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ISSN 2471-142X Open Journal http://dx.doi.org/10.17140/POJ-1-e003

Editorial

Corresponding author
Jaya Padmanabhan, PhD
Assistant Professor
Department of Molecular Medicine
USF Health Byrd Alzheimer's Institute
Morsani College of Medicine
University of South Florida, 4001 E. Fletcher Ave., Tampa, FL 33613, USA
Tel. 813-396-0721
E-mail: jpadmana@health.usf.edu

Volume 1 : Issue 2
Article Ref. #: 1000POJ1e003

Article History
Received: January 25th, 2016
Accepted: January 26th, 2016
Published: January 28th, 2016

Citation
Padmanabhan J. ADAM10 proteases and pancreatic cancer. *Pancreas Open J*. 2016; 1(2): e8-e10. doi: 10.17140/POJ-1-e003

ADAM10 Proteases and Pancreatic Cancer

Jaya Padmanabhan, PhD*

Department of Molecular Medicine, USF Health Byrd Alzheimer's Institute, Morsani College of Medicine, University of South Florida, 4001 E. Fletcher Ave., Tampa, FL 33613, USA

Pancreatic ductal adenocarcinoma (PDAC) is the 4th leading cause of cancer-related deaths in the United States and is expected to rise to the second rank by 2020.[1] The survival rate of PDAC is estimated at less than 5% and the high mortality rate is attributed to the asymptomatic progression and aggressive nature of the tumor, which exhibit locally advanced or metastatic disease at the time of diagnosis. Majority of the pancreatic cancers are PDACs and are characterized by a fibrotic tumor stroma.

The nucleoside analog Gemcitabine is the standard therapy used for treatment of PDAC but it shows only marginal therapeutic benefit.[2,3] The limited accessibility of the drugs to the tumors is one of the major issues with PDAC, given the dense, highly fibrotic nature of the stroma. Tumor stroma comprises of Extracellular matrix (ECM) proteins, growth factors such as fibronectin and collagen, stromal fibroblasts, stellate cells, immune cells, and blood vessels.[4] The strong desmoplastic tumor stroma inhibits transvascular transport of drugs to the tumors, and therefore the tumors continue to grow and metastasize. Though the newly developed combinatorial therapies such as Nab-Paclitaxel (colloidal suspension of paclitaxel and human serum albumin) and FOLFIRINOX (combination of oxaliplatin, 5-FU, lucovorin and irinotecan) have shown significant improvement in survival in patients with metastatic cancer, they are associated with severe toxicity issues, and therefore additional strategies are being developed to effectively treat PDAC.[5,6]

It is known that matrix-degrading enzymes affect cell adhesion and migration. Several transmembrane proteins that are involved in cell adhesion are cleaved by matrix degrading enzymes like matrix metalloproteinases, allowing detachment, migration and metastasis of cancer cells. Among the proteases, A Disintegrin And Metalloprotease (ADAM) family member ADAM10 has recently gained considerable attention for its role in tumor progression and metastasis.[7,8] The metalloprotease domain of ADAM10 is involved in proteolysis and ectodomain shedding of extracellular matrix-associated proteins whereas its disintegrin and cysteine rich domains are known to have adhesive activities.[9] Proteins such as cadherins, CD44, Notch, Ephrin B1, amyloid precursor protein, and the chemokine CXCL16 are a few examples, whose ectodomain release contributes to migration and invasion of cancer cells.[10-13] Recent studies by others and us have shown that ADAM10 inhibition or down-regulation enhances the chemosensitivity of PDAC cells to gemcitabine and prevents their anchorage independent growth and migration.[13-16] PDACs over express ADAM10, and down-regulation of ADAM10 in PDAC cells have shown to significantly reduce the secreted levels of the soluble ectodomains of its substrates. We recently demonstrated that ADAM10 inhibition enhances cell-cell adhesion and formation of cadherin positive tight adherens junctions, indicating that activation of ADAM10 plays an important role in loss of cadherin-dependent adhesions. Studies in other cellular systems have shown that inhibition or knockdown of ADAM10 prevents proteolytic processing and secretion of CD44 and cadherin. CD44 is a receptor for the glycoprotein hyaluronan, which is one of the major Extracellular Matrix (ECM) components of pancreatic tumor stroma.[17] Therefore, cleavage of CD44 leads to dissociation of the cells from the hyaluronan substrata and facilitation of migration. Another possible mechanism by which ADAM10-mediated cadherin proteolysis promotes cancer cell proliferation or stemness is by promoting β-catenin-nuclear signaling and TCF-LEF-dependent gene transcription.[12] We recently reported that ADAM10 inhibition significantly reduces β-catenin-target gene expression, which included cyclin D1,

ISSN 2471-142X Open Journal http://dx.doi.org/10.17140/POJ-1-e003

CD44, and c-myc.[18] Another interesting finding is that β-catenin nuclear signaling can induce transcription of ADAM10, thereby playing a feed forward role in the vicious cycle of tumor promotion. Thus, inhibition of ADAM10 protease could be a promising strategy for the prevention of cancer cell migration and invasion and overcoming drug resistance.

One strategy that will help to reduce PDAC-related mortality is to develop methods for early detection of the cancer and initiate the treatment at an early stage. Serum biomarkers are being sought as a diagnostic tool and currently CA19-9 is the only serum biomarker clinically used for monitoring pancreatic cancer in patients. Since ADAM10-mediated proteolysis of transmembrane substrates lead to secretion of their ectodomains, it is possible that an analysis of the body fluids for secreted ectodomains of ADAM10 substrates could provide valuable information on the activity state of this protease, and possible early detection of cancers. Supporting this notion, a recent study suggested that soluble forms of secreted Giant Cadherin FAT Atypical Cadherin 1 (Fat1) might serve as a potential serum biomarker for early detection of PDAC.[19] Fat cadherins are extremely large cell adhesion proteins (>500 kDa) that are present on the cell surface. Studies have shown that Fat1 at the cell membrane binds to another large cadherin known as Dachsous (Ds) and activates the Hippo tumor suppressor pathway and Planar Cell Polarity (PCP) organization.[20] Fat1 is active only when present at the cell surface, where it is capable of activating the Hippo tumor suppressor pathway, which in turn inhibits Yki-dependent transcription and tumor growth. It is possible that the ectodomain shedding of Fat1 leads to its dissociation from Dachsous and inactivation of the Hippo tumor suppressive pathway, thereby promoting tumor growth. It has also been shown to regulate actin cytoskeletal organization and tight cell-cell adhesion, which is dependent on the classic cadherins.[21] Fat1 is cleaved extra-membranously by ADAM10 protease, releasing its ectodomain; ADAM10 inhibition significantly reduces the ectodmain cleavage and secretion of FAT1.[19] Here, the authors analyzed serum samples from 11 PDAC and 10 normal human subjects, and the results showed that secreted Fat1 is increased in 2 patient samples but not in any of the normal, as analyzed by western blot as well as mass-spectrometry. Further, analysis of 30 patient samples and 28 normal samples using Enzyme Linked Immuno Sorbent Assay (ELISA) showed an increase in the levels of Fat1 in patient samples. Additionally, comparative studies in 4 of the patient samples with only modest levels of Cancer antigen 19-9 (CA19-9) showed high levels of soluble Fat1, suggesting that this secreted protein might serve as a biomarker for early detection of pancreatic cancer. While many of the ADAM10 substrates are also cleaved by ADAM17, it is possible that other ADAM family members or proteases also need to be analyzed for their potential role in the generation of soluble Fat1.

While ADAM10 activity is necessary for normal cellular function, strategies directed towards modulating its activity or levels could prove to be beneficial in overcoming its growth promoting and metastatic functions, and for enhancing drug sensitivity. Studies have implicated that calcium influx activates ADAM10 and we found that calcium channel inhibitors interfere with ADAM10 cellular distribution at the membrane and promote formation of tight cell-adhesions.[18] Additional studies will enable elucidation of calcium-dependent or independent mechanisms that activate ADAM10. An understanding of the specific role of ADAM10 in PDAC progression or metastasis would enable us to determine if targeted inhibition of ADAM10 is a viable option for overcoming drug resistance and metastasis associated with PDAC.

ACKNOWLEDGEMENTS

The studies in JP's lab is supported by grants from Anna Valentine Collaborative Grant and Byrd Institute Small Grant Program.

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