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Review

Paracrine and autocrine interactions in the human islet: More than meets the eye

Alejandro Caicedo [a,b,c,d,*]

[a] Department of Medicine, Miller School of Medicine, University of Miami, Miami, FL 33136, USA
[b] Department of Physiology and Biophysics, Miller School of Medicine, University of Miami, Miami, FL 33136, USA
[c] Program in Neuroscience, Miller School of Medicine, University of Miami, Miami, FL 33136, USA
[d] Diabetes Research Institute, Miller School of Medicine, University of Miami, Miami, FL 33136, USA

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ABSTRACT

The pancreatic islet secretes the hormones insulin and glucagon to regulate glucose metabolism. To generate an adequate secretory response, islet endocrine cells must receive multiple regulatory signals relaying information about changes in the internal and external environments. Islet cells also need to be made aware about the functional status of neighboring cells through paracrine interactions. All this information is used to orchestrate a hormonal response that contributes to glucose homeostasis. Several neurotransmitters have been proposed to work as paracrine signals in the islet. Most of these, however, have yet to meet the criteria to be considered *bona fide* paracrine signals, in particular in human islets. Here, we review recent findings describing autocrine and paracrine signaling mechanisms in human islets. These recent results are showing an increasingly complex picture of paracrine interactions in the human islet and emphasize that results from other species cannot be readily extrapolated to the human context. Investigators are unveiling new signaling mechanisms or finding new roles for known paracrine signals in human islets. While it is too early to provide a synthesis, the field of islet research is defining the paracrine and autocrine components that will be used to generate models about how islet function is regulated. Meanwhile, the identified signaling pathways can be proposed as therapeutic targets for treating diabetes, a devastating disease affecting millions worldwide.

Contents

* Tel.: +1 305 978 8319.
E-mail address: acaicedo@med.miami.edu

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1. Introduction

Diabetes mellitus is a common, disabling, and life-threatening disease. According to the Centers for Disease Control and Prevention, if current trends continue, 1 of 3 adults in the US will have diabetes by 2050. Today there is no cure for diabetes, but treatments include replacing the pancreatic hormone insulin, stimulating pancreatic beta cells to produce more insulin, or transplanting pancreatic islets of Langerhans. Thus, preserving glucose homeostasis and preventing diabetes critically depend on a well-functioning endocrine pancreas, the islets of Langerhans. Not surprisingly, the pancreatic islet has been intensively investigated. We know a great deal about how islet endocrine cells respond to glucose and how they couple these responses to hormone secretion. The basic mechanisms of islet function, however, have mainly been elucidated using animal models. As a result, our understanding of islet biology reflects anatomical and physiological features of islets from species other than the human, and in particular mice. Recent studies have revealed that islets from different species are so different that it is difficult to generalize findings from any particular species. An emphasis of this review is that to be relevant to human health, models of islet biology need to be reassessed by taking into account new findings about human islet structure and function.

As a consequence of a major effort aimed at moving therapeutic islet transplantation into the clinic, the incidence and quality of human islet isolations increased in the last decade [1]. Laboratories began using human islets to develop quality assays for transplantable human islet preparations [2]. This made human islets increasingly available for research purposes and ignited a new wave of studies of their functional properties. In the past, results on human islets were anecdotal. Now, however, with islet distribution programs, many groups world-wide are able to perform detailed mechanistic studies of human islet physiology in vitro. This has generated results that are often at odds with previous information gained from studying non-human species. Indeed, in a recent keynote lecture a renowned islet physiologist questioned whether he had wasted 25 years of his career conducting research on mouse islets! But thus far, detailed studies of human islets are only possible in vitro, and manipulation is limited to pharmacological tools. Cell-specific genetic interventions in islets in living mice will still be the gold standard for years to come for studying the role of particular signaling pathways in glucose homeostasis. Nevertheless, there is an impressive amount of new data that is providing an image of human islet biology not foreseen from rodent studies.

From the expression of voltage-gated channels to islet cell composition, from the basic mechanisms of beta cell division to autonomic neural control, investigators are revisiting the human islet [3–11]. The newly acquired information is slowly permeating the field, but it may take years for these findings to become accepted common knowledge. Needless to say, many results need to be confirmed, and there is skepticism, too. The rodent islet model is so ingrained that there is reluctance to view discrepant findings as real differences. There is a tendency to dismiss structural differences between islets from different species by considering them variations of a prototype that is based on the mouse islet. Thus, the porcine islet has been described as consisting of several mouse-like islets, and the human islet is viewed as a mouse islet with invaginations [12,13]. The mouse has been such a spectacular animal model in islet research that it has "murinized" our view of islet biology.

Yet human islets are different, and because diabetes is reaching epidemic levels they require special attention. One striking difference between human and mouse islets is that endocrine cells of different types intermingle more in the human islet. In the mouse islet, most insulin-producing beta cells only abut other beta cells, whereas most beta cells in the human islet are in contact with alpha cells, delta cells, or both [8,9,11]. These anatomical arrangements likely have consequences for cell-to-cell communication within the islet to the point where paracrine interactions may play a dominating role in orchestrating hormone secretion in the human islet.

The major theme of this review is autocrine and paracrine signaling mechanisms in human islets. We examine results showing how molecules known to work as paracrine or neural signals in rodent islets have unexpected roles in the human islet. While it is too early to provide a synthesis on how paracrine and autocrine signaling shapes human islet biology, the new results point at signaling pathways that could be interventional targets for the treatment of diabetes.

2. Anatomy of pancreatic islets

2.1. Paracrine interactions in human islets

Pancreatic islets are islands of endocrine tissue dispersed in the exocrine pancreas. They are composed not only of hormone-secreting endocrine cells but also of vascular cells, resident immune cells, and, in many species, neurons and glial cells of the neuroinsular complex (Fig. 1). Human islets are surrounded by a complex double basement membrane [14]. Each islet is a functional unit; it has all the elements to produce adequate responses to changes in glucose concentration. Indeed, in vitro hormone responses to glucose from isolated islets faithfully reflect the secretory activity of the endocrine pancreas in the organism [15]. When transplanted into diabetic individuals, islets take over glucose homeostasis and restore normoglycemia [1]. Examining the structure of islets provides important clues about how they perform this function.

Endocrine cells of the pancreas include insulin-secreting beta cells, glucagon-secreting alpha cells, somatostatin-secreting delta cells, and cells that secrete pancreatic polypeptide. The relative population of these cells varies from islet to islet, from individual to individual, from species to species, and from study to study [16,17]. In most species studied to date, beta cells are predominant. Human islets have a larger proportion of alpha cells than mouse islets (38% versus 18%) [11]. These numbers are disputed in the field of islet research, but perhaps more relevant than the relative proportion of these cells is how they are distributed within the islet. In human islets, alpha and delta cells are not segregated to the periphery as they are in the mouse islet. This has profound implications for islet function, as discussed next.

First, in human islets most if not all beta cells directly appose alpha cells, delta cells, or both (Fig. 1). The association of beta cells with alpha cells in human islets is so close that, after dispersion of islets into single cells, most beta cells remain attached to an alpha cell [9]. These intimate contacts have multiple effects for endocrine cell function. Interactions between membrane-bound molecules expressed in these cells promote function and survival [18]. Indeed, beta cells that are associated with alpha cells secrete more insulin when stimulated with glucose [19]. The proximity of beta cells with alpha cells further enables paracrine interactions.