



Deciphering cellular and molecular mechanism of MUC13 mucin involved in cancer cell plasticity and drug resistance

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Abstract

There has been a surge of interest in recent years in understanding the intricate mechanisms underlying cancer progression and treatment resistance. One molecule that has recently emerged in these mechanisms is MUC13 mucin, a transmembrane glycoprotein. Researchers have begun to unravel the molecular complexity of MUC13 and its impact on cancer biology. Studies have shown that MUC13 overexpression can disrupt normal cellular polarity, leading to the acquisition of malignant traits. Furthermore, MUC13 has been associated with increased cancer plasticity, allowing cells to undergo epithelial-mesenchymal transition (EMT) and metastasize. Notably, MUC13 has also been implicated in the development of chemoresistance, rendering cancer cells less responsive to traditional treatment options. Understanding the precise role of MUC13 in cellular plasticity, and chemoresistance could pave the way for the development of targeted therapies to combat cancer progression and enhance treatment efficacy.

Keywords MUC13 · Mucin · Drug resistance · Cancer cell plasticity · Metastasis · Cancer stem cell · EMT

1 Introduction

Cancer is one of the leading causes of mortality throughout the world, and it is projected to account for 10 million fatalities in the year 2020 [1]. The main cancer treatments that

are currently available are targeted therapy, radiation, laser, immunotherapy, gene therapy, hormone therapy, and chemotherapy. The most common and promising cancer treatment is chemotherapy [2–4]. Chemotherapeutic drug resistance is the leading cause of relapses and low survival rates in cancer patients, despite recent breakthroughs in cancer therapy. Most of the drugs that are used to treat the severe forms of cancer have been demonstrated to be resistant to chemotherapy. Metastases cancer cell resistant to chemotherapy causes 90% of failed cancer treatments, making it a major obstacle to cancer treatment [5]. For instance, a relapse of breast cancer caused by resistance to doxorubicin, paclitaxel, 5-fluorouracil, cyclophosphamide, and carboplatin is linked with a worse prognosis and shorter survival time [6–13].

Studies have shown that treatment resistance is either directly or indirectly responsible for between 80 and 90% of cancer patients' deaths [14]. It is widely held that therapeutic medications can only destroy actively dividing cancer cells; however, quiescent cancer cells, also called as cancer stem cells (CSCs), are believed to be resistant to these treatments and continue to thrive. According to the findings of studies, these CSCs are to blame for cancer's ability to recur, to relapse, to metastasize, and to become resistant to treatment medicines [15–17]. After

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seeing the histological similarities that exist between cancers and embryonic tissues, the notion of CSCs was originally described for the very first time in the early nineties, which is more than a century ago. On the other hand, it was demonstrated in 1937 that a cell transplanted from a mouse tumor can result in the development of a new tumor in the recipient mouse [18, 19]. It has been shown that CSCs may survive chemotherapy and even regenerate following treatment, despite the fact that the majority of chemotherapy medicines are effective to kill the tumor cells [20]. For instance, use of temozolomide results in the death of differentiated GBM cells but leads to an increase in the number of glioma stem cells in patient-derived cell lines [21]. The methods by which CSCs avoid the effects of chemotherapy are not well known. CSCs are responsible for orchestrating chemoresistance by regulating a number of different processes, including EMT, ROS production, hypoxia, and ABC transporters [22]. CSCs have been shown to express several different transporter proteins, including the multidrug resistance protein, phosphoglycoprotein, and breast cancer resistant protein (BCRP) [23, 24]. During cancer progression, tumors adopt several changes including accumulation of CSCs, metabolism, stromal-tumor cell interactions, and epithelial mesenchymal transition (EMT) to offer plasticity to harboring tumor cells. This comprehensive review will focus on deciphering the significance of MUC13 mucin in cancer cell

plasticity and drug resistance to provide valuable insights for the generation of innovative therapeutic methods.

2 Role of mucins in cancer biology

Mucins, a type of glycoproteins, have been found to play a significant role in cancers, particularly in their development and progression [25, 26]. Mucins are normally responsible for maintaining the mucus layer in different organs, such as the digestive, respiratory, and reproductive systems [25, 27–32]. In cancers, however, aberrant mucin expression and altered glycosylation patterns have been observed [33]. These changes can lead to the formation of a dense mucin-rich extracellular matrix, which promotes tumor growth, invasion, and metastasis (Fig. 1) [33–39]. Mucins have also been linked resistance to chemotherapy and immune evasion, further leads to the aggressiveness and treatment challenges posed by many cancers [40, 41]. Understanding the specific roles and mechanisms of mucins in different cancer types holds great potential for the development of targeted therapies and improved cancer management strategies [33–39].

There is an increasing body of research that points to a relationship between mucins and the plasticity of cancer cells. Mucins have been shown to influence the epithelial-mesenchymal transition (EMT), a process often associated

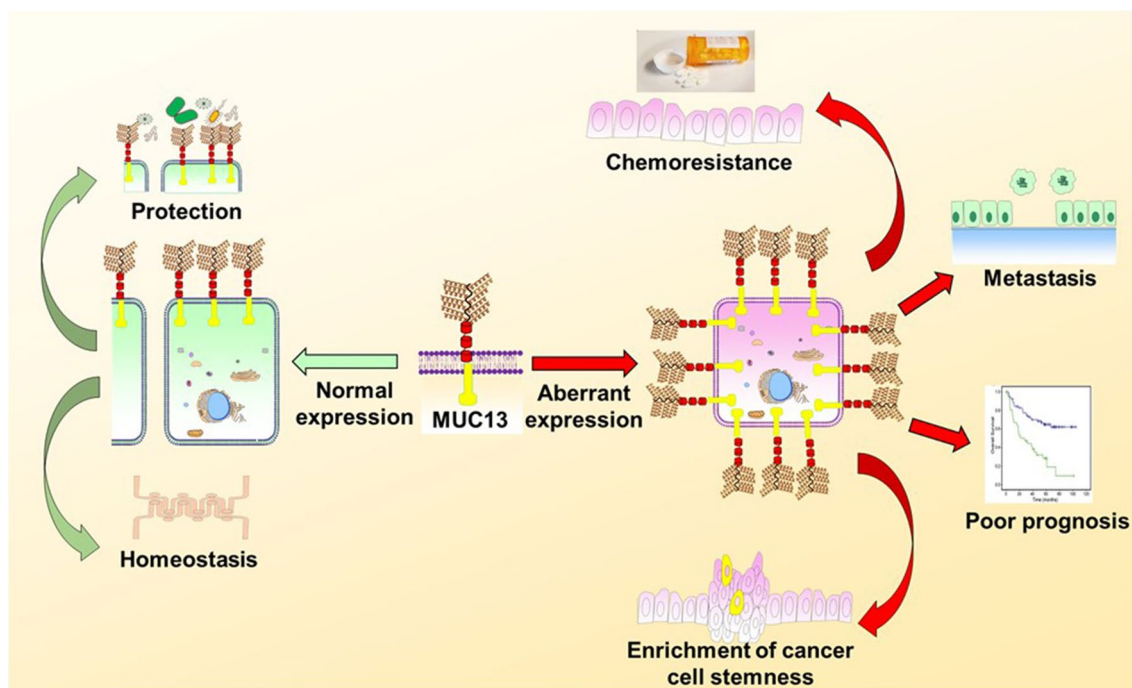


Fig. 1 Schematic representation of function of normal and aberrant MUC13 expression. The role of normal MUC13 is to provide protection from environmental toxin, pathogenic microbe insults, and

homeostasis. If aberrant, MUC13 induces chemoresistance, metastasis, poor prognosis, and enrichment of cancer cell stemness

with increased cancer cell plasticity and metastatic potential [42]. Certain mucin proteins can induce or suppress EMT, thereby influencing cancer cell behavior [43]. Moreover, mucins can interact with various signaling pathways involved in cell plasticity regulation, such as the transforming growth factor-beta (TGF- β) pathway. It is widely recognized that TGF- β signaling stimulates the epithelial to mesenchymal transition and cancer cell plasticity. Understanding the relationship between mucins and cancer cell plasticity is important for designing specific therapies and improving patient outcomes. By deciphering the mechanisms underlying mucin-mediated plasticity, researchers can potentially identify new therapeutic targets and strategies to better control tumor progression and metastasis. This comprehensive review primarily focusses on MUC13, an emerging oncogene that plays crucial role in cancer cell plasticity and drug resistance, particularly in the context of its interaction with CSCs, provides valuable insights for the development of novel therapeutic approaches.

3 The structural features of MUC13

Mucins are broadly classified into two categories: secreted mucins and membrane-bound mucins. Secreted mucins, such as MUC2, MUC5AC, MUC5B, MUC6, and MUC19, primarily comprise viscoelastic gels. They form a protective network that defends the epithelial cells against various aggressors like inflammation, bacteria, viruses, pollutants, and pH changes [40, 44–46]. On the other hand, membrane-bound mucins are a group of protein anchored to the cell membrane. They include MUC1, MUC3, MUC4,

MUC12, MUC13, MUC15, MUC16, MUC17, MUC20, and MUC21. These mucins play roles in cell-to-cell and cell-to-extracellular matrix interactions, as well as in cell signaling processes, owing to their specific structure and localization on the cell surface [47–49]. MUC13 is most notably characterized for protective functions in epithelial tissues and its large molecular weight (Fig. 2). MUC13 plays a crucial role in the intestinal epithelium by regulating tight junctions [50]. MUC13, like other mucins, has a tandem repeat (TR) domain rich in serine and threonine glycosylation sites. It has a cytoplasmic domain with putative phosphorylation sites and three epidermal growth factor domains. MUC13 has been found in the esophagus, trachea, kidney, small intestine, gastric epithelium, and large intestine under normal physiologic conditions [51]. According to its protective and lubricating role on the mucosal surface, MUC13 protein is generally found on the apical surface of epithelial cells. Mucin production, both secreted and linked with the cell membrane, offers a barrier against the colonization of harmful bacteria. Recent research has demonstrated the importance of altered MUC13 activity in variety of malignancies [51–57] (Table 1). Additionally, Filippou and colleagues conducted significant research on MUC13's ability as a marker for cancer and other disorders [58]. Therefore, the role of MUC13 is beginning to be redefined through its expression in various cancers from a protective glycoprotein to a potential oncogene. In our recent article, the various isoforms of MUC13 were discussed. A total of five transcripts of MUC13 were identified and among all, two were protein coding transcripts. These two protein coding isoforms further structurally identified as short form MUC13 (non-tumorigenic), and long form (tumorigenic). Multiple sequence

Fig. 2 Illustrative figure depicting the various factors associated with chemoresistance

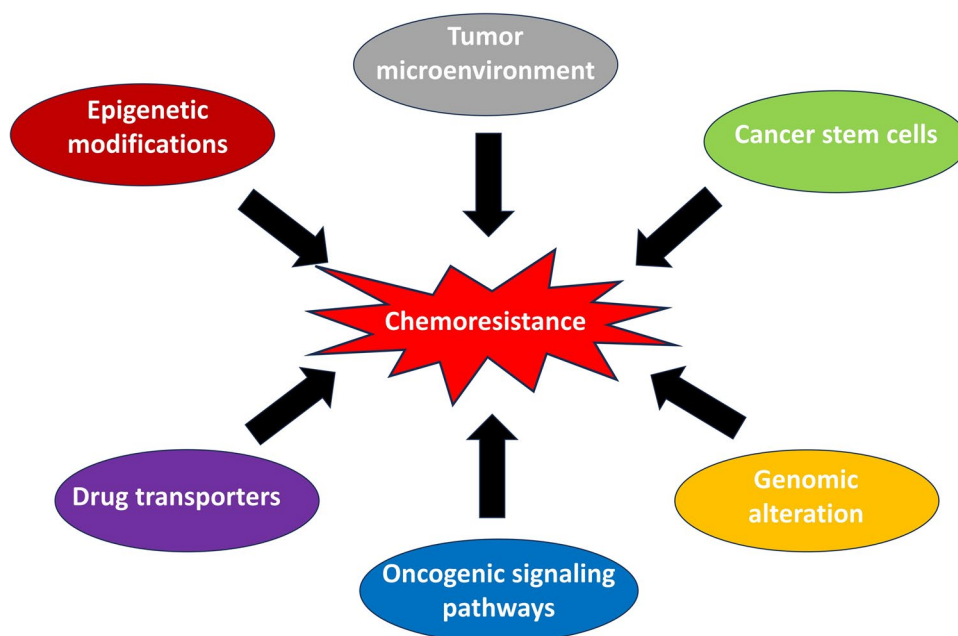


Table 1 The expression of MUC13 in a variety of human malignancies

Sr. no	Type of cancer	Role of MUC13 studied	References
1	Pancreatic cancer	Oncogenic, therapeutic target, prognosis, biomarker	[52, 56, 59–64]
2	Colon cancer	Oncogenic, metastasis	[55, 65, 66]
3	Liver cancer	Oncogenic	[58, 67–69]
4	Lung cancer	Oncogenic,	[70]
5	Renal cell carcinoma	Prognosis, chemoresistance	[71, 72]
6	Gastric cancer	Oncogenic, differentiation marker	[73–75]
7	Esophageal carcinoma	Prognosis	[76]
8	Glioblastoma	Oncogenic	[77]
9	Ovarian cancer	Oncogenic, prognosis	[54, 72, 78]
10	Cutaneous melanoma	Serum biomarker	[58]

alignment (MSA) was performed for better sequential elucidation of these forms of MUC13. The short of MUC13 having three functional domains while long form having five functional domains.

The presence of cytoplasmic domain in long form of MUC13 could be a main reason of tumorigenic effect. These structural and sequential features confirm the significance of MUC13 as a potential oncogene [79].

4 Oncogenic expression of MUC13 in various cancers

Prior research has suggested the significance of MUC13 overexpression in a number of malignancies [41–47, 80] (Table 1). MUC13 has gained attention for its potential use in prognostic applications. Studies have utilized datasets from The Cancer Genome Atlas (TCGA) to investigate MUC13 correlation with patient survival in different types of cancers. Higher levels of MUC13 expression in tumor tissues have been linked to poorer patient outcomes, such as reduced overall survival or disease-free survival rates in stomach, esophageal, and lung adenocarcinoma [80]. Dai and colleagues explored the protein expression profile of MUC13 in liver cancer (HCC) and examined its relationship with cell survival pathways [54]. They ultimately observed that MUC13 is significantly overexpressed in HCC tissues. They illustrated that the overexpression of MUC13 was strongly correlated with the size of the tumor, stage, invasion, and encapsulation. From this, it is evident that MUC13 interacts with several cell survival signaling pathways to promote the proliferation and invasion in various cancers [41–47]. In a similar manner, functional assays have shown that MUC13 possesses strong oncogenic activity in liver cancer. Interestingly, Axin2 levels are modulated with MUC13 overexpression. It is assumed the cytoplasmic tail of MUC13 is involved in β -catenin nuclear localization. The clinical significance of MUC13 in liver cancer was also

analyzed. It was observed that out of 119 patient samples, 51 samples had high MUC13 expression (42.9%). Furthermore, the expression of MUC13 has been associated to the number of copies of HBV and poor overall survival. A conducted ROC curve showed that in liver cancer, the connection of MUC13 upregulation and localized β -catenin has a stronger prognostic potential than alone. Emerging research for the potential of MUC13 in biomarker studies was performed by Fillppou and colleagues [52]. By employing ELISA assay, they performed an unprecedented quantification of serum MUC13 in healthy and liver cancer patients and observed a significantly elevated level in patients with liver cancer. These findings suggest that MUC13 holds promise for its use in prognostic applications. Moreover, further study is needed to determine the correlation of MUC13 in stage specific pathogenesis of various cancers.

4.1 MUC13 in pancreatic cancer

The prevalence of pancreatic cancer is abundant and is associated with extremely poor prognosis. Early diagnosis of this disease can be rather difficult to fulfill due to common misdiagnosis and lack of early representation [61]. In pancreatic cancer, MUC13 is aberrantly expressed and involved in tumor progression through various mechanisms such as *HER2*, *PAK1*, *ERK*, and *Akt* [57, 59] (Fig. 3). Recent studies suggest that upregulation of MUC13 increases cell growth, invasion, and migration of pancreatic cancer cells, which can be further enhanced by the addition of lactate [57, 59, 60]. Furthermore, MUC13 enhances glucose metabolism in cancer cells [60]. In another study, the tumor suppressor miR-145 was found to be associated with MUC13 upregulation in pancreatic cancer (Fig. 3). In short, the expression of miR-145 leads to the downregulation of MUC13, resulting in moderate growth of tumor cells [56]. MUC13 caused significant biophysical alterations in pancreatic cancer cells, and these cells displayed the distinctive phenotypic changes observed in prior research conducted from our lab.

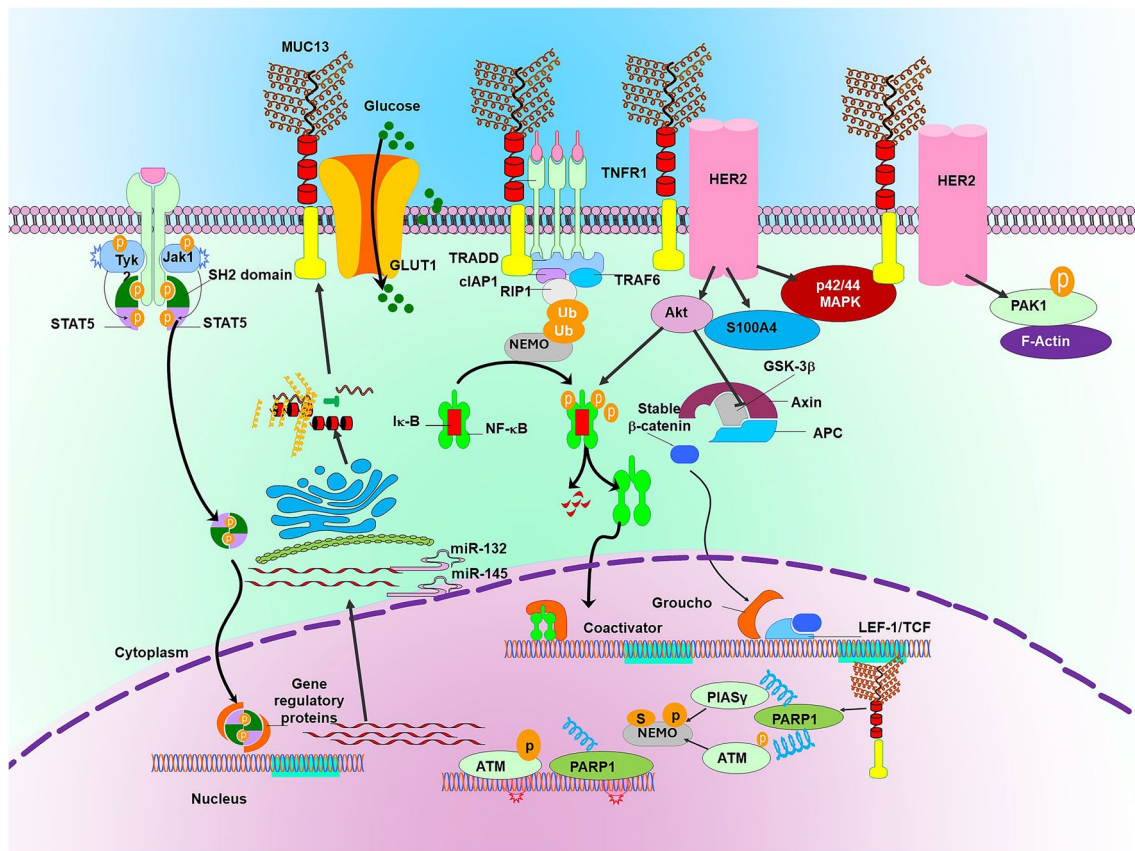


Fig. 3 Functional interaction of MUC13 glycoprotein with cell survival signaling pathways. HER2, human epidermal growth factor receptor 2; TNFR1, tumor necrosis factor- α receptor 1; TYK2, tyrosine kinase 2; JAK1, Janus kinase 1; TRADD, tumor necrosis factor receptor 1-associated death domain protein; RIP1, receptor-interacting protein kinase 1; TRAF6, TNF receptor Associated Factor 6; MAPK, mitogen-activated protein kinase; PAK1, p21-activated

kinase 1; GSK-3 β , glycogen synthase kinase-3 β ; APC, adenomatous polyposis coli protein; IK- β , inhibitor of nuclear factor kappa B; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; ATM, ataxia-telangiectasia; PARP1, poly[ADP-ribose]polymerase 1; NEMO, mediator of cell motility; PIA, polymorphism interaction analysis; LEF-1/TCF, lymphoid enhancer factor 1/T cell factor; miR, microRNA

This study sheds light on the potential utility of biophysical measurements in cancer diagnosis and monitoring, as well as in elucidating the mechanistic consequences of genetic modification [61]. MUC13 expression was found in 94.6% of pancreatic ductal adenocarcinoma samples and 100% of pancreatic intraepithelial neoplasia (PanIN) lesions. In contrast, MUC13 expression was found to be low in tumor-adjacent tissues and to be faint or absent in normal pancreatic tissues. Positive correlations were found between nuclear MUC13 expression and nodular metastasis ($P < 0.05$), malignant intrusion of peripheral tissues ($P < 0.5$), and poor survival of patient ($P < 0.05$; prognostic AUC = 0.9) [59]. Intraductal papillary mucinous neoplasms (IPMN) were found to have higher MUC13 activity than non-mucinous cysts. This study indicates that MUC13 could serve as a diagnostic marker for distinguishing between low and high risk IPMNs [63]. Additionally, our recent integrative big transcriptomic analytic data suggests important function for MUC13 in pancreatic cancer. In a cohort of 179 tumors and

171 normal samples, MUC13 was observed to be a highly expressed gene with 3.73 log₂ fold change and 92 ranked out of all upregulated genes [79]. The pairwise gene correlation analysis of MUC13, MUC1, and S100A4 shows a strong positive correlation. This analysis indicated that the MUC13 isoform analysis contained a total of 05 transcripts. Only two of the five transcripts—long and short—are protein-coding transcripts. It is intriguing to note that the long form of MUC13 was much more common in tumors than the short form [79]. The prognostic implications of MUC13 in cancer have sparked controversy, as various studies present contrasting findings. Thompson et al. [81] reported a study showing that higher expression of a specific splice variant of MUC13 is associated with significantly longer survival in pancreatic cancer. Contrary to these findings, other research groups have demonstrated that MUC13 expression is linked to a more aggressive phenotype in pancreatic ductal adenocarcinoma (PDAC) cell line models. The disparate findings may be attributed to various factors, including unique

post-translational modifications such as glycosylation on the MUC13 protein or cytoplasmic tail-mediated mechanisms. These factors could influence the functional status of the MUC13 protein during tumorigenesis, leading to different outcomes in terms of survival and disease progression.

4.2 MUC13 in colon cancer

Less than 20% of colorectal cancer patients survive five years [82]. Studies suggest that the overexpression of mucins can lead to catastrophic diseases such as cancer [83, 84]. As discussed, mucins play a significant and invasive role in many cancers, and colon cancer has shown to be one of these [83, 85]. In colorectal cancer, MUC13 is frequently upregulated and shows abnormal localization [86]. This overexpression of MUC13 increases tumorigenesis and metastasis [55]. Moreover, the upregulation and aberrant localization of MUC13 may prevent cancer cells from adhering to the cell's extracellular matrix and promote cell motility and invasion; therefore, indicating that MUC13 showing a dissatisfying involvement in colorectal tumorigenesis and metastasis [86, 87]. Furthermore, we recently reported the broad significance of MUC13 and YAP1 in colorectal cancer metastasis by targeting YAP1. Anchorage-independent circulating tumor cells gain a significant survival advantage *via* a novel molecular mechanism that is MUC13-YAP1 driven, resulting in efficient extravasation and aggressive cancer metastatic spread at unique peripheral sites [88].

4.3 MUC13 in stomach/gastric cancer

Gastric cancer, the fourth most leading cause of cancer deaths worldwide, also exhibits poor prognosis [89]. The 5-year survival rate for patients diagnosed with this disease is 33% since the representation of stomach cancer can easily be mistaken for indigestion or heartburn. In result, stomach cancer is often diagnosed in its advanced stages leading to catastrophic outcomes [90]. The expression level of MUC13 in gastric cancer tissues is notably higher than in normal tissues. Research demonstrates that MUC13 expression in gastric cancer tissues is considerably upregulated; however, results also indicate that decrease of miR-132 leads to an increase of MUC13 expression and elevated levels of HER2 and phosphorylation of ERK and Akt in gastric cancer cells [74]. Moreover, the overexpression of MUC13 enhances cell invasion, migration, HER2 levels, and phosphorylation of ERK and Akt.

4.4 MUC13 in liver cancer

Liver cancer, a fast spreading disease that continues to affect many individuals throughout the USA annually, seems to have an ever-rising mortality rate [91]. It has been noted

that the rate of liver cancer-related mortality is chronically transcending other cancers [92]. Hepatocellular Carcinoma (HCC), as briefly mentioned, is the main subtype of liver cancer responsible for many deaths in the USA [93]. Studies have shown that MUC13 is significantly overexpressed in HCC tissues [69]. The overexpression of MUC13 is significantly involved in various assays such as tumor growth, vascular invasion, and encapsulation. Furthermore, MUC13 also plays a pivotal role in oncogenic activity thus encouraging cell proliferation, migration, and invasion in HCC tissues [69]. While it has been suggested that MUC13 overexpression is a major factor in the onset and spread of hepatocellular carcinoma (HCC), its exact function in this process is still unknown [69]. Another study indicates that abnormal hypermethylation-induced downregulation of miR-212-3p leads to an increase in the expression of MUC13 in intrahepatic cholangiocarcinoma (iCCA). This upregulation in MUC13 activates the EGFR/PI3K/AKT signaling pathway, thereby promoting metastasis [68]. Nevertheless, an adequate amount of research is needed to better apprehend the role of MUC13 in the pathological processes of liver cancer.

4.5 MUC13 in ovarian cancer

Ovarian cancer, specifically epithelial ovarian cancer, is another type of cancer associated with poor diagnosis, with 5-year survival rates of less than 45%, making it the eighth most prevalent cancer-related mortality and seventh-most frequent cancer in women [94]. To challenge this, studies are striving to find methods in which to identify ovarian cancers in their beginning stages. As such, the identification of a biomarker would aid in achieving this goal. MUC13, as explored with multiple other cancers, has been identified to show a positively correlated trend with the expression of ovarian cancers [95]. To explore this, our team produced clone PPZ0020, a monoclonal antibody, to verify the general expression and chemical characteristics of MUC13 in ovarian cancer. Utilizing tissue samples of ovarian cancer, epithelial ovarian cancer, benign tumor growths, and normally functioning tissue, the study found the expression of MUC13 to be notably greater in the tissues affected with cancer [54]. Furthermore, the expression of MUC13 was especially prevalent in epithelial ovarian cancer, further supporting the initial notion that MUC13 shares a positive trend with ovarian cancer. Interestingly, the addition of MUC13 into SK-OV-3, a void ovarian cancer cell line, initiated molecular characteristic changes, such as the separation of cells through a depletion of cell–cell adhesion molecules. This resulting data suggests the functional effects of MUC13 in ovarian cancer and SK-OV-3 has great potential in being a successful indicator of ovarian cancer [54].

4.6 MUC13 in glioblastoma

A recent study exploring the role of MUC13 in glioblastoma, an extremely deadly cancer with very poor prognosis, supports the notion that the overexpression of MUC13 relates to cancerous activity. More specifically, it was observed that its overexpression resulted in the increase in glioblastoma stem cell migratory capabilities. As a result, the metastasis of glioblastoma was greatly magnified. Additionally, it was noted that the expression of MUC13 heightened the phosphorylation of protein kinase B and P38 mitogen-activated protein (MAP) kinase. This idea was further supported by the censorship of MUC13 expression in the system, which resulted in the suppression of protein kinase B and P38 MAP kinase phosphorylation. The levels of MUC13 expression were regulated through the presence and absence of upstream stimulatory factor 1 (USF1), which binds to the MUC13 promoter region. The relationship between MUC13 and USF1 was noted to be positively correlated, which explains the increased expression of MUC13 upon the addition of USF1. Overall, this study further adds to and supports the novel concept that MUC13 expression is directly related to cancerous activity [77].

4.7 MUC13 in renal cell carcinoma

A recent study perceiving the role of MUC13 in renal cell carcinoma (RCC), a cancer that affects many individuals annually with poor prognosis and chemoresistance, proclaims that MUC13 plays a potential role in therapeutics and prognosis of RCC. Although early presentation of this disease is unlikely, due to late presentation and screenings, activation of MUC13 may have a potential role in the detection and prognosis of RCC and clear cell RCC (ccRCC)—a main subtype that affects more than 75% of the population annually. Through clinical trials, they observed that high expressions of MUC13 are related to worse overall survival than lower MUC13 expressions [71]. Furthermore, high expressions of MUC13 are present in stage 1 tumors with even more expression in stages 2–4 tumors; however, stage 1 patients who express more MUC13 show a considerably lower survival rate than those who express less MUC13. Overall, they concluded that lower survival rates are associated with upregulation of MUC13. Patients with high MUC13 expression had a 5-year survival rate of 51%, while those with low MUC13 expression had an overall survival rate of 86% [71].

4.8 MUC13 in lung cancer

Lung cancer is a highly aggressive malignancy and the leading cause of cancer-related deaths worldwide [96, 97]. In a study conducted by Yao Pang et al. in 2021 [70], the

expression levels of MUC13 were investigated in lung tumor tissues and adjacent normal tissues. The researchers utilized RT-qPCR to analyze the expression levels of MUC13, and reported that MUC13 levels were significantly higher in the lung tumor tissues compared to the adjacent normal tissues. Further examination through Western blotting confirmed that the protein expression of MUC13 was also increased in the lung tumor tissues compared to the adjacent normal tissues. To validate these findings, MUC13 expression was assessed in 526 cancer samples and 59 normal samples obtained from patients with lung adenocarcinoma using datasets. Immunohistochemistry (IHC) analysis revealed an upregulation of MUC13 expression in the lung tumor tissues compared to the adjacent normal tissues. These findings suggest that MUC13 expression levels are abnormally elevated in lung cancer.

5 Unraveling influence of MUC13 on drug/chemo-resistance: a barrier to effective cancer treatment

Chemotherapy resistance occurs when cancer cells can endure and even thrive despite of chemotherapy exposure. Tumor-specific features in each patient influence this failure, ultimately dictating resistance and cancer growth in unanticipated. Chemotherapeutic drug resistance is the leading cause of relapses and low survival rates in cancer patients, despite recent breakthroughs in cancer therapy. Many of the drugs that are used to treat the severe forms of cancer have been demonstrated to have developed resistant to therapy. Resistance of metastasis cancer to chemotherapeutic compound is responsible for 90% of all failed cancer treatments, making it a significant barrier to cancer care [5]. For instance, it has been proven that breast cancer re-occurrence is driven by resistance to treatment with doxorubicin, paclitaxel, 5-fluorouracil, cyclophosphamide, and carboplatin, which is linked with a poor outcome and shortened survival time [6–13].

5.1 Intrinsic and acquired resistance

Multiple clinically relevant factors and their mechanisms of action have been described (Fig. 2). Intrinsic resistance and acquired resistance are the two main types of resistance. When tumor cells already have a resistance to chemotherapy medications before a patient starts treatment, this is called intrinsic chemoresistance [98]. Numerous elements affect intrinsic chemoresistance. To begin, chemoresistance may be caused by a tumor's innate genetic alterations. The KEAP1-NFE2L2 pathway is one such example; it controls redox and metabolic balance. Overexpression of NFE2L2 may come from mutations in these genes, which can cause

resistance to chemotherapeutic treatments. Lung, breast, bladder, ovarian, and liver cancers are only some of the many forms of malignancy that have been linked to these alterations [99–102]. Also, contributing to intrinsic chemoresistance is the fact that tumor cell populations tend to be rather diverse. Cancer stem cells (CSCs) that make up a tiny fraction of cancer cells are notoriously difficult to kill with chemotherapy. Recurrence of cancer and poor clinical outcomes may result from the enrichment of these CSCs after therapy [103–107]. Thirdly, chemoresistance might be facilitated by the stimulation of intrinsic mechanisms in tumor cells [108]. Multiple oncogenic signaling pathways, including mitogen-activated protein kinase (MAPK), hedgehog, PI3K/Akt, nuclear factor kappa B (NFkB), and notch, have been linked to the development of treatment resistance in malignant tumors. Angiogenesis, cell proliferation, drug distribution, apoptosis, and survival are all impacted by their activation [109]. Finally, pharmacological factors might play a part in the emergence of chemoresistant conditions. Chemotherapy efficacy may be diminished by a number of factors [110]. These include inadequate amounts of drugs at the tumor location, changed target molecules, and modifications to drug absorption, distribution, metabolism, or excretion. Drug resistance may develop when certain drug transporters, such as MRP1 and LRP, actively remove medicines from tumor cells, resulting in reduced intracellular drug concentrations [111]. In order to optimize treatment options and reduce hazardous side effects, knowing the causes of intrinsic chemoresistance is crucial for early detection of drug resistance. Personalized therapy techniques may enhance patient outcomes by identifying the individual resistance mechanisms in a patient's tumor cells [112].

Acquired chemoresistance refers to the development of resistance to chemotherapy drugs after treatment has been initiated. This type of resistance is characterized *via* emergence of treatment resistant cell populations and a reduction in the effectiveness of the anticancer therapy. Several mechanisms contribute to acquired chemoresistance. One mechanism is the mutation of drug targets. Changes in the genes encoding the targets of chemotherapy drugs can render them less susceptible to the drugs, reducing their effectiveness. Proto-oncogene stimulation is another process which may result in abnormal growth and proliferation of cells. When these genes are turned on, it results in the emergence of chemotherapy drug resistance [4, 14]. Alterations in the microenvironment of the tumor may also contribute to acquired chemoresistance. The microenvironment can provide a protective niche for cancer cells, allowing them to evade the effects of chemotherapy drugs. Furthermore, histone modification, DNA methylation and miRNA expression, epigenetic modifications can contribute to acquired chemoresistance. These changes can affect the activity of genes associated with drug response, either by activating

oncogenes or inhibiting tumor suppressor genes [113]. Chemoresistance can also result through modifications to DNA repair processes, disruptions to apoptosis, and changes in the cell cycle and its checkpoints [114]. Acquired chemoresistance is also linked to non-coding RNAs, particularly lncRNAs and miRNAs. Dysregulation of these RNA molecules may impact the synthesis of proteins involved in drug resistance [114–120].

5.2 Significance of MUC13 in key chemoresistance signaling pathways

CSCs' carcinogenic characteristics necessitate several developmental pathways that were previously connected to the regulating of normal stem cells [121]. Among these, EMT and CSCs exhibit dysregulation of the WNT pathway [122]. Although colorectal malignancies were the first to show mutations in WNT signaling molecules such as β -catenin APC, AXIN, and WNT ligands, but these changes have been discovered in other varieties of solid tumors [123–129] and hematologic cancers, like multiple myeloma and leukemia [130–132]. To defend themselves from and resist chemotherapy treatments, cancer stem cells evolve drug resistance mechanisms. [121, 133]. In addition to the ways of understanding tumor heterogeneity, two distinct approaches accounted for the development of cancer chemotherapy resistance. Stem cells, including CSC, demonstrate high levels of ABCB1 and ABCG2 expression, the two major MDR genes [133]. Moreover, the human ABCB1 gene promoter has many TCF4/LEF binding domains, rendering it a targeted gene for the β -catenin and TCF4 transcriptional factors. The WNT/ β -catenin circuit is linked to chemoresistance, as evidenced by the fact that β -catenin stimulation elevates ABCB1 expression.

In addition, a number of studies have shown that there is a relationship between this and the development of a multidrug resistant phenotype in tumor cells [134, 135]. This protein, along with other members of the family, has a physiological function in the blood–brain barrier *via* transporting substances through the placenta, gut, and another sites [136]. Additionally, these kinds of transporters effectively efflux xenobiotics to protect the cells from harmful compounds [133, 137]. Several solid tumors and hematological cancers develop chemoresistance due to their ability to expel drugs from cancer cell [122, 138, 139]. ABCB1 enables the development of multi drug resistance character because it may entangle and expel wide variety of medicines, hence causing treatment futility and tumor recurrence. Additionally, these proteins promote cell growth, invasion, and dysregulation of the pathways involved in apoptosis or complement-mediated cell toxicity [138–143] as well as transport ABC proteins to intracellular or extracellular regions to enhance product retention to enhance drug retention [144, 145].

Accumulating studies suggest that MUC13 expression has been linked to tumor differentiation. For example, MUC13 is especially upregulated in pancreatic neoplasms, in comparison to undetectable or poor expression in the normal pancreas [52]. In a similar vein, comparable expression, and localization trends of MUC13 were also seen in malignant and non-malignant colon cancer samples [65]. MUC13's cytoplasmic/nuclear localization may contribute to colon cancer's growth, progression, and spread to distant sites. MUC13 expression was shown to vary between the linked colorectal cancer cells SW620 and SW480. Two types of cells were taken from a diabetic patient: non-metastatic SW480 cells and metastasized SW620 cells from the patient's lymph node metastatic lesion 1 year later [146]. This strongly suggests that MUC13 may contribute to the colon cancer growth. These findings are consistent with our lab reports demonstrating that MUC13 is expressed more often and is localized abnormally in colon cancer tissues [65].

Our laboratory has demonstrated the molecular signaling pathways that control MUC13 regulation, such as the JAK2/STAT5 pathway [55] (Fig. 3). In renal cancer, high expression of MUC13 was shown to have a positive correlation with increased Fuhrman grade, a pathological grading of renal cell cancers, and with reduced overall survival. Following surgery, increased MUC13 activation was identified as a novel distinct risk factor for the clinical prognosis of non-metastatic clear cell renal cell carcinoma [147]. Additionally, silencing of MUC13 in combination with multi-kinase inhibitors, sorafenib, and sunitinib has showed enhanced sensitization of renal carcinoma cells to respond to the therapy [71], thus indicating the function of MUC13 in chemosensitivity. Moreover, research conducted in our laboratory has proven that upregulation of MUC13 is related with increased activity of HER2 in pancreatic cancer [52]. This was elucidated further in our follow-up investigation, which indicated that MUC13 functions as a ligand for HER2 and activates key oncogenic signaling pathways in pancreatic cancer [57]. In a different investigation, our lab identified that miR-145 plays a tumor suppressor role in a tumor-promoting network that also contains MUC13 [148]. Therefore, our lab further developed a novel formulation of miR-145 that restores miR-145 levels in cells and inhibits MUC13 [149]. These studies affirm that MUC13 is a very important oncogenic target in pancreatic cancer, the therapeutic strategies against which warrants suppressing tumorigenic and metastatic phenotypes of pancreatic cancer cells. MUC13 overexpression has been also observed in hepatocellular carcinoma and associated with poor outcomes. An interesting study shows that c-myc and cyclin D, the downstream effector of Wnt/ β -catenin signaling cascade, were found positively correlated with MUC13 levels. High β -catenin nuclear transition was found correlating with enhanced MUC13 overexpression, while

the regulatory downstream targets of β -catenin decreased following MUC13 silencing/inhibition [69]. In addition, we and other researchers have defined how MUC13 works in ovarian cancer. Expression and functional studies conducted by our laboratory on MUC13 in ovarian cancer have demonstrated its direct correlation with this disease. Moreover, we found that its overexpression significantly impacts cellular characteristics [54]. All the studies discussed above are consistent with other studies that suggest the vital aspect of MUC13 upregulation in tumors development, including ovary [54, 150], gastric [73, 151], liver [69], colon [55], and pancreatic cancer [56, 57, 149, 152].

6 Implications of MUC13 in cancer stem cell plasticity in maintaining tumor heterogeneity

Cancer stem cells, also known as CSCs, play an important part in the development of intrinsic chemoresistance in a variety of cancer types. These cells make up a small subset of the cancer cells that have undergone terminal differentiation. Following therapeutic treatment, this particular subset of cells becomes predominant in a wide variety of malignancies. For instance, breast cancer stem cells exhibit characteristics such as quiescence, increased DNA repair, overexpression of drug efflux transporters, self-renewal and differentiation, and immune system evasion. These characteristics facilitate cancer invasion, metastasis, and recurrence in patients following chemotherapy, which ultimately accounts for the unfavorable clinical results, increased mortality, and chemoresistance in patients with breast cancer [106, 107]. Cell plasticity describes how a cell can be reprogrammed to develop an alternative fate in response to internal or external influences [153, 154]. Stem cells' plasticity allows them to self-renew and transform into a variety of cell lineages. The ability of terminally differentiated cells like fibroblasts to revert to pluripotency reveals that plasticity is not limited to stem cells [155, 156]. Cancer cells exhibit plasticity through dedifferentiation, trans-differentiation, and EMT, when epithelial cells shift to a mesenchymal phenotype and lose features including cell–cell junctions and polarity [157] (Fig. 3). Plasticity and therapy resistance are two significant challenges in cancer treatment. They pose a major obstacle to successful treatment of cancer, especially in cases when it has spread (metastatic setting). These challenges are accountable for 90% of treatment failures [5]. There are two basic types of drug resistance: inherent, which occurs even before a drug is given to the patient, and acquired, which develops during therapy. Therapeutic treatments are assumed to only eliminate cancer cells that are actively proliferating, but CSCs stay impotent and persist. Resistance to therapy, tumorigenesis, tumor heterogeneity,

tumor recurrence, and metastasis have all been linked to cancer stem cells (CSCs) [158, 159]. The mechanisms that allow CSCs to elude chemotherapy are not fully understood currently. This has been revealed that while most chemotherapy drugs destroy the majority of tumor cells, CSCs typically persist and develop following chemotherapy [20]. For instance, treatment of temozolomide enhances glioma stem cells in patient-derived cell lines but kills differentiated GBM cells [160]. Studies have shown that MUC13 expression enhances the CD133 + /CD44 + self-renewing CSC populations. It is notable that CSC populations have a vital impact in inducing chemoresistance and tumor recurrence [161]. Of note, MUC13 knockdown decreased the CD133 + /CD44 + population's relative abundance and, more specifically, the enrichment of CSC that occurs after 5-FU therapy. Difference in CSC survival between MUC13-expressing and MUC13-deficient cells is paving a new way for combination therapy for involving the MUC13 siRNA along with available chemotherapy [71]

7 Role of MUC13 and epithelial to mesenchymal transitions (EMT)

Trans differentiation processes known as epithelial to mesenchymal transitions (EMT) is necessary for tissue morphogenesis in the developing embryo. According to recent research, EMT can trigger the formation of CSCs by sending signals to tumor stromal components. During the growth of tumors, oncogenically altered cells have the ability to override these developmental pathways [162]. Importantly, EMT has the unique ability to cause reversal to a CSC-like phenotype [163, 164], demonstrating a connection between therapy resistance, CSCs, and EMT. EMT is a developmental process that has been conserved throughout the process of evolution [165]. Through the process of EMT induction, pathophysiological events like tissue injury or cancer can cause differentiated cells to adopt on the characteristics of multipotent stem cells. This could reflect developmentally controlled EMT signaling pathways, which promote normal and CSC formation and regeneration [166–168]. Based on particular studies, cancer cells that have undergone EMT and have spread to distant sites may also have the characteristics of a CSC [169]. It is interesting to note that CD44 is a promising candidate for both β -catenin and TCF-4, which lends support to the notion that the EMT-associated Wnt pathway linked in the upkeep of CSCs [170]. Mesenchymal-like cells with the CD133 + chemokine receptor predominate in the intrusive front of pancreatic cancers, which may ready them for metastatic dissemination [171]. There are reports suggesting that alterations in cell adhesion properties caused by MUC13 can promote the invasion and spread of cancer [52, 54]. The extracellular tandem repeat domain of MUC13

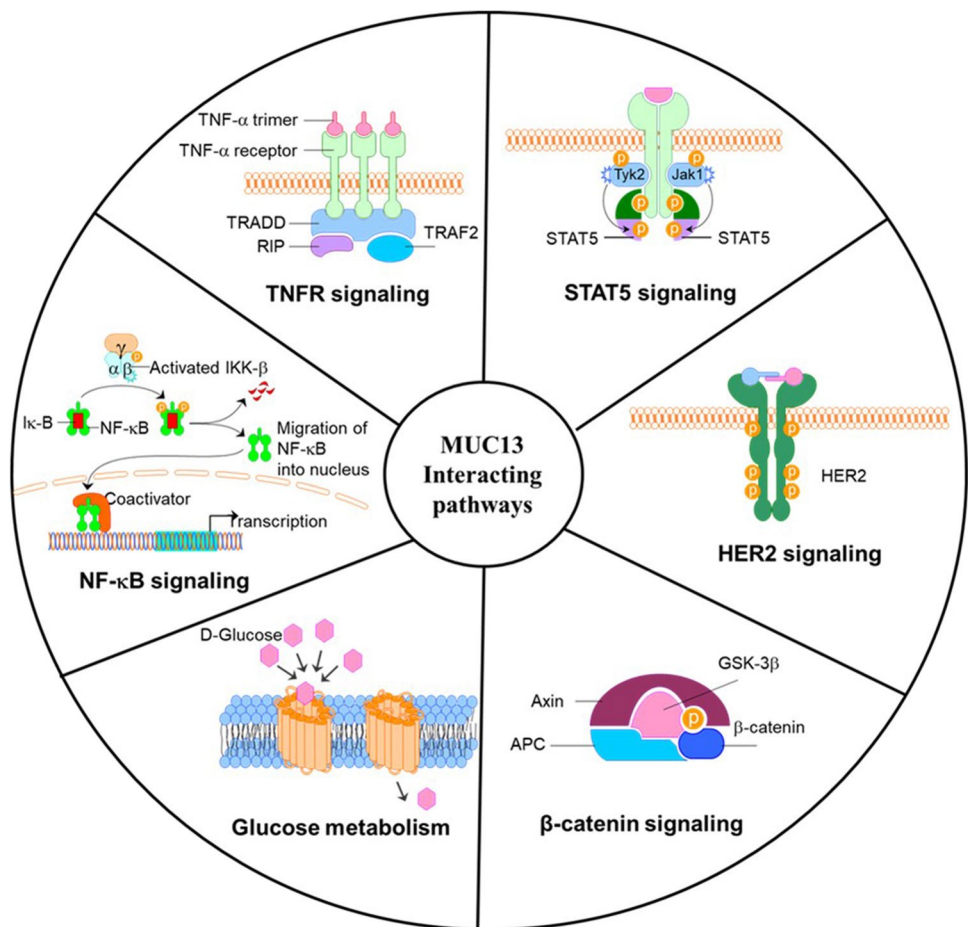
is highly glycosylated and contribute to anti-adhesiveness property of cells [34, 51]. Notably, MUC13 overexpression in pancreatic carcinoma reduced cell–cell and cell–matrix adhesion.

Our findings provide valuable information about how MUC13 influences the growth of pancreatic cancer by modulation of PAK1 and S100A4. PAK1 upregulation promotes cell migration and controls the actin cytoskeleton during motility in HCC, breast, and colon cancer cells [172, 173]. Of note, S100A4 has also been linked to metastasis and invasion [174, 175]. Similarly, MUC13 overexpression in ovarian cancer decreased cell–cell interaction, increased cell migration, and facilitated F-actin reconfiguration. In order to migrate, a cell must form cell membrane projections with actin filaments and a continuous phase of actin polymerization near its prominent surfaces [176]. MUC13 localization in the basal area and along the basement membrane in ovarian cancer cells has been confirmed to promote ovarian cancer cell detachment from the primary location, as well as tumor cell invasion into ovarian stromal tissue [54]. These results indicate a clear correlation between MUC13 and enhanced cellular motility.

8 Role of MUC13 in tumor cell metabolism

Accumulating studies suggest that the impact of Warburg effect, occurs when cancer cells increase their aerobic glycolysis, establishes an acidic micro-environment that encourages invasion of tumor cells in the surroundings area [177]. Furthermore, the Warburg effect is primarily influenced by glucose, and Glut-1 increases the cellular glucose transport essential to drive anaerobic metabolism in developing tumor cells. Enhanced lactate synthesis, on the other hand, increases tumorigenic characteristics including cell invasion, proliferation, which metastasis, and is linked to tumor recurrence [178]. Importantly, cancer cells develop an oncogene addiction, making them extremely reliant on an oncogene's action for survival and proliferation [179]. We have reported MUC13's novel function in pancreatic cancer metabolic reprogramming [60]. We demonstrated that MUC13 alters cancer cells' metabolism and the fundamental molecular pathways that underlie the tumorigenic features. Additionally, we discovered for the first time a substantial relationship between MUC13 and Glut-1 in patient tissue samples (Figs. 3 and 4). This indicates that MUC13 plays an important role in the tumor microenvironment, which promotes the growth of a more violent and invasive phenotype. Though more research is needed, we anticipate that a MUC13 cytoplasmic domain interacts to Glut-1 since the MUC13 cytoplasmic domain is believed to have a function in cell signaling. Low survival rates and poor outcomes are linked to hypoxia in the tumor environment, which typically

Fig. 4 Schematic illustration of oncogenic signaling pathways augmented by MUC13 in variety of malignancies. MUC13 modulates TNF- α , STAT5, HER2, Wnt/ β -catenin, glucose metabolism, and NF- κ B signaling pathways



occurs in later stage of cancer [180, 181]. A growing body of research has revealed that hypoxia can trigger the invasion, metastasis, and epithelial-mesenchymal transition of cancer cells, hence fostering stem-like properties in these cells [182, 183]. HIF-1 is essential for regulating CSCs through controlling the transcription of specific genes. It also contributes to tumor growth, evasion of the immune system, metabolic reprogramming, and resistance to drugs [181, 183, 184]. According to studies, HIF-1 has been linked with the development of CSCs. It has been reported that the production of various stem cell markers, such as Krüppel-like factor 4, OCT4, SOX2, and NANOG, can be promoted by HIF-1 [185–187]. Additionally, by inhibiting the production of stem cell markers, HIF-1 silencing can slow the spread of cancer. Low survival rates and poor outcomes are linked to hypoxia in the tumor environment, which typically occurs in later stage of cancer [188]. It has been discovered that HIF-1 directly binds to the CD47 promoter in order to enhance gene transcription. This serves in avoiding macrophage phagocytosis and retaining the stem phenotype of breast CSCs [184, 189]. The promoter of CD24 is recruited by endogenous HIF-1, which enhances CD24 activity and also tumor development and metastasis [190]. HIF-1 α interacts

with the CD133 promoter, activating CD133 + glioma, colorectal, and pancreas CSCs through OCT4 and SOX2 [188, 191–194]. Angiogenesis, tumorigenesis, immunological response, cancer metastasis, and recurrence, as well as EMT progression and CSC formation, are all controlled by hypoxia [188, 189, 195]. Determining the methods via CSCs develop and sustain stemness may assist in overcoming the limitations of current cancer treatments.

9 Role of MUC13 and cell PI3K/Akt signaling pathways

The mTOR and PI3K/Akt pathways are essential for numerous physiologic and pathologic situations, such as, cell growth, differentiation, metabolism, angiogenesis, and survival [196]. In most cases of human cancer, the activation of mTOR is often regulated incorrectly. Among ovarian malignancies, for instance, the PI3K/Akt/mTOR pathway is active in around 70% of cases [197]. In addition, Tapia and colleagues [198] discovered that the PI3K/Akt/mTOR signaling is active in the tissues of individuals who had progressed gastric cancer, in contrast to the non-tumor mucosa

[198]. Aside from the focus on cancer cells, an increasing number of recent studies have demonstrated the connections involving PI3K/Akt/mTOR signaling and CSCs [199, 200]. Number of studies showed the role of mTOR pathway in CSC maintenance. Prostate cancer radio resistance has been linked to EMT and increased cancer stem cells characteristics through the signaling pathway of PI3K/Akt/mTOR [201]. Induction of the mTOR pathway is necessary for colony-forming ability and tumor growth in breast cancer stem-like cells [202]. mTOR inhibition may diminish the activity of ALDH1, an indicator of colon cancer stem cells [203, 204]. When mTORC2 was inhibited, the activity of liver CSC marker decreased, and hepatocellular cancer stem cells demonstrated minimal or no ability to form tumors [205]. According to Sunayama et al., cancer stem-like cells' ability to self-renew and proliferate is maintained through cross-inhibitory modulation between the MEK/ERK and PI3K/mTOR pathways in glioblastoma [206]. It has been discovered that in glioma tumor stem-like cells, Akt modulates the activity of ATP-binding cassette transporters (ABCG2) but does not control its downstream target mTOR [207]. The PI3K/Akt/mTOR pathway has a clear relationship with cancer stem cells, and its components are strong candidates for potential treatment. MUC13 interacts with cell-survival signaling pathways both actively and implicitly, leading to cell survival and proliferation. Ectopic expression of MUC13 was shown to have a greater capacity for colony formation and increased cellular proliferation, as well as a shorter doubling period of cells, as opposed to control cells. As a result, there were more cells in the S phase of the cell cycle. Furthermore, it was observed that increase in the proliferation was mediated by involvement of p38 MAPK pathways. Of note, ectopic expression of MUC13 leads to an upregulation of PAK1 and HER2, suggesting having a role in stabilization of EGFRs. Interestingly, it was reported that MUC13 expression also modulates the cell morphology as evident in ovarian cancer cells [54].

10 Conclusion

In conclusion, the study of MUC13 and its multifaceted functions in drug/chemo-resistance and cancer cell plasticity has offered valuable insights into the complex nature of cancer progression. It is evident that MUC13 overexpression disrupts normal cellular polarity, promoting the acquisition of malignant traits and facilitating metastasis through epithelial-mesenchymal transition (EMT). Additionally, MUC13 has been found to contribute to chemoresistance, presenting a significant challenge in cancer treatment. The unraveling of the molecular complexity surrounding MUC13 opens new opportunities for targeted therapies that address these mechanisms and offer improved outcomes for patients. By

understanding the intricate biology of MUC13, researchers can develop strategies to restore cellular polarity, inhibit plasticity, and overcome chemoresistance. Further research is needed to explore this molecule's potential as a therapeutic target, while considering its intricate network of interactions within the cancer microenvironment. Ultimately, unraveling the mysteries of MUC13's role in cancer biology holds great promise for advancing our ability to combat cancer progression and enhance the efficacy of treatment strategies.

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Declarations

Competing interests The authors declare no competing interests.

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