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The Pancreatic Renin-Angiotensin System: Does It Play a Role in Endocrine Oncology?

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Summary

The characterization of a local renin-angiotensin system in the pancreas has attracted much attention because of its potential clinical applications. A pancreatic renin-angiotensin system may be present in humans and may interact with islet cells. Nevertheless, our knowledge of the renin-angiotensin system in the human pancreas is still in its infancy, especially in the field of endocrine oncology. Much of our knowledge stems from the study of the pancreas and pancreatic endocrine tumors of rodents. Thus, the direction of future research should be based on in-depth and collaborative efforts between researchers in the various disciplines in order to apply the newly acquired scientific knowledge to the patient.

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The pancreatic islet consists of different types of hormone-secreting cells. It is the classic endocrine unit in the pancreas. The two most common diseases arising from the pancreatic islet are diabetes mellitus and pancreatic endocrine (islet cell) tumors [1, 2]. Recent data have shown the existence of another endocrine unit in the pancreas, the renin-angiotensin system (RAS) [3, 4, 5, 6, 7]. An interaction may exist between these two endocrine units in the pancreas. In fact, the RAS in the pancreas may be important in the regulation of islet blood flow and points to a pivotal role of islet blood perfusion for an adequate insulin release [8, 9]. In the clinical setting, the systemic RAS has largely been concerned because of its relationship to hypertension with diabetes and its complications [10, 11]. The pancreatic RAS may act in a similar manner and may have a role in acute pancreatitis [12]. However, the role of this local RAS in the pathogenesis of pancreatic endocrine tumors is unknown.

Pancreatic endocrine tumors are endocrine tumors arising from the cells in the pancreatic islet. They account for approximately 10% to 15% of primary pancreatic tumors. The tumors are divided into two groups, functional and non-functional tumors [13]. Functional tumors are those with clinical or biochemical evidence of hormonal production. These tumors are typed according to the hormonal syndromes they produce and are called by names such as insulinoma, glucagnonoma, gastrinoma, etc. Pancreatic endocrine tumors present an important challenge to the clinical management team because of their proteic manifestations, potential lethality and difficulty in predicting the clinical behavior (uncertain malignant potential) [14, 15].

Pancreatic endocrine tumor cell lines with variable hormonal phenotypes have been derived from pancreatic endocrine tumors of rodents [16, 17]. These cell lines provide a model for analyzing the factors that regulate hormone biosynthesis and cellular differentiation. They have been shown to be multi-potential in their capacity for hormone gene transcription. Angiotensinogen gene expression has also been found in a cell line derived from a pancreatic endocrine tumor of a rat [18, 19]. Thus, the effect of the RAS in pancreatic endocrine tumors may be a potential feature in the complex manifestation of this tumor.

The different components of the RAS have been documented and localized by in-situ hybridization or immunohistochemistry in the pancreas of the mouse, rat and dog. Tahmasebi and colleagues showed, for the first time, the presence of angiotensin I receptors and (pro)renin in the beta cells (insulin-secreting cells) of the human pancreatic islet [7]. Therefore, the pancreatic RAS may be present in humans and may interact with the classical endocrine unit, the islet cells. This pancreatic RAS may contribute to the pathogenesis of some human diseases.

Renin is secreted by cells in the juxtaglomerular apparatus of the kidney. Juxtaglomerular tumors (JGT), also known as reninomas, are uncommon renal tumors arising from these renin-secreting cells in the kidney [20]. Elevation of plasma renin levels and hypertension are typical features in patients with JGTs. Extra-renal JGTs have also been reported [21]. Unlike pancreatic endocrine tumors, all JGTs are benign. JGTs did not show metastasis, local invasion or recurrence, multifocality or bilaterality. To date, no JGT has been reported in the pancreas. On the other hand, JGTs are uncommon and the tumors may be misdiagnosed and confused with other more common tumors. The discovery of a local RAS in the pancreas alerts us to the possibility of detecting JGT in the pancreas in the future.

Further experiments should be done to elucidate the roles of pancreatic RAS in endocrine oncology. In-situ testing of the various components of the RAS in human pancreatic endocrine tumors should be performed. The expression of angiotensinogen, in particular, should be tested as it has been detected in the rodent pancreatic cell lines. Also, much of our knowledge stems from rodent pancreatic endocrine tumors. Up to now, no cell lines derived from human pancreatic endocrine tumor have been present. Such cell lines are essential for future research dealing with the relationship between the RAS and islet cells, the multi-hormonal secretory potential of endocrine tumors and the effect of various treatments on the tumors, etc.

The characterization of the local RAS in the pancreas has attracted much attention because of its potential clinical applications. Nevertheless, our knowledge of this is still in its infancy, especially in the field of endocrine oncology. The direction of future researches should be based on in-depth and collaborative efforts (molecular biologists, endocrinologists, pathologists, surgeons, etc) in order to apply the newly acquired scientific knowledge to the patient himself.

Key words Islets of Langerhans; Pancreatic Neoplasms

Abbreviations JGT: juxtaglomerular tumor

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