Pancreatic Cancer–Associated Diabetes Is an "Exosomopathy"

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Diabetes may be a consequence of pancreatic cancer, preceding cancer diagnosis. The underlying mechanism is the release of exosomes delivering adrenomedullin to β cells, inducing endoplasmic reticulum stress and perturbations in the unfolded protein response, leading to β-cell dysfunction and death. This knowledge could lead to improved diagnostic strategies for pancreatic cancer. Clin Cancer Res; 21(7); 1508–10. ©2015 AACR.

In this issue of Clinical Cancer Research, Javeed and colleagues (1) demonstrate that exosomes released by pancreatic cancer cells (PCCs) in culture and in patients with pancreatic ductal adenocarcinoma (PDAC) carry adrenomedullin, which is delivered to the β cell, inducing endoplasmic reticulum (ER) stress, a failure of the unfolded protein response (UPR), increased β-cell dysfunction and death, and PDAC-associated diabetes mellitus.

Most cases of diabetes mellitus are classified as type I or type II diabetes. The former, termed T1DM, is associated with undetectable insulin levels due to autoimmune-mediated destruction of the β cells and a propensity to develop ketoacidosis. The latter, termed T2DM, is associated with insulin resistance; elevated, normal, or slightly decreased insulin levels; a failure of the β cell to overcome insulin resistance, and an inability of the liver to suppress inappropriate hepatic glucose release. Among the population of diabetic patients in the United States, it is estimated that approximately 5% have T1DM and approximately 90% have T2DM. Importantly, the Centers for Disease Control and Prevention (CDC) estimates that approximately 29 million people in the United States had diabetes mellitus in 2012, and that in 8 million of these individuals, diabetes had not yet been diagnosed (2).

Long-standing T2DM is a risk factor for PDAC (3). Additional risk factors include inherited familial disorders, tobacco smoking, obesity, chronic pancreatitis, heavy alcohol intake, and diets rich in saturated fats and low in fruits and vegetables (3). However, the relationship between diabetes mellitus and PDAC is complex, and loss of glyemic control and diabetes mellitus can occur as a consequence of PDAC and can precede the diagnosis of PDAC by a few weeks, to a few months, to 2 to 3 years (4). This type of diabetes, termed pancreaticogenic diabetes, or type 3c diabetes (T3cDM), is much less common than either T1DM or T2DM. The underlying etiology in most cases is chronic pancreatitis, and it has been estimated that chronic pancreatitis and PDAC contribute to approximately 80% and 8% of T3cDM, respectively, while the remaining cases occur as a result of other types of pancreatic exocrine pathologies, such as pancreatic trauma and cystic fibrosis (5, 6).

In this issue of Clinical Cancer Research, Javeed and colleagues (1) make the point that PDAC-associated T3cDM, termed PC-DM, is associated with insulin resistance and increased peripheral insulin levels, whereas T3cDM observed in chronic pancreatitis is associated with decreased insulin levels due to the loss of insulin-secreting β cells. Having previously shown that PCC-derived adrenomedullin inhibits insulin secretion by the β cell, they now focused on how adrenomedullin targets the β cell. They first demonstrated that PCC lines preferentially release exosomes over other forms of extracellular vesicles, and that exosomes were present in both the portal and peripheral venous blood of patients with PDAC. They next determined that exosomes derived from PANC-1 PCCs can be internalized by β cells within 48 hours following their coincubation. Given that exosomes are of endosomal origin and that endosomes express tumor susceptibility gene 101 (Tsg101), they next confirmed that the exosomes they were isolating expressed Tsg101. Validation of their pancreatic cancer origin was demonstrated by showing that these exosomes expressed the PDAC-associated protein CA19-9. PCC-derived exosomes were then shown to inhibit insulin secretion in human islets and in INS-1 rat insulinoma cells. Importantly, adrenomedullin receptor blockade abrogated the inhibitory effect of exosomes on insulin secretion, whereas medium depleted of exosomes by ultracentrifugation had no effect on the β cells.

Adrenomedullin was originally identified as a hypotensive hormone isolated from pheochromocytoma and subsequently shown to exert proliferative and proangiogenic effects and to inhibit insulin secretion (7). There are three adrenomedullin receptors (ADMR), and all three belong to the 7-transmembrane superfamily of g-protein–coupled receptors, but each has a different affinity for adrenomedullin (8). Among these, the calcitonin receptor-like receptor (CRLR) requires single transmembrane modulating proteins known as receptor activity modifying proteins (RAMP). It was important, therefore, to investigate the interactions between exosomal adrenomedullin and ADMR. Accordingly, Javeed and colleagues (1) used a fluorescent-based Duolink assay system in which fluorescent proximity ligation...
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Figure 1.
PCCs express and release adrenomedullin into the circulation as well as into exosomes (shown as small yellow circles), which derive from multivesicular bodies (MVB), which in turn originate from endosomes (not shown). Although adrenomedullin released into the circulation does not achieve sufficiently high levels to affect the β cells, when packaged into exosomes it is delivered into β cells by endocytosis and micropinocytosis, resulting in sufficient quantities of intracellular adrenomedullin for the induction of ER stress, perturbations in the unfolded protein response, suppression of insulin secretion, and ultimately β-cell death.

To determine why adrenomedullin interferes with β-cell function even though it upregulates insulin mRNA and cyclic AMP levels, Javeed and colleagues (1) examined the effects of adrenomedullin on ER stress and the unfolded protein response. They observed that incubation of INS-1 cells with adrenomedullin peptide for 48 hours, followed by glucose stimulation for 4 to 6 hours, led to an increase in Bip and Chop mRNA levels, indicating that there was enhanced ER stress. This effect was reversed by AM 22-52, confirming that it was mediated by adrenomedullin. PCC-derived exosomes also induced increased BIP and CHOP mRNA expression in INS-1 cells, while enhancing apoptosis and Bip–proinsulin interactions, indicating that, in addition to enhanced ER stress, there was an adrenomedullin-induced failure of the UPR pathway (Fig. 1).

This study is important for several reasons. First, it underscores the complex connections between diabetes and PDAC. Second, it demonstrates that PDAC is associated with preferential production of exosomes over other extracellular vesicles. Third, it provides novel insights on how exosomes lead to β-cell dysfunction, raising the possibility that PDAC-associated diabetes is caused, in part, by exosomes and pointing to a novel exosome-based disease mechanism or “exosomopathy.” Thus, PC-DM induces both insulin resistance and β-cell dysfunction. Fourth, the study draws our attention to the direction of earlier PDAC diagnosis. (11), the current findings could raise new hope for moving in the direction of earlier PDAC diagnosis.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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References


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