

Alpha the versatile: Guardians of the islets

NEWLY REVEALED ROLES FOR α -CELLS BY BASIC RESEARCH

Glucagon secreted by pancreatic α -cells plays pivotal roles in systemic energy homeostasis mainly by regulating systemic glucose mobilization together with another important metabolic hormone, insulin. Recent application of incretin-based therapies to clinical diabetes refocused on the central roles of glucagon in the development of diabetic hyperglycemia. This revival of glucagon also enhanced the progress of basic research in α -cell biology, as targeting glucagon is now expected to be the next therapeutic approach in diabetes treatment.

α -Cell function is tightly regulated by various physiological inputs, including systemic energy status, central and autonomic nervous systems, and endocrine systems. In addition to those, the intra-islet microenvironment, where α -cells are located, has recently been shown to be important in the regulation of cellular functions, including glucagon secretion¹. Indeed, the anatomical analyses of human pancreatic islets show a tight positional association between α - and β -cells that enables communication with each other through their secretions by paracrine effects.

Many basic research studies have also sensationally revealed unexpected functions of α -cells. For a long time, α -cells had been believed to produce and secrete only glucagon to simply counteract the effect of insulin during hypoglycemia. Recent molecular biology studies of α -cells discovered that α -cells produce other hormones, including glucagon-like peptide (GLP)-1, glucose-dependent

insulinotropic polypeptide (GIP) and acetylcholine. They have a certain effect on the neighboring β -cell function of insulin secretion and survival through intra-islet effects². The central role of this α -cell-derived GLP-1 on GLP-1-mediated systemic glucoregulation has recently been suggested by *in vivo* genetic studies³. In other words, α -cell function, such as glucagon secretion, is regulated in an intra-islet manner by inputs from other endocrine cells, including insulin from β -cells and somatostatin from δ -cells, meanwhile α -cells certainly influence their neighboring cells through various outputs.

In addition, α -cells have also been shown to transdifferentiate into β -cells by the presence of insulin-positive cells with α -cell origin in lineage tracing analyses, confirming the role of α -cells as a source of β -cell regeneration². α -Cells are also reported to have an abundant proliferation capacity in cellular proliferation, and it is plausible that α -cells quantitatively control the islets mass in both β -cells and themselves. α -Cells could maintain their own population volume by their own proliferation. Simultaneously, α -cells might monitor the overall condition of the islets, including β -cell mass, possibly through intra-islet input from β -cells, and sometimes transdifferentiate into β -cells or an insulin-producing state to maintain β -cell volume and enough insulin supply.

These data suggest that α -cells possess versatile abilities to secrete multiple important hormones for energy homeostasis together with the preservation of islet mass. The roles of α -cells are bidirectional; α -cells are regulated by other islet cells, together regulating other islet cells. Thus, α -cells are suggested to play a central role in both the quality and quantity of islets by serving as 'guardians' of the islets (Figure 1)². These

also show the anatomical significance of the islet architecture and environment by which the α -cell is placed in the pancreatic islet together with other endocrine cells.

HUMAN EVIDENCE OF HIGH-PROLIFERATION CAPACITY OF α -CELLS AND THE NEW CONCEPT OF CELLULAR PLASTICITY IN α -RELATED CELLS

Recently, the versatile abilities of α -cells beyond glucagon secretion have been shown, indicating the possibility of α -cell-based regeneration therapy for β -cells in type 1 diabetes. However, these are proposed mainly based on observations in animal models, so the direct clinical or human evidence for these critical properties of α -cells, especially their proliferating capacity and its contribution to islet maintenance, has been lacking and awaited. Under the circumstances, the Kushner laboratory of Baylor College of Medicine, Houston, TX, USA, provided direct histological evidence of the high proliferative property of α -cells and related cells.

The report from Lam *et al.*⁴ clearly showed certain amounts of cellular proliferation of islet endocrine cells in adolescent and young adult type 1 diabetes patients, and also in the same generation of controls without diabetes. Among pancreatic endocrine cells, glucagon-producing cells were most proliferative compared with other cell types, such as β -cells, somatostatin-producing δ -cells, pancreatic polypeptide-producing PP-cells and ghrelin-producing ϵ -cells, showing the abundant proliferative potential of human α -cells. The α -cell proliferation was unexpectedly decreased in type 1 diabetes patients compared with controls. Interestingly, only one-third of proliferating islet cells were hormone-positive, and the other two-thirds were negative. These

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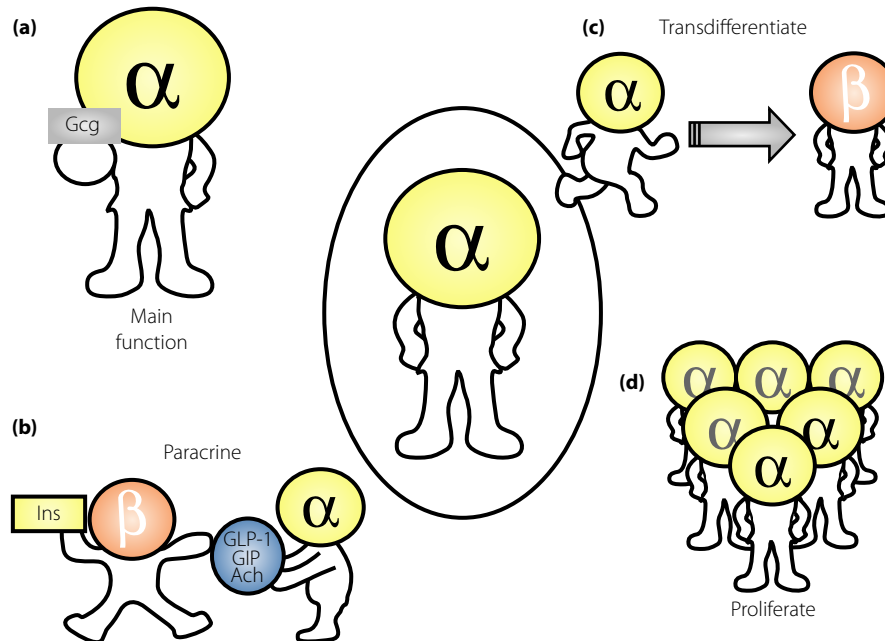


Figure 1 | Model of newly discovered multiple roles for α -cells as 'guardians' of the islets. (a) The main role is to produce and secrete glucagon (Gcg). (b) In addition to glucagon, α -cells also produce and secrete other hormones, including glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and acetylcholine (Ach), then modulate functions of surrounding β -cells including insulin (Ins) secretion through the paracrine effect. (c) α -Cells transdifferentiate into other type endocrine cells including β -cells. (d) α -Cell-related cells possess strong potentials of cellular proliferation. Some of the proliferating cells do not express glucagon (gray).

hormone-negative proliferating cells expressed a transcription factor, aristaless-related homeobox (ARX), that represents the α -cell signature, together with cytoplasmic expression of sex-determining region Y-box 9 (SOX-9), which is one of the critical factors for organ development. In other words, the majority of intra-islet proliferating endocrine cells in adult humans are α -cells, regardless of the glucagon-producing state or non-functioning state. It is still unclear whether this non-functioning state is in a transition phase from or to α -cells. In contrast, no possible sign of β -cell neogenesis or regeneration from α -related cells was detected in type 1 diabetes patients, whereas the islet cellular proliferation was comparable with control subjects. From these data, the authors suggested a fascinating new concept of α -cell plasticity that is not a simple tracing of the developmental stages of pancreatic islets.

The authors' detailed histological analyses of human pancreata revealed a novel population of highly proliferating glucagon-negative cells carrying α -cell

characters. The positive expression of SOX-9 in the islet proliferating cells would indicate the acquisition of multipotency, which is preferable to proliferate and transdifferentiate. The data not only confirm the proliferative potentials of α -cells, they also suggest the critical involvement of α -cells (or relatives) in islet cell growth. There is still a large controversy as to which cell is responsible for islet cell growth, maintenance or neogenesis – duct cells, acinar cells, endocrine stem cells, dedifferentiated cells, hematopoietic stem cells or extra-islet stem cells. Now, this newly discovered population composed of α -related cells seems to overtake others and come to the center stage of islet regeneration.

Importantly, this active proliferation in α - and related cells could induce an increase in the absolute or relative mass of glucagon-secreting α -cells compared with other endocrine cells, including critical β -cells. The change of islet α -cell mass in diabetes could not reach any certain consensus, despite many reports analyzing the α -cell mass in human

pancreas samples. As those studies were mainly using autopsy samples, it is possible that they are showing results in different stages of islet destruction/restructuring/regeneration or others. Given the results in rodent studies together with the current report, it is highly possible that α - and related cells are absolutely or relatively increased in diabetes patients. In type 2 diabetes in which β -cells are decreased but still remain, a relatively higher proportion of α -cells could induce an imbalance between glucagon and insulin, resulting in dysregulation in energy homeostasis. In type 1 diabetes patients in which β -cells are highly injured, remaining islets, composed mainly of α -cells, could secrete glucagon in a disorderly manner due to the absence of controls by β -cells. Indeed, we have recently found dysregulated plasma glucagon levels in Japanese young-adult type 1 diabetes patients⁵. The plasma glucagon levels evaluated by a newly-developed 'sandwich' enzyme-linked immunosorbent assay were generally higher and totally uncorrelated with

plasma glucose levels, suggesting dysregulated and excessive secretion. Taken together, it should be noted that the abundant proliferation properties of α - and related cells could be beneficial for preservation of islet mass in a healthy state, but, paradoxically, adverse by inducing an uncontrolled increase in α -cell mass and glucagon secretion. Further investigations would clarify the pathological significance of α -cell proliferation in the disease.

The current report provided direct histological evidence of the active proliferation of α -cells in humans, which has been previously reported in rodents. This is substantial progress in not only understanding the nature of α -cells, but also considering its possible application to regeneration therapy. In conclusion, recent progress in both basic and clinical research regarding glucagon and α -cells emphasizes the physiological and patho-

logical consequences of α -cells, and thus suggests important clues for future therapeutic approaches to diabetes.

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DISCLOSURE

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