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Original Article

Mucins in pancreatic cancer: biological role, implications in carcinogenesis and applications in diagnosis and therapy

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Abstract: Pancreatic cancer is the fourth highest cause of cancer mortality in the world. It has very low survival rates owing to late diagnosis resulting from the absence of accurate diagnostic tools and effective therapies. Hence, there is a pressing need to develop new diagnostic and therapeutic tools. In the recent years, there has been new evidence implicating the importance of mucins in pancreatic carcinogenesis. Mucins belong to a group of heavily glycosylated proteins, and are often aberrantly expressed in a number of cancers such as pancreatic cancer. Therefore, this literature review will summarise the role of mucins and mucin expression in pancreatic neoplasms. Subsequently the paper will also discuss the most recent advances in the biological properties of mucins and their role in carcinogenesis and resistance to chemotherapy. Then it will conclude on the newest developments in diagnosis and therapy based on mucins for pancreatic cancer.

Keywords: Mucins, pancreatic cancer, carcinogenesis, resistance, prognostic biomarker, cancer therapy

Introduction

Pancreatic cancer is the fourth highest cause of cancer deaths in the United States and has contributed to over 40,000 deaths in 2016 [1], despite advances in cancer diagnosis and treatment methods. 95% percent of pancreatic cancer is classified as pancreatic ductal adenocarcinoma (PDAC), and more rarely it is acinous or endocrine in origin [2, 3].

In 85% of cases, PDAC arises from pancreatic intraepithelial neoplasia (PanIN), categorised into PanIN 1A, PanIN 1B, PanIN 2 and PanIN 3. The remaining 15% arises from intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN) [3-5].

Survival is poor, as the 5-year survival rate is less than 5% [6], whilst the median survival is less than 6 months. Surgery is the primary treatment, however only a minority are eligible for this treatment as 80% of patients have either metastatic or locally advanced tumours at diagnosis, leaving chemotherapy and radiotherapy with palliative intent as the only option [3, 5, 7-9]. Although the standard chemotherapy drug used is gemcitabine, less than 30% of patients respond to the treatment due to resistance [3, 10]. Other alternative drugs include albumin-bound paclitaxel (nab paclitaxel), erlotinib or combination of leucovorin, 5-FU, irinotecan and oxaliplatin (FOLFIRINOX). However, these combination treatments have shown minimal survival advantage over gemcitabine monotherapy, and have serious adverse effects such as neutropenia and peripheral neuropathy [4, 10, 11]. Mucins, which are able to form a protective coat around cancer cells, are critical in the pathogenesis of pancreatic cancer, and are associated with resistance to cytotoxic drugs, invasiveness, metastases and cell proliferation. In recent years, there has been a number of studies on the irregular expression of mucins in malignancies such as pancreatic cancer and its potential as a drug target or prognostic biomarker [5]. This review aims to summarise the most recent evidence regarding the function of mucins in the development and advancement of pancreatic neoplasms.

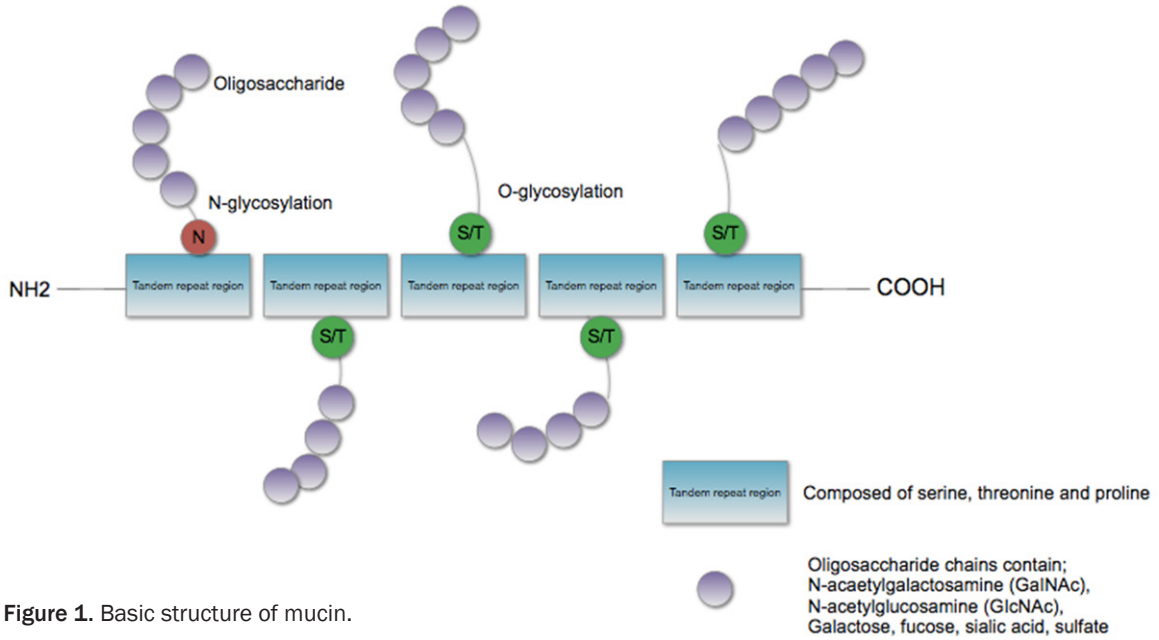

Figure 1. Basic structure of mucin.

Overview of mucins

Mucins are a family of heavy weight glycoproteins produced by the gastrointestinal, respiratory, reproductive, hepatic, pancreatic and renal epithelium [7, 12]. They consist of a varying number of tandem repeat regions prolific in proline, serine and threonine [13] with abundant oligosaccharide chains attached by either N-glycosylation or O-glycosylation to serine or threonine residues [3, 5, 14] as represented in **Figure 1**. Due to the abundance of glycans that extend out from the peptide core, mucins can extend out to 200 nm into the lumen of ducts and glands [15].

There are 21 mucin members and they can be categorised into secreted and transmembrane mucins based upon their structural and functional roles. Secreted mucins form a viscoelastic gel on the surface of apical cells to protect the epithelium from inflammation, pH changes, toxins and pathogens [13, 16]. The gel like property of secreted mucins is due to the fact that they are able to polymerize through the formation of glycosidic and disulphide bonds. The members include MUC2, MUC5AC, MUC5B, MUC6, MUC7, MUC8, MUC9 and MUC19 [17-19]. Membrane-bound or transmembrane mucins contain a hydrophobic region in the phospholipid bilayer and include MUC1, MUC3A/B, MUC4, MUC11, MUC12, MUC13, MUC15, MUC16, MUC17, MUC20, MUC21 and MUC22. They contain a number of distinguishing components such as the N-glycans, O-glycans and the functional domains of epidermal growth factor, nidogen-like domain, sea urchin sperm protein-enterokinase-agrin, von Willebrand factor D domain, cysteine knots and the cytoplasmic tail, which are able to interact with receptors, signalling molecules and the extracellular matrix [3, 5, 9, 15, 18].

Carcinogenetic significance of mucins in pancreatic malignancies

Pancreatic cancer, along with a number of other malignancies including breast, ovarian, lung and gastrointestinal, are characterised by the aberrant expression, glycosylation and localisation of mucins as they develop from normal tissue to malignant cells as outlined in **Figure 2** and **Table 1** [17, 18, 20-22]. These alterations in mucin expression confer oncogenic properties, playing a critical role in carcinogenesis, metastasis and resistance to therapy [5]. Mucins can play a variety of roles in oncogenesis, such as limiting intracellular drug uptake, antagonising drug targets, evasion of the immune system and upregulating survival pathways [15, 18, 23-27]. This is supported by a number of clinical studies that link the aberrant expression of mucins to poor clinical prognosis [15, 23-25, 28]. Healthy pancreatic tissue may express low levels of mucins such as MUC1, however histological studies show that there is

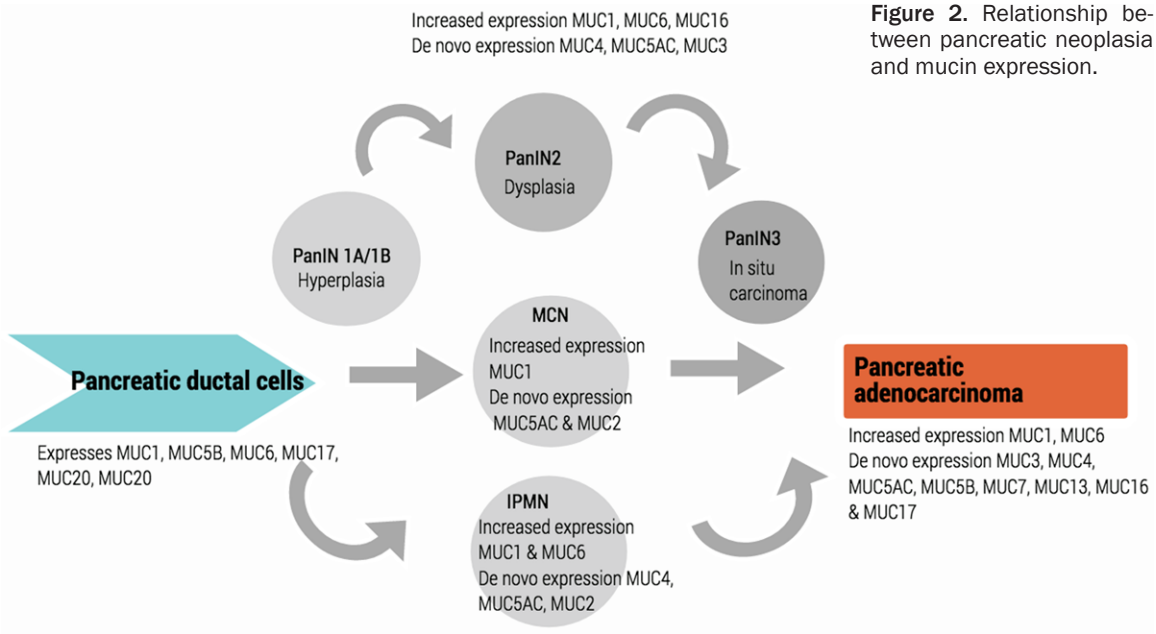

Figure 2. Relationship between pancreatic neoplasia and mucin expression.

Table 1. Degree of expression of mucins in the different types of pancreatic neoplasms, [15]*

Mucin	Normal	PanIN			PDAC	Invasive IPMN		MCN	Studies
		PanIN-I	PanIn-II	PanIN-III		Gastric	Intestinal		
MUC1	L	L	M	H	H	H	H	M	[7, 77, 97, 98]
MUC2	N	N	N	N	ND	H	H	ND	[52, 69, 99, 100]
MUC3	C	L	L	L	M	C	C	ND	[38, 60, 69, 101]
MUC4	N	L	M	H	H	M	M	H	[14, 36, 38, 41, 42, 56, 73]
MUC5AC	N	H	H	H	H	H	H	H	[14, 55, 56, 61, 64, 102]
MUC5B	C	ND	ND	ND	H	ND	M	ND	[16, 69, 99]
MUC6	L	M	M	M	H	M	M	ND	[56, 61, 69, 97, 99]
MUC7	N	ND	ND	ND	L	N	N	ND	[69, 74, 99]
MUC13	C	ND	ND	ND	H	ND	ND	ND	[54, 58, 59, 103]
MUC16	N	L	M	M	H	ND	ND	ND	[16, 17, 48, 51, 104, 105]
MUC17	M	H	H	H	M	ND	ND	ND	[38, 62]
MUC20	L	ND	ND	ND	ND	ND	ND	ND	[106]
MUC21	L	ND	ND	ND	ND	ND	ND	ND	[107]

*ND: no data is available. N = negative expression, L = low or minimal expression, M = moderate expression, H = high or abundant expression, C = contradicting studies.

neo-expression and upregulation of mucins such as MUC4, MUC5AC & MUC16 in PanIN, IPMN and MCN [15, 24, 25, 29]. Additionally major genetic mutations such as K-RAS are also implicated in alteration of mucin expression patterns [30].

MUC1

MUC1 is a 300-600 kDA membrane bound mucin expressed by both pancreatic ductal and acinar cells. MUC1 plays a variety of physiological roles in the healthy pancreas involving both cell signalling and differentiation. However, MUC1 is atypically expressed in higher than 60% of PDAC and positively correlates with tumour size and dysplasia, which may suggest that it has a pivotal role in pancreatic cancer progression [5, 7, 31-33]. In addition, there are a number of clinical studies that link greater MUC1 expression with poorer prognosis [34]. In cancer cells, MUC1 binds to Epidermal Growth Factor Receptor (EGFR), ß-catenin and NF-KB to enhance cell proliferation through the MAPK,

Akt or Wnt/ß-catenin pathways [7, 33, 35]. It also upregulates cdc-25c to increase cell division and increases the expression of glycolytic genes to enhance metabolism [14, 33]. MUC1 also activates MMP13, Stat3 and PDGFR-ß, which induce epithelial mesenchymal transition (EMT) hence facilitating metastasis [7, 18, 31]. Additionally, MUC1 inhibits apoptosis through suppressing p53 [33] and activating anti-apoptotic pathways (Akt and Bcl-xL) [7]. Furthermore, it decreases caspase-3-activation, a mitochondrial apoptotic enzyme [18, 36]. MUC1 also induces chemoresistance [4] through increasing expression of multidrug resistant genes [5, 37].

MUC4

MUC4 is a large membrane bound glycoprotein that is over expressed in the majority of pancreatic cancers, detected as early as the PanIN-IA stages [14, 38, 39]. It is an independent marker of poor clinical prognosis [10] and imparts a number of oncogenic properties. MUC4 activates a number of proliferative pathways such as MAPK, PKC and RAS-REK, all of which induces cell growth and differentiation [5, 40, 41]. Cell proliferation is also aided by the large extracellular domain of MUC4, which allows it to evade recognition by the immune system [9, 42]. Furthermore, MUC4 facilitates EMT through activating Akt, JNK/2 pathway and Src kinase and Wnt/ß catenin pathways [3, 8, 9, 14, 42, 43]. These help promote extravasation and metastasis, playing a critical role in invasive cancer [10, 44]. In addition, MUC4 allows cancer cells to evade apoptosis through sequestration of pro-apoptotic proteins and inhibition of anti-apoptotic proteins such as cytochrome C present in the mitochondria and caspase-9 [5, 18, 45, 46]. Moreover, MUC4 imparts resistance to tumour cells against gemcitabine through upregulating anti-apoptotic pathways [47].

MUC16

Similar to MUC4, MUC16 is a transmembrane mucin that is also a predictor of poor prognosis and high recurrence rate [48, 49]. However, it is expressed in both pancreatitis and pancreatic neoplasms [50], which can limit its role as a specific biomarker. MUC16 has been implicated in a number of oncogenic pathways, such as increasing nuclear translocation of JAK2 and upregulation of LMO2 to increase cell proliferation. Furthermore, it has been shown that inhibition of MUC16 decreases mTOR and c-MYC activity, both of which stimulates cell growth [17, 48]. MUC16 also helps promote metastasis through activating matrix metalloproteinase-7 and the Akt and MAPK pathways. Furthermore, it is a ligand to E- and L-selectin, which helps promote adhesion and metastases [17, 49]. Indeed inhibiting MUC16 decreases migration and survival of pancreatic tumour cells [16]. Additionally, MUC16 induces cancer cells to switch to anaerobic metabolism and also inhibits apoptosis, both of which increase survival [48, 51].

Other mucins

MUC2

MUC2 is occasionally present at low levels in healthy pancreatic tissue and IPMN, however it is absent in PDAC and MCN [5, 14]. In IPMN intestinal type, expression of MUC2 is correlated with high grade dysplasia and invasiveness [52], whilst for the IPMN gastric type MUC2 is a marker of favourable prognosis [32].

MUC5AC/AB

MUC5AC is a secreted mucin that can be overexpressed in early neoplastic lesions such as PanIN and PDAC [53, 54]. However, it is more commonly found in non-invasive IPMN and MCN [5]. As it is absent in the healthy pancreas, it is used as an indicator for distinguishing malignant from non-neoplastic cells [32]. Knockdown of MUC5AC in xenograft studies resulted in decreased growth and metastasis, suggesting it plays a role in tumour development [55]. However MUC5AC expression in PDAC and IPMN is associated with better clinical outcome [56, 57].

MUC13

MUC13 is a transmembrane glycoprotein associated with proliferation, motility, invasion and tumour growth [18, 54]. It can be expressed at low levels in the non-neoplastic pancreas, however is upregulated in pancreatic cancer as early as the PanIN stages [58]. MUC13 phosphorylates HER2 in PDAC, regulating growth, motility and differentiation of PDAC. Furthermore it activates PAK1, resulting in increased metastases [59]. MUC13 is also associated

with expression of a number of other oncogenes including ERK, Akt and S100A4 and reduced expression of tumour suppressor genes such as p53 [54].

MUC3, MUC 6, MUC15, MUC17, MUC20

Cysteine domains present in MUC3 can suppress the intrinsic apoptotic pathway and increase invasion [60]. Expression of MUC3 also correlates with the level of dysplasia in cancer cells [5, 38]. MUC6 can be present in the non-neoplastic tissue and is not associated with either clinical prognosis or outcome [5, 61]. There are limited studies on MUC15, 17 and 20, however some studies have indicated that they are increased in pancreatic cancer cell lines as compared to the healthy pancreas [62, 63].

Mucins as diagnostic biomarker in pancreatic malignancies

The unavailability of reliable biomarkers for the timely diagnosis of pancreatic cancer is a major contributor to the high mortality rates. Current available biomarkers have limited sensitivity and specificity [5, 64, 65]. Cancer Antigen 19-9 (CA-19-9) is the most widely used biomarker [66], whilst others include, pyruvate kinase isoenzyme type 2, MIC-1, CEA and CA242. However the expression of these antigens in benign conditions such as chronic pancreatitis, along with variable sensitivity and specificity limits their utility as a diagnostic tool [64, 67]. As a result, mucins have garnered attention as promising biomarkers to be utilised in the clinical setting, as certain mucins have a high specificity for pancreatic cancer cells [14, 16].

EUS-DNA and circulating tumour markers

Endoscopic ultrasonography-guided, fine-needle aspiration (EUS-FNA) is a relatively harmless method for staging and diagnosing pancreatic malignancies. In previous studies using EUS-FNA, MUC1 (CA15-3), MUC2, MUC7, MUC4, MUC16 (CA125) and MUC5AC has been shown to be overexpressed compared to benign conditions or the healthy pancreas [18, 68-71]. In EUS, the use of MUC4 and MUC16 were 100% specific in diagnosing malignant pancreatic cancer from benign conditions with 63% and 67% sensitivity [71]. Circulating tumour markers have also been explored as a potential approach. A recent study evaluating a panel of serum tumour markers (such as CA19-9, CEA, CA242, CA72-4, CA50 and CA125) has shown that MUC16 had the highest association with metastatic disease and was able to best predict recurrent disease after surgical resection [67]. To improve the diagnostic sensitivity of the CA19-9 test, it has been used in combination with mucins such as MUC1 and MUC5AC [64, 72]. Mucins have been used to predict prognosis, and elevated serum CA125 levels were strongly associated with a shorter survival time [65]. Similarly tumours that expressed a high level of MUC4 were more likely to metastasize [36, 73, 74], whereas patients with a low MUC4 expression receiving adjuvant gemcitabine treatment had a longer survival time [13]. In summary, MUC1, MUC4 and MUC16 may be able to diagnose pancreatic cancer, forecast prognosis and monitor treatment with the intention of improving patient survival.

Mucins as a therapeutic target

Since mucins play an important role in oncogenesis, immune system evasion, metastasis and chemotherapeutic resistance [75], they are a target for the development of new therapies as well as to enhance the potency of cytotoxic drugs [7, 37, 76, 77].

Agents that can affect the structural features of mucin and production of glycol-oncoproteins

Several studies have shown that the dense mucin mesh, due to heavy O-glycosylation, decreases the efficacy of cytotoxic drugs. It is postulated that the mucin forms a physical barrier thus inhibiting the intracellular drug uptake and thereby affecting cytotoxicity of the drug [78]. Hence, there has been investigation into dissolving mucin using mucolytic agents bromelain and N-acetylcysteine (NAC) [79-81]. Bromelain is a cysteine proteinase from *Ananas comosus* that is composed of thiol endopeptidases as well as other enzymes such as phosphatases, glucosidases and cellulases and is able to break the glycosidic bonds within mucin. NAC, a mucolytic agent used in respiratory conditions is able to denature the disulphide bonds in mucins through reduction reactions [19]. The use of bromelain and NAC in suitable combination, also resulted in decreased expression of mucin in vitro and in vivo. The advantage of this treatment is that they have very low toxicity profiles and also contributed to increased chemo-

sensitivity, laying the basis for its use as an adjunct to cytotoxic drugs [82].

Agents involving the immune system

Agents involving the immune system range from the use of peptide vaccinations, adoptive immunotherapy or the use of mucin specific antibodies [14]. Peptide vaccinations enhance the T helper cell or cytotoxic T cell response against tumour cells expressing mucins [5, 33]. A vaccination comprising of a MUC1 peptide with five TRR, with either a BCG (Bacillus Calmette-Gurein) or Freund's adjuvant, has been explored through a Phase 1 trial on patients with metastatic or localised pancreatic cancer. Patients had minimal side effects and results showed that they had an increase in mucin specific cytotoxic T cells [83-85]. In adoptive immunotherapy, patients are injected with dendritic cells expressing the mucin peptides or cytotoxic T cells sensitized to mucin [86]. Single treatment with either approach showed negligible improvement in survival rates, but in metastatic disease, the one-year survival was greater than 20% for the combination approach [87]. PankoMab, an anti-tumour MUC1 antibody, has also been investigated in pancreatic cancer. The advantage of these antibodies is that it differentiates between malignant MUC1 and non-malignant MUC1 antigens whilst generating a strong antibody dependent killing response [88]. Anti-mucin antibodies, conjugated to radioactive iodine, technetium or yttrium, have also been evaluated in clinical trials. However, patients only develop a partial response to this treatment and were exposed to unacceptable levels of radioactivity resulting in neutropenia and thrombocytopenia [89-91]. Although many of these studies and trials show promising results, they are limited in that they are mainly targeting MUC1, besides only involving a small cohort of patients.

Gene based

Currently there are no clinically available forms of gene therapy. However, there are a number of laboratory based and clinical studies that have down-regulated mucin through direct targeting and epigenetic regulation at the transcriptional level [28, 54, 92, 93]. Down regulation of MUC13 through transfecting human pancreatic cancer cells with microRNA-145 has resulted in decreased tumour growth and invasion [54]. Similarly, tumour expression of mucins has been targeted with short interfering RNA that resulted in reduced tumour invasion and metastasis in *in vitro* and *in vivo* models [94, 95]. Apart from the silencing of mucin genes, another approach involves taking advantage of the mucin gene promoter. This technique involves inserting suicide genes, for example the herpes simplex thymidine kinase, into the promoter region, therefore up-regulating the enzyme. This enzyme helps convert prodrugs into more potent cytotoxic agents, that has been tested in a number of neoplastic pancreatic cell lines successfully, resulting in increased cell death [96]. Although these studies indicate the potential efficacy of gene therapies, they do not address the challenge of delivering the gene in vivo and thus warrants future work on the practicalities of the treatment.

Conclusion and directions for future research

Pancreatic cancer is notorious for its low survival rates. Effective treatment remains a challenge due to lack of effective therapy and resistance. Over the past forty years, the significance of mucins in the carcinogenesis, progression and metastasis of pancreatic neoplasms has been established. Whilst the role of MUC1, MUC4 and MUC16 in pancreatic cancer is well elucidated, there is a lack of data on the significance of other mucins in this disease. However, gaining a deeper understanding of mucins will be critical to developing improved diagnostic tools and novel therapies. Additionally, whilst there has been a number of studies on MUC1 therapy, there is an urgent need to target other mucins such as MUC4 and MUC16, perhaps through combination therapy with the mucolytic agents, bromelain and N-acetylcysteine. Although therapy in pancreatic cancer has not improved, with growing knowledge on the role of mucins in pancreatic cancer, the development of a therapy aimed at improving the survival and outcomes of pancreatic cancer in the near future is inevitable.

Review criteria

Relevant literature on mucins and pancreatic cancer was identified by searching PubMed for articles published until March 2017. Search terms used in combination with mucin included "pancreatic cancer", "carcinogenesis", "expression", "therapy", "diagnosis" and "biomarker".

Full text articles published in peer reviewed journals were used.

Disclosure of conflict of interest

None.

Abbreviations

PDAC, pancreatic ductal adenocarcinoma; PanIN, Pancreatic intraepithelial neoplasia; IPMN, Intraductal papillary mucinous neoplasms; MUC, mucin; EMT, epithelial mesenchymal transition.

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