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Contribution of DUSP28 to Regulation of Mucins in Human Pancreatic Cancer Cells

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Abstract

Pancreatic cancer remains one of the most deadly cancers, and once diagnosed, the prognosis for patient survival is poor. Patient outcomes have not been improved despite considerable and continuous efforts. We have suggested that dual-specificity phosphatase 28 (DUSP28) is a potential anti-cancer target to inhibit malignant pancreatic cancers. In this context, atypical DUSP28 can affect the regulation of mucins such as mucin5B (MUC5B) and mucin16 (MUC16). To investigate this correlation, we analysed mRNA levels of DUSP28 and mucins using the Gene Expression Omnibus public microarray database in pancreatic cancer, which indicated higher DUSP28, MUC1, MUC4, MUC5B, MUC16 and MUC20 mRNA levels in pancreatic cancers compared with normal pancreas tissue. In addition, DUSP28 expression in human pancreatic cancers correlated positively with those of MUC1, MUC4, MUC5B, MUC16 and MUC20. In contrast, there were no significant correlations between DUSP28 and mucins in normal pancreas tissues. Decreased DUSP28 expression resulted in down regulation of MUC5B and MUC16 at both the mRNA and protein levels. Furthermore, blockade of MUC5B or MUC16 expression inhibited migration and survival of cancer cells through the inhibition of phosphorylated FAK and ERK1/2. Collectively, we propose that DUSP28 uniquely links regulation of MUC5B and MUC16 to migration and survival of pancreatic cancer cells, which strongly support a rationale for targeting DUSP28 to inhibit development of malignant pancreatic cancer.

Keywords: DUSP28; MUC5B; MUC16; Survival; Migration

Introduction

Pancreatic cancer is one of the most dangerous cancers, and its overall 5 year survival rate is <1% [1]. This poor outcome is due to its aggressive biological features, such as migratory nature and resistance to chemotherapy and radiotherapy [2,3]. An advanced understanding of the molecular and cellular backgrounds of pancreatic cancers may promote potential clinical strategies. However, new therapies have not been successful in improving clinical outcomes to date [4]. The resistance of pancreatic cancers to treatment might originate from intrinsic or acquired features, via various genetic and cellular mechanisms [5], epithelial-mesenchymal transition [6], hypoxia [7] and pancreatic cancer stem cells [8].

Dual-specificity phosphatases (DUSPs) are protein phosphatases that tune the activities of mitogen-activated protein kinases (MAPKs) and play a crucial role regulating cancer cell features [9,10]. To date, 25 DUSP genes are listed in the Human Genome Organization database due to overlapping DUSP17, 20 and 23 with DUSP19, 18, and 25, respectively. DUSPs can be classified into three groups by their localizations. DUSP1, 2, 4 and 5 are situated to the nucleus (class I), while DUSP6, 7, and 16 are found in the cytoplasm (class II). DUSP8, 9 and 10 can be localized in the nucleus or the cytoplasm (class III). The dominant substrates of class I and II DUSPs are ERK, p38 and JNK and class III DUSPs recognize p38 and JNK as substrates. The strict divisions of substrate specificity and localization make DUSPs suitable targets to understand the malignant cancers involved in complex MAPK signaling networks [11-13]. DUSPs can be sub-divided into functional groups: typical and atypical DUSPs with or without an additional MAP kinase binding (MKB) domain [14]. Similar to this category, DUSPs also can be classified by their specific functions: oncogenic or anti-cancer effect in various cancer cells [15-19]. Our previous reports suggest that DUSP28 promotes malignancy of pancreatic cancer through various signaling pathways including intracellular signaling regulation and synchronized expression modification of other molecules [15,20].

Mucins are high-molecular-weight glycoproteins comprising 21 members in two groups. The membrane-bound members include MUC1, MUC3A/B, MUC4, MUC11, MUC12, MUC13, MUC15, MUC16, MUC17, MUC20 and MUC20. Based on their structure and localisation, these proteins play essential biological functions in cell-cell and cell-extracellular matrix interactions with critical signalling pathways in cancer cells [21,22]. Secreted mucins are divided into gel-forming and non-gel-forming groups. Gel-forming mucins include MUC2, MUC5AC, MUC5B, MUC6 and MUC19, which participate in mucus formation by forming a 3-D network via the oligomerization domain to protect the epithelial layer against various factors, such as inflammation, bacteria, viruses, pollutants, etc. [23,24]. Multiple mucins are erroneously expressed in pancreatic cancer, in contrast to healthy pancreas which is devoid of mucins or expresses them at low levels. With emerging recognition of the role of mucins in malignancy

of tumors, it is becoming evident that pancreatic cancer cells exploit the properties of mucins to interact with their microenvironment, survive in an inhospitable local environment, and metastasise to distant sites [25]. Numerous reports have suggested that MUC1 [26], MUC4 [27], MUC16 [28] and MUC20 [29] expression is increased in pancreatic cancers. In agreement with previous reports, our results revealed that transcriptional levels of MUC1, MUC4, MUC16 and MUC20 were enhanced in pancreatic cancers; moreover, we further demonstrated unique overexpression of MUC5B at both the mRNA and protein levels in pancreatic cancer cells. The role of MUC5B in pancreatic cancer malignancy has been overlooked compared with MUC5AC [30].

Correlations between DUSP28 expression and mucins whose expression was increased — i.e., MUC1, MUC4, MUC5B, MUC16 and MUC20 — in pancreatic cancers were assessed. The expression levels of these five mucins had significant positive correlations with that of DUSP28. Of interest, MUC5B and MUC16 were regulated by DUSP28 expression at both the mRNA and protein levels.

Pancreatic cancer initiation and progression remains poorly understood. The need for a more-effective pancreatic cancer treatment strategy is urgent and the link between DUSP28 and MUC5B and MUC16 expression may enhance understanding of the development of malignant pancreatic cancer. MUC16 has been reported previously to be a key factor in pancreatic cancer malignancy [27,28]. However, we suggest the importance of MUC5B in pancreatic cancer cells for the first time and that MUC5B and MUC16 are involved more closely in human pancreatic cancer malignancy than previously recognized.

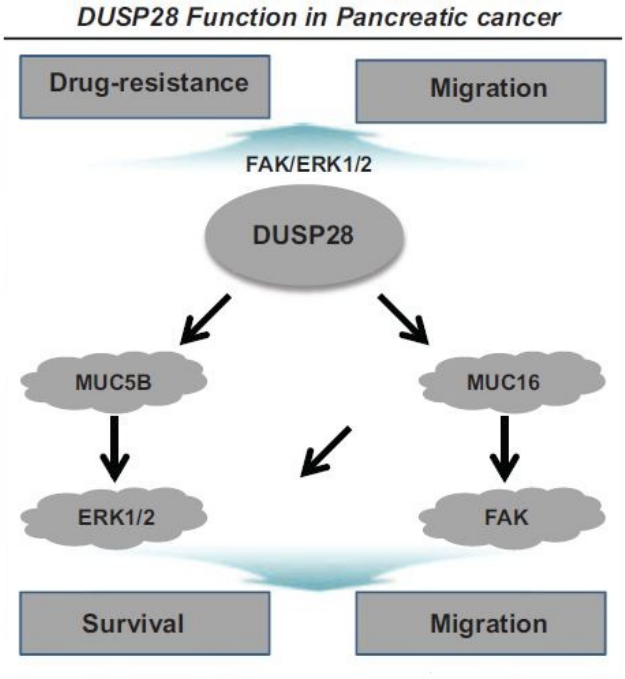

Figure 1: Schematic diagram of DUSP28 related survival, migration and chemo-resistance in pancreatic cancer cells.

Several studies have suggested that mucins regulate the ERK1/2, p38, mTOR and c-Myc intracellular signalling pathways in pancreatic cancer cells. The regulation of MUC5B and MUC16 expression by DUSP28 therefore might affect various MAPK signalling pathways [15,27,28]. Silencing of MUC5B and MUC16 caused reduction of phospho-ERK1/2 levels compared with those of phospho-FAK. We also showed that FAK phosphorylation was regulated by knockdown of MUC16, but not MUC5B in human pancreatic cancer cells, suggesting a complex relationship between DUSP28 and MUC5B/MUC16 expression in pancreatic cancer cells. Collectively, we establish that DUSP28 uniquely links regulation of MUC5B and MUC16 to malignancy of pancreatic cancer cells, which strongly supports a rationale for further investigating DUSP28 as pivotal regulator in pancreatic cancer (Figure 1).

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