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Evolving function and potential of pancreatic alpha cells

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The alpha cells that co-occupy the islets in association with beta cells have been long recognized as the source of glucagon, a hyperglycemia-producing and diabetogenic hormone. Although the mechanisms that control the functions of alpha cells, glucagon secretion, and the role of glucagon in diabetes have remained somewhat enigmatic over the fifty years since their discovery, seminal findings during the past few years have moved alpha cells into the spotlight of scientific discovery. These findings obtained largely from studies in mice are: Alpha cells have the capacity to trans-differentiate into insulin-producing beta cells. Alpha cells contain a GLP-1 generating system that produces GLP-1 locally for paracrine actions within the islets that likely promotes beta cell growth and survival and maintains beta cell mass. Impairment of glucagon signaling both prevents the occurrence of diabetes in conditions of the near absence of insulin and expands alpha cell mass. Alpha cells appear to serve as helper cells or guardians of beta cells to ensure their health and well-being. Of potential relevance to the possibility of promoting the transformation of alpha to beta cells is the observation that impairment of glucagon signaling leads to a marked increase in alpha cell mass in the islets. Such alpha cell hyperplasia provides an increased supply of alpha

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cells for their transdifferentiation into new beta cells. In this review we discuss these recent discoveries from the perspective of their potential relevance to the treatment of diabetes.

Introduction

Over nine decades ago the alpha cells were identified as the source of the hyperglycemia-producing "contaminant" factor contained in the pancreas extracts used to isolate insulin [1]. The hyperglycemic factor was named glucagon and subsequently shown to arise from alpha cells that co-occupy the islets of Langerhans in the pancreas along with the beta cells that produce insulin, and accompanying delta and PP cells that produce the hormones somatostatin and pancreatic polypeptide, respectively. The biological actions of glucagon are counter-regulatory to those of insulin. Insulin lowers prandial blood glucose levels by stimulating glucose uptake in peripheral tissues whereas glucagon raises postprandial (fasting) blood glucose levels by stimulating hepatic glucose production (gluconeogenesis). As a consequence of its glucose-elevating actions, glucagon was proposed 45 years ago to be diabetogenic, an important contributor to the fasting hyperglycemia that occurs in patients with diabetes [2].

The prevalence of diabetes, both type 1 (T1D) and type 2 (T2D), is increasing throughout the world at an alarming rate [3]. The fundamental cause of both types of diabetes is a failure of the beta cells in the pancreas to produce insulin in the amounts needed to efficiently modulate nutrient utilization. Both T1D and T2D are characterized by a reduction in beta cell mass; T1D as a result of near complete destruction of beta cells by autoimmunity and T2D as a result of a gradual loss of beta cells, and loss of function of remaining beta cells due to insulin resistance, hyperglycemia, and oxidative stress (glucotoxicity). The treatment of diabetes has involved both pharmacologic and cellular approaches [4]. Pharmacologic approaches include the use of insulin in T1D and drugs that increase insulin sensitivity and improve glycemic control in T2D. Cellular approaches include pancreas transplants and the transplantation of donor islets into the livers of T1D patients. Although helpful, these exogenous treatments currently in use for the treatment of diabetes are not fully effective in their normalization of glucose homeostasis. A major effort is directed at finding the means to stimulate the endogenous formation and growth of new beta cells in the pancreas to replace those destroyed by autoimmunity and by glucolipotoxicity. Such formation of new beta cells is believed to be possible by the stimulation of beta cell neogenesis from stem/progenitor cells that exist in the pancreatic ducts, or by the differentiation of exocrine stem-like cells into beta cells [5,6]. Most remarkable has been the recent discovery that the glucagon-producing alpha cells (and somatostatin-producing delta cells) of the islets are capable of trans-differentiation into insulin-producing beta cells [7–12]. This process of beta cell neogenesis and trans-differentiation (BCNT) for the creation of new beta cells in the pancreas opens up new avenues for research into devising a lasting treatment for diabetes, and is the topic of this review. Several review articles on the biology of alpha cells are available [1,13–20].

Proglucagon gives rise to proglucagon-derived peptides (PGDPs)

It is important to emphasize that the "glucagon" gene (Gcg) encodes a mRNA for a prohormone, proglucagon, that when translated into protein, contains several peptide hormones in addition to glucagon [21–23]. These hormones include glucagon-like peptides 1 and 2 (GLP-1, GLP-2), oxyntomodulin, glicentin, glicentin-related polypeptide (GRPP), and the intervening peptides 1 and 2. (Fig. 1). GLPs 1 and 2, and oxyntomodulin have demonstrated biological activities in the promotion of cell growth. These peptides are formed from the proglucagon precursor by selected enzymatic cleavages mediated by specific endopeptidases. These endopeptidases include the prohormone convertases (PCs) of the subtilisin-kexin class (Pcsks) that cleave proglucagon at sites of basic residues, lysine and arginine, and thereby liberate the parent peptide hormones, glucagon, oxyntmodulin, GLP-1, and GLP-2 from the prohormone [24]. The parent peptide GLP-1, produced from the PC-mediated cleavage of proglucagon, is further post-translationally modified by the removal of two amino-terminal amino acids by