Peculiarities of distribution of patterns with high and low expression of c-Kit protein in the pancreas of rats with experimental 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

The c-Kit protein, also known as CD117, is a membrane receptor tyrosine kinase, and plays an important role in various cellular processes including cell proliferation, survival and differentiation. In particular, at the embryonic stage of pancreatogenesis, c-Kit protein participates in the process of beta-cell differentiation from pancreatic progenitor cells, and controls the subsequent migration and invasion of endocrinocytes with the formation of new pancreatic islets. Activation of c-Kit-mediated receptor mechanisms triggers intracellular molecular signalling pathways, that promote beta-cell proliferation and differentiation, leading to an increase in the pool of endocrinocytes in the pancreas and enhancing their functional activity.

Aim: to identify quantitative distribution patterns of c-Kit protein with high and low expression levels in endocrinocytes and pancreatic exocrinocytes in rats' streptozotocin-induced diabetes.

Materials and methods. The study was conducted on 20 white Wistar rats, which were divided into 2 groups of 10 animals each. Animals of group 1 were included in the control (intact) group. To model experimental diabetes mellitus, animals of group 2 were injected intraperitoneally with streptozotocin (Sigma-Chemical, USA) at a dose of 50 mg/kg dissolved in 0.5 ml of 0.2 M citrate buffer pH = 4.5.

Results. The study of immunoreactivity to c-Kit protein in intact rats and in diabetic animals showed the presence of patterns with high and low expression levels both in endocrinocytes of pancreatic islets and in the exocrine part of the pancreas. Among the endocrinocytes of intact rats, cells with a high level of c-Kit protein expression prevailed and in the exocrine part of the pancreas – cells with a low level of protein expression. The development of diabetes resulted in a significant increase in the number of c-Kit-immunopositive alpha cells with a low level of protein expression (3.6-fold, $p < 0.001$), as well as pancreatic exocrinocytes (by 38 %, $p < 0.001$). At the same time, the formation of diabetes did not lead to changes in c-Kit protein concentration in all pancreatic cells with a low level of c-Kit protein expression.

Conclusions. c-Kit-immunopositive cells of the pancreas form two patterns of cells – with a high level of c-Kit protein expression, and with a low level of its expression. In intact animals, endocrinocytes with a high level of c-Kit protein expression predominate, and in the exocrine part of the pancreas – cells with and low level of protein expression. Alpha-endocrinocytes of intact rats have a 30 % higher ($p < 0.001$) c-Kit protein expression level compared to beta-cells and exocrinocytes. The development of diabetes in rats was accompanied by a significant increase in the number of c-Kit-immunopositive beta cells with a high level of protein expression, as well as an increase in the number of alpha cells and exocrinocytes with both high and low levels of c-Kit protein expression. In the pattern of beta cells with a high level of protein expression in diabetes, an increase in the concentration of the c-Kit protein was observed (by 17 %, $p < 0.001$) compared to intact endocrinocytes, while in alpha cells and exocrinocytes a similar pattern of the concentration of the c-Kit protein was observed significantly decreased (by 44 % and 30 %, respectively).

Keywords: pancreas, diabetes mellitus, genes, insulin, glucagon, c-Kit, automated cell counting.

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Особливості розподілу патернів із високим і низьким рівнем експресії білка c-Kit у підшлунковій залозі щурів при експериментальному діабеті

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Білок c-Kit, також відомий як CD117, – мембранний рецепторний тирозинкіназний фермент, що відіграє важливу роль у різноманітних клітинних процесах, зокрема у проліферації, виживанні та диференціації клітин. Так, на ембріональній стадії панкреатогенезу білок c-Kit бере участь у процесі диференціації β-клітин із панкреатичних прогеніторних клітин, а також контролює подальшу міграцію та інвазію ендокриноцитів з утворенням нових острівців підшлункової залози. Активація рецепторних механізмів, опосередкованих c-Kit, запускає внутрішньоклітинні молекулярні сигнальні шляхи, що стимулюють проліферацію та диференціацію β-клітин, спричиняючи збільшення пулу ендокриноцитів у підшлунковій залозі та підвищення їхньої функціональної активності.

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Мета роботи – визначити кількісні закономірності розподілу білка c-Kit із високим і низьким рівнем експресії в ендокриноцитах та екзокриноцитах підшлункової залози при стрептозотоциновому цукровому діабеті в щурів.

Матеріали і методи. Дослідження здійснено на 20 білих щурах лінії Wistar, яких поділили на 2 групи по 10 тварин у кожній. Тварини 1 групи сформували контрольну (інтактну) групу. Для моделювання експериментального цукрового діабету тваринам 2 групи внутрішньоочеревинно вводили стрептозотоцин (Sigma-Chemical, США) у дозі 50 мг/кг, розчинений у 0,5 мл 0,2 М цитратного буфера з pH = 4,5.

Результати. Дослідження імунореактивності до білка c-Kit в інтактних і діабетичних тварин дало змогу виявити клітинні патерни і з високим, і з низьким рівнем експресії серед ендокриноцитів острівців підшлункової залози та в екзокринній частині органа. Серед ендокриноцитів інтактних щурів переважали клітини з високим рівнем експресії білка c-Kit, а в екзокринній частині підшлункової залози домінували клітини з низьким рівнем експресії. Розвиток діабету зумовлював значне збільшення кількості c-Kit-імунопозитивних α-клітин із низьким рівнем експресії білка (у 3,6 раза, p < 0,001), а також екзокриноцитів (на 38 %, p < 0,001). Водночас розвиток діабету не спричиняв змін концентрації білка c-Kit у всіх клітинах підшлункової залози з низьким рівнем його експресії.

Висновки. c-Kit-імунопозитивні клітини підшлункової залози формують два типи клітинних патернів – із високим і низьким рівнем експресії білка c-Kit. В інтактних тварин серед ендокриноцитів переважали клітини з високим рівнем експресії білка c-Kit, а в екзокринній частині підшлункової залози – клітини з низьким рівнем експресії. Альфа-ендокриноцити інтактних щурів мали на 30 % вищий рівень експресії білка c-Kit (p < 0,001) порівняно з β-клітинами й екзокриноцитами. Розвиток діабету у щурів супроводжувався значним збільшенням кількості c-Kit-імунопозитивних β-клітин із високим рівнем експресії білка, а також збільшенням кількості α-клітин та екзокриноцитів і з високим, і з низьким рівнем експресії білка c-Kit. У патерні β-клітин із високим рівнем експресії при діабеті визначено збільшення концентрації білка c-Kit (на 17 %, p < 0,001) порівняно з інтактними ендокриноцитами, а в α-клітинах та екзокриноцитах концентрація білка значно зменшувалася (на 44 % і 30 % відповідно).

Ключові слова: підшлункова залоза, цукровий діабет, гени, інсулін, глюкагон, c-Kit, автоматизований підрахунок клітин.

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The c-Kit protein, also known as CD117, is a membrane receptor tyrosine kinase, and plays an important role in various cellular processes including cell proliferation, survival and differentiation. In particular, at the embryonic stage of pancreatogenesis, c-Kit protein participates in the process of beta-cell differentiation from pancreatic progenitor cells, and controls the subsequent migration and invasion of endocrinocytes with the formation of new pancreatic islets [1,2].

Activation of c-Kit-mediated receptor mechanisms triggers intracellular molecular signalling pathways, that promote beta-cell proliferation and differentiation, leading to an increase in the pool of endocrinocytes in the pancreas and enhancing their functional activity [3,4]. In beta-cells, c-Kit protein can also activate signalling molecules that regulate insulin release from beta-cells and thus influence the mechanisms of glucose-stimulated insulin exocytosis [2,4]. It has been shown that impaired function or expression of c-Kit protein in endocrinocytes can lead to a decrease in the number of functioning beta cells, impaired glucose tolerance and insulin secretion capacity [2,4,5], which, in turn, contributes to an increased risk of developing type 2 diabetes mellitus.

Aim

To identify quantitative distribution patterns of c-Kit protein with high and low expression levels in endocrinocytes and pancreatic exocrinocytes in rats' streptozotocin-induced diabetes.

Materials and methods

The study was conducted on 20 white Wistar rats, which were divided into 2 groups of 10 animals each. Animals of group 1 were included in the control (intact) group. To model experimental diabetes mellitus, animals of group 2 were injected intraperitoneally with streptozotocin (Sigma-Chemical, USA) at a dose of 50 mg/kg dissolved in 0.5 ml of 0.2 M citrate buffer pH = 4.5. Animals of group 2 were monitored weekly for blood glucose levels for 4 weeks after streptozotocin administration using a GlucoCard-II glucometer (Japan) and animals with fasting glucose levels of more than 10.0 mmol/l were selected for further study.

After the animals were withdrawn from the experiment under thiopental anaesthesia (50 mg/kg), the pancreas was harvested, fixed in Buena solution (20 hours) and, after standard histological processing, embedded in paraplast (MkCormick, USA). Serial histological sections of the pancreas (5 μm thick) were deparaffinised and demasked in citrate buffered saline (pH = 9.0) in a PT module (Thermo Scientific, USA). Insulin, glucagon, and c-kit protein were detected by immunofluorescence using antibodies from Santa Cruz Biotecnology (USA). To do this, a mixture of antibodies to insulin or glucagon conjugated to AlexaFluor-546 and, respectively, to c-Kit conjugated to FITC was prepared at a dilution of 1:200, followed by incubation in a humid chamber (T = +4 °C, 24 hours). The sections, washed in phosphate buffer (pH = 7.4), were fixed in UltraCruz™ Mounting Medium in a mixture of phosphate buffer and glycerol with DAPI (Santa Cruz Biotechnology, USA) and covered with glass slides (Menzel-Glaser, Germany). The specificity of antibody binding was controlled in the same way, except for incubation with primary antibodies.

The immunofluorescence reaction was studied using an AxioImager-M2 fluorescence microscope (Carl Zeiss, Germany), equipped with an AxioCam-5HRm camera (Carl Zeiss, Germany), using 38NE and 43NE high emission filters (Carl Zeiss, Germany). For fluorescence imaging, the digital image analysis system AxioVision-4.8.2 (Carl Zeiss, Germany) was used according to the method [6]. The digital image analysis system ImageJ version 2.1.0 / 1.53c (public open license) was used for image analysis.

Table 1. Distribution of endocrinocytes in pancreatic islets

Groups	Relative number of endocrinocytes in islets (%)		Hormone concentration in endocrinocytes (IFU/mcm²)	
	beta cells	alpha cells	insulin	glucagon
Intact	78.801 ± 1.052	21.198 ± 1.052	2.025 ± 0.031	1.514 ± 0.046
Diabetes	37.274 ± 1.795*	62.977 ± 1.787*	1.645 ± 0.061*	2.172 ± 0.102*

*: reliability of differences $p < 0.001$.

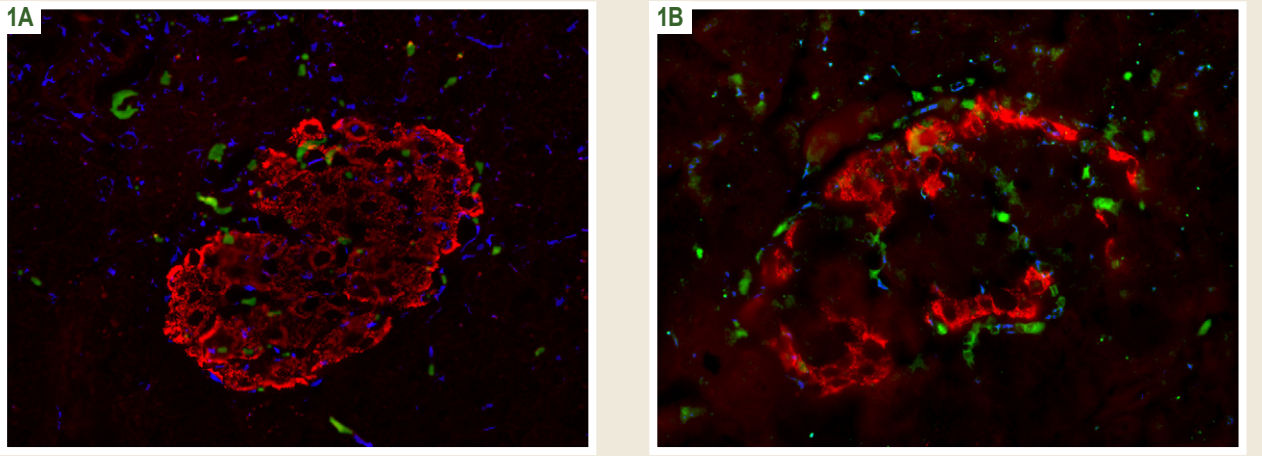

Fig. 1. Immunoreactivity with high (green fluorescence) and low (blue fluorescence) expression levels of c-Kit protein in pancreatic islets stained (red fluorescence) for insulin (**A**) and glucagon (**B**).

For each pancreatic islet, the area of the material immunoreactive to the studied biomarkers was measured automatically. For insulin and glucagon, the area of immunoreactive material was calculated in relation to the total area of the islet and this parameter was further considered an indicator of the relative number of beta- and alpha-endocrinocytes in the pancreatic islet (%). For the c-Kit protein, the area of immunoreactive material in the pancreatic islets was calculated in relation to the area of immunoreactive material to insulin or glucagon, respectively, and this parameter was considered an indicator of the relative number of c-Kit-expressing beta or alpha cells (%).The area of the material immunoreactive to c-Kit protein in the exocrine part of the pancreas was calculated in relation to its area and was subsequently considered an indicator of the relative number of c-Kit-expressing exocrinocytes (%). We understood, that this cell pool includes not only acinar exocrinocytes, but also ductal epithelial cells. The concentration of insulin, glucagon, and c-Kit in pancreatic cells was measured in relative immunofluorescence units (IFU/mcm²) relative to nonspecific background fluorescence [6]. At least 5 cm² of the total area of pancreatic sections of each animal was examined. At least 100 pancreatic islets were analysed for each marker.

Obtained results were statistically processed in Excel Office365. Differences between the compared parameters at $p < 0.05$ by Student's t-test were considered significant. The data in the tables are presented in the form of the mean value and its error (M ± m). The data in the figures are presented as mean and confidence interval.

Results

The development of streptozotocin diabetes in rats led to a regular development of hyperglycaemia up to 17.69 ± 1.10 mmol/l against 3.94 ± 0.09 mmol/l in intact animals. In pancreatic islets in diabetes there was a 53 % ($p < 0.001$) decrease in the number of beta-cells and, on the contrary, an almost 3-fold increase in the number of alpha-endocrinocytes *(Table 1)*. At the same time, the concentration of insulin in beta-cells decreased by about 20 % ($p < 0.001$), and glucagon in alpha-cells increased by more than 40 % ($p < 0.001$).

The study of immunoreactivity to c-Kit protein in intact rats and in diabetic animals showed the presence of patterns with high and low expression levels both in endocrinocytes of pancreatic islets and in the exocrine part of the pancreas *(Fig. 1)*. Among endocrinocytes of intact rats, cells with a high level of c-Kit protein expression prevailed, and in the exocrine part of the pancreas – cells with a low level of protein expression *(Fig. 2)*.

It was found that in intact rats in the pattern with a high level of c-Kit expression the protein concentration in beta-cells and exocrinocytes was approximately the same ($p > 0.05$), whereas in alpha-cells this index was 30 % higher ($p < 0.001$).

The formation of diabetes in rats was accompanied by a significant increase in the number of c-Kit-immunopositive cells with a high level of protein expression in the pancreas *(Fig. 2A)*. At the same time, c-Kit protein concentration moderately increased (by 17 %, $p < 0.001$) exclusively in pancreatic beta-endocrinocytes, whereas c-Kit protein con-

Table 2. Concentration of c-Kit protein in cells with high expression levels

Groups	Beta cells	Alpha cells	Exocrinocytes
Intact	2.335 ± 0.042	3.577 ± 0.177	2.518 ± 0.110
Diabetes	2.727 ± 0.040*	2.472 ± 0.069*	1.771 ± 0.053*

*: reliability of differences – $p < 0.001$.

Table 3. Concentration of c-Kit protein in pancreas with low expression levels

Groups	Beta cells	Alpha cells	Exocrinocytes
Intact	0.224 ± 0.062	0.505 ± 0.145	1.235 ± 0.017
Diabetes	0.153 ± 0.086	0.655 ± 0.093	1.221 ± 0.011

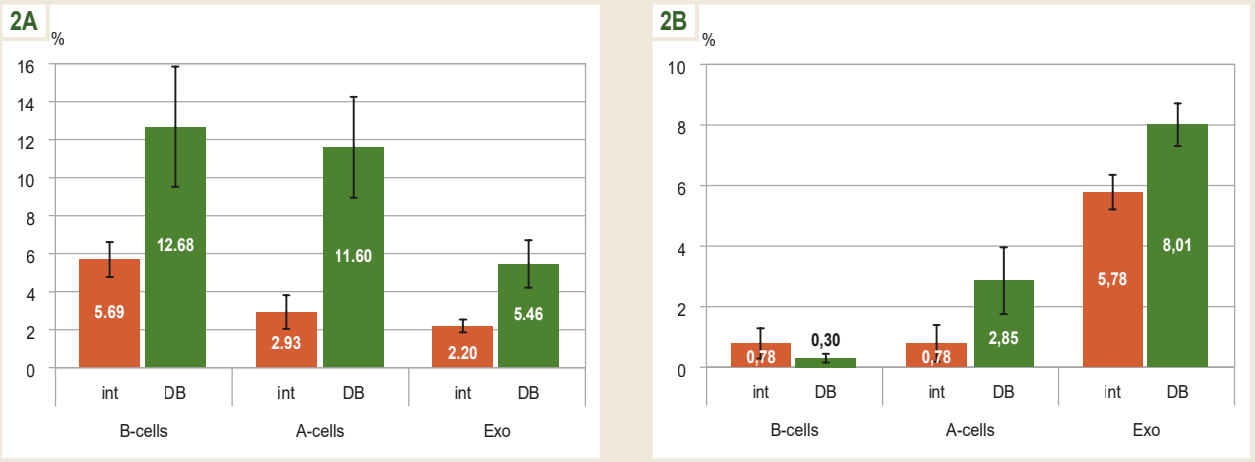

Fig. 2. Relative number of c-Kit-immunopositive beta (B-cells), alpha (A-cells) cells and exocrinocytes (Exo) with high (**A**) and low (**B**) levels of protein expression.

centration decreased in alpha cells by 44 % ($p < 0.01$), and in exocrinocytes by 30 % ($p < 0.001$) *(Table 2)*.

The study of the distribution of immunoreactivity with a low level of c-Kit protein expression showed, that in intact rats the number of such c-Kit-immunopositive endocrinocytes was significantly lower, than cells with a high level of c-Kit protein expression *(Fig. 2)*. At the same time, this pattern of beta-cells was characterized by the lowest protein concentration, whereas in alpha-cells this index was approximately 2 times higher, and in exocrine cells of the pancreas even higher and more than 2 times higher than in alpha-endocrinocytes *(Table 3)*.

The development of diabetes led to a significant increase in the number of c-Kit-immunopositive alpha cells with a low level of protein expression (3.6-fold, $p < 0.001$), as well as pancreatic exocrinocytes (by 38 %, $p < 0.001$) *(Fig. 2B)*. At the same time, the formation of diabetes did not lead to changes in c-Kit protein concentration in all pancreatic cells with a low level of c-Kit protein expression *(Table 3)*.

Discussion

The use of streptozotocin for modelling diabetes in rodents was proposed by A. A. Like and A. A. Rossini in 1976 [7]. Until today this model remains the most common for experimental studies. By the nature of hormonal and metabolic changes streptozotocin-induced diabetes in rats is very similar to type 1 diabetes in humans [8]. The data obtained in the present study on the nature of endocrinocyte distribution in pancreatic islets also correspond to the classical model of type 1 diabetes and are consistent with both our own earlier data [9,10] and the results of foreign researchers [11,12]. Accordingly, we assume that the results of changes in immunoreactivity to c-Kit protein in the pancreas also fully correspond to the pathogenetic features of type 1 diabetes.

Previously, we conducted studies of immunoreactivity to c-Kit protein in endocrinocytes of pancreatic islets and gave a preliminary quantitative assessment of its distribution in beta- [13] and alpha-cells [14]. At the same time, these studies did not take into account the peculiarity of immunoreactive material distribution taking into account the presence of two patterns of immunoreactivity to c-Kit protein both in endocrinocytes of different types and in exocrine cells of the pancreas: a pattern with a high level of c-Kit protein expression and, accordingly, its higher concentration in cells, and a pattern with an order of magnitude lower (10 times lower) level of its expression. The study of intact animals revealed the dominance of endocrinocytes with a high level of c-Kit protein expression: the number of such c-Kit-immunopositive beta cells was 7 times higher

than cells with a low level of expression, and the number of similar patterns of c-Kit-immunopositive alpha cells differed by 4 times. This fact seems to be important in view of scientifically established c-Kit-mediated molecular mechanisms of pancreatic islets cytoarchitectonics maintenance. It was shown that the extracellular region of the membrane protein c-Kit is a receptor for stem cell factor (SCF) and its binding to c-Kit leads to the activation of physiological mechanisms of survival, migration and proliferation of pancreatic endocrinocytes [2]. It was found out, that c-Kit protein expression in endocrine cells increases the production of VEGF-A, which is the most important regulator of pancreatic islets angiogenesis [15]. This explains the important role of c-Kit protein in the remodelling of pancreatic islets, ensuring the survival of beta cells and in the regulation of islet function under normal physiological conditions.

In contrast to islets, the exocrine part of the pancreas was dominated by cells with a low level of c-Kit protein expression, including both acinar exocrinocytes and ductal epithelial cells. It is believed that c-Kit protein expression is predominantly observed in ductal progenitor cells in the exocrine part of the pancreas (progenitor endocrinocytes), where c-Kit protein is a stimulator of islet neogenesis in the embryonic and early postnatal period [2,16].

The development of diabetes led to qualitative and quantitative changes in c-Kit protein expression in the pancreas. Thus, in pancreatic islets there was a 2-fold increase in the number of c-Kit-immunopositive beta cells with a high level of protein expression and a 4-fold increase in the number of c-Kit-immunopositive alpha cells with both high and low levels of c-Kit protein expression. Similar, but less quantitatively expressed, changes in the nature of immunoreactivity to c-Kit protein were also observed on the part of exocrine cells of the pancreas in response to the development of diabetes. Thus, the formation of streptozotocin-induced diabetes in rats was accompanied by a significant increase in immunoreactivity to protein c-Kit on the part of all cells of the pancreas.

Given the important role of c-Kit protein in the neogenesis of pancreatic islets, we believe that a significant increase in immunoreactivity to c-Kit may have a protective value in diabetic beta-cell destruction. In turn, it was shown that decreased expression of c-Kit protein in c-KitW-v mice with a mutation in the c-kit gene leads to a significant decrease in the levels of PDX1 protein and insulin, inhibits endocrinocyte proliferation and increases their apoptosis [17]. We believe, that increased expression of c-Kit protein in beta-cells in diabetes may contribute to the activation of molecular mechanisms of endocrinocyte protection from apoptosis, which is activated against the background of increased concentration of proapoptotic protein p53, decreased concentration of anti-apoptotic protein Bcl2 in endocrinocytes [10,18] and a significant deficit of beta-cell mass in the pancreas [9,10,11,12]. An important factor of pancreatic islets neogenesis in diabetes is c-Kit-stimulated expression of molecular markers of proliferation of homeobox proteins PDX-1 and Nk2 family [2,16].

It was shown that simultaneous increase of c-Kit and PDX-1 expression in pancreatic islets in rats with streptozotocin-induced diabetes can promote beta-cell regeneration [19]. At the same time, we previously analysed the activity of genes associated with the development of streptozotocin-induced diabetes by real-time reverse transcription polymerase chain reaction using the RTl ProfilerTM PCR Array Rat Diabetes (QIAGEN) kit and found a significant increase in the expression of the Nkx2.1 gene against the background of inhibition of the expression of the proliferation regulator Pdx1 and angiogenesis stimulator Vegfa [20]. Thus, the facts presented in the present study indicate that the development of experimental diabetes in rats leads to the formation of dysregulatory pathology of c-Kit-mediated mechanisms of beta-cell regeneration and does not affect the neogenesis of alpha-endocrinocytes.

Conclusions

1. c-Kit-immunopositive cells of the pancreas form two patterns of cells – with a high level of c-Kit protein expression, and with a low level of its expression. In intact animals, endocrinocytes with a high level of c-Kit protein expression predominate, and in the exocrine part of the pancreas – cells with and a low level of protein expression.

2. Alpha-endocrinocytes of intact rats have a 30 % higher ($p < 0.001$) c-Kit protein expression level compared to beta-cells and exocrinocytes.

3. The development of diabetes in rats was accompanied by a significant increase in the number of c-Kit-immunopositive beta cells with a high level of protein expression, as well as an increase in the number of alpha cells and exocrinocytes with both high and low levels of c-Kit protein expression.

4. In the pattern of beta cells with a high level of protein expression in diabetes, an increase in the concentration of the c-Kit protein was observed (by 17 %, $p < 0.001$) compared to intact endocrinocytes, while in alpha cells and exocrinocytes a similar pattern of the concentration of the c-Kit protein was observed significantly decreased (by 44 % and 30 %, respectively).

Ethical approval
The Bioethics Committee of Zaporizhzhia State Medical and Pharmaceutical University has reviewed the materials presented in the article. Based on the results of the review, all ethical standards were found to be met, and the study was conducted in accordance with international guidelines for research involving living subjects and with national legislation (meeting protocol No. 10, dated September 18, 2025).

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