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The human α cell in health and disease

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Abstract

In commemoration of 100 years since the discovery of glucagon, we review current knowledge about the human α cell. Alpha cells make up 30–40% of human islet endocrine cells and play a major role in regulating whole-body glucose homeostasis, largely through the direct actions of their main secretory product – glucagon – on peripheral organs. Additionally, glucagon and other secretory products of α cells, namely acetylcholine, glutamate, and GLP-1, have been shown to play an indirect role in the modulation of glucose homeostasis through autocrine and paracrine interactions within the islet. Studies of glucagon's role as a counterregulatory hormone have revealed additional important functions of the α cell, including the regulation of multiple aspects of energy metabolism outside that of glucose. At the molecular level, human α cells are defined by expression of conserved islet-enriched transcription factors and various enriched signature genes, many of which have currently unknown cellular functions. Despite these common threads, notable heterogeneity exists amongst human α cell gene expression and function. Even greater differences are noted at the interspecies level, underscoring the importance of further study of α cell physiology in the human context. Finally, studies on α cell morphology and function in type 1 and type 2 diabetes, as well as other forms of metabolic stress, reveal a key contribution of α cell dysfunction to dysregulated glucose homeostasis in disease pathogenesis, making targeting the α cell an important focus for improving treatment.

Keywords

alpha cell; pancreatic islet; type 1 diabetes; type 2 diabetes

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTEREST

The authors have no conflicts of interest to disclose.

INTRODUCTION

Twenty-five years after the discovery of glucagon in 1923, the pancreatic α cell was identified as its source (Sutherland & Duve 1948). Since then, the α cell has gained recognition for its physiologic role in preventing life-threatening hypoglycemia via the actions of glucagon on peripheral organs, thereby opposing the peripheral effects of β cell-derived insulin on glucose homeostasis. Additionally, multiple lines of evidence have implicated the α cell in disease, most notably diabetes. Early reports revealed improvements in fasting and postprandial glucose levels following glucagon suppression in animal models of and humans with type 1 diabetes (T1D), illustrating an integral role of altered α cell function in disease-associated hyperglycemia (Gerich et al. 1974; Sakurai et al. 1974). Later studies supported this notion and implicated glucagon in the development of other clinical manifestations of diabetes, including ketosis (Raskin & Unger 1978; Lee et al. 2011). These studies and numerous others led to introduction of the “bihormonal hypothesis” by Unger and Orci in 1975, whereby excess glucagon contributes to hyperglycemia in conditions of insulin deficiency or insufficiency, and even the proposal of a glucagonocentric view of diabetes pathogenesis later in 2012 (Unger & Orci 1975; Unger & Cherrington 2012). Despite this, relatively fewer studies have been conducted with a focus on the α cell compared to the β cell (Figure 1).

Here, we review what is known about α cells under normal and pathophysiologic states, with a focus on the human α cell. We begin with a discussion of the healthy α cell, including cell morphology, molecular profile, and function. We summarize studies characterizing how the α cell adapts to changes in metabolic demand during pregnancy, aging, and obesity. Finally, we compare and contrast how α cell physiology is altered in T1D and type 2 diabetes (T2D). Though the focus of this review is on the human α cell, we acknowledge the limitations in studying human tissue and draw upon studies performed in animal models where appropriate, while also outlining key inter-species differences in α cell physiology. Finally, we conclude with opportunities for future studies of human α cell biology and physiology that will further our knowledge of diabetes pathophysiology leading to new strategies for therapeutic interventions.

THE HEALTHY α CELL

Islet composition and morphology

Pancreatic islets of Langerhans are heterogenous clusters of cells that work together to promote whole-body glucose homeostasis. Endocrine cells are the major cell type within the islet including β, α, δ, γ, and ϵ cells (in order of abundance) defined by their production of the hormones insulin, glucagon, somatostatin, pancreatic polypeptide (PP), and ghrelin, respectively. Additionally, multiple non-endocrine cell types are present within the islet that have been shown to play important roles in islet function, including endothelial cells, pericytes, immune cells, and nerve terminals. In the human pancreas, islet composition varies by location: the posterior head of the pancreas possesses a “PP-rich” lobe in which islets are made up of mostly γ cells at the expense of the other endocrine cell types, particularly α cells (Malaisse-Lagae et al. 1979; Stefan et al. 1983). In contrast, γ cells are sparse throughout the body and tail of the pancreas, where α and β cells are most abundant.

Endocrine cell subpopulations within human islets are spatially intermingled, forming frequent heterotypic contacts (Brelje et al. 1989; Brissova et al. 2005; Cabrera et al. 2006); however, this cellular organization varies significantly by species (see "*Interspecies differences"* below). The close contact between different endocrine cell types serves as a structural basis for the important paracrine interactions that occur in the human islet. In particular, α cells make up an average of 30–40% of the endocrine cell population in the human islet, depending on the individual, and receive numerous inputs from other islet endocrine cells that regulate α cell secretion (Hartig & Cox 2020). Abundant levels of β cell-derived insulin and δ cell-derived somatostatin bind to surface receptors on the α cell to decrease glucagon secretion; additionally, other secreted products, such as β cell-derived GABA, also influence α cell secretion. While much less is known about the function of γ and ϵ cells within the human islet, exposure of mouse islets to exogenous PP suggests it may also exert an inhibitory effect on glucagon release (Aragón et al. 2015). Further, α cells secrete hormones and neurotransmitters that act in a paracrine manner to regulate islet function. Secreted products of the α cell and their effects on the islet, as well as neuroendocrine receptors expressed in human α cells, are further discussed in detail later in the article. Additionally, physical contacts between cells have also been shown to influence α cell function. For example, human α cells express *EphA4*, which encodes the EphA4 receptor that binds the membrane-associated ephrin A5 ligand on adjacent β cells; further, signaling through ephrin receptors has been shown to modulate glucagon secretion in a juxtacrine manner (Dorrell et al. 2011; Hutchens & Piston 2015). Regarding their association with non-endocrine cell types, human α cells appear to preferentially lie directly next to vascular cells as compared with β cells (Bosco et al. 2010); in contrast, sympathetic fibers only sparsely contact endocrine cells directly, and only few parasympathetic axons seem to penetrate the human islet (Ahrén 2000; Rodriguez-Diaz et al. 2011; Dolenšek et al. 2015).

Morphologically, α cells contain secretory granules approximately 250–300 nm in diameter with an electron-dense core surrounded by a halo of relatively less dense material (Deconinck et al. 1971; Pelletier 1977) (Figure 2). The appearance of the halo is somewhat controversial, with its size and electron density varying by fixation method, but it is generally accepted as being less prominent than that of β cell secretory granules (Deconinck et al. 1971). It is possible that organelles in α and β cells exhibit ultrastructural differences, as mouse α cells display more extensive endoplasmic reticulum (ER), less prominent Golgi apparatus, and narrower mitcochondria; further studies are necessary to determine if this is the case in human islets (Pfeifer et al. 2015). Some human α cells are also ciliated, with stimulation of cilia-enriched G protein-coupled receptors (GPCRs) shown to potentiate glucagon secretion (Wu et al. 2021); however, the extent to which α cells are ciliated and the role cilia play in the integration of extracellular signals from within or outside of the islet remains to be fully determined. Moreover, lipid-rich structures, which may include both lipofuscins and lipid granules, are also present in human α cells and may increase with age and in T2D, although the role they play in α cell function is not well understood (Cnop et al. 2011; Tong et al. 2020).

Alpha cell function

Glucagon—The main function of pancreatic α cells is to secrete glucagon, a 29 amino acid peptide hormone that is the product of posttranscriptional processing of preproglucagon (Bell et al. 1983). Preproglucagon is a 180 amino acid precursor encoded by the *GCG* gene that contains sequences for glucagon and glucagon-related peptides. Preproglucagon is cleaved to proglucagon in the ER, transported through the Golgi apparatus to the trans-Golgi network, and packaged into immature secretory granules, where it undergoes further processing (Guizzetti et al. 2014). Proglucagon is first cleaved into 2 major fragments: glicentin and major proglucagon fragment (MPGF) (Dey et al. 2005). Further processing within mature secretory granules occurs in a tissue-dependent manner: in pancreatic α cells, glicentin is cleaved into glucagon and glicentin-related polypeptide (GRPP) by prohormone convertase (PC) 2 (Mojsov et al. 1986; Rouillé et al. 1994). In contrast, PC1/3 is highly enriched in intestinal L cells, where MPGF is further processed into glucagon-like peptide-1 (GLP-1), GLP-2, and oxyntomodulin (Mojsov et al. 1986) (Figure 3A).

The promoter for the preproglucagon gene (*GCG*) contains four DNA elements identified as G1 through G4, with G3 and G2 lying most upstream and G4 and G1 most proximal to the transcription start site (Figure 3A). Elements G2, G3, and G4 confer islet-specific expression (G4 shares binding sites with the insulin gene), while G1 restricts glucagon gene expression to α cells (Cordier-Bussat et al. 1995; Morel et al. 1995; Ritz-Laser et al. 1999). Element G1 is activated by PAX6 and indirectly suppressed by PAX4 (Ritz-Laser et al. 2002; Trinh et al. 2003). There are also several enhancer regions and cAMP-responsive elements within the promoter region (Philippe et al. 1988; Cordier-Bussat et al. 1995; Kieffer & Habener 1999). As single-cell assays are developing, recent studies have been able to investigate other context-specific regulators of α cell genes. In an RNAi screen using αTC1 cells, Casteels et al. identified Smndc1 as a regulator of chromatin remodeler Atrx, which maintains repressive H3K9me3 marks at the insulin gene. Although significant differences exist between this cell line and primary cells, results were recapitulated using shRNA knockdown in human α cells, strongly suggesting relevance to human α cell physiology (Casteels et al. 2022).

While less is known about the mechanisms of glucagon release compared to insulin, human α cell exocytosis relies on calcium influx through P/Q-type calcium channels as well as activity of voltage-dependent sodium channels (Ramracheya et al. 2010; Hughes et al. 2018). Studies of mouse islets suggest that synaptotagmin-7 mediates calcium-regulated exocytosis in α cells and that SNAP25 and syntaxin-1A are critical to docking, fusion, and exocytosis of secretory granules from the readily releasable and reserve pools (Gustavsson et al. 2009; Andersson et al. 2011). Glucagon secretion is modulated by blood glucose concentrations, amino acids, circulating hormones, and paracrine and autocrine signals within the islet (discussed later in “Neuroendocrine receptors”). Select aspects of glucagon production and components of α cell transduction and secretory pathways are summarized in Figure 3. For an in-depth review on mechanisms of glucagon secretion and α cell nutrient sensing, we refer to the reviews by Gao et al. and Armour et al. in this special collection.

Glucagon plays an integral role in the maintenance of glucose homeostasis, which is mediated by its impact both at the systemic and local intra-islet level. The vast majority of glucagon's role in maintaining normoglycemia during fasting is achieved through its actions on the liver (reviewed extensively by (Jiang & Zhang 2003)). Briefly, activation of hepatic glucagon receptors (GcgRs) initiates a cAMP-dependent cascade that leads to simultaneous activation of glycogen phosphorylase and inhibition of glycogen synthase, promoting glycogenolysis and blocking glycogen synthesis, respectively. In parallel, hepatic glucagon signaling promotes gluconeogenesis by enhancing the expression of phosphoenolpyruvate carboxykinase (PEPCK), which catalyzes the rate-limiting step of the gluconeogenic pathway. Additionally, glucagon also activates the enzyme fructose 1,6-bisphosphatase (FBPase)-2, which indirectly promotes gluconeogenesis and inhibits glycolysis. Studies in rodent models demonstrate that glucagon may also regulate extrahepatic gluconeogenesis through its actions on the kidney and intestines (Mutel et al. 2011; Rahim et al. 2021). Further, glucagon may also modulate glucose homeostasis via its actions in the brain, where intracerebral glucagon promotes hyperglycemia in rodents via both cholinergic and α-adrenergic-dependent pathways (Marubashi et al. 1985; Amir 1986).

In addition to exerting systemic effects, glucagon also has an indirect impact on glucose homeostasis through its paracrine effects on islet β and δ cells. Despite the opposing whole-body actions of glucagon and insulin, multiple lines of evidence point toward the ability of intra-islet glucagon to enhance insulin secretion. Elegant studies by Rodriguez-Diaz et al. demonstrate the ability of glucagon to modulate the glycemic setpoint in human islets, as human islets exposed to a human GcgR-specific antagonist following transplantation into immunodeficient mice led to reduced human insulin production and shift in blood glucose level (Rodriguez-Diaz et al. 2018). Additionally, rodent studies demonstrate the ability of glucagon to promote insulin secretion under fed conditions via both the GcgR and GLP-1R (Svendsen et al. 2018; Capozzi et al. 2019); it remains to be seen whether this occurs in human islets. The GcgR receptor is also expressed by δ cells, where it stimulates somatostatin secretion, forming a negative feedback loop on α cell glucagon secretion (Patton et al. 1977). Finally, the GcgR is expressed by α cells, serving as a positive autocrine regulator (Ma et al. 2004).

Outside that of glucose homeostasis, other impacts of glucagon on nutrient metabolism are numerous and involve promotion of β-oxidation, inhibition of lipogenesis, and amino acid metabolism via enhanced uptake and ureagenesis in the liver (Richter et al. 2022). Multiple *in vivo* studies in humans implicate a role for glucagon in feeding behavior, as exogenous glucagon reduces food intake; rodent studies administering intracerebral glucagon suggest this effect of glucagon may be mediated through its actions on the hypothalamus (Schulman et al. 1957; Penick et al. 1961; Quiñones et al. 2015). Finally, glucagon may act on the kidney and heart to modulate renal excretion and cardiac function, although these aspects of glucagon physiology are less understood (Bankir et al. 2016; Petersen et al. 2018).

Other secreted factors—Beyond glucagon, the human α cell secretes several factors important for overall human islet function. Human islets are only sparsely innervated with parasympathetic fibers; instead, the α cell is a major source of intra-islet acetylcholine, which is secreted in response to α cell-specific stimuli such as low glucose (Rodriguez-Diaz

et al. 2011). Acetylcholine enhances β cell secretory response to glucose in an M3 receptor-dependent manner; additionally, intra-islet acetylcholine stimulates somatostatin secretion from δ cells, providing negative feedback on insulin secretion (Molina et al. 2014).

Another neurotransmitter secreted by α cells is glutamate. Expressed exclusively in human α cells, vesicular glutamate transporter 1 (vGluT1) is necessary for glutamate secretion and has been shown to co-localize with glucagon secretory granules in rat islets (Hayashi et al. 2003; Cabrera et al. 2008). Glutamate secretion is activated by stimuli that also promote glucagon secretion, providing further evidence that the two peptides are co-secreted (Hayashi et al. 2003; Cabrera et al. 2008). In the islet, glutamate has been established as a positive autocrine regulator of α cell function. Human α cells express alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)/kainate ionotropic glutamate receptors, the activation of which leads to robust increases in glucagon secretion under low glucose conditions; in contrast, metabotropic receptor agonists have no effect on glucagon secretion, suggesting little to no expression of these receptor subtypes in human α cells, contrary to what has been reported in rat islets (Tong et al. 2002; Uehara et al. 2004; Cabrera et al. 2008; Omar-Hmeadi et al. 2020).

Alpha cells have also been implicated as a local source of glucagon-like peptide-1 (GLP-1) in the islet. A subset of human α cells express PC1/3, which alternatively cleaves the proglucagon peptide into GLP-1, GLP-2, oxyntomodulin, and glicentin (Marchetti et al. 2012; Campbell et al. 2020) (Figure 3A). Isolated human islets secrete higher levels of active GLP-1 than mouse islets, suggesting a greater impact of intra-islet GLP-1R signaling in human islets (Campbell et al. 2020). GLP-1 binds its G_s-coupled GPCR on β cells, where it potentiates glucose-stimulated insulin secretion (GSIS) in a cAMP-dependent manner. Blockade of signaling through the GLP-1R in isolated human islets significantly blunts insulin secretion, further suggesting paracrine signaling through the GLP-1R plays an important role in GSIS under normal conditions (Campbell et al. 2020; Souza et al. 2020). Studies also show that α cells may increase their capability to produce GLP-1 by upregulating PC1/3 expression under certain conditions, such as in type 2 diabetes or following exposure to GLP1-R agonists (Marchetti et al. 2012; Campbell et al. 2020; Galvin et al. 2021; Saikia et al. 2021). Despite this, the abundance of glucagon in human islets is greater than 100x that of GLP-1 as measured by liquid chromatography–mass spectrometry (LC-MS) (Galvin et al. 2021); thus, the relative contribution of glucagon and α cell-derived GLP-1 to GLP-1R signaling in human islets remains to be defined.

Molecular profile

Signature genes and identity markers—Advances in RNA-sequencing (RNA-seq) technology have enabled for the unbiased identification of α cell signature genes, a selection of which appears in Table 1 (all genes in this table appear as α cell-enriched in two or more independent studies of human islets (Wang et al. 2016; Xin et al. 2016; Enge et al. 2017; Shrestha et al. 2021; Gurp et al. 2022; Tritschler et al. 2022)). Transcriptomic profiles of human α cells share some similarities with other mammalian species and can be largely recapitulated in α-like cells derived from embryonic stem (ES) cells, though there are notable exceptions (Li et al. 2020; Sachs et al. 2020; Weng et al. 2020; Tritschler et

al. 2022). While the function of many of these α cell-specific or "identity" genes has not been fully elucidated, some have been shown to have significant roles in islet function. For example, *DPP4* encodes a peptidase whose role is to regulate the bioavailability of various peptides, most notably GLP-1 through cleavage into its inactive form (Deacon 2019). Given the importance of intra-islet GLP-1R signaling in insulin secretion, DPP-4 likely serves an important role in overall islet function by modulating local GLP-1 pools, as illustrated by the successful use of DPP-4 inhibitors to treat T2D. Some evidence also suggests that DPP-4 activity changes in T2D islets, which might implicate it in disease pathophysiology (Omar et al. 2014). In addition, *FAP* is a closely related peptidase shown to be co-expressed with DPP-4 exclusively in human α cells and while its role in α cell function is largely unknown, it may also work to influence intra-islet signaling (Busek et al. 2015). Efforts to further characterize α cell signature genes are ongoing, as evidenced by recent work by Viloria et al. to define the role of vitamin-D-binding protein (DBP; encoded by *GC*) in α cell function. Deletion of DBP in mice leads to smaller α cells with altered electrophysiologic properties and impaired responses to glucose, likely due to alternative functions outside that of vitamin D transport (Viloria et al. 2020). Interestingly, *GC* polymorphisms have been associated with altered glucose homeostasis (Viloria et al. 2022), illustrating the potential of investigations into basic α cell biology to inform our understanding of diabetes risk.

Multiple islet-enriched transcription factors (TFs) are involved in the establishment and maintenance of human α cell identity, including ARX, MAFB, and PAX6; a comprehensive list of human α cell-enriched transcripts, including several TFs, can be found in Table 2. Notably, most of these factors are conserved across species, highlighting their importance in α cell development, maturation, and/or function. For a full discussion of α cell specification and development, we refer readers to the review by Brooks and Sussel published in this collection.

Neuroendocrine receptors—Alpha cells respond to a variety of external signals that modulate glucagon secretion after binding to neuroendocrine receptors on the cell membrane. A summary of major neuroendocrine receptors expressed on the α cell, their subtypes, and their overall effect on glucagon secretion is summarized in Table 3.

Heterogeneity—Studies at the single cell level reveal significant heterogeneity in human α cell gene expression and function. Recent single cell (sc) RNA-seq studies identified multiple α cell subclusters whose signatures vary by the level of expression of α-enriched genes including *ARX, IRX2, TTR, ALDH1A1,* and even *GCG* (Saikia et al. 2021). This is supported by work identifying two distinct populations of human α cells that varied by their abundance of granular zinc and glucagon content (Zadeh et al. 2020). Moreover, rare populations of α cells with increased expression of proliferative genes have been identified in adult human islets, which is in line with aging studies that demonstrate little change in α cell mass beyond early adulthood –see "Aging" section below (Segerstolpe et al. 2016; Fang et al. 2019). Consequently, multiple studies report heterogeneity in functional characteristics of α cells as well. Mouse α cells display a wide distribution in voltage-activated Na^+ and Ca^{2+} currents, K_{ATP} conductance, and changes in plasma membrane Ca^{2+} concentrations in response to varying glucose concentrations (Huang et al. 2011; Shuai et al. 2016). In

human α cells, variations in electrophysiologic properties, specifically capacitance and Na^+ currents, correlate with higher expression of α cell maturity markers and secretory genes as well as downregulation of ER stress markers (Camunas-Soler et al. 2020). This observation is further supported by work from our own group, in which we showed that human α cells co-expressing the transcription factors *MAFB* and *ARX* had higher expression of genes involved in nutrient sensing and glucagon secretion, while α cells expressing neither transcription factor had upregulated stress response genes (Shrestha et al. 2021).

Inter-species differences

Multiple differences exist between species in terms of islet α cell distribution, gene expression, and some aspects of α cell physiology. Arguably the most obvious is the variability in the distribution and abundance of α cells in the islet: compared to adult human islets, mouse islets have a lower percentage of α cells that are topologically confined to the mantle of the islet along with non-β endocrine cells, whereas β cells exclusively lie within the core of the islet (Brelje et al. 1989; Brissova et al. 2005; Cabrera et al. 2006). In canine islets, this "core-mantle" arrangement of islet β and α cells is not conserved, as α cells are also observed in the islet core (Redecker et al. 1992). Non-human primate islets exhibit a reverse core-mantle structure, where α cells are mostly observed in the core and are less abundant (Wieczorek et al. 1998; Brissova et al. 2005). In pigs, α cell distribution varies at the pancreas and islet level: one lobe is characterized by a small number of α cells found primarily at the islet periphery, while the other lobe has significantly greater abundance of α cells located throughout the islet (Wieczorek et al. 1998). We refer readers to (Steiner et al. 2010) for a comprehensive review of islet morphology across a range of species.

Studies comparing gene expression in α cells across species reveal both conserved and species-specific patterns. While global patterns in gene expression are highly correlative between mouse and human α cells, a closer evaluation of α-enriched genes reveal significant variations in expression, with some genes being highly expressed in human α cells but not mouse α cells (ex. *LDHA)* or vice-versa (Xin et al. 2016). A recent study published by Tritshler et al. expands upon this notion by performing a cross-species RNA-sequencing analysis of human, mouse, and pig islets. Notably, only ~6% of identified human α-enriched marker genes were shared between all three species; others were either expressed but not considered marker genes, were more enriched in another endocrine cell type, or were not detected at all in α cells (Tritschler et al. 2022) (Table 1).

These highlighted inter-species differences in α cells underscore the need for validation studies in human islets to be performed whenever possible. Efforts have been made to generate stem cell-derived human α cells, which could serve as a model system for primary α cells (Rezania et al. 2011; Peterson et al. 2020). These α-like cells express canonical α cell genes such as *ARX* and *PCSK2* and respond appropriately to glucose; however, they are not without limitations, including diminished responses to some modulators of glucagon secretion and altered gene expression compared to primary cells (Tables 1 and 2). Further, it is unknown whether these cells respond similarly to primary α cells *in vivo*, emphasizing the need for more comprehensive studies. The development of an immunodeficient glucagon knockout (GKO-NSG) mouse model improves upon previous challenges to study primary

human α cells over time *in vivo*, as identical glucagon sequences in mice and humans historically prevented the detection of circulating graft-derived vs. endogenous glucagon following human islet transplantation. The GKO-NSG mice harbor an in-frame deletion of exon 3 of the *Gcg* gene, which corresponds to nucleotides encoding amino acids 2–29 of glucagon; this genetic strategy renders undetectable glucagon levels while preserving production of other proglucagon-derived peptides such as GLP-1 (Tellez et al. 2020). Further, transplantation of human islets ameliorates the previously reported negative effects of interrupted glucagon signaling, making this a suitable model for the study of normal human α cell physiology.

Adaptations to other physiologic states

Aging—Islet endocrine cells are long-lived, and thus may be susceptible to age-related changes in mass and/or function (Drigo et al. 2019). The vast majority of α cells are estimated to be established by 20 years of age, with little replication afterwards (Cnop et al. 2011). Studies examining the association between α cell mass and age in humans report no drastic changes in α cell mass across time (Henquin & Rahier 2011; Moin et al. 2020). However, aged human islet endocrine cells display higher rates of transcriptional noise, increased expression of stress response genes, and shortened telomeres, suggesting that age may influence cell identity and/or function (Tamura et al. 2016; Enge et al. 2017). Studies of non-human primate α cells support this, where downregulated genes in aged α cells were enriched for gene ontology terms associated with peptide secretion and multiple metabolic processes (Li et al. 2020). Similar large-scale studies have not yet been performed in human α cells, although a recent study showed that aged human β cells have altered gene expression that correlates with a decline in function (Shrestha et al. 2022), highlighting the possibility that a similar phenomenon may occur in α cells.

Pregnancy—Pregnancy represents a scenario of increased metabolic demand, where placenta-derived hormones promote peripheral insulin resistance to meet increased energy needs of the developing fetus (Catalano et al. 1993). Pregnancy in humans is associated with a rise in plasma glucagon levels during the second trimester that falls in the third; however, glucagon responses during oral glucose tolerance test are normal, suggesting minimal functional changes (Luyckx et al. 1975). Most of what we know about pregnancy-induced islet adaptations comes from rodent studies, where pregnant C57BL/6 mice show increased α cell size, fractional area per pancreatic section, and mass in late pregnancy; despite these changes, reduced secretion in response to low glucose was also observed (Quesada-Candela et al. 2020; Qiao et al. 2022). These findings were recapitulated in *in vitro* experiments after cultured α cells were exposed to prolactin and placental lactogen, suggesting the involvement of placental hormones in this process (Quesada-Candela et al. 2020). However, a conflicting study reported no changes to α cell area during pregnancy, underscoring the complexity of possible α cell changes (Moffett et al. 2014). Glucagon may also be required for normal pregnancy progression, as pregnancies in $GcgR^{-/-}$ mice show decreased fetal size, increased fetal demise, and structural placental abnormalities (Ouhilal et al. 2012). Pregnancy in mice has also been associated with altered proglucagon processing, where α cells express higher levels of GLP-1 and PC1/3, which is mirrored by an increase in pancreatic GLP-1 content (Moffett et al. 2014). Ablation of α cells during

pregnancy leads to impaired glucose tolerance and reduced GSIS that is rescued by GLP-1R agonism but not glucagon, implicating an important role for α-cell derived GLP-1 in GSIS during pregnancy (Qiao et al. 2022). Of note, inter-species differences in α cell adaptations to pregnancy may exist, as pregnant C57BL/6 mice also exhibit decreased plasma glucagon in late pregnancy versus non-pregnant controls, which has not been observed in humans (Moffett et al. 2014; Quesada-Candela et al. 2020).

THE HUMAN α CELL IN T1D

T1D is characterized by autoimmune-mediated β cell destruction, resulting in a loss of β cell mass and systemic hyperglycemia. In contrast, multiple studies report normal α cell abundance, highlighting the cell-specific nature of the autoimmune process (Rahier et al. 1983; Campbell-Thompson et al. 2016; Bonnet-Serrano et al. 2018). In a small study of whole pancreata from human donors with T1D, Rahier et al. (1983) found decreased volume density of endocrine tissue in PP cell-deficient regions of the pancreas, which was further characterized by the presence of smaller islets with poorly defined borders and a higher proportion of α cells present in small clusters outside of the islets. While the overall proportion of α cells was increased, this was largely due to β cell loss; further, due to the overall reduction in pancreas weight, estimated α cell mass was similar between donors with T1D and controls (Rahier et al. 1983). These observations were largely replicated in a study of pancreata from over 70 donors with T1D and without diabetes available through the Network for Pancreatic Organ Donors with Diabetes (nPOD), which revealed no significant differences in α cell area or mass, regardless of autoantibody status or the presence of insulitis (Campbell-Thompson et al. 2016). While an additional study utilizing nPOD samples reported decreased α cell mass in T1D (Bonnet-Serrano et al. 2018), the authors attributed this finding to the significantly decreased total pancreas weight associated with T1D in the context of preserved α cell area; these discrepant findings could be due to differences in quantification and sampling methods.

In spite of preserved α cell abundance in disease, impaired glucagon secretion in T1D is well established. Individuals with T1D display similar levels of fasting glucagon as nondiabetic controls, which is inappropriate given their elevated fasting blood glucose (Unger et al. 1970; Gerich et al. 1973). In a study on glucagon responses in the fed state, carbohydrate-rich meals failed to suppress glucagon secretion in T1D participants, as compared to nondiabetic individuals that showed a robust decline in circulating glucagon (Müller et al. 1970). Additionally, those with T1D have increased plasma glucagon levels in response to infused arginine and, given their elevated blood glucose, inappropriately normal circulating glucagon following a protein-rich meal (Müller et al. 1970; Unger et al. 1970; Sherr et al. 2014). Despite the relative and/or absolute hyperglucagonemia demonstrated by these studies, individuals with T1D have impaired responses to hypoglycemia as well. While hypoglycemia normally stimulates glucagon secretion, individuals with T1D fail to respond appropriately despite preserved or even exaggerated increases in other counterregulatory hormones; this impairment appears to worsen over time (Gerich et al. 1973; Bolli et al. 1983). Together, these studies demonstrate a loss of sensitivity in glucagon response to acute changes in blood glucose in T1D.

Recent studies by our group and others have sought to further define and understand α cell dysfunction in T1D through the study of primary islets and pancreatic tissue from human donors. Primary T1D islets show multiple functional impairments in glucagon secretion, including lack of high glucose-mediated glucagon suppression, reduced amino acid-stimulated glucagon secretion, and decreased Ca^{2+} currents (Brissova et al. 2018; Camunas-Soler et al. 2020; Doliba et al. 2022). These functional impairments are accompanied by an altered α cell identity signature marked by decreased expression of the α-enriched TFs MAFB and ARX, upregulation of the β cell-enriched TF NKX6.1, and altered expression of genes important for α cell function (Brissova et al. 2018; Wang et al. 2019; Camunas-Soler et al. 2020).

Given the complexity of T1D pathogenesis, potential factors contributing to α cell dysfunction are numerous. A partial recovery of α cell transcriptomic profile is observed after transplantation into nondiabetic immunodeficient mice (Brissova et al. 2018), implicating a potential role for autoimmunity and/or systemic hyperglycemia in altered α cell identity state in T1D. Further, purified α cells aggregates isolated from islets from nondiabetic human donors secrete glucagon appropriately under low glucose conditions but fail to reduce their secretion in response to high glucose exposure when compared to mixed α and β cell aggregates or primary human islets, suggesting a role of β cell contact in the maintenance of α cell function (Liu et al. 2019). A recent study by Doliba et al. (2022) adds further nuance, describing that α cells from single autoantibody glutamic acid decarboxylase antibodies (GADA)+ islets also showed altered gene expression and glucagon secretory responses, despite no difference in islet composition or insulin secretion. These studies would suggest that α cell dysfunction begins prior to the onset of overt β cell loss and hyperglycemia; however, the role that loss of β-to-α cell contact and/or hyperglycemia plays in the progression of α cell dysfunction remains to be defined.

THE HUMAN α CELL IN OBESITY AND T2D

Obesity

Obesity is highly correlated with insulin resistance and is a major independent risk factor for the development of T2D. Reports of α cell abundance in obese individuals are mixed. A study focused on α cell mass in obesity conducted in Japanese individuals found that obesity had no impact on α cell area in surgically resected pancreas samples independent of diabetes status (Inaishi et al. 2016). Similarly, analysis of pancreata obtained at autopsy from a European cohort found no correlation between BMI and α cell mass (Henquin & Rahier 2011). In contrast, a study of pancreata from nondiabetic organ donors with obesity and undefined ancestry found increased α cell mass (Ellenbroek et al. 2017). These findings may be influenced by the pancreatic sampling location, as the latter study identified increased α cells in samples from the pancreatic head only (Ellenbroek et al. 2017). Nevertheless, *in vivo* studies of α cell function in obese individuals report fasting hyperglucagonemia despite preserved glucose-mediated glucagon suppression (Borghi et al. 1984; Bonora et al. 1990). This finding is associated with peripheral insulin resistance, as insulin sensitivity is negatively correlated with fasting glucagon level and impaired early glucagon suppression following glucose challenge (Færch et al. 2016). The pro-inflammatory nature of obesity

may play a role in these changes in α cell function, as human islets upregulate proglucagon expression and glucagon secretion *in vitro* following exposure to IL-6, a proinflammatory cytokine that is elevated in obese individuals and associated with increased risk of developing T2D (Spranger et al. 2003; Ellingsgaard et al. 2008).

Type 2 diabetes

Alpha cell dysfunction is also a hallmark of T2D, where hyperglucagonemia is well recognized. Individuals with T2D have inappropriately normal glucagon levels in the fasted state, elevated non-fasted plasma glucagon, and delayed glucose-mediated glucagon suppression (Müller et al. 1970; Unger et al. 1970; Reaven et al. 1987; Færch et al. 2016). In a study measuring glucagon levels throughout the day, plasma glucagon was significantly elevated with blood glucose levels, highlighting the important contribution of altered α cell secretory responses to systemic hyperglycemia observed in T2D (Reaven et al. 1987). Despite these known impairments in α cell function, the literature investigating pancreatic α cell fractional area and/or mass is less consistent, with studies reporting increased (Yoon et al. 2003; Mizukami et al. 2014), decreased (Sato et al. 2015), or no difference between individuals with T2D and nondiabetic controls (Henquin & Rahier 2011; Inaishi et al. 2016). The discrepancies in those studies could result from experimental differences, including sample type (archived autopsy specimens, surgical samples, or fresh donor pancreatic tissue), study population, pancreatic sampling location, and/or quantification methods; additionally, clinical parameters such as disease duration could play a role. For example, Yoon et al. (2003) evaluated pancreatic tissue obtained from organ donors and surgically-resected pancreatic samples in a Korean cohort and found a significant increase in median islet size in patients with T2D. Additionally, islets were characterized by an overall increase in α:β cell ratio, especially in larger islets, and an increase in the relative contribution of α cells to islet area; however, the authors at least partially contributed these observations to selective loss of β cells. Similarly, a study of pancreatic autopsy samples in a Japanese cohort found increases in α cell fractional area and mass, where those with the most marked increases in α cell fractional area also had a decrease in β cell fractional area (Mizukami et al. 2014). In contrast, another study evaluating pancreatic autopsy samples in a separate Japanese cohort found decreased islet size, decreased α and β cell fractional area, and preserved α:β cell ratio (Sato et al. 2015). To further highlight the controversial nature of these findings, a third study of surgically resected samples from Japanese individuals found no effect of T2D on α cell fractional area and increased α:β cell ratio due to decreased β cell fractional area (Inaishi et al. 2016); similar observations were found in autopsy samples from a European cohort (Henquin & Rahier 2011).

At the cellular level, studies of α cells in T2D reveal functional alterations. In a study utilizing imaging techniques to measure human α cell secretion, α cells within intact islets isolated from donors with T2D exhibited a bimodal response to increasing glucose, where granule exocytosis was observed at both low and high glucose (Omar-Hmeadi et al. 2020). This is similar to the secretory profile seen in dispersed nondiabetic α cells, suggesting α cells may lose response to paracrine regulators of glucagon secretion in the T2D disease state. This was further supported by observations that α cells in islets from donors with T2D were less responsive to somatostatin and insulin-mediated inhibition

(Omar-Hmeadi et al. 2020). Altered α cell response to high glucose in T2D was also observed by Dai and colleagues, who utilized Patch-seq techniques to correlate inappropriate secretory responses with altered expression of genes involved in cell fate commitment and pancreas development (Dai et al. 2021). Interestingly, high expression of α cell identity and maturity markers including *ARX, ISL1, RFX6, and MAFB* was highly correlated with impaired electrophysiologic profile in α cells isolated from islets from donors with T2D. Alpha cells with high *ARX* expression also had higher expression of progenitor genes such as *NEUROD1*, suggesting these seemingly more mature α cells are more susceptible to T2D-induced changes. Together, these studies provide multiple potential mechanisms for α cell dysfunction in T2D, including impaired nutrient sensing, loss of paracrine regulation, and/or acquisition of a less mature phenotype (Wang et al. 2016).

As we have discussed, α cell dysfunction is a feature of both T1D and T2D; thus, mechanisms of α cell dysfunction may either be common or disease specific. A recent study by Bosi et al (2022) addresses this question by comparing genes and pathways altered in primary α cells from donors with diabetes versus those in age-matched nondiabetic controls. Alpha cells in T2D upregulate pathways involved in defense against reactive oxygen species and strongly downregulate various glucose metabolism pathways (Segerstolpe et al. 2016; Bosi et al. 2022). In contrast, T1D α cells strongly upregulate those involved in immunity and ER stress. Interestingly, fewer differentially expressed genes are shared between T1D and T2D α cells, yet genes that overlap (e.g., *ARX*, *MAFB*, *PCSK2*) relate to both α cell identity and function. This would suggest that some aspects of α cell dysfunction may be disease-specific but converge on common regulators or pathways.

CONCLUSIONS

In this review, we have provided an overview of current knowledge around the human α cell. Studies in animal models have provided a strong foundation on which to base human studies and while our understanding of human α cell biology is ever evolving, there are many opportunities for future studies. For example, the vast majority of α cell genes altered in T2D have no known role in islet cell growth or function, emphasizing the need for more studies in basic α cell biology (Xin et al. 2016). Molecular studies of α cells in both T1D and T2D support the role of an intrinsic α cell defect and call for further investigation to understand disease development and progression as it relates to glucagon secretion. This is further emphasized by recent work demonstrating impairments in α cell function that precede β cell loss in GADA+ individuals, which underscore the need for molecular studies across T1D stages (Doliba et al. 2022). In particular, studies of islets from autoantibody positive individuals may reveal opportunities for new diagnostic tools for T1D and therapies for disease prevention. Additionally, comparative studies may further advance our understanding of human β cell biology, as some work suggests that the α cell is more resistant to undergoing senescence and stress-induced apoptosis than β cells in diabetes (Marroqui et al. 2015; Brawerman et al. 2022).

Given the role of α cell dysfunction in diabetes pathogenesis, targeting α cells may represent an avenue for diabetes treatment. Studies in rodents consistently demonstrate improvements in glucose homeostasis at baseline and in models of obesity, T1D, and

T2D following glucagon signaling blockade (Brand et al. 1994; Gelling et al. 2003; Sloop et al. 2004; Conarello et al. 2007). However, this is limited by significant side effects, including α cell hyperplasia and hepatic steatosis, that are directly due to blocking the other biologic functions of glucagon. Despite promising results, phase I and II trials of glucagon receptor antagonists reveal similar side effects, which would need to be further characterized prior to wide-scale usage (Sammons & Lee 2015). Further understanding of normal α cell physiology and mechanisms of dysfunction in T1D and T2D may reveal additional avenues for treatment.

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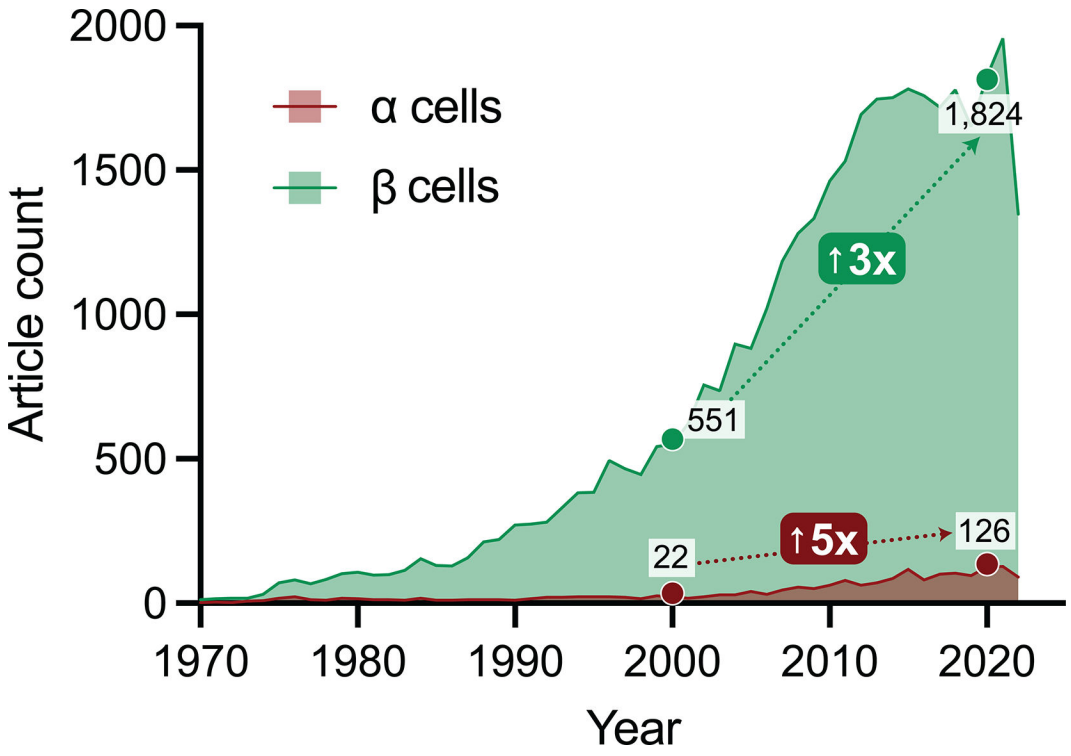

Figure 1. Articles published on α cells vs. β cells.

Graph shows a yearly count of research articles indexed in PubMed containing 'alpha cell' or 'beta cell' in the Title/Abstract field. Though α cells are mentioned far less frequently than β cells in paper titles and abstracts, there has been a rapid rise in research studies of both cell types in the past two decades (from 2000 to 2020, a three-fold increase for β cells and five-fold increase for α cells). The authors emphasize that this dataset represents only a small sample of α and β cell-related research but nonetheless reflects overall trends in the field.

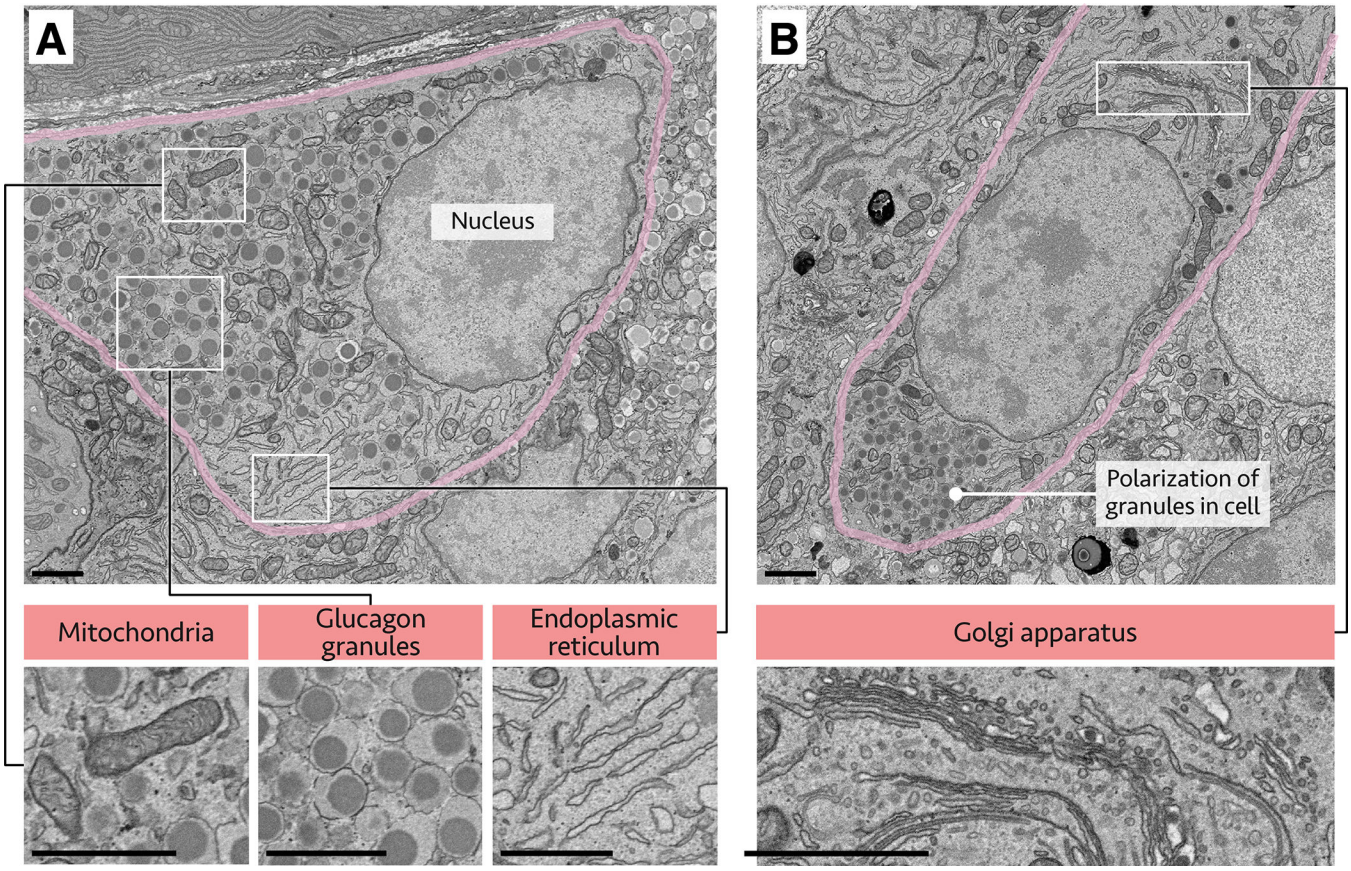

Figure 2. Ultrastructure of the human α cell.

Human pancreatic tissue imaged by electron microscopy; α cells are outlined in pink, with white outlined regions shown at higher magnification below. (A) Alpha cell with annotated nucleus, mitochondria, endoplasmic reticulum, and glucagon granules. (B) Polarized α cell with granules concentrated in one pole of the cell; Golgi apparatus also annotated. Scale bars, 5 μm. Images courtesy of Rafael Arrojo e Drigo (Vanderbilt University) and Thomas Deerinck and Mark Ellisman (UCSD).

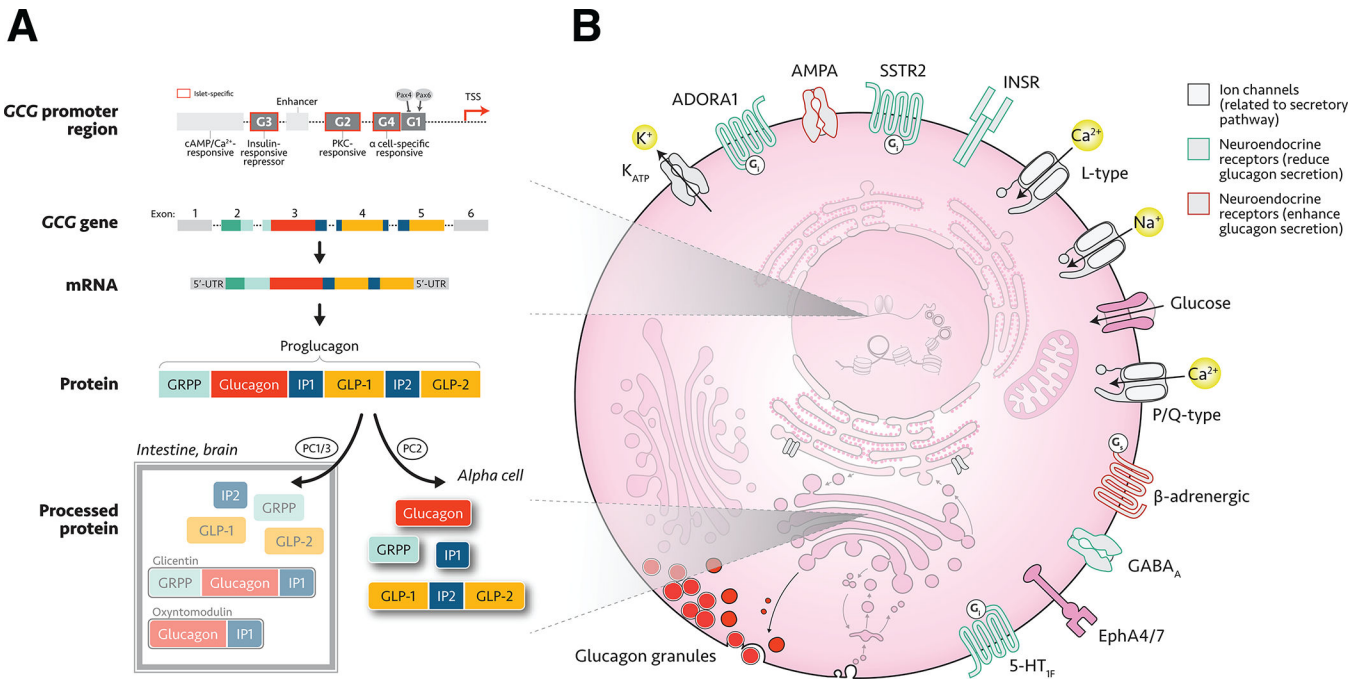

Figure 3. Glucagon gene expression and secretion in the human α cell.

(A) Overview of expression and post-transcriptional processing of proglucagon in the α cell, also showing differential processing in other tissues (boxed inset). Abbreviations: cAMP, cyclic adenosine monophosphate; PKC, protein kinase C; TSS, transcription start site; UTR, untranslated region; GRPP, glicentin-related pancreatic polypeptide; IP, intermediate peptide; GLP, glucagon-like peptide; (B) Schematic of major human α cellular components, including neuroendocrine cell surface receptors. For effects of these receptors on α cell physiology, see Table 3. Abbreviations: K^+, potassium; K_{ATP}, ATP-sensitive potassium channel; ADORA1, adenosine A1 receptor; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; SSTR2, somatostatin receptor 2; INSR, insulin receptor; Ca^{2+}, calcium; Na^+, sodium; GABA, gamma-aminobutyric acid; Eph, ephrin; 5-HT, serotonin.

Table 1.

Select human α cell signature genes from single cell RNA-sequencing studies

Gene	Description	Protein class	Human ES	Primate	Pig	Mouse
ALDH1A1	Aldehyde dehydrogenase 1 family member A1	Dehydrogenase	Exp	Exp	Switch	ND
CFC1	Cripto, FRL-1, cryptic family 1	Intercellular signal molecule	Exp	Exp		ND
CLU	Clusterin	*Intercellular signal molecule*	Exp	Switch	Exp	Exp
CRYBA2	Crystallin beta A2	Structural protein	Exp	Exp	Exp	Exp
DPP4	Dipeptidyl peptidase 4	Serine protease	Exp	ND	Exp	Exp
F10	Coagulation factor X	Serine protease	Exp	Switch	ND	ND
FAP	Fibroblast activation protein alpha	Serine protease	Exp	Exp	ND	ND
FXYD3	FXYD domain-containing ion transport regulator 3	Primary active transporter	Exp	Switch	Exp	Exp
FXYD5	FXYD domain-containing ion transport regulator 5	Primary active transporter	Exp	Switch	Exp	ND
GC	GC vitamin D binding protein	Transfer/carrier protein	Exp	Exp	Switch	Exp
GCG	Glucagon	*Peptide hormone*	Exp	Exp	Exp	Exp
GLS	Glutaminase	Hydrolase	Exp	Exp	Exp	Exp
HIGD1A	HIG1 hypoxia inducible domain family member 1A	Scaffold/adaptor protein	Exp	Exp	Exp	Exp
IRX2	Iroquois homeobox 2	Homeodomain transcription factor	Exp	Exp	Exp	Exp
KCTD12	Potassium channel tetramerization domain containing 12	Scaffold/adaptor protein	Exp	*	*	Exp
LOXL4	Lysyl oxidase like 4	Oxidase	Exp	ND	*	Exp
MUC13	Mucin 13, cell surface associated	*Transmembrane signal receptor*	Exp	ND	ND	ND
PALLD	Palladin, cytoskeletal associated protein	Scaffold/adaptor protein	Exp	Switch	ND	Switch
PCSK2	Proprotein convertase subtilisin/kexin type 2	Serine protease	Exp	Exp	Exp	Exp
PLCE1	Phospholipase C epsilon 1	Phospholipase	Exp	ND	ND	ND
PLIN3	Perilipin 3	Scaffold/adaptor protein	Exp	ND	ND	Exp
RGS4	Regulator of G protein signaling 4	GTPase-activating protein	Exp	Exp	Exp	Exp
SLC7A2	Solute carrier family 7 member 2	Amino acid transporter	Exp	Exp	Exp	Exp
SMIM24	Small integral membrane protein 24	*Transmembrane signal receptor*	Exp	Exp		ND
TMEM176A	Transmembrane protein 176A	*Transmembrane signal receptor*	Exp	Exp	Exp	Exp
TTR	Transthyretin	Hydrolase	Exp	Exp	Exp	Exp

Table 2.

Select human α cell identity markers from single cell RNA-sequencing studies

Gene	Description	Protein class	Human ES	Primate	Pig	Mouse
ARX	Aristaless related homeobox	Homeodomain transcription factor	Exp	ND	*	Exp
CHGA	Chromogranin A	*Intercellular signal molecule*	Exp	Exp	Exp	Exp
CHGB	Chromogranin B	*Intercellular signal molecule*	Exp	Exp	Exp	Exp
FOXA2	Forkhead box A2	Winged helix/forkhead transcription factor	Exp	Exp	Exp	Exp
FOXO1	Forkhead box O1	Winged helix/forkhead transcription factor	ND	Exp	Exp	Exp
GATA6	GATA binding protein 6	DNA-binding transcription factor	ND	ND	Exp	Exp
ISL1	ISL LIM homeobox 1	*Homeodomain transcription factor*	Exp	Exp	Exp	Exp
MAFB	MAF bZIP transcription factor B	Basic leucine zipper transcription factor	Exp	ND	ND	Exp
NEUROD1	Neuronal differentiation 1	Basic helix-loop-helix transcription factor	Exp	Exp	Exp	Exp
NKX2–2	NK2 homeobox 2	Homeodomain transcription factor	ND	Exp	Exp	Exp
PAX6	Paired box 6	Homeodomain transcription factor	Exp	Exp	Exp	Exp
POU6F2	POU class 6 homeobox 2	DNA-binding transcription factor	ND	ND	Exp	Exp
PTPRT	Protein tyrosine phosphatase receptor type T	Protein phosphatase	ND	ND	*	Exp
RFX6	Regulatory factor X6	Winged helix/forkhead transcription factor	Exp	Exp	Exp	Exp
SCG5	Secretogranin V	*Intercellular signal molecule*	Exp	Exp	Exp	Exp
SLC38A4	Solute carrier family 38 member 4	Amino acid transporter	Exp	Exp	Exp	Exp
WNT4	Wnt family member 4	Intercellular signal molecule	Exp	Exp	Exp	Exp

Table 3.

Select neuroendocrine cell receptor types expressed by the α cell

Receptor	Receptor type	Impact on glucagon secretion	References – rodent	References – human
Adenosine A1 receptor (ADORA1)	G_i-coupled	↓	(Johansson et al. 2007)	(Yip et al. 2013)
			(Yip et al. 2013)	
Epinephrine receptors	β-adrenergic: G_s-coupled α_1 adrenergic: G_q-coupled	↑	(Gromada et al. 1997)	(Hamilton et al. 2018)
			(Vieira et al. 2004)	
			(Hamilton et al. 2018)	
$GABA_A$ receptor	Ionotropic	↓	(Rorsman et al. 1989)	(Yang et al. 1994)
			(Wendt et al. 2004)	
Glucagon receptor (GcgR)	G_s-coupled	↑	(Ma et al. 2004)	
Glutamate receptor	AMPA/kainate subtype: ionotropic	↑	(Weaver et al. 1996)	(Cabrera et al. 2008)
Insulin receptor	Tyrosine kinase	↓	(Maruyama et al. 1984)	(Elliott et al. 2015)
			(Kawamori et al. 2009)	
			(Elliott et al. 2015)	
Somatostatin receptor (SSTR2, predominant)	G_i-coupled	↓	(Ludvigsen et al. 2003)	(Gerich et al. 1974)
				(Kumar et al. 1999)
				(Portela-Gomes et al. 2000)
$5\text{-}HT_{1F}$ serotonin receptor	G_i-coupled	↓		(Almaça et al. 2016)

Level of evidence: bold; RNA, italic; protein, underline; function