Editorial

Exosomes containing adrenomedullin mediate new onset diabetes and weight loss in pancreatic cancer

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New onset diabetes and concurrent weight loss often occur several months before the clinical presentation of pancreatic cancer (PC). The authors suggest that both of these are paraneoplastic phenomena caused by the tumor-secreted product adrenomedullin (AM). In a prior report (1), they provide evidence for how AM causes new onset diabetes. In the current report, they give rationale for how AM causes weight loss. They propose that AM, delivered by exosomes to the pancreas, can explain both clinical effects.

As the authors note, most patients with PC die within six months of diagnosis (2), and a major contributor to early mortality is a loss of adipose tissue and muscle mass. They evaluated a possible rationale for the loss of adipose tissue. Using exosomes from patient derived cell lines and plasma from individuals with PC, they observed lipolysis in murine and human adipocytes. Lipolysis was also observed with AM, which decreased when the AM receptor was blocked. They posit that AM is a candidate mediator of PC induced lipolysis.

The authors previously reported that exosomes were the predominant extracellular vesicles secreted by PC, that PC exosomes contained AM as well as CA19-9, a known PC marker, and that the exosomes readily entered pancreatic β cells and inhibited insulin secretion (1). Moreover, AM in PC exosomes interacted with the AM receptor on β cells, and AM receptor blockade removed the inhibitory effect of exosomes on insulin secretion. AM or PC exosomes upregulated ER stress genes and increased reactive oxygen/nitrogen species (1).

AM was first reported in 1993, being isolated from a pheochromocytoma (3). AM is produced by many types of tumor cells but also by diverse types of normal cells (4). AM serves as a growth factor, prevents apoptosis, increases tumor cell motility and metastasis, induces angiogenesis (5), and suppresses the immune system. It increases tumor aggressiveness by inducing epithelial mesenchymal transition (6). AM is activated by hypoxia, acting as a survival factor for tumor cells. AM is found in a variety of body fluids including plasma, urine, saliva, sweat, milk, amniotic fluid and cerebrospinal fluid (4). AM levels in plasma are elevated in cardiovascular diseases, pulmonary hypertension, type 2 diabetes and in eye pathologies and is altered (in some cases increased, others decreased) in renal disorders (1). AM levels are elevated in many malignancies, though decreased in a few (4).

Of course, there are other known lipolytic factors which could be active in PC. To argue for AM, they authors indicate that their data demonstrate that PC exosomes induce lipolysis and the effect is abolished by blocking the AM receptor, suggesting that lipolysis induced by PC exosomes is dependent on exosomal AM. They suggest that PC exosomes lack sufficient TNF-α for this agent to be a major source of PC exosomal lipolysis. They acknowledge that other mediators, such as IL-6, could be at work in PC exosome-induced lipolysis, which could act either independently or in conjunction with PC exosomal AM.

The recent reports by the Mukhopadhyay lab extend the already robust evidence that AM is pleiotropic, influencing multiple mechanisms to drive a variety of human diseases. Moreover, the authors provide rationale for a new method of AM delivery, through exosomal transfer. The authors argue that circulating levels of AM are not sufficient to

explain the actions seen in PC. They argue that, on the other hand, when packaged into exosomes AM is delivered intracellularly in sufficient quantities to induce ER stress, cause perturbations in the unfolded protein response, suppression of insulin secretion, and ultimately pancreatic β cell death (1,7). The authors examined how exosomes were internalized in adipocytes, testing inhibitors of various endocytic pathways. They found evidence for caveolin-mediated endocytosis and macropinocytosis as possible mechanisms for exosome internalization in adipocytes (2). One wonders if exosomal transfer, rather than an increase or decrease in circulating levels, is the primary mechanism by which AM influences the development and progression of other cancers, as well as non-neoplastic diseases.

The study highlights the interconnections between diabetes and PC. Moreover, it gives insight into how exosomes can lead to pancreatic β cell dysfunction, suggesting multiple roles of AM in PC, including insulin resistance, beta cell dysfunction, leading to DM and weight loss due to lipolysis. Finally, it highlights how the loss of glucose control often presages PC (7).

The role of extracellular vesicles, of which exosomes is one type, in oncogenesis continues to expand (8). Virtually all cell types appear able to produce exosomes. Exosomes provide a means of intercellular communication for both normal and malignant cells and have been detected in many body fluids, including urine, semen, saliva, amniotic fluid, cerebrospinal fluid, bile, ascites, tears, breast milk and blood (8). Tumor cells use exosomes to promote their survival (9).

This article points out that tumor cells use exosomes to mediate paraneoplastic effects that are often seen with PC, new-onset diabetes and concurrent weight loss. One of the best studied paraneoplastic effects that is brought about through exosomes is immunosuppression. This is brought about through apoptosis of activated cytotoxic T cells and induction of myeloid-suppressive cells and T regulatory cells (2). Tumor exosomes are also involved in angiogenesis promotion, stromal remodeling, signaling pathway activation through growth factor/receptor transfer, chemoresistance, and genetic intercellular exchange (10).

Exosomes are considered potentially ideal for the delivery of various biomolecules and small molecule drugs. They are also being considered as a tool to treat cancer, either by downregulating gene expression or by increasing the immune system's tumor response (11). Exosomes can in theory be loaded either endogenously or exogenously, with passive loading enabled by a cell's native exosomal production mechanisms, whereas active loading requires co-incubation or electroporation of exosomes (11).

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