REVIEW ARTICLE

A Star of Connection Between Pancreatic Cancer and Diabetes: Adrenomedullin

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ABSTRACT

Pancreatic cancer belongs to the most aggressive cancer types, with an incidence rate equallig mortality rate. It is well-known that type 2 diabetes is a significant risk factor for pancreatic cancer. Interestingly, several studies have shown that pancreatic cancer can also lead to type 2 diabetes, as part of the pancreatic cancer induced paraneoplastic syndrome. Multiple factors have been proposed to be involved in the interaction between pancreatic cancer and diabetes. Adrenomedullin, a multifunctional hormone, is nominated as a strong candidate influencing the connection of pancreatic cancer with diabetes. Evidence so far suggest that adrenomedullin upregulation is linked with pancreatic cancer growth, invasion, metastasis, and angiogenesis. Most importantly, adrenomedullin exerts paracrine effects on pancreatic β cells impairing insulin secretion, causing glucose intolerance, and thus leading to β cell dysfunction. This review will explain recent advances regarding the involvement of adrenomedullin in pancreatic cancer and pancreatic cancer-associated diabetes.

INTRODUCTION

Pancreatic cancer bears a poor prognosis and dismal survival rate representing the twelfth most common cancer in the world. Indeed, overall five-year survival rate of pancreatic cancer patients is below 5%, with a median survival of 4 to 6 months [1, 2]. Pancreatic cancer is typically diagnosed at an advanced stage, reducing efficient treatment strategies. An important risk factor for pancreatic cancer is type 2 diabetes. Interestingly, studies indicate that pancreatic cancer can also cause diabetes along with weight loss and cachexia, as part of the cancer-induced paraneoplastic syndrome. Pancreatic cancer-induced diabetes has been shown to be present in 34% of patients (177of 512) [3]. Even though, the pathogenesis of these cancer-associated metabolic syndromes is only beginning to be understood, they present potential avenues in enhancing the survival and growth of pancreatic cancer, especially as pancreatic cancer is characterized by an abundant and desmoplastic microenvironment. Adrenomedullin (ADM) is a multifunctional hormone, which is expressed in different tissues of the human body including the pancreas. Researchers have shown that ADM is involved in regulating growth of normal and carcinogenic cells, both with antiproliferative and mitogenic activities. Recently, ADM has been described as a candidate diagnostic marker of pancreatic cancer in association with diabetes mellitus. Furthermore, many studies have highlighted the importance of ADM in pancreatic cancer and diabetes. For a general overview on ADM function, see an informative review [4]. This review will describe the involvement of ADM in pancreatic cancer and pancreatic cancer-associated diabetes. For the literature research Pubmed was used, no restrictions were applied and the time frame covered was from 1994-2015. The keywords used for the research included “Adrenomedullin cancer”, “adrenomedullin pancreatic cancer”, “pancreatic cancer and diabetes”. In some cases, references from cited papers have been included in the analysis.

Received February 05th, 2015-**Accepted** May 25th, 2015
Keywords Adrenomedullin; Diabetes Mellitus; Pancreatic Neoplasms
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Adrenomedullin and Its Role in Malignant Growth

Adrenomedullin (ADM) is a 52 amino acid peptide known to inhibit insulin secretion. Receptors of this pluripotent hormone are found on β cells in the pancreas. ADM expression is sighted particularly in the F cells of pancreatic islets. ADM expression has also been identified

in the embryonic pancreas at the beginning and throughout organ development. The first study implicating ADM in the regulation of pancreatic physiology described an ADM-mediated decrease in insulin secretion from isolated rat islets [5].

ADM has been implicated as a regulator of several types of tumors including breast cancer, colorectal cancer, prostate cancer, cervical cancer, renal cell carcinoma, and multiple myeloma. Most recently, Lim *et al*. have shown that oncostatin M, a member of the Interleukin-6 family, stimulates ADM expression in astroglioma cells via induction of signal transducer and activator of transcription-3 (STAT-3) [6]. ADM peptides then enhance astroglioma cell migration and invasion, as analyzed by wound healing assay [6]. Moreover, ADM seems indispensable for cancer cell growth, survival and angiogenesis. Sena *et al*. analyzed the influence of hypoxia-inducible factors (HIF) on ADM isoforms. Their study demonstrated that HIF stimulates splicing of ADM pre-mRNA, thus regulating ADM expression [7]. Furthermore, ADM has been associated with carcinogenesis in an oncogenic *Kras* dependent manner. Importantly, researchers have shown that ADM plays a substantial role during tumor cell growth and invasion especially in mutant KRAS colon cancer cells cultured in hypoxic conditions. In this study, ADM was also upregulated in tumor samples from colorectal cancer patients. The authors thus concluded that ADM is a novel target of oncogenic KRAS in conditions of hypoxia [7]. Additionally, the significance of ADM and its receptors in colorectal cancer has been highlighted via using anti-adrenomedullin antibody (αADM) treatment. Indeed, αADM treatment led to inhibition of tumor growth and angiogenesis [8]. Glioblastoma is one of the most devastating and common brain tumors in adults. Sun *et al*. have suggested that Interleukin-1β (IL-1β) along with hypoxia-inducible factor 1 (HIF-1) and ADM, could be used to predict the progression of glioblastoma in patients. They have found that IL-1β effectively induces apoptosis in ADM expressing glioblastoma cells, by blocking HIF-1 mediated ADM production [9]. Similarly, αADM suppresses proliferation of Du145 and PC3 prostate cancer cells *in vitro* by cAMP/CRAF/MEK/ERK pathway. Importantly, αADM effectively blocks lymphangiogenesis in tumor tissue and induces lymphatic endothelial cell apoptosis, without affecting vasculature and lymphatic vessels in normal adult mice [10]. In another study, ADM was found overexpressed in the stroma of cervical cancer, localized to the blood and lymphatic vessels. Moreover, the above study suggested a crosstalk between stroma and cervical cancer in enhancing repression of miR-126 while upregulating ADM to enable invasion, growth and angiogenesis [11].

The G-protein-coupled receptor (GPCR) calcitonin receptor-like receptor (CLR) and its ligand peptide ADM are established inducers of tumor angiogenesis in mouse models but have been inadequately analyzed in human cancers. Nikitenko *et al*. revealed upregulation of CLR in an ADM signaling loop in renal cell carcinoma and thus nominated CLR as a new potential target for future studies [12]. Recently, it has been demonstrated that secretion of ADM can be an essential driver of the angiogenic switch surveyed during multiple myeloma progression, which highlights the potential importance of ADM as a target in multiple myeloma therapy [13]. The major focus of these studies was to delineate the importance of ADM in diagnostic and prognostic approaches. Overall, reported data from all studies illustrate that the multifunctional peptide ADM is a crucial regulator of multiple cancer cell hallmarks in numerous cancer types.

Adrenomedullin and Its Role in Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is highly aggressive and various therapeutic methods, including chemotherapy and radiotherapy have very limited effects on patient survival. Thus, the need to elucidate the mechanisms underlying pancreatic carcinogenesis is great. Many research projects have illustrated that ADM is associated with different aspects of carcinogenesis, such as prevention of apoptosis by different pathways e.g., CGRP1, cAMP, AKT-GSK, and MEK-ERK pathway [14-17], stimulation of angiogenesis by increasing VEGF secretion, and regulation of hypoxia (see previous section). For the first time, Ishikawa *et al*. have shown that an ADM antagonist (ADMA) significantly decreased the *in vivo* growth of pancreatic cancer cells in SCID mice [18]. In this study, immunohistochemical analysis demonstrated that the mean diameter of blood vessels was crucially smaller in mice treated with an ADM N-terminal fragment. Moreover, Keleg *et al*. have shown that ADM is induced by hypoxia and overexpressed in PDAC. According to their results, in PDAC the median ADM mRNA expression levels were higher in LN (lymph node)-positive compared to LN- negative patients [19]. Importantly, recombinant ADM (rADM) stimulated VEGF secretion by some of the utilized human pancreatic cancer cell lines. Moreover, by treating COLO-357 pancreatic cancer cells with TGF-B1 and rADM, they showed that rADM antagonized the antiproliferative effect of TGF- B1 on COLO-357 cells [19]. In addition, Miseki *et al*. have reported that the intra-tumoral or intra- muscular transfer of naked DNA encoding ADMA significantly reduced the *in vivo* growth of pancreatic cancer cells in SCID mice [20]. Indeed, they observed that after treatment with naked DNA encoding ADMA, tumor tissues did not contain CD-31 positive cells [20]. Accordingly, Logsdon and his group have indicated that treatment of different pancreatic cancer cells with ADM *in vitro* stimulates cell proliferation, invasion and nuclear factor kB activity. Also, they illustrated that

Table 1. Studies connecting Adrenomedullin with Pancreatic Cancer

Hallmarks of Cancer	Mechanism	Experiments	Reference
Tumor growth	Reduced blood vessel diameter using ADM-antagonist(ADMA)	*In vitro* and *in vivo*	[10]
Invasion and angiogenesis	Induction of ADM by hypoxia stimulated VEGF secretion	*In vitro* and clinical data	[11, 14]
Tumor growth and neovascularization	Reduced tumor growth by transfer of ADMA encoding DNA	*In vivo*	[12]
Cell proliferation, invasion, nuclear factor kB activity, tumor growth, metastasis	Autocrine action ofexogenous ADM via ADM receptor	*In vivo* and *in vitro*	[13]
Paraneoplastic syndrome, i.e. new-onset diabetes	Inhibition of insulin secretion from β cells and glucose intolerance by tumor secreted ADM	*In vitro*, *in vivo* and clinical data	[16]
Cancer derived exosomes	Impaired insulin secretion by tumor derived exosomes and β cell dysfunction	*In vitro* and clinical data	[17]

ADM increases pancreatic cancer growth and metastasis *in vivo* [21]. Finally, Kobayashi *et al*. supported for the first time that ADM is a hypoxia inducible gene and expressed at higher levels under glucose-deprived hypoxic conditions [22].

In conclusion, all the above studies (Table 1) demonstrate that ADM is a crucial regulator of pancreatic carcinogenesis and pancreatic cancer aggressiveness *in vitro* as well as *in vivo*.

Adrenomedullin: Connecting Pancreatic Cancer and Type 2 Diabetes

Overall, reported data demonstrate that most patients with pancreatic cancer have hyperglycaemia or diabetes. Similarly, patients with new-onset diabetes have an escalated risk of being diagnosed with pancreatic cancer. The connection between pancreatic cancer and diabetes has been explained by several translational, clinical and epidemiological studies. The majority of translational studies described new-onset diabetes in pancreatic cancer as a paraneoplastic syndrome originating from tumor secreted products, including ADM [23], islet amyloid polypeptide (IAPP) [24], and S-100A8 N-terminal peptide [25]. Importantly, recent studies have determined ADM as a strong candidate for connecting pancreatic cancer with new-onset diabetes [26]. A collaborative study between Mayo Clinic and M.D. Anderson Cancer Center has shown that ADM is upregulated in patients with pancreatic cancer. Moreover, diverse *in vitro* and *in vivo* experiments pointed towards ADM as a strong inhibitor of β cell-mediated insulin secretion in pancreatic cancer.

Indeed, ADM overexpression caused glucose intolerance in subcutaneous and orthotopic pancreatic cancer models [23]. As mentioned in the first paragraph of this section, ADM is a strong candidate biomarker of new-onset diabetes in pancreatic cancer. A recent experimental study indicated that pancreatic cancer-derived exosomes containing ADM and CA19-9 reach β cells and decrease insulin secretion, providing a potential explanation for the association of ADM with pancreatic cancer- dependent β cell dysfunction. ADM binds ADMR on β cells and causes upregulation of Bip (ER chaperone protein) and Chop (inducer of apoptosis) which are endoplasmic reticular (ER) stress associated genes. Importantly, ADM-induced ER stress compromises the unfolded protein response in β cells impairing β cell insulin secretion in the presence of ADM [27].

Thus, all of the above studies highlight the central role of ADM in the development of pancreatic cancer-associated diabetes. Pancreatic cancer-derived ADM seems to block insulin secretion from β cells by direct, receptor-mediated interaction.

CONCLUSION

So far multiple studies provide evidence that diabetes can be considered a pancreatic cancer-associated paraneoplastic syndrome. However, the mechanisms underlying the connection between diabetes and pancreatic cancer have not been clarified. ADM is known to positively regulate multiple hallmarks of malignant cancer cell growth (e.g., angiogenesis, proliferation, invasion, etc) in various cancer types including pancreatic cancer. Recently, ADM emerged also as a potential diagnostic biomarker for pancreatic cancer-dependent diabetes. Indeed, studies have shown that pancreatic cancer-derived ADM blocks insulin secretion from pancreatic β cells by directly interacting with the ADM receptor on β cells **(Figure 1)**. On the other hand, studies on ADM and its role in pancreatic cancer and pancreatic cancer associated diabetes still have some limiting aspects in terms of lack of large cohort and translational studies. Pancreatic cancer induced paraneoplastic diabetes is very rare compared to type 2 diabetes mellitus. Thus, it is of great importance to clearly differentiate these clinical manifestations in order to discern the main mechanism behind the connection between pancreatic cancer and diabetes. Unfortunately, most of the ADM related studies have focused on *in vitro* experiments. Researchers should use transgenic animal models to support the above findings as well as *in vivo* systems with isolated cancer and islet cells. Thus, ADM represents a promising new therapeutic target in the fight against pancreatic cancer, especially in combination with new onset diabetes. Future studies should be directed towards elucidating the mechanistic details behind the association of ADM with pancreatic cancer and diabetes.

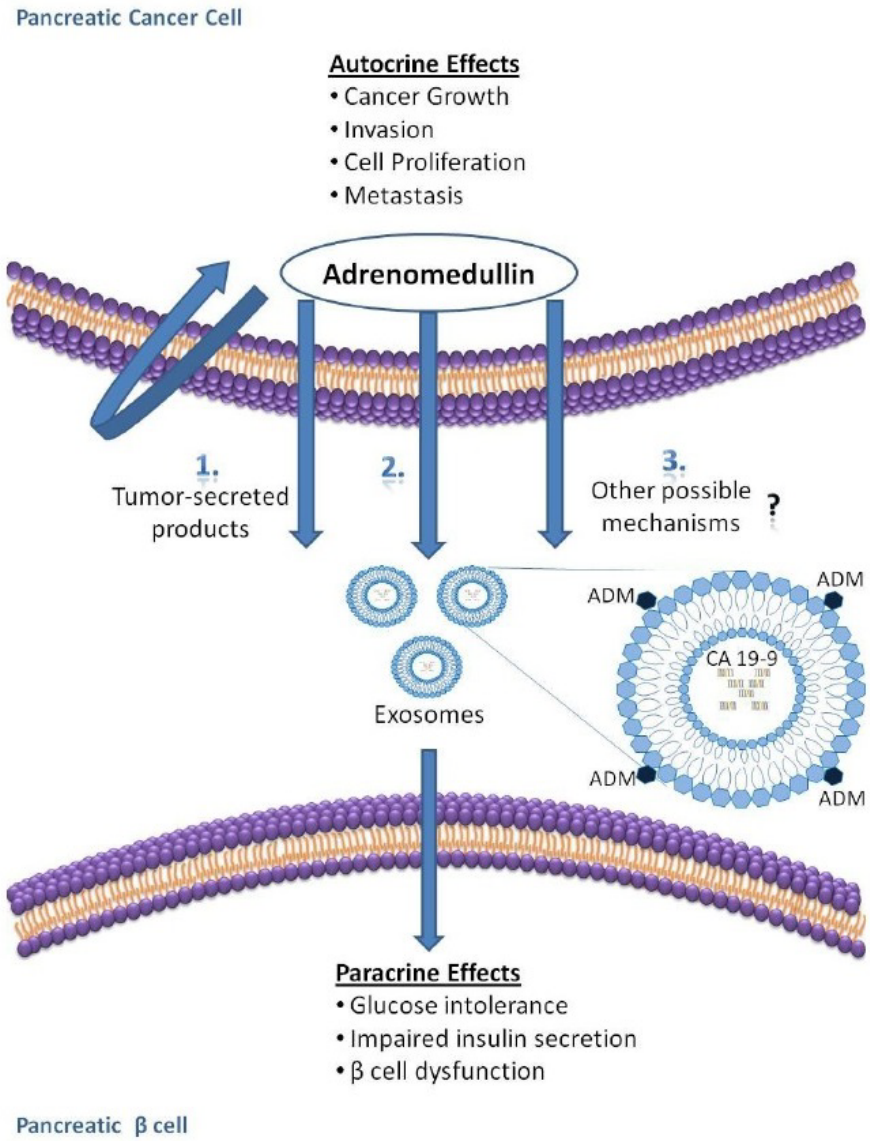

Figure 1. Effect of ADM on pancreatic cancer cells and β cells: Scheme illustrating the potential mechanism of action of pancreatic cancer cell-derived ADM on pancreatic cancer cells and β cells. ADM may be directly secreted (1) or bind to CA 19-9 containing exosomes (2) produced by pancreatic cancer cells. Alternative routes are also possible and remain to be discovered (3). ADM may then act on pancreatic cancer cells in an autocrine manner and on β cells in a paracrine manner with various pro-tumorigenic and pro-diabetes inducing effects, respectively. See text for details. ADM=Adrenomedullin

Conflicts of Interest

The authors declare no conflicts of interest.

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