthy women (P<0.001) (32), suggesting that the levels of autoantibodies against MUC1 in the serum and saliva of patients with breast cancer may provide references in cancer screening. Researchers have used quantitative (q)PCR to detect the mRNA level of MUC1 in the blood from healthy volunteers mixed with breast cancer cells (MCF-7) to simulate the CTCs of breast cancer, which indicated that this method had a sensitivity of detecting 1 CTC among $1x10^6$-10^7 white blood cells

and a high specificity of 96.8% (detected 1 MUC1-positive individual among 30 healthy volunteers) (33). The qPCR method also found that after the first cycle of chemotherapy, the treatment efficiency in patients lacking MUC1 expression (60%; 6/10) was higher than that in MUC1-positive patients (12.5%; 3/24) (33). These results suggest that MUC1 can provide clinical significance in the diagnosis of CTCs and the prediction of chemotherapy efficacy for patients with breast cancer. Other studies have indicated that upregulation of the MUC1 gene is associated with a poor prognosis in patients with breast cancer (34,35). MUC1 may also be a valid target for predicting and improving the prognosis of patients.

Expression of MUC1 in ovarian cancer. Ovarian cancer is one of the most lethal gynaecological malignancies, and the prognosis of affected patients is often poor due to its inconspicuous early symptoms and its tendency to invade surrounding organs (36). The MUC1 oncogene is involved in the progression, metastasis and drug resistance of ovarian cancer cells (37).

The immunohistochemical results of a clinical study revealed that all tumour specimens were MUC1-positive (19/19; 100%), with 47.4% (9/19) of these cases expressing high MUC1 levels (+++) in more than one-half of the cancer tissues (positive staining of cancer tissue >50%), and another

52.6% (10/19) of these cases expressing very high MUC1 levels (++++) (38). Another study on 60 primary ovarian cancer paraffin-embedded and sectioned tissue specimens showed that the positive expression rate of MUC1 was 95.0% (57/60), and the high expression rate of MUC1 was associated with tumour stage and postoperative residual tumour tissue (39). It has been suggested that MUC1 is involved in the progression of ovarian tumours and the poor prognosis of patients. Therefore, the MUC1 gene has great potential in the clinical diagnosis and treatment of patients with ovarian cancer (40). The intracellular segment of MUC1 (MUC1-CT) has also been reported as a potential site for ovarian cancer immunotherapy (41).

Expression of MUC1 in cholangiocarcinoma. The clinical outcome of patients with cholangiocarcinoma is generally poor, as cholangiocarcinoma cells are highly invasive and prone to lymph node and vascular metastasis (42).

In a previous study, an immunohistochemical staining analysis was performed to assay cancer tissues from 85 patients with cholangiocarcinoma. The study reported that the positive staining rate of MUC1 was 65.9% (56/85), and the positive expression rate of MUC1 was associated with tumour differentiation (poorly differentiated, 91%; moderately differentiated, 84%; highly differentiated, 43%), tumour stage (T1 stage, 50%; ≥T2 stage, 80%), neurological invasion (positive, 83%; negative, 57%) and patient survival time (median survival time of MUC1-positive patients, 29.21 months; median survival time of MUC1-negative patients, 56.48 months) (43). The results of another study showed that the positive immunohistochemical staining rate of MUC1 in the cholangiocarcinoma tissues of 25 patients was 44% (11/25) (44). Thus, these findings suggested that the upregulation of MUC1 plays an important role in the progression of cholangiocarcinoma and is expected to be a valid marker for the diagnosis of affected patients.

Cholangiocarcinoma can be divided into intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma depending on the site. One study showed that the positive expression rate of MUC1 was 25, 57 and 80 in patients with three staging types of intrahepatic cholangiocarcinoma, namely, intraductal, peri-biliary infiltrative and mass type, respectively (43). These results suggest that the abnormal expression of MUC1 has clinical value in the diagnosis of intrahepatic cholangiocarcinoma of different stages. Survival analysis of 61 patients with intrahepatic cholangiocarcinoma revealed that the median survival time of the MUC1 low expression group (qPCR: MUC1/GAPDH <0.056) was significantly higher (55.06 months) than that of the MUC1 high expression group (17.25 months); the overall survival rates at 1, 3 and 5 years were 73, 57 and 45%, respectively, for patients in the MUC1 low expression group, whereas the overall survival rates for the same periods in the MUC1 high expression group were 35, 26 and 20%, respectively, with a significantly higher recurrence rate in the MUC1 high expression group (54.8%) than in the low expression group (30.0%) (45). Another study found that, in 50 tissues of mass-type intrahepatic cholangiocarcinoma, the positive expression rate of MUC1 was 76.0% (38/50), and the abnormal expression of MUC1 was a prognosis-related risk factor for the disease (P=0.0011) (46). These findings suggest

that MUC1 is associated with a low survival time and high recurrence rate in patients with intrahepatic cholangiocarcinoma, which may be a valid predictor of prognostic status for these patients.

Another study demonstrated that the positive expression rate of MUC1 in the intraductal and peribiliary infiltrative types of extrahepatic cholangiocarcinoma was 47 and 85% (P=0.006), respectively (43), suggesting that MUC1 is also differentially expressed in different stages of extrahepatic cholangiocarcinoma, which is expected to assist in the diagnosis, prognosis prediction and treatment of cholangiocarcinoma in clinical practice (47).

Expression of MUC1 in gallbladder cancer. Gallbladder cancer has insidious symptoms in the early stage and is prone to invade other surrounding organs; therefore, patients are often in the middle and late stages when they are diagnosed, resulting in poor treatment outcomes (48).

MUC1 has been found to be strongly positively expressed in primary cancer cells derived from the ascites of patients with gallbladder cancer (49). A study collected 629 specimens from patients with gallbladder cancer for analysis, and the results showed that the positive expression rate of MUC1 in gallbladder cancer tissue specimens was 85.71% (18/21), which was significantly higher than its expression level in 605 patients with non-neoplastic gallbladder disease (5.29%; 32/605) (50).

Gallbladder adenocarcinoma is the most common type of gallbladder cancer in clinical practice, accounting for 85% of all gallbladder cancer cases. One study showed that the positive expression of MUC1 in the cancerous tissues of 108 patients with gallbladder adenocarcinoma (57.4%; 62/108) was significantly higher than its expression in paraneoplastic tissues (21.7%; 10/46), chronic cholecystitis (5.7%, 2/35) and adenomatous polyps (20.0%; 3/15) (51). These results suggest that MUC1 has a high specificity and accuracy in the diagnosis of gallbladder cancer, especially gallbladder adenocarcinoma, and that it can be used as a marker for clinical diagnosis. Another study also indicated that the positive expression rate of MUC1 was correlated with tumour size (tumour maximum diameter <2 cm, 38.7%; maximum diameter ≥2 cm, 64.9%; P<0.05), tumour stage (T1 stage, 28.6%; T2 stage, 42.9%; T3 stage, 59.5%; T4 stage, 77.3%; P<0.01) and lymph node metastasis (with lymph node metastasis, 69.5%; without metastasis, 42.9%; P<0.01) (51). These results further suggest that the abnormal expression of MUC1 is involved in promoting the progression and metastasis of gallbladder cancer, and that it may be of clinical significance in the diagnosis and prediction of clinical stage and metastasis for patients with gallbladder cancer.

Expression of MUC1 in bladder cancer. MUC1 plays a role in maintaining mucosal integrity and inhibiting urinary bacterial invasion in the normal urinary epithelium, and its abnormal expression is involved in promoting the progression and metastasis of bladder cancer in cancerous tissues (52).

A previous study showed that the positive expression rate of MUC1 was 61.8% (333/539) in tissue specimens from patients with bladder cancer, and its positive expression rate was associated with patient sex (female, 24.3%; male, 75.7%; P=0.044) and tumour pathological grade (high grade, 50.8%;

low grade, 49.2%; P=0.013) (53). A study on 97 bladder cancer tissue specimens found that the positive expression rate of MUC1 was 89.7% (87/97); of these specimens, 57 had >50% tumour cells positive for MUC1, indicating strong positive expression of MUC1 (54). Similarly, another study found an increasing trend of MUC1 expression in normal bladder mucosa, benign bladder disease and bladder tumours (55). It is suggested that MUC1 is involved in the development and drug resistance of bladder cancer (56). Thus, MUC1 may be an important clinical marker and targeted therapeutic molecule due to its high accuracy in the diagnosis of bladder cancer.

Expression of MUC1 in hepatocellular carcinoma. Hepatocellular carcinoma is one of the most common malignancies in clinical practice. The high aggressiveness and recurrence rate of this disease are important reasons for the low survival rate of patients (57).

One study showed that the positive expression rate of MUC1 in 96 patients with primary hepatocellular carcinoma was 77.1% (74/96), 68 specimens of which had strong positive immunohistochemical staining (++; positive cells >25%); MUC1 was only weakly positively expressed (+; positive cells <25%) in 20.0% (4/20) of patients with cirrhosis and there was no MUC1 expression in 10 normal liver tissue samples (58). In the aforementioned specimens of liver cancer, the positive expression rate of MUC1 was correlated with the degree of tumour differentiation (positive expression rate of MUC1: 53% highly differentiated, 85% moderately differentiated and 92% hypofractionated; strong positive expression rate: 47% highly differentiated, 80% moderately differentiated and 85% hypofractionated) and lymph node metastasis (positive, 90%; negative, 61%), suggesting that MUC1 is involved in the development and metastasis of hepatocellular carcinoma.

Another study found that the positive expression rate of MUC1 in 186 hepatocellular carcinoma specimens was 45.7% (85/186), and its positive expression rate was correlated with tumour differentiation (P=0.0001) and lymph node metastasis (P=0.0419) (59). A similar study showed that MUC1 was differentially expressed in hepatocellular carcinoma and paraneoplastic tissues, and that its expression rate was correlated with low patient survival rates (60). These findings suggest that MUC1 may be a diagnostic marker and a potential therapeutic target for hepatocellular carcinoma.

Expression of MUC1 in thyroid cancer. A previous report showed that MUC1 was positively expressed in 75.8% (219/289) of 289 patients with thyroid cancer, which was significantly higher than its expression level in non-malignant thyroid tissue (28/121; 23.1%) (61). Another study showed that the positive expression of MUC1 was significantly higher in thyroid cancer tissues (78.3%) than in paraneoplastic (24%) and normal (10%) tissues, and that its expression was associated with tumour stage (stage III+IV, 92.9%; stage I+II, 65.6%) and lymph node metastasis (positive, 90.5%; negative, 50%) (62). A previous study also showed that the positive expression rate of MUC1 in thyroid cancer was 77.6%, and its expression was associated with peripheral tumour invasion (P=0.035) and lymph node metastasis (P=0.013) (63). These results suggest that MUC1 is involved in the development and metastatic invasion of thyroid

cancer, indicating that it is a potential specific marker for clinical diagnosis.

Thyroid cancer is classified into papillary, follicular, undifferentiated and medullary carcinoma (64). RT-PCR analysis revealed that the expression of MUC1 in papillary thyroid cancer tissues was significantly higher than that in follicular carcinoma (P<0.05) (65), suggesting that there may be variability in the expression of MUC1 in different types of thyroid carcinoma. Additional clinical data are required to support these findings.

Expression of MUC1 in colorectal cancer. Colorectal cancer is one of the most common malignancies in China, and is prone to occur in the sigmoid colon and rectum. In recent years, a number of reports have confirmed that MUC1 may be a dominant antigen for the diagnosis and targeted therapy for colorectal cancer (66,67).

A previous study showed that the positive expression rate of MUC1 was 55.6% (25/45) in the cancer tissues of 45 patients with colorectal cancer, but that this rate was 0.0% in paracancerous tissues (0/20); the expression rate in cancer tissues was significantly correlated with lymph node metastasis (with metastasis, 84.2%; without metastasis, 34.6%) (68). Another study reported that the levels of MUC1 mRNA in colorectal cancer tissues were significantly higher than those in normal tissues (P=0.004) (69). These results suggest that MUC1 is involved in colorectal carcinogenesis and metastasis, indicating that MUC1 has a high specificity and accuracy in the diagnosis and prediction of colorectal cancer.

Another study showed that the positive expression rate of MUC1 in 202 colorectal cancer specimens (43.6%; 88/202) was significantly higher than its positive expression rate in 202 normal colorectal mucosa specimens (8.9%; 18/202), and the positive expression rate of MUC1 showed a significant increasing trend in tumour stages I (20%), II (35%), III (54%) and IV (60%) (P=0.006) (70). In addition, the expression rate of MUC1 was also associated with lymph node metastasis in patients (N0, 31%; N1, 61%; N2, 47%; N3, 100%) (70). These studies suggest that the abnormal expression of MUC1 is involved in the occurrence, development and invasive metastasis of colorectal cancer (71), indicating that MUC1 may aid in the clinical diagnosis of progression and postoperative metastasis. In addition, MUC1 may also serve as a specific target for colorectal cancer drugs or vaccines (72).

Expression of MUC1 in cervical cancer. Cervical cancer is a malignant disease caused by human papillomavirus infection, and it is divided into two main histological types, namely, cervical adenocarcinoma and cervical squamous carcinoma. The incidence of cervical adenocarcinoma is higher than that of cervical squamous carcinoma and the prognosis of patients with cervical adenocarcinoma is even worse than that of patients with cervical squamous carcinoma (73).

Among 52 patients with cervical adenocarcinoma, a study showed that the positive expression rate of MUC1 was 59.6% (31/52), which was associated with cervical cancer stage (FIGO stage 1a, 33%; FIGO stage 1b1, 50%; FIGO stage 1b2, 67%; FIGO stage 2a, 63%; FIGO stage 2b, 100%), lymph node metastasis (positive, 91%; negative, 51%) and ovarian metastasis (positive, 100%; negative, 55%) (74). Thus, MUC1 is

Table I. Expression of MUC1 in different tumours.

Cancer type	Positive expression rate of MUC1, % (n/total n) (Ref.)	Positive expression rate of MUC1 in patients with different stages, (%) (Ref.)	Overall survival time, months
Lung adenocarcinoma	86.3 (44/51) (20)	T1a-c, 16.2; T2a-b+T3+T4, 40.6 (22)	
Breast cancer	94.2 (49/52) (29)		
Ovarian cancer	100.0 (19/19) (38); 95.0 (57/60) (39)		
Cholangiocarcinoma	65.9 (56/85) (43)	Poorly differentiated, 91; moderately differentiated, 84; highly differentiated, 43; T1, 50; ≥T2, 80 (43)	MUC1 positive, 29.21; MUC1 negative, 56.48 (43)
Gallbladder carcinoma	57.4 (62/108) (51)	T1, 28.6; T2, 42.9; T3, 59.5; T4, 77.3 (51)	
Liver cancer	77.1 (74/96) (58)	Poorly differentiated, 92; moderately differentiated, 85; highly differentiated, 53 (58)	
Thyroid carcinoma	78.3 (47/60) (62)	I+II, 65.6; III+IV, 92.9 (62)	
Colorectal cancer	43.6 (88/202) (70)	I, 20; II, 35; III, 54; IV, 60 (70)	
Cervical carcinoma	59.6 (31/52) (74)	FIGO 1a, 33; FIGO 1b1, 50; FIGO 1b2, 67; FIGO 2a, 63; FIGO 2b, 100 (74)	

T1-T4 represent the size and range of the primary tumor using TNM staging (96,97). MUC1, mucin 1; FIGO, International Federation of Gynecology and Obstetrics.

involved in the malignant process of cervical adenocarcinoma and may be a target molecule for diagnosis and treatment.

As cervical cancer cells are prone to metastasis to other organs (75), it is important to detect early metastases of cervical cancer for clinical treatment. qPCR analysis of 179 lymph nodes from 21 patients with primary cervical cancer revealed that the MUC1 mRNA levels in lymph nodes with a positive histological diagnosis of metastasis were significantly higher than those in lymph nodes with negative histology (P<0.001); the specificity and sensitivity of MUC1 for the diagnosis of cervical cancer lymph node metastasis was 78% (percentage of negative qPCR tests in 162 negative lymph nodes) and 76% (percentage of positive qPCR tests in 17 positive lymph nodes), respectively (76). These results suggest that MUC1 level indicates lymph node metastasis in cervical cancer and provides a reference for the extent of surgical lymph node dissection.

Expression of MUC1 in pancreatic cancer. Pancreatic cancer is one of the most rapidly progressing malignancies with the worst prognosis. Most pancreatic cancer patients have poor treatment outcomes due to missing the optimal time for surgery (77).

A previous study showed that abnormal upregulation of MUC1 can be detected in >60% of pancreatic cancer cases, which correlates with the poor prognosis of the patients. It has been suggested that MUC1 is involved in the development and progression of pancreatic cancer, and that it may be an important marker in the clinical diagnosis of the disease (78). In addition, the pro-cancer mechanism of MUC1 may be associated with its promotion of glucose metabolism in pancreatic cancer cells (79).

A previous study showed that among 101 patients with pancreatic cancer, the median survival time of the patients in

the low MUC1 expression group (39.7 months) was significantly higher than that of patients in the high MUC1 expression group (13.4 months) (80). These findings indicated that MUC1 is associated with a poor prognosis and low survival time in patients with pancreatic cancer, suggesting that it may be an important target molecule to determine and improve the prognosis of patients.

4. Progress and perspectives

In summary, the MUC1 oncogene is aberrantly expressed in a variety of tumours, and its expression is mostly associated with tumour progression (Table I). Therefore, MUC1 may play an important role in the clinical diagnosis of tumours. Some researchers have attempted to use radiolabelled MUC1 antibodies or aptamers for targeted tumour imaging, which is expected to achieve a rapid diagnosis with high specificity when used in combination with traditional pathological biopsy methods (81). Studies have found that targeting the MUC1 antigen can be used for the radiographic diagnosis of breast cancer, which can be used to diagnose 90% of breast cancer cases, including TNBC (82,83). As CTCs also carry the MUC1 oncogene, the detection of MUC1 levels in the peripheral blood can also be applied in the clinical diagnosis of patients with cancer. The present review illustrates that the level of MUC1 in the peripheral blood of patients with NSCLC and breast cancer is associated with the treatment outcome and prognosis of patients, and that it is expected to be widely used in clinical practice in the future for the *in vitro* diagnosis of cancer, for chemotherapy efficacy assessment, and for postoperative recurrence and metastasis monitoring, due to its advantages of being an easy and non-invasive sampling method (26). Although, to the best of our knowledge, there are

few related reports to date, the level of MUC1 mRNA in the patient serum is a significant reference for the initial diagnosis of tumours (84).

In tumour immunotherapy, the exposed glycosylation sites can be recognized by the immune system as TAAs. Therefore, MUC1 has been an important target for tumour vaccine design and development in recent years. Tumour vaccines based on MUC1 effectively prevent cancer progression and metastasis. At present, MUC1-based tumour vaccines mainly include DNA vaccines, dendritic cell (DC) vaccines, virus vaccines and subunit vaccines. A variety of MUC1 DNA vaccines have been developed to date. Studies have confirmed that the MUC1 DNA vaccine induces a specific immune response against MUC1, produces an obvious tumour suppression effect and prolongs patient survival time (85-87). In phase I/II clinical trials, MUC1-loaded DC vaccines in the combination therapy of patients with advanced pancreatic cancer enhanced the disease suppression rate and effectively extended the survival period (88,89). TG4010, which is a viral vaccine expressing MUC1 has attracted much attention in recent years. In a phase II clinical trial, the vaccine extended the survival period of patients with NSCLC and no serious adverse reactions were found. At present, TG4010 has entered phase III clinical trials and is expected to enhance the efficacy of radiotherapy and chemotherapy for patients with cancer (16,90). Studies have confirmed that MUC1 subunit vaccines enhance specific immune responses, and these vaccines are expected to enter clinical trials in the future (91,92). In addition, studies have confirmed that chimeric antigen receptor-T cells targeting MUC1 have good antitumour function in tumour models *in vivo* and *in vitro*, which may provide new strategies for tumour treatment (93-95). Although MUC1-based tumour vaccines have not been successfully applied to clinical treatment at present, MUC1 has great potential in tumour treatment. In the process of vaccine development, it is very important to design vaccines according to the expression characteristics of MUC1 in different tumor tissues. In addition, the safety and effectiveness of tumour vaccines still need to be further verified, especially for patients with advanced cancer whose T-cell functions are severely damaged. MUC1 is expected to generate new hope for the clinical diagnosis and treatment of a number of tumors in the near future.

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Authors' contributions

YL drafted the initial manuscript, and edited and critically revised the manuscript. WN contributed substantially in drafting the manuscript, and in editing and critically revising the manuscript for intellectual content. GT put forward the concept, critically revised the article for intellectual content, and was responsible for the organization, revision and submission of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Wi DH, Cha JH and Jung YS: Mucin in cancer: A stealth cloak for cancer cells. BMB Rep 54: 344-355, 2021.
2. Xu F, Liu F, Zhao H, An G and Feng G: Prognostic significance of mucin antigen MUC1 in various human epithelial cancers: A meta-analysis. Medicine (Baltimore) 94: e2286, 2015.
3. Bose M, Grover P, Sanders AJ, Zhou R, Ahmad M, Shwartz S, Lala P, Nath S, Yazdanifar M, Brouwer C and Mukherjee P: Overexpression of MUC1 induces non-canonical TGF-β signaling in pancreatic ductal adenocarcinoma. Front Cell Dev Biol 10: 821875, 2022.
4. Khodabakhsh F, Merikhian P, Eisavand MR and Farahmand L: Crosstalk between MUC1 and VEGF in angiogenesis and metastasis: A review highlighting roles of the MUC1 with an emphasis on metastatic and angiogenic signaling. Cancer Cell Int 21: 200, 2021.
5. Supruniuk K and Radziejewska I: MUC1 is an oncoprotein with a significant role in apoptosis (Review). Int J Oncol 59: 68, 2021.
6. Chen W, Zhang Z, Zhang S, Zhu P, Ko JK and Yung KK: MUC1: Structure, function, and clinic application in epithelial cancers. Int J Mol Sci 22: 6567, 2021.
7. Beatty PL and Finn OJ: Preventing cancer by targeting abnormally expressed self-antigens: MUC1 vaccines for prevention of epithelial adenocarcinomas. Ann N Y Acad Sci 1284: 52-56, 2013.
8. Guo M, You C and Dou J: Role of transmembrane glycoprotein mucin 1 (MUC1) in various types of colorectal cancer and therapies: Current research status and updates. Biomed Pharmacother 107: 1318-1325, 2018.
9. Cascio S and Finn OJ: Intra- and extra-cellular events related to altered glycosylation of MUC1 promote chronic inflammation, tumor progression, invasion, and metastasis. Biomolecules 6: 39, 2016.
10. Gao T, Cen Q and Lei H: A review on development of MUC1-based cancer vaccine. Biomed Pharmacother 132: 110888, 2020.
11. Li W, Han Y, Sun C, Li X, Zheng J, Che J, Yao X and Kufe D: Novel insights into the roles and therapeutic implications of MUC1 oncoprotein via regulating proteins and non-coding RNAs in cancer. Theranostics 12: 999-1011, 2022.
12. Hagiwara M, Fushimi A, Bhattacharya A, Yamashita N, Morimoto Y, Oya M, Withers HG, Hu Q, Liu T, Liu S, et al: MUC1-C integrates type II interferon and chromatin remodeling pathways in immunosuppression of prostate cancer. Oncoimmunology 11: 2029298, 2022.
13. Yasumizu Y, Rajabi H, Jin C, Hata T, Pitroda S, Long MD, Hagiwara M, Li W, Hu Q, Liu S, et al: MUC1-C regulates lineage plasticity driving progression to neuroendocrine prostate cancer. Nat Commun 11: 338, 2020.
14. Hosseinzadeh A, Merikhian P, Naseri N, Eisavand MR and Farahmand L: MUC1 is a potential target to overcome trastuzumab resistance in breast cancer therapy. Cancer Cell Int 22: 110, 2022.

15. Utispan K and Koontongkaew S: Mucin 1 regulates the hypoxia response in head and neck cancer cells. J Pharmacol Sci 147: 331-339, 2021.

16. Quoix E, Lena H, Losonczy G, Forget F, Chouaid C, Papai Z, Gervais R, Ottensmeier C, Szczesna A, Kazarnowicz A, *et al*: TG4010 immunotherapy and first-line chemotherapy for advanced non-small-cell lung cancer (TIME): Results from the phase 2b part of a randomised, double-blind, placebo-controlled, phase 2b/3 trial. Lancet Oncol 17: 212-223, 2016.

17. Ning Y, Zheng H, Zhan Y, Liu S, Yang Y, Zang H, Luo J, Wen Q and Fan S: Comprehensive analysis of the mechanism and treatment significance of Mucins in lung cancer. J Exp Clin Cancer Res 39: 162, 2020.

18. Kwan TY and Chowdhury EH: Clinical outcomes of chemotherapeutic molecules as single and multiple agents in advanced non-small-cell lung carcinoma (NSCLC) patients. Medicina (Kaunas) 57: 1252, 2021.

19. Kaira K, Nakagawa K, Ohde Y, Okumura T, Takahashi T, Murakami H, Endo M, Kondo H, Nakajima T and Yamamoto N: Depolarized MUC1 expression is closely associated with hypoxic markers and poor outcome in resected non-small cell lung cancer. Int J Surg Pathol 20: 223-232, 2012.

20. Situ D, Wang J, Ma Y, Zhu Z, Hu Y, Long H and Rong T: Expression and prognostic relevance of MUC1 in stage IB non-small cell lung cancer. Med Oncol 28 (Suppl 1): S596-S604, 2011.

21. Palladino P, Papi F, Minunni M, Nativi C and Scarano S: Structurally constrained MUC1-tn mimetic antigen as template for molecularly imprinted polymers (MIPs): A promising tool for cancer diagnostics. Chempluschem 87: e202200068, 2022.

22. Kato T, Ujiie H, Hatanaka KC, Nange A, Okumura A, Tsubame K, Naruchi K, Sato M, Kaga K, Matsuno Y, *et al*: A novel Tn antigen epitope-recognizing antibody for MUC1 predicts clinical outcome in patients with primary lung adenocarcinoma. Oncol Lett 21: 202, 2021.

23. Xie Q, Zhao S, Liu W, Cui Y, Li F, Li Z, Guo T, Yu W, Guo W, Deng W and Gu C: YBX1 enhances metastasis and stemness by transcriptionally regulating MUC1 in lung adenocarcinoma. Front Oncol 11: 702491, 2021.

24. Liu S, Zhang X, Jiang Q and Liang T: Detection of circulating natural antibodies against CD25, MUC1, and VEGFR1 for early diagnosis of non-small cell lung cancer. FEBS Open Bio 10: 1288-1294, 2020.

25. Warawdekar UM, Sirajuddin MM, Pramesh CS and Mistry RC: An approach of selecting appropriate markers from the primary tumor to enable detection of circulating tumor cells in patients with non-small cell lung cancer. J BUON 20: 782-790, 2015.

26. Li J, Hu YM, Du YJ, Zhu LR, Qian H, Wu Y and Shi WL: Expressions of MUC1 and vascular endothelial growth factor mRNA in blood are biomarkers for predicting efficacy of gefitinib treatment in non-small cell lung cancer. BMC Cancer 14: 848, 2014.

27. Savarese-Brenner B, Heugl M, Rath B, Schweizer C, Obermayr E, Stickler S and Hamilton G: MUC1 and CD147 are promising markers for the detection of circulating tumor cells in small cell lung cancer. Anticancer Res 42: 429-439, 2022.

28. Borri F and Granaglia A: Pathology of triple negative breast cancer. Semin Cancer Biol 72: 136-145, 2021.

29. Siroy A, Abdul-Karim FW, Miedler J, Fong N, Fu P, Gilmore H and Baar J: MUC1 is expressed at high frequency in early-stage basal-like triple-negative breast cancer. Hum Pathol 44: 2159-2166, 2013.

30. Maeda T, Hiraki M, Jin C, Rajabi H, Tagde A, Alam M, Bouillez A, Hu X, Suzuki Y, Miyo M, *et al*: MUC1-C induces PD-L1 and immune evasion in triple-negative breast cancer. Cancer Res 78: 205-215, 2018.

31. Yamashita N, Long M, Fushimi A, Yamamoto M, Hata T, Hagiwara M, Bhattacharya A, Hu Q, Wong KK, Liu S and Kufe D: MUC1-C integrates activation of the IFN-gamma pathway with suppression of the tumor immune microenvironment in triple-negative breast cancer. J Immunother Cancer 9: e002115, 2021.

32. Laidi F, Bouziane A, Errachid A and Zaoui F: Usefulness of salivary and serum auto-antibodies against tumor biomarkers HER2 and MUC1 in breast cancer screening. Asian Pac J Cancer Prev 17: 335-339, 2016.

33. Cheng JP, Yan Y, Wang XY, Lu YL, Yuan YH, Jia J and Ren J: MUC1-positive circulating tumor cells and MUC1 protein predict chemotherapeutic efficacy in the treatment of metastatic breast cancer. Chin J Cancer 30: 54-61, 2011.

34. Jing X, Liang H, Hao C, Yang X and Cui X: Overexpression of MUC1 predicts poor prognosis in patients with breast cancer. Oncol Rep 41: 801-810, 2019.

35. Li J, Liu L, Feng Z, Wang X, Huang Y, Dai H, Zhang L, Song F, Wang D, Zhang P, *et al*: Tumor markers CA15-3, CA125, CEA and breast cancer survival by molecular subtype: A cohort study. Breast Cancer 27: 621-630, 2020.

36. Gaitskell K, Hermon C, Barnes I, Pirie K, Floud S, Green J, Beral V, Reeves GK and Million Women Study Collaborators: Ovarian cancer survival by stage, histotype, and pre-diagnostic lifestyle factors, in the prospective UK million women study. Cancer Epidemiol 76: 102074, 2022.

37. Ma Q, Song J, Wang S and He N: MUC1 regulates AKT signaling pathway by upregulating EGFR expression in ovarian cancer cells. Pathol Res Pract 224: 153509, 2021.

38. Budiu RA, Mantia-Smaldone G, Elishaev E, Chu T, Thaller J, McCabe K, Lenzner D, Edwards RP and Vlad AM: Soluble MUC1 and serum MUC1-specific antibodies are potential prognostic biomarkers for platinum-resistant ovarian cancer. Cancer Immunol Immunother 60: 975-984, 2011.

39. Wang L, Ma J, Liu F, Yu Q, Chu G, Perkins AC and Li Y: Expression of MUC1 in primary and metastatic human epithelial ovarian cancer and its therapeutic significance. Gynecol Oncol 105: 695-702, 2007.

40. Barani M, Bilal M, Sabir F, Rahdar A and Kyzas GZ: Nanotechnology in ovarian cancer: Diagnosis and treatment. Life Sci 266: 118914, 2021.

41. Hu XF, Yang E, Li J and Xing PX: MUC1 cytoplasmic tail: A potential therapeutic target for ovarian carcinoma. Expert Rev Anticancer Ther 6: 1261-1271, 2006.

42. Elvevi A, Laffusa A, Scaravaglio M, Rossi RE, Longarini R, Stagno AM, Cristoferi L, Ciaccio A, Cortinovis DL, Invernizzi P and Massironi S: Clinical treatment of cholangiocarcinoma: An updated comprehensive review. Ann Hepatol 27: 100737, 2022.

43. Park SY, Roh SJ, Kim YN, Kim SZ, Park HS, Jang KY, Chung MJ, Kang MJ, Lee DG and Moon WS: Expression of MUC1, MUC2, MUC5AC and MUC6 in cholangiocarcinoma: Prognostic impact. Oncol Rep 22: 649-657, 2009.

44. Mall AS, Tyler MG, Ho SB, Krige JEJ, Kahn D, Spearman W, Myer L and Govender D: The expression of MUC mucin in cholangiocarcinoma. Pathol Res Pract 206: 805-809, 2010.

45. Chen FY, Zhou C, Zhang XY, Zhou KQ, Peng YF, Yu L, Fan J, Zhou J, Hu J and Wang Z: Integrated Bioinformatics analysis and clinical validation reveals that high expression of mucin 1 in intrahepatic cholangiocarcinoma predicts recurrence after curative resection. Exp Ther Med 20: 50, 2020.

46. Matsumura N, Yamamoto M, Aruga A, Takasaki K and Nakano M: Correlation between expression of MUC1 core protein and outcome after surgery in mass-forming intrahepatic cholangiocarcinoma. Cancer 94: 1770-1776, 2002.

47. Supimon K, Sangsuwannukul T, Sujjitjoon J, Phanthaphol N, Chieochansin T, Poungvarin N, Wongkham S, Junking M and Yenchitsomanus PT: Anti-mucin 1 chimeric antigen receptor T cells for adoptive T cell therapy of cholangiocarcinoma. Sci Rep 11: 6276, 2021.

48. Bosch DE, Salipante SJ, Schmidt RA, Swanson PE, Bryan A, SenGupta DJ, Truong CD and Yeh MM: Neutrophilic inflammation in gallbladder carcinoma correlates with patient survival: A case-control study. Ann Diagn Pathol 56: 151845, 2022.

49. Garcia P, Bizama C, Rosa L, Espinoza JA, Weber H, Cerda-Infante J, Sánchez M, Montecinos VP, Lorenzo-Bermejo J, Boekstegers F, *et al*: Functional and genomic characterization of three novel cell lines derived from a metastatic gallbladder cancer tumor. Biol Res 53: 13, 2020.

50. Bhoge A, Khandeparkar SGS, Joshi AR, Gogate B, Kulkarni MM and Bhayekar P: Immunohistochemical study of MUC1 and MUC5AC expression in gall bladder lesions. J Clin Diagn Res 11: EC12-EC16, 2017.

51. Xiong L, Yang Z, Yang L, Liu J and Miao X: Expressive levels of MUC1 and MUC5AC and their clinicopathologic significances in the benign and malignant lesions of gallbladder. J Surg Oncol 105: 97-103, 2012.

52. Kaur S, Momi N, Chakraborty S, Wagner DG, Horn AJ, Lele SM, Theodorescu D and Batra SK: Altered expression of transmembrane mucins, MUC1 and MUC4, in bladder cancer: Pathological implications in diagnosis. PLoS One 9: e92742, 2014.

53. Stojnev S, Ristic-Petrovic A, Velickovic LJ, Krstic M, Bogdanovic D, Khanh DT, Ristic A, Conic I and Stefanovic V: Prognostic significance of mucin expression in urothelial bladder cancer. Int J Clin Exp Pathol 7: 4945-4958, 2014.

54. Gonul II, Cakir A and Sozen S: Immunohistochemical expression profiles of MUC1 and MUC2 mucins in urothelial tumors of bladder. Indian J Pathol Microbiol 61: 350-355, 2018.

55. Tao TT, Chen J, Hu Q, Huang XZ, Fu J, Lv BD and Duan Y: Urothelial carcinoma of the bladder with abundant myxoid stroma: A case report and literature review. Medicine (Baltimore) 99: e21204, 2020.

56. Shigeta K, Hasegawa M, Kikuchi E, Yasumizu Y, Kosaka T, Mizuno R, Mikami S, Miyajima A, Kufe D and Oya M: Role of the MUC1-C oncoprotein in the acquisition of cisplatin resistance by urothelial carcinoma. Cancer Sci 111: 3639-3652, 2020.

57. Anwanwan D, Singh SK, Singh S, Saikam V and Singh R: Challenges in liver cancer and possible treatment approaches. Biochim Biophys Acta Rev Cancer 1873: 188314, 2020.

58. Yuan SF, Li KZ, Wang L, Dou KF, Yan Z, Han W and Zhang YQ: Expression of MUC1 and its significance in hepatocellular and cholangiocarcinoma tissue. World J Gastroenterol 11: 4661-4666, 2005.

59. Ichikawa T, Yamamoto T, Uenishi T, Tanaka H, Takemura S, Ogawa M, Tanaka S, Suehiro S, Hirohashi K and Kubo S: Clinicopathological implications of immunohistochemically demonstrated mucin core protein expression in hepatocellular carcinoma. J Hepatobiliary Pancreat Surg 13: 245-251, 2006.

60. Jiang QL, Feng SJ, Yang ZY, Xu Q and Wang SZ: CircHECTD1 up-regulates mucin 1 expression to accelerate hepatocellular carcinoma development by targeting microRNA-485-5p via a competing endogenous RNA mechanism. Chin Med J (Engl) 133: 1774-1785, 2020.

61. Morari EC, Silva JR, Guilhen AC, Cunha LL, Marcello MA, Soares FA, Vassallo J and Ward LS: Muc-1 expression may help characterize thyroid nodules but does not predict patients' outcome. Endocr Pathol 21: 242-249, 2010.

62. Zhan XX, Zhao B, Diao C, Cao Y and Cheng RC: Expression of MUC1 and CD176 (Thomsen-Friedenreich antigen) in papillary thyroid carcinomas. Endocr Pathol 26: 21-26, 2015.

63. Hu YJ, Luo XY, Yang Y, Chen CY, Zhang ZY and Guo X: Characterization and significance of MUC1 and c-myc expression in elderly patients with papillary thyroid carcinoma. Genet Mol Res 14: 15325-15330, 2015.

64. Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, LiVolsi VA, Papotti MG, Sobrinho-Simões M, Tallini G and Mete O: Overview of the 2022 WHO classification of thyroid neoplasms. Endocr Pathol 33: 27-63, 2022.

65. Baek SK, Woo JS, Kwon SY, Lee SH, Chae YS and Jung KY: Prognostic significance of the MUC1 and MUC4 expressions in thyroid papillary carcinoma. Laryngoscope 117: 911-916, 2007.

66. Guo M, Luo B, Pan M, Li M, Xu H, Zhao F and Dou J: Colorectal cancer stem cell vaccine with high expression of MUC1 serves as a novel prophylactic vaccine for colorectal cancer. Int Immunopharmacol 88: 106850, 2020.

67. Guo M, You C, Dong W, Luo B, Wu Y, Chen Y, Li J, Pan M, Li M, Zhao F and Dou J: The surface dominant antigen MUC1 is required for colorectal cancer stem cell vaccine to exert anti-tumor efficacy. Biomed Pharmacother 132: 110804, 2020.

68. Wang HS and Wang LH: The expression and significance of Gal-3 and MUC1 in colorectal cancer and colon cancer. Onco Targets Ther 8: 1893-1898, 2015.

69. Kasprzak A, Siodla E, Andrzejewska M, Szmeja J, Seraszek-Jaros A, Cofta S and Szaflarski W: Differential expression of mucin 1 and mucin 2 in colorectal cancer. World J Gastroenterol 24: 4164-4177, 2018.

70. Hazgui M, Weslati M, Boughriba R, Ounissi D, Bacha D and Bouraoui S: MUC1 and MUC5AC implication in Tunisian colorectal cancer patients. Turk J Med Sci 51: 309-318, 2021.

71. Niv Y and Rokkas T: Mucin expression in colorectal cancer (CRC): Systematic review and meta-analysis. J Clin Gastroenterol 53: 434-440, 2019.

72. Schimanski CC, Kasper S, Hegewisch-Becker S, Schröder J, Overkamp F, Kullmann F, Bechstein WO, Vöhringer M, Öllinger R, Lordick F, et al: Adjuvant MUC vaccination with tecemotide after resection of colorectal liver metastases: A randomized, double-blind, placebo-controlled, multicenter AIO phase II trial (LICC). Oncoimmunology 9: 1806680, 2020.

73. Shimada M, Tsuji K, Shigeta S, Nagai T, Watanabe Z, Tokunaga H, Kigawa J and Yaegashi N: Rethinking the significance of surgery for uterine cervical cancer. J Obstet Gynaecol Res 48: 576-586, 2022.

74. Togami S, Nomoto M, Higashi M, Goto M, Yonezawa S, Tsuji T, Batra SK and Douchi T: Expression of mucin antigens (MUC1 and MUC16) as a prognostic factor for mucinous adenocarcinoma of the uterine cervix. J Obstet Gynaecol Res 36: 588-597, 2010.

75. Gardner AB, Charo LM, Mann AK, Kapp DS, Eskander RN and Chan JK: Ovarian, uterine, and cervical cancer patients with distant metastases at diagnosis: Most common locations and outcomes. Clin Exp Metastasis 37: 107-113, 2020.

76. Samouëlian V, Mechtouf N, Leblanc E, Cardin GB, Lhotellier V, Querleu D, Révillion F and Rodier F: Sensitive molecular detection of small nodal metastasis in uterine cervical cancer using HPV16-E6/CK19/MUC1 cancer biomarkers. Oncotarget 9: 21641-21654, 2018.

77. Cai J, Chen H, Lu M, Zhang Y, Lu B, You L, Zhang T, Dai M and Zhao Y: Advances in the epidemiology of pancreatic cancer: Trends, risk factors, screening, and prognosis. Cancer Lett 520: 1-11, 2021.

78. Wang S, You L, Dai M and Zhao Y: Mucins in pancreatic cancer: A well-established but promising family for diagnosis, prognosis and therapy. J Cell Mol Med 24: 10279-10289, 2020.

79. Fu X, Tang N, Xie WQ, Mao L and Qiu YD: MUC1 promotes glycolysis through inhibiting BRCA1 expression in pancreatic cancer. Chin J Nat Med 18: 178-185, 2020.

80. Sierzega M, Mlynarski D, Tomaszewska R and Kulig J: Semiquantitative immunohistochemistry for mucin (MUC1, MUC2, MUC3, MUC4, MUC5AC, and MUC6) profiling of pancreatic ductal cell adenocarcinoma improves diagnostic and prognostic performance. Histopathology 69: 582-591, 2016.

81. Maleki F, Rezazadeh F and Varmira K: MUC1-targeted radiopharmaceuticals in cancer imaging and therapy. Mol Pharm 18: 1842-1861, 2021.

82. Alirezapour B, Ashkezari MD, Fini MM, Rasaee MJ, Mohammadnejad J, Paknejad M, Maadi E, Yousefnia H and Zolghadri S: Preparation and preclinical characterization of (111)In-DTPA-Anti-MUC1 as a radioimmunoconjugate for diagnosis of breast cancer by single-photon emission computed tomography. J Cancer Res Ther 18: 158-167, 2022.

83. Stergiou N, Nagel J, Pektor S, Heimes AS, Jäkel J, Brenner W, Schmidt M, Miederer M, Kunz H, Roesch F and Schmitt E: Evaluation of a novel monoclonal antibody against tumor-sassociated MUC1 for diagnosis and prognosis of breast cancer. Int J Med Sci 16: 1188-1198, 2019.

84. Pierga JY, Bidard FC, Denis MG and de Cremoux P: Prognostic value of peripheral blood double detection of CK19 and MUC1 mRNA positive cells detected by RT-quantitative PCR in 94 breast cancer patients with a follow up of 9 years. Mol Oncol 1: 267-268, 2007.

85. Liu C, Xie Y, Sun B, Geng F, Zhang F, Guo Q, Wu H, Yu B, Wu J, Yu X, et al: MUC1- and survivin-based DNA vaccine combining immunoadjuvants CpG and interleukin-2 in a bicistronic expression plasmid generates specific immune responses and antitumour effects in a murine colorectal carcinoma model. Scand J Immunol 87: 63-72, 2018.

86. Ruan J, Duan Y, Li F and Wang Z: Enhanced synergistic anti-Lewis lung carcinoma effect of a DNA vaccine harboring a MUC1-VEGFR2 fusion gene used with GM-CSF as an adjuvant. Clin Exp Pharmacol Physiol 44: 71-78, 2017.

87. Gong YF, Zhou QB, Liao YD, Mai C, Chen TJ, Tang YQ and Chen RF: Optimized construction of MUC1-VNTRn DNA vaccine and its anti-pancreatic cancer efficacy. Oncol Lett 13: 2198-2206, 2017.

88. Ogasawara M, Miyashita M, Yamagishi Y and Ota S: Dendritic cell vaccination combined with a conventional chemotherapy for patients with relapsed or advanced pancreatic ductal adenocarcinoma: A single-center phase I/II trial. Ther Apher Dial 25: 415-424, 2021.

89. Ota S, Miyashita M, Yamagishi Y and Ogasawara M: Baseline immunity predicts prognosis of pancreatic cancer patients treated with WT1 and/or MUC1 peptide-loaded dendritic cell vaccination and a standard chemotherapy. Hum Vaccin Immunother 17: 5563-5572, 2021.

90. Tosch C, Bastien B, Barraud L, Grellier B, Nourtier V, Gantzer M, Limacher JM, Quemeneur E, Bendjama K and Préville X: Viral based vaccine TG4010 induces broadening of specific immune response and improves outcome in advanced NSCLC. J Immunother Cancer 5: 70, 2017.

91. Glaffig M, Stergiou N, Hartmann S, Schmitt E and Kunz H: A synthetic MUC1 anticancer vaccine containing mannose ligands for targeting macrophages and dendritic cells. ChemMedChem 13: 25-29, 2018.

92. Hu B, Wang J, Guo Y, Chen T, Ni W, Yuan H, Zhang N, Xie F and Tai G: Pre-clinical toxicity and immunogenicity evaluation of a MUC1-MBP/BCG anti-tumor vaccine. Int Immunopharmacol 33: 108-118, 2016.

93. Zhang H, Zhao H, He X, Xi F and Liu J: JAK-STAT domain enhanced MUC1-CAR-T cells induced esophageal cancer elimination. Cancer Manag Res 12: 9813-9824, 2020.
94. Mei Z, Zhang K, Lam AK, Huang J, Qiu F, Qiao B and Zhang Y: MUC1 as a target for CAR-T therapy in head and neck squamous cell carinoma. Cancer Med 9: 640-652, 2020.
95. Zhou R, Yazdanifar M, Roy LD, Whilding LM, Gavrill A, Maher J and Mukherjee P: CAR T cells targeting the tumor MUC1 glycoprotein reduce triple-negative breast cancer growth. Front Immunol 10: 1149, 2019.
96. Pang L, Wang J, Fan Y, Xu R, Bai Y and Bai L: Correlations of TNM staging and lymph node metastasis of gastric cancer with MRI features and VEGF expression. Cancer Biomark 23: 53-59, 2018.
97. Jeong O, Jung MR and Kang JH: Prognostic value of the anatomic region of metastatic lymph nodes in the current TNM staging of gastric cancer. J Gastric Cancer 21: 236-245, 2021.