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CHANGES IN MITOCHONDRIAL FUNCTION AND STRUCTURE WITHIN PANCREATIC BETA CELLS OF INDIVIDUALS WITH TYPE 2 DIABETES

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Abstract

Aims: There is limited knowledge regarding the insulin secretion characteristics of pancreatic islets derived from individuals with type 2 diabetes. Given that mitochondria play a central role in generating key metabolites that regulate insulin release, we investigated both insulin secretion and mitochondrial function and morphology in islets isolated from type 2 diabetic patients.
Methods: Pancreatic islets were isolated using collagenase digestion followed by density gradient purification. Insulin secretion in response to glucose and arginine was measured using the batch incubation method. Additionally, adenine nucleotide levels, mitochondrial membrane potential, expression of UCP-2, respiratory chain complexes I and V, and nitrotyrosine content were assessed and analyzed in relation to insulin secretion.
Results: Compared with control islets, islets from diabetic patients exhibited diminished insulin secretion in response to glucose. This defect was accompanied by reduced ATP content, a decreased ATP/ADP ratio, and impaired mitochondrial membrane hyperpolarization. Type 2 diabetic islets also showed increased protein expression of UCP-2, complexes I and V, and elevated nitrotyrosine levels. Morphological analysis revealed that while the number of mitochondria in beta cells was similar between diabetic and control groups, mitochondrial volume density was significantly greater in diabetic beta cells.
Conclusions: In pancreatic beta cells from type 2 diabetic subjects, impaired glucose-stimulated insulin secretion is closely associated with substantial alterations in mitochondrial function and structure. Notably, upregulation of UCP-2—likely reflecting a state of nutrient excess—results in decreased ATP production and a reduced ATP/ADP ratio, ultimately contributing to diminished insulin release.
Keywords
Type 2 diabetes mellitus, Pancreatic beta cells, Insulin secretion, Mitochondrial dysfunction, ATP/ADP ratio, Uncoupling protein-2 (UCP-2), Electron transport chain, Oxidative stress, Mitochondrial morphology, Glucose-stimulated insulin release.

Аннотация
Цели: Существует ограниченное количество данных о характеристиках секреции инсулина в панкреатических островках у пациентов с сахарным диабетом 2 типа. Поскольку митохондрии играют центральную роль в генерации ключевых метаболитов, регулирующих высвобождение инсулина, мы исследовали секрецию инсулина, а также функцию и морфологию митохондрий в островках, изолированных у пациентов с диабетом 2 типа.
Методы: Панкреатические островки были выделены с использованием коллагеназного переваривания с последующей очисткой по градиенту плотности. Секреция инсулина в ответ на глюкозу и аргинин оценивалась методом пакетного инкубирования. Дополнительно измерялись уровни адениновых нуклеотидов, мембранный потенциал

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митохондрий, экспрессия белка UCP-2, комплексов I и V дыхательной цепи и содержание нитротирозина, которые анализировались в связи с секрецией инсулина.
Результаты: По сравнению с контрольными островками, островки диабетических пациентов демонстрировали сниженную секрецию инсулина в ответ на глюкозу. Этот дефект сопровождался уменьшением содержания АТФ, снижением соотношения АТФ/АДФ и нарушением гиперполяризации митохондриальной мембраны. В островках диабетических пациентов также наблюдалось увеличение экспрессии белка UCP-2, комплексов I и V и повышение уровней нитротирозина. Морфологический анализ показал, что, хотя количество митохондрий в бета-клетках было сходным у диабетиков и контрольной группы, плотность митохондриального объёма была значительно выше у бета-клеток пациентов с диабетом 2 типа.
Выводы: В бета-клетках поджелудочной железы у пациентов с диабетом 2 типа нарушенная глюкозо-стимулируемая секреция инсулина тесно связана с существенными изменениями функции и структуры митохондрий. В частности, повышение экспрессии UCP-2 — вероятно, отражающее состояние избытка питательных веществ — приводит к снижению продукции АТФ и уменьшению соотношения АТФ/АДФ, что в конечном итоге способствует снижению высвобождения инсулина.

Ключевые слова

Сахарный диабет 2 типа, Бета-клетки поджелудочной железы, Секреция инсулина, Дисфункция митохондрий, Соотношение АТФ/АДФ, Белок UCP-2, Дыхательная цепь, Окислительный стресс, Морфология митохондрий, Глюкоз-стимулируемая секреция инсулина.

Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic and vascular disorder that has reached epidemic proportions and poses a significant global health challenge. Its prevalence is projected to rise from approximately 150 million individuals currently to 225 million by the end of the decade. Alarmingly, incidence rates are also increasing among children and adolescents. Long-term complications of T2DM impose a substantial burden of morbidity and mortality, with cardiovascular events being the leading cause of premature death in affected patients.

T2DM is primarily characterized by impaired insulin secretion from pancreatic beta cells in response to glucose, coupled with insulin resistance in target tissues. Clinical observations have highlighted the crucial role of beta cell dysfunction in disease development. Insulin resistance alone is insufficient to trigger T2DM in the absence of a beta cell defect, and patients with impaired glucose tolerance or early-stage T2DM consistently exhibit deficiencies in beta cell insulin secretion. The onset of clinical diabetes occurs when compensatory hypersecretion of insulin by beta cells is no longer adequate. The UK Prospective Diabetes Study (UKPDS) further demonstrated that insulin secretion progressively declines as the duration of T2DM increases.

Direct assessment of beta cell function in diabetic subjects could therefore provide valuable insight into the mechanisms underlying impaired insulin secretion. However, data on insulin release from islets isolated from T2DM patients remain limited. Previous studies on isolated pancreatic islets from diabetic subjects have reported conflicting findings: some observed normal glucose-stimulated insulin secretion ex vivo despite in vivo defects, suggesting the influence of extrapancreatic factors, while others reported significantly reduced insulin secretion, particularly in response to glucose, though responses to other secretagogues were less affected. Recent evidence indicates that islets from diabetic donors exhibit both reduced insulin output and an elevated threshold for glucose-stimulated insulin release.

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Altered insulin secretion in T2DM may result from genetic or acquired factors, including chronic hyperglycemia and elevated circulating non-esterified fatty acids, which can induce glucotoxicity and lipotoxicity. In normal beta cells, glucose regulates insulin release through its metabolism, with mitochondria serving as the site where key metabolites that control insulin secretion are generated. Several studies have emphasized the critical role of adenine nucleotides in this process, with an increased ATP/ADP ratio closely associated with glucose-stimulated insulin granule exocytosis. Beyond mitochondrial glucose oxidation, ATP production and the ATP/ADP ratio are modulated by the expression of uncoupling protein 2 (UCP-2), a mitochondrial inner membrane protein that acts as a proton channel, uncoupling oxidative phosphorylation, dissipating energy as heat, and reducing cellular ATP synthesis.

Given these considerations, the present study aimed to investigate insulin secretion alongside mitochondrial function and morphology in pancreatic islets from patients with T2DM. We assessed adenine nucleotide levels, mitochondrial membrane potential, expression of UCP-2, respiratory chain complexes I and V, nitrotyrosine content, and mitochondrial ultrastructure, and examined their correlation with insulin secretion. Our findings reveal notable differences between islets from diabetic and non-diabetic individuals, providing insights into the mitochondrial mechanisms contributing to impaired insulin secretion in T2DM.

Materials and Methods:

Human Islet Preparation: Pancreatic islets were isolated using collagenase digestion followed by density gradient purification, according to established protocols. All procedures were approved by the local Ethics Committee. For this study, islets were obtained from 11 non-diabetic multi-organ donors (mean age 58 ± 5.4 years; BMI 24.6 ± 1.4 kg/m², mean ± SEM) and from seven patients with type 2 diabetes (mean age 65 ± 6 years; BMI 27.4 ± 2.2 kg/m², mean ± SEM). The average duration of diabetes among patients was 5.6 ± 0.6 years, with plasma glucose at admission of 273.3 ± 38.5 mg/dL. Four diabetic donors were managed with dietary interventions only, two received sulfonylurea therapy, and one was treated with both sulfonylurea and metformin. Screening for GAD antibodies in three diabetic and three control donors yielded negative results. The digestion times were comparable between control (38 ± 3 min) and diabetic (36 ± 4 min) islet isolations. Isolated islets were resuspended in M199 culture medium containing 5.5 mmol/L glucose, supplemented with 10% adult bovine serum, antibiotics (penicillin 100 U/mL; streptomycin 100 μg/mL; gentamicin 50 μg/mL; amphotericin B 0.25 μg/mL), and cultured at 37°C in 5% CO_2.

Insulin Secretion: Insulin secretion was evaluated using the batch incubation method as previously described. Islets were pre-incubated for 45 minutes at 37°C in medium containing 3.3 mmol/L glucose. Subsequently, groups of approximately 30 islets of comparable size were incubated for 45 minutes in Krebs–Ringer bicarbonate (KRB) solution containing 0.5% albumin (pH 7.4) and 3.3 mmol/L glucose. After this basal period, the medium was collected to assess basal insulin secretion and replaced with KRB containing either 16.7 mmol/L glucose or 3.3 mmol/L glucose plus 20 mmol/L arginine. Following a further 45-minute incubation, medium was collected for analysis of stimulated insulin release. Insulin secretion was expressed as absolute concentration, as a percentage of total islet insulin content, and as a stimulation index (SI), defined as the ratio of stimulated to basal secretion. Insulin levels were quantified using a commercially available immunoradiometric assay (Pantec Forniture Biomediche, Turin, Italy).

Adenine Nucleotide Measurement: Adenine nucleotide levels were measured following established protocols. After islet incubation with either 3.3 or 16.7 mmol/L glucose, reactions were terminated by the addition of 0.125 mL of trichloroacetic acid (TCA) (Sigma, St. Louis, MO, USA), and extracts were stored at −80°C until analysis. ATP and ADP concentrations were

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determined in triplicate using a luminometric method. Total ATP+ADP was measured by first converting ADP to ATP, with parallel controls confirming complete conversion. ATP quantification was performed using a luciferase-luciferin reagent (Sigma, St. Louis, MO, USA), and emitted light was measured with a luminometer (Junior LB 283 9509-Berthold Technologies, Germany). For measurement of ATP alone, the same procedure was applied without the initial addition of pyruvate kinase, and ADP concentrations were subsequently calculated by subtracting ATP from total ATP+ADP. Blanks and ATP standards were included throughout the extraction and assay procedures to ensure accuracy.

Mitochondrial Membrane Potential: Mitochondrial membrane potential ($\Delta\Psi m$) was assessed using rhodamine-123 (Rh123) (Sigma, St. Louis, MO, USA) as a fluorescent indicator in islet cell suspensions under glucose stimulation (16.7 mmol/L). Cells were obtained from approximately 3,000 human pancreatic islets according to previously described methods. Briefly, islets were transferred into Ca^{2+}-free Krebs–Ringer bicarbonate (KRB) solution at 30°C containing 1 mmol/L EGTA, 16.5 µg/mL trypsin, and 2 µg/mL DNase (Boehringer, Mannheim, Germany), and gently dissociated using a Pasteur pipette. The extent of dissociation was monitored microscopically. Single-cell suspensions were cultured overnight in M199 medium at 37°C under 95% O_2/5% CO_2. For $\Delta\Psi m$ measurement, cells were incubated for 30 minutes at 37°C in KRB containing 3.3 mmol/L glucose and 10 µg/mL Rh123, then washed and resuspended in dye-free buffer. Fluorescence was measured in a fluorometer (Hitachi F-2000) at 37°C with excitation at 490 nm and emission at 530 nm, and results were expressed as a percentage of basal fluorescence measured at 3.3 mmol/L glucose.

Nitrotyrosine Determination: Nitrotyrosine levels in islet cell lysates were quantified by ELISA. Ninety-six-well plates were coated overnight at 4°C with standard curve solutions (0.166–15 nmol/L) and 1 µg/µL lysate samples (65 µL/well) in 0.1 mol/L carbonate–bicarbonate buffer (pH 9.6). Non-specific binding sites were blocked with 1% BSA in PBS-T (0.05% Tween-20) for 1 hour at 37°C, followed by incubation with monoclonal anti-nitrotyrosine mouse IgG for 1 hour at 37°C. Plates were washed and incubated with peroxidase-conjugated goat anti-mouse IgG for 45 minutes at 37°C. Color development was achieved using tetramethylbenzidine (TMB) substrate, followed by termination with 0.5 mol/L H_2SO_4, and absorbance was read at 492 nm.

Western Blot Analysis: Protein expression of UCP-2, NADH-ubiquinone oxidoreductase (complex I), F_1-ATP synthase (complex V), and SREBP-1c was evaluated by western blot. Groups of ~300 islets were homogenized by sonication in SDS-PAGE sample buffer. Equal amounts of protein were separated by SDS-polyacrylamide gel electrophoresis (Mini-Protean, Bio-Rad) and transferred onto nitrocellulose membranes (Amersham Pharmacia Biotech). Membranes were blocked and incubated overnight at 4°C with primary antibodies: rabbit polyclonal anti-UCP-2 (1:2,000), monoclonal anti-complex I (1:1,000), goat polyclonal anti-F_1-ATP synthase (1:1,000), or monoclonal anti-SREBP-1c (1:1,000). After washing, membranes were incubated with appropriate peroxidase-conjugated secondary antibodies. Signal detection was performed using enhanced chemiluminescence (ECL, Amersham Pharmacia Biotech).

Electron Microscopy: Ultrastructural analysis of pancreatic tissue was performed using transmission electron microscopy. Samples were fixed in 2.5% glutaraldehyde in 0.1 mol/L cacodylate buffer (pH 7.4) for 1 hour at 4°C, post-fixed in 1% osmium tetroxide for 2 hours at room temperature, dehydrated through graded ethanol, transferred to propylene oxide, and embedded in Epon-Araldite. Ultrathin sections (60–80 nm) were cut using a diamond knife, mounted on formvar-carbon coated copper grids (200 mesh), and stained with uranyl acetate and lead citrate.

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Statistical Analysis: Data are presented as mean ± SEM. Statistical significance was determined using Student's t-test for two-group comparisons or one-way ANOVA followed by Newman–Keuls post hoc test for multiple comparisons. A p-value < 0.05 was considered statistically significant.

Results:

Insulin Secretion: As summarized in Table 1, glucose-induced insulin release (16.7 mmol/L) was markedly reduced in islets from type 2 diabetic patients compared with non-diabetic controls. Because diabetic islets contained approximately 34% less total insulin than control islets (78 ± 4.7 vs. 118 ± 4.2 µU/islet, $p < 0.01$), insulin secretion was also expressed as a percentage of total islet insulin content (Table 2). Even when normalized in this manner, glucose-stimulated insulin release remained significantly lower in diabetic islets. In contrast, arginine-stimulated insulin secretion did not differ significantly between diabetic and control islets in either absolute or relative terms. These findings indicate a selective impairment in glucose-responsive insulin secretion in beta cells from type 2 diabetic subjects.

Adenine Nucleotide Content: The ATP/ADP ratio is a critical determinant of glucose-stimulated insulin secretion in human beta cells. Adenine nucleotide levels were therefore measured in islets under basal (3.3 mmol/L) and stimulatory (16.7 mmol/L) glucose conditions (Fig. 1). At baseline, diabetic islets exhibited higher ATP content than controls (14.22 ± 1.58 vs. 9.82 ± 0.31 pmol/µg islet DNA; n = 30 replicates for diabetic vs. 45 for controls; $p < 0.01$) and an elevated ATP/ADP ratio. Following glucose stimulation, ATP levels significantly increased in control islets (from 9.82 ± 0.31 to 16.11 ± 0.27 pmol/µg islet DNA; $p < 0.001$), whereas no significant increase was observed in diabetic islets (from 14.22 ± 1.58 to 13.22 ± 1.31 pmol/µg islet DNA). Consequently, the ATP/ADP ratio in response to glucose was significantly lower in diabetic islets than in controls (15.85 ± 0.98 vs. 24.14 ± 1.77; $p < 0.001$), reflecting impaired mitochondrial energy generation.

Mitochondrial Membrane Potential: Given that ATP synthesis depends on the proton gradient across the inner mitochondrial membrane, glucose-induced changes in mitochondrial membrane potential were assessed using Rh123 fluorescence. In control islet cells, raising glucose concentration to 16.7 mmol/L induced a hyperpolarization of $\Delta\Psi m$, reflected by a decrease in fluorescence (−9.6 ± 0.1%, mean ± SEM, n = 5; Fig. 2a). In contrast, islet cells from diabetic subjects exhibited attenuated hyperpolarization under the same conditions (−6.5 ± 0.54%, mean ± SEM, n = 4; $p < 0.001$; Fig. 2b). Addition of the uncoupler FCCP (1 µmol/L) depolarized $\Delta\Psi m$ in both diabetic and control cells, confirming mitochondrial responsiveness (Fig. 2). These results indicate that mitochondrial membrane polarization in response to glucose is compromised in beta cells from type 2 diabetic patients.

Mitochondrial Protein Expression and Nitrotyrosine Levels: To assess the expression of mitochondrial proteins involved in pancreatic beta cell energy metabolism, Western blot analysis was performed for uncoupling protein-2 (UCP-2) and respiratory chain complexes I (NADH-ubiquinone oxidoreductase) and V (F_1-ATP synthase). UCP-2 protein levels were significantly elevated in islets from type 2 diabetic subjects compared with controls (+24 ± 6%, mean ± SEM, n = 4; $p < 0.01$; Fig. 3). Similarly, the expression of both complex I and complex V proteins was increased in diabetic islets (+14 ± 4.5% and +31 ± 13%, respectively; n = 4; $p < 0.01$; Fig. 3). To determine whether the upregulation of UCP-2 was associated with increased expression of the transcription factor SREBP-1c, its protein levels were measured; no significant differences were observed between diabetic and control islets (Fig. 4).

Because enhanced respiratory chain activity can generate reactive oxygen species, oxidative stress was assessed by measuring nitrotyrosine, a stable marker formed by the reaction of

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superoxide with nitric oxide. Nitrotyrosine concentrations were significantly higher in diabetic islets (9.9 ± 0.4 nmol/L, n = 6) compared with control islets (7.2 ± 0.4 nmol/L, n = 7; $p < 0.05$), indicating increased oxidative stress in pancreatic beta cells from type 2 diabetic subjects.

Electron Microscopy Studies: Analysis of pancreatic endocrine cell composition revealed that in control preparations, beta, alpha, and delta cells constituted 69 ± 4%, 22 ± 4%, and 9 ± 2% of the islet population, respectively (mean ± SEM, n = 4). In diabetic subjects, the corresponding proportions were 61 ± 3%, 25 ± 7%, and 14 ± 5%. Cell viability, assessed by trypan blue exclusion, exceeded 90% in both controls (n = 5) and diabetic samples (n = 3).

Ultrastructural examination demonstrated that mitochondria in beta cells from type 2 diabetic patients were round-shaped and hypertrophic (Fig. 5). Although the total number of mitochondria per microscopy field was comparable between diabetic and control beta cells (12.0 ± 0.9 vs. 12.4 ± 0.6; n = 108 vs. n = 112 cells from three pancreases each), mitochondrial volume density was significantly increased in diabetic beta cells (4.7 ± 0.3 ml %) compared with controls (3.1 ± 0.4 ml %; $p < 0.01$). These findings indicate a substantial alteration in mitochondrial morphology in beta cells from type 2 diabetic subjects.

Discussion: In pancreatic islets isolated from seven multiorgan donors with type 2 diabetes, we observed a pronounced reduction in glucose-stimulated insulin secretion, whereas insulin release in response to the non-nutrient secretagogue arginine was only minimally affected. To elucidate the mechanisms underlying this selective defect, we focused on mitochondrial metabolism, as the rise in ATP and the ATP/ADP ratio is a key determinant of glucose-induced insulin release. Several critical steps in mitochondrial ATP generation were measured and correlated with insulin secretion.

ATP production relies on the oxidation of reducing equivalents via the electron transport chain, which comprises complexes I through V located in the inner mitochondrial membrane. Electron flux along the respiratory chain establishes a proton gradient, generating the mitochondrial membrane potential ($\Delta\Psi m$). In response to glucose, reducing equivalents are transferred to the respiratory chain, causing hyperpolarization of $\Delta\Psi m$ and stimulating ATP synthesis. In islets from diabetic subjects, glucose-induced mitochondrial hyperpolarization was attenuated, accompanied by lower ATP levels and a blunted ATP/ADP ratio.

These defects could theoretically result from reduced electron flux through the respiratory chain or from overexpression of proteins, such as uncoupling protein-2 (UCP-2), which diminish the proton gradient. Assessment of respiratory chain protein expression revealed increased levels of complexes I and V, making impaired electron flux an unlikely explanation. In contrast, UCP-2 protein expression was significantly elevated in diabetic islets. UCP-2, located in the inner mitochondrial membrane, uncouples oxidative phosphorylation by dissipating the proton gradient as heat, thereby reducing ATP synthesis. Its upregulation may be triggered by increased reactive oxygen species (ROS), consistent with the elevated nitrotyrosine levels observed in diabetic islets, indicating heightened oxidative stress.

Taken together, these findings suggest that in beta cells from type 2 diabetic patients, increased UCP-2 expression contributes to reduced mitochondrial hyperpolarization, decreased ATP production, a lower ATP/ADP ratio, and consequently impaired glucose-stimulated insulin secretion.

This mechanistic sequence aligns with previous in vitro and animal studies. Elevated UCP-2 levels in beta cells are consistently associated with reduced insulin secretion, and overexpression of UCP-2 in rat pancreatic islets inhibits glucose-stimulated insulin release by decreasing ATP formation. In rodent islets chronically exposed to high glucose or non-esterified fatty acids, impaired insulin secretion correlates with mitochondrial dysfunction, UCP-2 overexpression, and

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diminished ATP production. Similarly, hyperglycaemic rat models and human islets exposed to high glucose demonstrate increased UCP-2 mRNA or protein levels along with reduced glucose-induced insulin release. In beta cell lines, chronic exposure to elevated NEFA decreases insulin secretion while increasing UCP-2 expression, thereby altering glucose-stimulated ATP production. Conversely, studies in Zucker diabetic fatty (ZDF) rat islets suggest that modulating UCP-2 to enhance the ATP/ADP ratio can restore insulin secretion, highlighting its central role in beta cell dysfunction.

Further Insights from Mitochondrial Morphology and Beta Cell Function: Morphological analyses provide additional evidence that mitochondria in beta cells from type 2 diabetic patients exist in an altered state. Electron microscopy revealed that mitochondrial volume density was significantly higher in diabetic beta cells compared with controls. Mitochondrial structural changes often reflect functional adaptations under both physiological and pathological conditions. Enlargement of mitochondria, which can manifest as either swelling or the formation of megamitochondria, is generally considered an adaptive response to cellular stress. For instance, exposure to excessive reactive oxygen species can induce mitochondrial enlargement, which decreases oxygen consumption and reduces ROS production, thereby serving as a protective mechanism. Such adaptive processes are likely relevant to beta cell function in diabetes. Supporting this notion, mitochondrial swelling has been reported in sural nerve biopsies from patients with diabetic neuropathy. Additionally, impaired glucose-stimulated insulin secretion in isolated rat islets has been associated with mitochondrial enlargement, and exposure of human pancreatic islets to cytotoxic cytokines induces both mitochondrial swelling and beta cell dysfunction.

Functionally, our data demonstrate a selective impairment in insulin secretion in response to glucose, whereas arginine-stimulated secretion was only minimally affected. This highlights an intrinsic, glucose-specific beta cell defect in type 2 diabetes. Importantly, arginine-induced insulin release is largely independent of ATP synthesis, acting directly on membrane potential and ion flux in beta cells.

Collectively, these findings indicate that in pancreatic beta cells from type 2 diabetic individuals, defective glucose-stimulated insulin secretion is closely associated with significant mitochondrial dysfunction. Excessive nutrient availability increases substrate flux through mitochondrial metabolic pathways, generating high levels of ATP and reactive oxygen species. Under these conditions, UCP-2 expression is upregulated, leading to decreased ATP production and a reduced ATP/ADP ratio, ultimately impairing insulin release. Understanding these mechanisms in greater detail, and identifying specific molecular targets, could substantially improve strategies for preserving beta cell function in patients with type 2 diabetes.

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