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Commentary

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Commentary on Paracrine GABA and insulin regulate pancreatic alpha cell proliferation in a mouse model of type 1 diabetes

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Abstract

A significant increase in pancreatic α-cells is observed in patients and animal models with recent-onset type 1 diabetes (T1D). Our recent studies suggest that the increase in α-cell proliferation in recent-onset T1D results, at least partially, from a decline of the paracrine factor γ-aminobutyric acid as a consequence of β-cell deficiency.

Five (α-, β-, δ, PP-, and ε) subtypes of endocrine cells are located closely within the pancreatic islets of Langerhans and they are responsible for the production and release of specific hormones that regulate glucose levels. Among these endocrine cells, α- and β-cells are mostly studied as they operate cooperatively under physiological conditions, secreting the 'counter-regulatory' hormones glucagon and insulin respectively thus ensuring normoglycaemia. Autoimmune destruction of the β-cells results in type 1 diabetes mellitus (T1D) because of a significant decline of insulin production. Intriguingly, in patients [1] and animal models [2] with recent-onset T1D, a significant increase in α-cells (α-cell hyperplasia) appears within pancreatic islets. However, treating T1D mice with insulin neither protects against β-cell loss nor inhibits α-cell proliferation [3]. The mechanisms underlying α-cell hyperplasia in recent-onset T1D has long been unclear.

Gamma-aminobutyric acid (GABA), a well-known inhibitory neurotransmitter is widely utilised as a signalling molecule by cells outside the central nervous system, including pancreatic β-cells [4-6], immune cells [7] and epithelial cells in the intestine [8], the lung [9-11] and the liver [12,13]. Unlike neurons, pancreatic β-cells produce GABA mainly through a pathway referred to as the GABA shunt [14], a closed-loop metabolic process occurring in mitochondria with the dual purpose of producing and conserving the supply of GABA. The GABA shunt starts with the transamination of α-ketoglutarate formed from glucose metabolism via the tricarboxylic acid cycle, by GABA/α-oxoglutarate transaminase, into L-glutamic acid. The latter is then catalyzed into GABA by decarboxylation via the enzymatic activity of glutamic acid decarboxylase (GAD). Early studies showed that the β-cells express GAD and produce GABA. In addition, type A GABA receptors ($GABA_AR$s), a class of ligand gated chloride channels, are expressed in both β- and α-cells [4,15,16]. Because of the disparity in expression levels of Cl^--intruding and chloride-extruding transporters, the intracellular Cl^-concentration is high in β-cells but low in β-cells [17,18]. As a result, stimulation of $GABA_AR$s in the β-cells causes Cl^- efflux and membrane depolarisation, increasing Ca^{2+} entry and insulin secretion [4,15,19], whereas activation of $GABA_AR$s in α-cells results in Cl^-influx and membrane hyperpolarisation, decreasing Ca^{2+} entry and glucagon release [16,20].

We recently explored whether GABA, as a paracrine factor, regulates α-cell proliferation using a mouse model with streptozotocin (STZ)-induced T1D [21]. We demonstrated that intraperitoneal STZ causes a rapid decline of GAD and insulin in β-cells, which is followed by elevated mTOR activity in α-cells (glucagon$^+$) 1 day after STZ and increased Ki67$^+$/glucagon$^+$ cells 2 days after STZ. By two weeks after STZ, a significantly increased α-cell mass appears in pancreatic islets, in which the GAD$^+$/insulin$^+$ cells decreases while the ALDH1a3$^+$/insulin$^+$ cells increases. Cells expressing high levels of ALDH1a3 display progenitor/stem cell-like features. Excitingly, treating the STZ-injected mice with GABA not only significantly reduces ALDH1a3$^+$/insulin$^+$ cells and increases the GAD$^+$/insulin$^+$ cells, but also prevents α-cell hyperplasia and hyperglucagonaemia. These findings suggest that in normal pancreatic islets, the autocrine GABA protects β-cell from injuries and/or phenotypic dedifferentiation while the paracrine GABA inhibits α-cell proliferation. Whereas, in early-onset T1D the increased α-cell proliferation might be initiated by a decline in the paracrine factor GABA and/or insulin, as a result of β-cell loss.

To explore whether the paracrine factor GABA or insulin restrains α-cell proliferation, we tested the effect of the selective $GABA_AR$ agonist muscimol and insulin, respectively, on proliferation of αTC1-6 cells, a widely used mouse pancreatic α-cell line. Our assays showed that muscimol alone has no effect on αTC1-6 cell proliferation while insulin significantly increases αTC1-6 proliferation as previously reported

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[22]. Remarkably, muscimol effectively prevents αTC1-6 proliferation in the presence of insulin. Given that insulin increases $GABA_AR$s on the surface of αTC1-6 cells [16], we propose that under physiological conditions, insulin maintains $GABA_AR$s on α-cells, where GABA, via $GABA_AR$s, retains α-cell proliferation.

How does the paracrine GABA signalling restrain α-cell proliferation? The Ca^{2+}-dependent activity of mTOR upregulates the proliferation and renewal of pancreatic endocrine cells [22,23]. Activation of $GABA_AR$s hyperpolarises α-cells [16] hence decreases voltage-gated Ca^{2+} channel activity. Indeed, our Ca^{2+}-imaging analyses show that GABA significantly lowered cytosolic Ca^{2+} of αTC1-6 cell. In addition, our immunoblotting assays showed that insulin increases the levels of p-mTOR and its downstream kinase p-P70S6K in αTC1-6 cells, whereas these effect of insulin are blocked by muscimol. Together, these data suggest that activating $GABA_AR$s reduces Ca^{2+} entry and lowers mTOR activity in α-cells hence inhibiting their proliferation.

On the basis of available data, we propose that in normal pancreatic islets, insulin signalling maintains a stable expression of $GABA_AR$s on the surface of α-cells, whereas GABA, through $GABA_AR$s, keeps these cells hyperpolarised hence restraining their cytosolic Ca^{2+}, mTOR activity and proliferation. Under conditions of T1D, however, severe β-cell loss and/or β-cell "dedifferentiation" result in a decline in intraislet insulin and GABA causing α-cell hyperplasia. Administration of GABA to rodents with STZ-induced diabetes facilitates β-cell generation [15] and prevents α-cell proliferation [21] hence improving glucose tolerance. Severe β-cell injury/loss induces α-to-β cell transdifferentiation [24]. In this regard, a recent study demonstrated that long-term stimulation of $GABA_AR$s facilitates α-to-β cell transdifferentiation in normal mice by regulating Pax4 expression [25]. The issue as to whether GABA inhibits α-proliferation but enhances α-to-β cell transdifferentiation in T1D conditions remains to be addressed by future studies.

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