

Mechanism(s) of Pancreatic Cancer-induced Diabetes

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While long-standing diabetes (DM) modestly increases the risk of pancreatic ductal adenocarcinoma (PC), there is growing evidence that PC frequently causes DM. Up to 85% of PC patients have DM or hyperglycemia, which frequently manifests in the 2 to 3 years preceding the diagnosis of cancer. Conversely, subjects with new-onset DM have a high probability (5-8 folds higher than the population) of being diagnosed with PC within 1-3 years of DM onset. Resection of the PC leads to amelioration of DM. Type 2 DM occurs due to beta cell failure following decades of obesity-associated insulin resistance. As in type 2 DM, beta cell dysfunction and peripheral insulin resistance are seen in PC-induced DM (PC-DM). However, in contrast to type 2 DM, onset and progression of glucose intolerance in PC-DM occur in the face of ongoing, often profound, weight loss. The weight loss precedes the development of DM in PC and occurs months before the onset of cancer cachexia. Studies show that PC is associated with profound insulin resistance that resolves following PC resection. However, the very high frequency of DM suggests that there is associated beta cell dysfunction. There are many hypotheses for how PC might cause DM:

a) Is PC-DM simply type 2 DM? Canonical risk factors for DM (age, BMI and family history of DM) are also risk factors for PCDM. However, the fact that new-onset DM and hyperglycemia occur in 85% of PC suggest a PC-specific stressor that profoundly and consistently decompensates glucose homeostasis.

b) Could PCDM be a consequence of profound cachexia seen in PC? Cachexia is associated with insulin resistance which could potentially decompensate glucose homeostasis, especially in the elderly. This is unlikely to explain PCDM as.

c) Could obstruction of the pancreatic duct and consequent pancreatic atrophy cause PCDM? PC is frequently associated with obstructive pancreatitis and distal atrophy. However, onset of DM occurs at a time when CT does not even show a mass. Additionally, insulin levels would be expected to be low in patients with DM due to destruction of islet mass. Insulin levels are relatively high in PCDM, reflecting insulin resistance.

d) The most likely explanation for the frequent occurrence of DM in PC is that it is a paraneoplastic phenomenon caused by tumor secreted products. Apart from the clinical and epidemiological evidence noted above, this notion is supported by laboratory data that supernatant from PC cell lines inhibit insulin secretion.

Although much remains to be learned, new insights on the pathogenesis of these metabolic alterations in PC have recently emerged. Adrenomedullin, which is over-expressed in PC, was identified as a potential mediator of beta-cell dysfunction in PCDM. Adrenomedullin is a pluripotent hormone with homology semblance to amylin. In the pancreas, its receptors are found on beta cells and its expression is seen specifically in the F cells of the islets. Inhibition of insulin secretion in beta cells induced by supernatant from PC cell lines was replicated by external addition of adrenomedullin and abrogated by its genetic knockdown. Similar effects were seen in orthotopic and subcutaneous *in vivo* tumor models using adrenomedullin expressing PC cell lines. Further, plasma adrenomedullin levels were higher in PC compared to controls and even higher levels were seen in PCDM. Overexpression of adrenomedullin was seen in surgically resected specimens of PC. These data strongly support the notion that adrenomedullin mediates beta cell dysfunction. The cause of insulin resistance and PCDM-associated weight loss remains unclear, though these appear to be paraneoplastic phenomena as well. PC is associated with a unique mechanism of DM. The onset of DM occurs between 6 months and 365 months before PC diagnosis in 20-25% of patients. At this time patients are otherwise asymptomatic. This suggests that new-onset DM could be biomarker of asymptomatic PC. However, the strategy to use new-onset DM as a marker of asymptomatic PC will succeed only if PC-DM can be distinguished from the more common type2 DM. Identifying the mediators of PC-DM could lead to discovery of novel biomarkers of PC.
