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Molecular mechanisms of regulation and damage of β-cells in the development of experimental dexamethasone-induced diabetes

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

According to the World Health Organization (WHO), diabetes mellitus remains one of the most prevalent and rapidly increasing non-communicable chronic diseases worldwide. Over the past few decades, there has been a consistent trend towards an increase in the number of patients in developed, as well as low- and middle-income countries. This trend is driven by a complex set of factors, including urbanization, sedentary lifestyles, poor nutrition, overweight and obesity, population aging, as well as comorbid pathology.

The aim of this study was to identify and analyse the expression of genes involved in the morphological and secretory regulation of β-cells and their alterations in response to damage under conditions of the development of experimental dexamethasone-induced diabetes.

Materials and methods. The analysis of gene expression involved in the morphological and secretory regulation of β-cells, as well as changes associated with their damage, was performed using real-time reverse transcription polymerase chain reaction on a CFX-96 Touch™ amplifier (Bio-Rad, USA) with the RT²Profiler™ PCR Array Rat Diabetes kit (QIAGEN, Germany).

Results. Based on the PCR analysis, the activity of the investigated genes involved in the morphological and secretory regulation of β-cells can be categorized as follows: *Parp1* – a gene exhibiting increased expression compared to the control group of animals; *Enpp1, Ide*, *Trib3*, *Ucp2, Ccl5*, *Cd28*, *Icam1*, *Il12b*, *Tgfb1, Tnfrsf1a* – genes demonstrating decreased expression compared to the control group of animals; *Ceacam1, Dusp4, Retn, Ctla4, Ifng, Ikbkb, Il10, Il4r, Il6, Igfbp5, Tnf* – genes in which no significant changes were detected in the samples relative to the control group of animals; *Adra1a, Agt, Foxc2, Slc2a4, Srebf1, Tnfrsf1b* – genes whose expression was not detected.

Conclusions. The development of dexamethasone-induced diabetes significantly increased expression (ΔΔCt < 30) of the *Parp1* gene by 3.06-fold compared with the control group of animals. Under dexamethasone-induced diabetes, significantly decreased expression (ΔΔCt < 30), relative to the control group, was observed for the following genes: *Enpp1* (12.55-fold), *Ide* (3.31-fold), *Trib3* (7.74-fold), and *Ucp2* (9.76-fold), which are involved in the mechanisms of insulin secretion regulation, *Ccl5* (2.27-fold), *Cd28* (23.98-fold), *Icam1* (4.54-fold), *Il12b* (4.38-fold), and *Tgfb1* (3.76-fold), which are associated with autoimmune destruction of β-cells; and *Tnfrsf1a* (130.97-fold), which is implicated in survival and apoptosis mechanisms. The expression of *Adra1a, Agt, Foxc2, Slc2a4, Srebf1, and Tnfrsf1b* was not detected under conditions of dexamethasone-induced diabetes.

Keywords: pancreas, diabetes mellitus, genes, insulin, insulin resistance, differentiation, β-cells, apoptosis, proliferation, autoimmune destruction, laboratory diagnostics.

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Молекулярні механізми регуляції та ушкодження бета-клітин при розвитку експериментального дексаметазонового діабету

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Згідно з даними Всесвітньої організації охорони здоров'я, цукровий діабет залишається однією з найпоширеніших і найшвидше зростаючих неінфекційних хронічних патологій у світі. За останні десятиліття спостерігається стійка тенденція до збільшення кількості хворих як у розвинених, так і в країнах із низьким та середнім рівнем доходу. Така динаміка зумовлена комплексом чинників, серед яких — урбанізація, малорухливий спосіб життя, нераціональне харчування, надмірна маса тіла та ожиріння, старіння населення, а також супутня патологія

Мета роботи – визначення та аналіз експресії генів, що беруть участь у морфологічній та секреторній регуляції бета-клітин та зміни при їх ушкодженні за умов розвитку експериментального дексаметазонового цукрового діабету.

Матеріали і методи. Аналіз експресії генів, що беруть участь у морфологічній та секреторній регуляції бета-клітин та зміни при їх ушкодженні проводили за допомогою метода полімеразної ланцюгової реакції зі зворотною транскрипцією в режимі реального часу на ампліфікаторі CFX-96 Touch ™ (Bio-Rad, США) за допомогою набору RT²Profiler™ PCR Array Rat Diabetes (QIAGEN, Німеччина).

Результати. За результатами проведеного ПЛР дослідження можна розподілити активність досліджуваних генів, що беруть участь у морфологічній та секреторній регуляції бета-клітин наступним чином: *Parp1* – ген з високою експресією в порівнянні з контрольною групою тварин; *Enpp1, Ide*, *Trib3*, *Ucp2, Ccl5*, *Cd28*, *Icam1*, *Il12b*, *Tgfb1, Tnfrsf1a* – гени з низькою експресією в порівнянні з контрольною групою тварин; *Ceacam1, Dusp4, Retn, Ctla4, Ifng, Ikbkb, Il10, Il4r, Il6, Igfbp5, Tnf* – гени в яких не виявлені зміни в зразках по відношенню до контрольної групи тварин; *Adra1a, Agt, Foxc2, Slc2a4, Srebf1, Tnfrsf1b* – гени експресія яких не була виявленою.

Ключові слова: підшлункова залоза, цукровий діабет, гени, інсулін, інсуліно-резистентність, диференціювання, бета-клітини, апоптоз, проліферація, аутоімунна деструкція, лабораторна діагностика.

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Висновки. Розвиток дексаметазонового діабету достовірно (де ΔΔCт < 30) підвищує експресію гена *Parp1* в 3,06 рази в порівнянні до контрольної групи тварин. При розвитку дексаметазонового діабету достовірно (де ΔΔCт < 30), по відношенню до контрольної групи тварин, демонстрували низьку експресію гени *Enpp1* в 12,55, *Ide* в 3,31, *Trib3* в 7,74, *Ucp2* в 9,76 разів, які беруть участь у механізмах регуляції секреції інсуліна, гени *Ccl5* в 2,27, *Cd28* в 23,98, *Icam1* в 4,54, *Il12b* в 4,38, *Tgfb1* в 3,76 разів, які беруть участь у механізмах аутоімунної деструкції бета-клітин та ген *Tnfrsf1a* в 130,97 рази, який бере участь у механізмах виживання та апоптозу. Експресія генів *Adra1a, Agt, Foxc2, Slc2a4, Srebf1, Tnfrsf1b* при розвитку дексаметазонового діабету не була виявленою.

According to the World Health Organization (WHO), diabetes mellitus remains one of the most prevalent and rapidly increasing non-communicable chronic diseases worldwide. Over the past decades, there has been a consistent trend towards an increase in the number of patients in developed, as well as low- and middle-income countries. This trend is driven by a complex set of factors, including urbanization, sedentary lifestyles, poor nutrition, excessive body weight and obesity, population aging, as well as comorbid pathology [1,2,3].

The constant increase in disease prevalence imposes a significant burden on healthcare systems, as the treatment of diabetes and its complications requires substantial financial, human, and material and technical resources. Consequently, the problem of diabetes mellitus is regarded not only as a medical but also as a socio-economic challenge, necessitating multisectoral collaboration, the enhancement of preventive programmes, and the development of effective strategies for early detection and comprehensive treatment aimed at reducing morbidity, disability, and mortality rates [4].

Particular scientific attention has been directed towards the mechanisms underlying the regulation and impairment of pancreatic β-cells, given their role in insulin production and their morphological and functional alterations during the development of diabetes. Identification and characterisation of the genetic mechanisms regulating these processes are of crucial importance for a deeper understanding of the molecular basis of diabetes pathogenesis, as well as for the development of innovative strategies for its prevention, laboratory diagnostics, and therapy.

The expression of genes involved in the regulatory mechanisms of pancreatic β-cells can change under the influence of various exogenous and endogenous factors, including metabolic disorders, arterial hypertension, hypoxia, and others. Existing data on quantitative and qualitative alterations in β-cells, automated cell-counting results, and insights into the molecular processes of β-cell damage in the context of experimental dexamethasone-induced diabetes provide an opportunity to gain a deeper understanding of the genetic mechanisms underlying disease development and to determine relevant criteria and approaches for the laboratory diagnosis of this pathology.

Aim

The purpose of the work was to determine and analyse the expression of genes involved in the morphological and secretory regulation of β-cells, and to characterise their alterations during β-cell injury in experimental dexamethasone-induced diabetes mellitus.

Materials and methods

The study was conducted on 10 male Wistar rats, which were divided into two groups (five animals per group). The first group comprised the control (intact) animals. Experimental type 2 diabetes mellitus was induced in the second group as follows: 18-month-old male Wistar rats received, for 30 consecutive days, a modified diet consisting of hydrogenated vegetable fats (5% of the total food mass) and, on alternate days, replacement of drinking water with a 20% aqueous fructose solution. In parallel with the dietary modification, subcutaneous injections of dexamethasone were administered at a dose of 0.125 mg/kg from day 1 to day 7 and from day 24 to day 30.

For the reliability of the experiment and laboratory confirmation of the development of dexamethasone-induced diabetes, which represents one of the established models of type 2 diabetes mellitus in humans, blood glucose concentration was measured in all experimental animals of the second group two weeks after the initiation of dexamethasone administration, and again on day 30 of the experiment. Glucose levels were assessed using a Gluco Card-II glucometer (Japan).

Following decapitation of the experimental animals under thiopental anaesthesia (50 mg/kg), blood samples were collected for the biochemical determination of insulin, and pancreatic tissue was excised. The pancreas was fixed in Bouin's solution for 20 hours and, after standard histological processing, embedded in Paraplast (McCormick, USA).

Total RNA was isolated from paraffin-embedded tissue blocks using the PureLink™ FFPE Total RNA Isolation Kit (Thermo Fisher Scientific, USA) according to the manufacturer's instructions. Prior to extraction, tissue sections were deparaffinized, digested with proteinase K, and RNA was purified using silica spin columns. To prevent genomic DNA contamination, samples were treated with DNase I.

Complementary DNA (cDNA) synthesis was performed using 100–500 ng of total RNA with the RevertAid™ Reverse Transcriptase Kit (Thermo Fisher Scientific, USA) following the manufacturer's protocol. Reverse transcription was carried out using random hexamer primers under the following conditions: 25 °C for 5 min, 42 °C for 60 min, followed by enzyme inactivation at 70 °C for 5 min. The resulting cDNA was stored at –20 °C until use.

Gene expression analysis, with genes listed in Table 1, was performed using the RT² Profiler™ PCR Array Rat Diabetes (QIAGEN, Germany) according to the manufacturer's instructions. Real-time PCR reactions were carried out on a CFX-96 Touch™ system (Bio-Rad, USA) under the following conditions: initial denaturation at 95 °C for 10 min, followed by 50 cycles of 95 °C for 15 s, primer annealing at 60 °C for 30 s, and elongation at 72 °C for 30 s. Fluorescence intensity was recorded automatically

Table 1. Molecular markers of insulin secretion regulation and mechanisms of β-cell regeneration and death

Genes involved in the regulation of insulin secretion by β-cells	Genes involved in the mechanisms of autoimmune destruction of β-cells	Genes involved in the mechanisms of β-cells proliferation, survival, and apoptosis
Enpp1, Ide, Trib3, Ucp2, Ceacam1, Dusp4, Retn, Adra1a, Agt, Foxc2, Slc2a4, Srebf1	*Ccl5, Cd28, Icam1, Il12b, Tgfb1, Ctla4, Ifng, Ikbkb, Il10, Il4r, Il6*	*Parp1, Tnfrsf1a, Igfbp5, Tnf, Tnfrsf1b*

Table 2. Gene expression activity involved in the regulation of insulin secretion by β-cells in rats with experimental pathology relative to the intact control group and normalization relative to internal reference genes (Ct/ΔCt/ΔΔCt)

Genes with increased expression compared to the control group (ΔΔCt < 30)	Genes with decreased expression compared to the control group (ΔΔCt < 30	Genes without detectable changes relative to the control group	Genes with undetectable expression
Not detected	*Enpp1* (fold change: D* – 0.024170, C* – 0.303292), *Ide* (fold change: D* – 0.026999, C* – 0.089374), *Trib3* (fold change: D* – 0.004625, C* – 0.035817), *Ucp2* (fold change: D* – 0.001095, C* – 0.010691).	*Ceacam1, Dusp4, Retn*	*Adra1a, Agt, Foxc2, Slc2a4, Srebf1*

D*: diabetes, **C*:** control.

Table 3. Gene expression activity involved in the mechanisms of autoimmune destruction of β-cells in rats with experimental pathology relative to the intact control group and normalization relative to internal reference genes (Ct/ΔCt/ΔΔCt)

Genes with increased expression compared to the control group (ΔΔCt < 30)	Genes with decreased expression compared to the control group (ΔΔCt < 30)	Genes without detectable changes relative to the control group	Genes with undetectable expression
Not detected	*Ccl5* (fold change: D* – 0.004714, C* – 0.010691), *Cd28* (fold change: D* – 0.004638, C* – 0.111242), *Icam1* (fold change: D* – 0.002353, C* – 0.010691), *Il12b* (fold change: D* – 0.002444, C* – 0.010691), *Tgfb1* (fold change: D* – 0.002843, C* – 0.010691).	*Ctla4, Ifng, Ikbkb, Il10, Il4r, Il6*	Not detected

D*: diabetes, **C*:** control.

Table 4. Gene expression activity involved in the mechanisms of proliferation, survival, and apoptosis of β-cells in rats with experimental pathology relative to the intact control group and normalization relative to internal reference genes (Ct/ΔCt/ΔΔCt)

Genes with increased expression compared to the control group (ΔΔCt < 30)	Genes with decreased expression compared to the control group (ΔΔCt < 30)	Genes without detectable changes relative to the control group	Genes with undetectable expression
Parp1 (fold change: D* – 0.032715, C* – 0.010691).	*Tnfrsf1a* (fold change: D* – 0.005396, C* – 0.706769).	*Igfbp5, Tnf*	*Tnfrsf1b*

D*: diabetes, **C*:** control.

at the end of the elongation step of each cycle using the SYBR Green channel. Amplification specificity was confirmed by melt curve analysis.

The analysis included genes with significantly increased expression compared to the control group, genes with significantly decreased expression compared to the control group, genes with no statistically significant changes relative to controls, and genes with undetectable expression levels. Statistical analysis of PCR data was performed using GeneGlobe software (QIAGEN, Germany) with the ΔΔCt method [5]. Fold-Change ($2^{(-\Delta\Delta C_T)}$) is the normalized gene expression ($2^{(-\Delta C_T)}$) in the Test Sample divided the normalized gene expression ($2^{(-\Delta C_T)}$) in the Control Sample. Fold-Regulation represents fold-change results in a biologically meaningful way. Fold-change values greater than one indicate a positive- or an up-regulation, and the fold-regulation is equal to the fold-change. Fold-change values less than one indicate a negative or down-regulation, and the fold-regulation is the negative inverse of the fold-change.

Results

The performed PCR analysis enabled the classification of gene expression activity involved in the regulation of insulin secretion by pancreatic β-cells as follows: genes with increased expression compared to the control group (ΔΔCt < 30), genes with decreased expression compared to the control group (ΔΔCt < 30), genes without statistically significant changes relative to the control group, and genes with undetectable expression (*Table 2*).

The activity of genes involved in the morphological mechanisms of autoimmune destruction of β-cells was distributed as follows (*Table 3*).

The functionality of genes involved in the mechanisms of β-cell proliferation, survival, and apoptosis was distributed as follows (*Table 4*).

Discussion

The decreased expression of the genes *Enpp1*, *Ide*, *Trib3*, and *Ucp2* (see Table 2) in rats with experimental dexamethasone-induced diabetes, all of which are involved in the regulating of insulin secretion by β-cells, can be interpreted as a manifestation of a complex adaptive and pathological response of the islet apparatus to metabolic stress. Each of these genes performs a specific molecular function that influences the insulin-secretory phenotype of β-cells, and alterations in their expression may reflect both complementary and compensatory mechanisms.

Enpp1 is generally regarded as an inhibitory factor in insulin signalling: increased expression of *Enpp1* is associated with insulin resistance in peripheral tissues and exerts a negative impact on insulin receptor signalling. In the context of β-cells, decreased *Enpp1* expression may represent a compensatory mechanism aimed at enhancing the intracellular insulin signalling cascade to sustain secretion under conditions of peripheral insulin resistance [6].

The *Ide* gene regulates both intracellular and extracellular insulin turnover. A decrease in *Ide* expression may lead to reduced intracellular degradation of proinsulin and mature insulin, which could theoretically result in a transient increase in insulin content within secretory granules. However, it simultaneously imposes an increased burden on the endoplasmic reticulum (ER). Such alterations may contribute to short-term compensation of insulin secretion but, in the long term, may impair β-cell survival through ER stress and the activation of inflammatory signalling pathways [7].

Trib3 is an adaptive regulator that modulates the *PI3K/Akt* pathway and is associated with ER stress and glucotoxicity. In numerous models, *Trib3* expression is elevated under conditions of overnutrition, obesity, and acute glucose stress, where it inhibits *Akt*-dependent pathways and impairs β-cell survival and function [8]. Therefore, the decrease in Trib3 observed in our diabetes model may be interpreted in two ways: 1. as a reactive "release of inhibition" of the Akt pathway, aimed at preserving the survival and secretory capacity of the endocrine apparatus; 2. as a marker of disrupted ER-stress regulatory circuits, reflecting the exhaustion of adaptive responses.

Ucp2 is a mitochondrial protein that uncouples oxidative phosphorylation, thereby reducing ATP production. In β-cells, *Ucp2* induction is associated with decreased glucose-stimulated insulin secretion due to a lower ATP/ADP ratio and, consequently, incomplete closure of KATP channels [9]. In this context, the decrease in *Ucp2* expression observed in diabetic rats may enhance ATP production and potentially augment glucose-stimulated insulin secretion. This finding can be interpreted as a compensatory mechanism in response to peripheral insulin resistance or β-cell mass reduction.

In summary, the concomitant downregulation of *Enpp1*, *Ide*, *Trib3*, and *Ucp2* observed in our study may reflect a complex interplay of adaptive and dysfunctional processes: 1. compensatory alterations aimed at preserving or temporarily enhancing the secretory capacity of β-cells (decrease in *Ucp2* and *Enpp1* expression); 2. indicators of proteostasis dysregulation and ER stress response (decrease in *Ide* and *Trib3* expression).

The downregulation of genes (see Table 3) associated with autoimmune β-cell destruction in rats with experimental diabetes indicates a complex reorganization of the islet immune microenvironment and may have dual implications, in particular it may reflect the suppression of the local proinflammatory profile, thereby potentially reducing the recruitment and activation of cytotoxic effector cells, or it may demonstrate the exhaustion of protective and regulatory mechanisms that normally maintain tolerance or restrain chronic inflammation.

Ccl5 is a key chemokine responsible for the recruitment of mononuclear cells and specific T-lymphocyte subpopulations into tissues. Increased local secretion of *Ccl5* has been associated with more pronounced insulitis in both experimental models and patients [10]. The reduced *Ccl5* expression observed in our study may indicate compensatory suppression of chemokine signaling within the islets to limit further effector cell recruitment, or alternatively, may reflect the exhaustion of the cellular capacity to produce chemokines as a consequence of chronic inflammation or cellular dysfunction.

Cd28 is a principal co-stimulatory molecule for T cells, critical for the activation of naive T lymphocytes and for the maintenance of the regulatory T cell (Treg) population. Reduced *Cd28* expression in the tissue context may reflect both a diminished local potential for stimulation (and thus reduced effector activation) and a disruption of Treg homeostasis, which, over time, may contribute to the loss of tolerance [11]. Therefore, the interpretation of our findings depends strongly on the spatial and cell-type-specific context: decreased *Cd28* expression directly in pancreatic β-cells (if such expression occurs) may have different consequences compared to alterations in parenchymal or infiltrating immune cells within the islet, a question that warrants further investigation.

Icam1 is a key molecular component mediating leukocyte adhesion and the formation of immunological synapses. In numerous models, increased *Icam1* expression in β-cells or in the endothelium has been correlated with enhanced immune infiltration and the progression of insulitis, whereas reduction or complete absence of *Icam1* suppresses the development of diabetes [12]. Therefore, the unexpected downregulation of *Icam1* observed in our study – contrary to most literature reports – may represent a protective response aimed at limiting effector cell adhesion and migration, or, alternatively, may reflect cellular injury or dysfunction resulting in the loss of responsiveness to proinflammatory signals.

The *Il12b* gene encodes the p40 subunit, which is a component of both IL-12 and IL-23 – cytokines that are pivotal for the differentiation of Th1 and Th17 responses. Elevated IL-12/IL-23 production has been linked to the induction of robust cell-mediated autoimmune responses [13]. Therefore, it can be postulated that the downregulation of *Il12b* in the studied context may attenuate Th1/Th17 polarization and temporarily reduce the aggressiveness of the immune response.

Tgfb1 is a multifunctional cytokine, central to the maintenance of immune tolerance, the induction and function of regulatory T cells, as well as the regulation of β-cell recovery and apoptosis. Reduced *Tgfb1* expression in the islets is typically interpreted as a loss of local immunoregulatory mechanisms, thereby increasing the risk of uncontrolled autoimmune activation. Conversely, excessive *Tgfb1* expression may limit autoimmunity but can also contribute to fibrosis [14]. The observed downregulation of *Tgfb1* in our study may represent one of the key factors promoting the progression of autoimmune destruction, particularly if accompanied by a concomitant reduction in regulatory T cells or an increase in effector Th1/Th17 markers.

The downregulation of *Ccl5*, *Cd28*, *Icam1*, *Il12b*, and *Tgfb1* observed in our experimental diabetes model points to a profound reorganization of the immune architecture within the studied samples, combining elements of transient anti-effector adaptation with potential exhaustion of regulatory mechanisms.

In rats with experimental diabetes, significant alterations were observed in the expression of genes regulating the mechanisms of proliferation, survival, and apoptosis of pancreatic β-cells (see *Table 4*). In particular, reduced *Tnfrsf1a* expression, the absence of *Tnfrsf1b*, and increased *Parp1* expression may critically affect on the functional state of β-cells.

The *Tnfrsf1a* and *Tnfrsf1b* genes encode receptors for tumor necrosis factor alpha (TNF-α), which play a pivotal role in the regulation of apoptosis and inflammatory processes. The TNFR1 receptor (*Tnfrsf1a*) is capable of inducing both survival and apoptotic signaling depending on the activation context [15]. The absence of *Tnfrsf1b* may disrupt the balance between these pathways, enhancing pro-apoptotic signaling and thereby contributing to β-cell death [16].

Parp1 is an enzyme responsible for DNA repair and the regulation of cellular metabolism. Elevated *Parp1* expression can result in excessive activation, resulting in the depletion of NAD^+ and ATP, disruption of energy homeostasis, and the initiation of apoptosis or necroptosis [17]. In the context of diabetes, excessive *Parp1* activity may contribute to the loss of functional β-cell mass and the progression of hyperglycemia [18].

The observed alterations in gene expression in rats with experimental dexamethasone-induced diabetes create an imbalance between survival and apoptotic signaling pathways, thereby promoting the loss of functional cell mass and the progression of hyperglycemia. These changes also lead to dysregulation of insulin secretion and autoimmune destructive processes, highlighting the potential of molecular laboratory diagnostics and subsequent targeted therapies for the protection of pancreatic islets.

Conclusions

1. The development of dexamethasone-induced diabetes significantly increased the expression of the *Parp1* gene by 3.06-fold compared to the control group of animals (ΔΔCt < 30).

2. In the development of dexamethasone-induced diabetes, relative to the control group of animals, significantly reduced expression (ΔΔCt < 30) was observed for the following genes: *Enpp1* (12.55-fold), *Ide* (3.31-fold), *Trib3* (7.74-fold), and *Ucp2* (9.76-fold), which are involved in the mechanisms of insulin secretion regulation; *Ccl5* (2.27-fold), *Cd28* (23.98-fold), *Icam1* (4.54-fold), *Il12b* (4.38-fold), and *Tgfb1* (3.76-fold), which participate in the mechanisms of autoimmune β-cell destruction; as well as *Tnfrsf1a* (130.97-fold), which is involved in the mechanisms of survival and apoptosis.

3. The expression of the genes *Adra1a*, *Agt*, *Foxc2*, *Slc2a4*, *Srebf1*, and *Tnfrsf1b* was not detected in the context of dexamethasone-induced diabetes.

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