

Review

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## The MUC gene family: Their role in diagnosis and early detection of pancreatic cancer

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### Abstract

The early diagnosis of pancreatic cancer, as well as distinguishing between chronic pancreatitis and malignant pancreatic disease, remains still a clinical problem. Presently, there is no specific tumor marker for diagnosing pancreatic cancer. Mucin-associated marker like CA 19-9 are the most widely available pancreatic cancer tumor marker, but its value as a screening marker is limited by its reduced specificity.

Mucins (MUCs) are heavily glycosylated, high molecular weight glycoproteins with an aberrant expression profile in various malignancies.

This review considers briefly the potential use of the mucin expression pattern in diagnosis of pancreatic neoplasm. The overview will point out the present knowledge about changes in the mucin gene expression in pancreatic intraepithelial neoplasia (PanINs) as precursor lesions and in pancreatic adenocarcinoma, compared to normal pancreas and chronic pancreatitis and the potential role for differentiating chronic pancreatitis from pancreatic cancer.

Furthermore, the potential use of MUCs in the diagnosis and differentiation of intraductal papillary-mucinous neoplasm's (IPMNs) will be discussed.

### Review

Pancreatic adenocarcinoma is a neoplasm with a relatively high incidence and an extraordinarily poor prognosis [1]. In Western countries, it is the fifth leading cause of cancer deaths and has the lowest 5-year survival rate of any cancer [2]. Despite advances in diagnostic imaging, methods like endoscopic ultrasonography, dualphase spiral computer tomography, magnetic resonance imaging, and endoscopic retrograde cholangiopancreatography, early diagnosis and differentiation between malignant pancreatic tumors and chronic pancreatitis is still a diagnostic problem for clinicians [3].

The most commonly used clinical tests for tumor markers are serum-based immunoassays for blood group-related antigens and glycoproteins like CA 19-9, DUPAN2, CA 50, CA 125, and more recently CA 242. In pancreatic cancer, the sensitivity of the CA19-9 serum assay has been shown to range from 69% to 93%, and the specificity varied between 46% and 98% [4,5]. Unfortunately, elevated levels of the CA 19-9 antigen were found in chronic pancreatitis and other cancer conditions [5,6].

Antigens such as CA 19-9, CA 50, CA 125, and CA 242 contain oligosaccharide structures present on heavily glycosylated high molecular weight mucins [7]. These mole-

cules are widely synthesized and expressed by epithelial cells of the gastrointestinal, respiratory, and genito-urinary tracts [8]. Mucins are synthesized either as membrane-bound or as secreted glycoproteins. The structure of epithelial mucins displays a protein backbone bearing numerous carbohydrate side chains. The structure of the apomucin backbone typically reveals the presence of Ser/Thr/Pro-rich regions containing tandemly repeated stretches of amino acids that constitute potential O-glycosylation sites [9].

So far 14 mucin genes have been described, eight are now well-characterized; these include *MUC1-4*, *MUC5B*, *MUC5AC*, *MUC6* and *MUC7* [8-10]. Two other mucins, *MUC8* and *MUC9* have also been described but their characterization is yet to be completed [11,12]. Recently, partial cDNA sequences for *MUC11* and *MUC12* have been published [13]. Currently, *MUC13* was identified as a cell surface mucin expressed by epithelial cells as well as hematopoietic cells [14]. *MUC16* is the most recent member to the MUC protein family. It was characterized from a partial cDNA sequence encoding a mucin that has long been known as the ovarian cancer marker CA125 [15,16].

Under normal circumstances, mucins are known to play a protective role for epithelial tissues. In addition, their involvement in the renewal and differentiation of the epithelium, modulation of cell adhesion, as well as cell signaling has also been proposed.

Alterations in the expression and in the structure of mucins have been reported in both pre-neoplastic and neoplastic lesions [17,18]. However, there is a growing incidence that mucins and their associated blood group antigens may assist in the diagnosis of malignancies. In that regard, MUCs may represent potential diagnostic markers for early detection of pancreatic cancer and specific discrimination between pancreatic cancer and benign pancreatic diseases.

#### **MUCs in normal pancreas**

Various studies have analyzed the expression profiles of mucins in human pancreas under normal and pathological conditions using various methods with differences in their specificity and sensitivity including immunocytochemistry, *in situ* hybridization, RT-PCR and Northern blot. In general, immunocytochemical data obtained by using antibodies raised against the tandem repeat peptide should be analyzed with caution because the staining intensity may be caused by a changed mucin protein expression or by an altered glycosylation. Therefore, immunocytochemistry should be correlated with another method such as *in situ* hybridization. Despite the different analyzing methods the studies differ also in the inclusion or exclusion of MUCs.

Reports have shown the expression of *MUC1* and *MUC6* in normal adult pancreas tissue [19-22]. Our recently published RT-PCR and Northern blot data support these data and demonstrate the absence of *MUC2*, *MUC3A*, *MUC4*, and *MUC7* mRNA in normal pancreatic tissue [19]. There are contrary data about the detection of *MUC5AC* and *MUC5B* in normal pancreas [19,22,23]. *MUC5B* mRNA was detected in normal pancreas tissue as well as in normal duct cells by *in situ* hybridization [19,23,24]. Recently *MUC5AC* mRNA was found by the highly sensitive RT-PCR and slot blot analyses in normal pancreas tissue [19]. Studies using Northern blot analyses, *in situ* hybridization and immunohistochemistry did not show any *MUC5AC* in pancreatic duct cells [22,23].

However, normal pancreatic duct cells seem to express predominantly *MUC1* and *MUC6* [7,37]. In general, *MUC1* is a member of the membrane-bound mucins, whereas *MUC6* is a secreted gel-forming mucin. *MUC6* as a member of the group of mucins including *MUC2*, *MUC5AC* and *MUC5B* is located within the 11p15 chromosomal locus. In addition, no *MUC2*, *MUC4*, or *MUC7* expression was detected in normal pancreas.

#### **MUC molecules in PanINs and ductal adenocarcinoma**

Approximately 80-90% of tumors of the exocrine pancreas are adenocarcinomas with ductal cell origin. However, a relationship between hyperplastic and dysplastic epithelial lesions of the pancreatic ducts and invasive ductal carcinoma are described for a long time. Therefore, similar to the adenoma-carcinoma sequence model for colon cancer development, the present ductal pancreatic cancer model is based on the concept of intraepithelial neoplasia and describes a series of lesions termed PanIN (pancreatic intraepithelial neoplasia). Each grade of PanINs (PanIN-1A, PanIN-1B, PanIN-2 and PanIN-3) based on morphological criteria, cytological and architectural atypia [25]. This classification scheme with increasing neoplastic potential parallels with the stepwise prevalence of genetic alterations. Studies have shown, that characteristic genetic changes of the invasive ductal carcinoma such like p53 mutations and the loss DPC4/SMAD4 are a late event in the PanIN development whereas the overexpression of p21WAF1/CIP1 is an early event in the precursor lesions [26].

According to the studies about the occurrence of mutations and other genetic alterations in PanINs and pancreatic ductal adenocarcinoma (DAC) there is an increasing knowledge about the expression of MUC mucins in DAC and the precursor lesions.

Studies have shown, that DACs and tumor cell lines commonly overexpress *MUC1* mucin [7,19,22,27]. This mucin was detected only at low levels in the most chronic

pancreatitis and normal pancreas tissues on RNA level [19]. Recently, overexpression of MUC1 was observed in all stages of PanINs indicating the early occurrence of MUC1 in the development of DACs. Furthermore, published data indicate qualitative differences between the expression patterns showing cytoplasmatic and membrane-bound MUC1 in malignant pancreatic cancer cells [27]. In contrast, no cytoplasmatic staining was seen in normal tissue and chronic pancreatitis [27]. Pancreatic cancer cells are characterized by an aberrant glycosylation pattern. In this context, sialynated MUC1 was detected in DACs whereas it was not observed in specimens from normal pancreas, chronic pancreatitis or ductal hyperplasia [28].

The *de novo* expression of MUC4 in pancreatic adenocarcinoma and cell lines has been reported, a mucin that is usually undetectable in normal pancreas [19,20,23,24]. Recently, we demonstrated the aberrant *MUC4* mRNA expression in 75% (12/16) of the pancreatic adenocarcinoma and 73% (11/15) established pancreatic cancer cell lines [19]. There was no expression of *MUC4* in normal pancreas (0/7) or in chronic pancreatitis tissues (0/10) [19]. This study introduces MUC4 as a tumor-associated mucin that was specific for pancreatic adenocarcinoma and that may serve as diagnostic marker to discriminate pancreatic adenocarcinoma from chronic pancreatitis. Recent published data about the MUC4 expression on protein level including samples from all PanIN grades and 25 invasive pancreatic adenocarcinoma detected MUC4 in all PanIN grades but with increasing percentage in PanIN-3 lesions (11/13) compared to PanIN-1 (5/30), PanIN-2 (10/28) [29]. 89% of the investigated DACs were MUC4 positive [29]. Interestingly, few nonneoplastic lesions including reactive ducts in chronic pancreatitis were immunoreactive. More comprehensive studies including the correlation of immunohistochemistry with other methods like in situ hybridization may be necessary to confirm these data.

Beside the expression of the full length precursor of MUC4 (sv0-MUC4) with the soluble glycoprotein subunit MUC4 $\alpha$  and the transmembrane growth factor-like subunit MUC4 $\beta$  pancreatic cancer cells express MUC4 various splice variants [30,31].

Another study corroborates the potential role of MUC4 as a diagnostic marker for pancreatic cancer. This pilot study demonstrates the presence of *MUC4* mRNA in peripheral blood mononuclear cells of pancreatic cancer patients whereas it was undetectable in PBMCs of healthy volunteers or patients with pancreatitis or patients affected by other cancer types [32].

At this time, the biological function of human MUC4 in epithelial cells and malignant cells is poorly understood

and remains under evaluation. In addition to its involvement in the covering of luminal epithelia, recent studies suggest that the overexpression of the MUC4 rat homologue sialomucin complex (SMC) disrupts integrin-mediated cell-matrix and cell-cell interaction and inhibits immune recognition [33]. The putative function of MUC4 as adhesion molecule was supported by the description of the new extracellular domain AMOP (adhesion-associated domain in MUC4 and other proteins) [34].

In a recent study, overexpression of MUC6 and the *de novo* expression of gastric secretory mucin MUC5AC in all stages of PanINs and in invasive DACs was described on RNA and protein level [22]. It suggests the early involvement of MUC6 and MUC5AC in the carcinogenesis of the DACs. Additionally, a correlation between the MUC6 detection and the degree of differentiation of the infiltrating pancreatic adenocarcinoma detecting MUC6 predominantly in well-differentiated and less in moderately differentiated neoplasms was seen. Poorly differentiated tumors were only in 9% MUC6 positive.

In contrast to former published data indicating an aberrant expression of MUC3 in pancreatic cancer probes a recent study using RT-PCR and primer located in the non-repetitive MUC3A specific sequence did not reveal any *MUC3* mRNA detection in normal pancreas, chronic pancreatitis nor pancreatic cancer tissue samples [19,24,35]. In contrast to the new study, former studies are based on data using repetitive-sequences. The authors suggest that the detection of MUC3A in previous studies is the result of cross-hybridization with the recently discovered mucins MUC11 and/or MUC12. MUC3A, MUC12 and the particular characterized MUC11 share sequence homologies. In support of this hypothesis *MUC11* and *MUC12* mRNA was found in all investigated pancreatic tissues [19].

#### **Mucin gene expression in intraductal papillary-mucinous pancreatic neoplasia and related lesions**

Intraductal papillary-mucinous pancreatic neoplasia (IPMN) also called Intraductal papillary-mucinous pancreatic tumors (IPMT) are a distinct and rare entity of pancreatic disease characterized by a proliferation of the epithelium lining the pancreatic ducts [36]. In contrast to the DACs IPMN have in general a better clinical prognosis and can be cured by surgery. Therefore, the correct diagnosis has an important clinical impact. Their relationship to the PanINs and DACs is still not well defined. IPMN may progress from adenomas stepwise to intraductal carcinomas and then to invasive carcinoma. However, molecular analyses demonstrate genetic alterations like the loss of *DPC4* in distinct invasive forms of IPMNs, PanIN-3 as well as in DACs. Various studies demonstrate a dysregulation of mucins in IPMNs, which might contribute to the neoplastic progression. Studies revealed that IPMNs in

general express MUC2, MUC5AC and mostly MUC4 whereas MUC1 is absent [36–39]. This is in contrast to the invasive DACs, which are characterized by an overexpression of MUC1 and the absence of MUC2. However, recent data suggest a more heterogeneous profile of IPMNs with different mucin patterns and different clinical prognosis. It seems to be that there are at least three groups of IPMNs differing in their mucin expression. The largest group is MUC2 positive and MUC1 negative. A second group of IPMNs is MUC1 positive and MUC2 negative with an increased tendency for invasion and seems to be related to DAC. The third group with an oncocytic histology is characterized by a focal MUC1 and MUC2 expression [36]. IPMNs with a high expression of MUC2 and MUC5AC have a lower invasion and metastasising potential in comparison to DACs and therefore a better clinical outcome [36–39]. In contrast, other data demonstrate that within the IPMNs MUC2 positive tumors have a higher incidence for malignant transformation and invasive behaviour than MUC2 negative tumors [38]. However, the authors point out that both groups of IPMNs have still a significant better clinical outcome than DACs.

Other rare neoplasms of the pancreas are the mucinous cystic neoplasms (MCNs). MCNs are unilocular or, more commonly, multilocular cysts lined by tall mucin producing cells. They affect almost woman and occur predominantly in the tail of the pancreas [40]. MCNs may be misdiagnosed as IPMNs or cystic forms of DACs. But in contrast to the most DACs non-invasive MCNs can be cured by surgery. A recent study has shown that non-invasive MCNs can be distinguished from IPMNs and DACs by the mucin profile that is characterized by expression of MUC5AC, whereas MUC2 expression is restricted to goblet cells [40]. Similar to DACs invasive forms of MCNs are MUC1 positive. In this regard, MUC1 expression in pancreatic lesions correlates with a more aggressive biological behaviour.

## Conclusion

In summary, the early diagnosis of pancreatic cancer, as well as distinguishing between benign (chronic pancreatitis) and malignant pancreatic disease, remains difficult and may require multiple approaches including the imaging studies and tissue sampling. The analysis of the mucin expression pattern might be a promising tool to improve the correct diagnosis of pancreatic cancer. Several studies have shown that the mucin profile correlates with the growth behaviour and the prognosis of DACs, IPMNs and MCNs. In general, MUC1 expression is associated with a more aggressive biological behaviour. Therefore, mucins might be an important prognostic marker.

Despite, increasing knowledge about the mucin expression profile in normal pancreas, PanINs and DACs,

chronic pancreatitis tissues were included only in few studies. However, the discrimination between pancreatic adenocarcinoma and chronic pancreatitis is still a pressing clinical problem. In this moment, MUC4 as a pancreas tumor-associated mucin seems to be a potential discrimination marker. But it has to be mentioned that despite the high frequency of MUC4 occurrence in pancreatic cancer a fraction is MUC4 negative.

The combined implementation of conventional imaging techniques and molecular diagnostic approaches including investigation of the mucin expression pattern may provide improved sensitivity and specificity of diagnosis of pancreatic cancer. Overall, further studies are necessary to confirm the clinical value of mucins in diagnosis of pancreatic diseases.

## List of abbreviations used

MUC, mucin; RT-PCR, reverse transcription polymerase chain reaction; PBMC, peripheral blood mononuclear cell; PanIN, pancreatic intraepithelial neoplasia; IPMT, intraductal papillary-mucinous tumors; IPMN, intraductal papillary-mucinous neoplasia; DAC, ductal adenocarcinoma; MCN, mucinous cystic neoplasms

## Authors' contribution

Jörg Ringel drafted the manuscript. Matthias Löhr finalized the review. All authors read and approved the final manuscript.

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