EXPANDED ABSTRACT

Extracellular purinergic signaling in pancreas

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ATP and other nucleotides/sides have now been recognized as important extracellular signaling molecules in many biological systems (1). In epithelia, ATP signaling is thought to regulate fluid transport, and exocrine glands are one of the first epithelia where the effect of ATP on ion channels and Ca^{2+} signaling was observed (2, 3). Nevertheless, many steps in ATP signaling, also known as purinergic signaling, remain to be clarified. This includes the questions of where and how ATP is released, which purinergic receptors are stimulated and where and how ATP is hydrolyzed by ecto-nucleotidases. In general, our studies aim to understand the role of purinergic signaling in communication between pancreatic acini and ducts. We have established that pancreatic acini release ATP and nucleotidases (4, 5) possibly from zymogen granules and we propose that pancreatic ducts are important sites for purinergic signaling, where the effect on specific receptors is translated into epithelial cell responses. Therefore, our recent studies focused on determining expression and effect of purinergic and adenosine receptors and their effect on Ca^{2+} and Cl^- transport.

For our studies we used freshly isolated rat pancreatic ducts and human duct cell lines often used for ion transport studies-PANC-1, Capan-1 and CFPAC-1. Investigation of the expression of proteins of interest included RT-PCR and Western blot analysis. Functionally, we monitored intracellular Ca^{2+} and Cl^- responses using Fura-2 and MQAE and electrophysiological responses.

Pancreatic ducts (rat and human) possess a number of purinergic P2 receptors from both the P2Y and P2X families. Human pancreatic duct cell lines express P2Y1, P2Y2, P2Y4, P2Y6 and P2Y11-14 receptors, as well as the P2X1, P2X2, P2X4, P2X5, P2X6 and P2X7 receptors (6). Responses in intracellular Ca^{2+} signals to certain agonists (UTP, BzATP and ivermectin) shows that at least P2Y2, P2Y4, P2X4 and P2X7 receptors are functional. Our latest study shows that these purinergic receptors may also regulate pancreatic Ca^{2+} transport, a process that involves the Na^+/Ca^{2+} exchanger and a number of Ca^{2+}-handling proteins, which both rodent and human pancreatic ducts express (7). Pancreatic ducts (rat and human) also express four types of adenosine receptors (A_1, A_{2A}, A_{2B} and A_3), though A_2 types are most abundant (8). Functionally, using intracellular Ca^{2+} and Cl^- measurements and electrophysiology we have determined that the A_{2A} receptors regulate the cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channels. Furthermore, these receptors are localized to the luminal membranes of pancreatic ducts. Taken together, the purinergic signaling plays an important role in regulation of exocrine function of the pancreas. P2 receptors affect Ca^{2+} signaling and homeostasis, Ca^{2+} regulated Cl^- and K^+ channels (9) and adenosine receptors can affect CFTR and thus secretion.

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