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Clinical course of extensively drug-resistant tuberculosis with HIV infection and tertiary syphilis: a case report
Features of Bcl2 and p53 proteins synthesis in pancreatic islets of normotensive and hypertensive rats with streptozotocin-induced diabetes

T. V. Abramova* A–D, F, T. V. Ivanenko B–E, O. V. Melnykova D, E, F

Zaporizhzhia State Medical University, Ukraine

In our previous studies it was established that the remodeling of pancreatic islets with decreasing β-cell population density is formed in hypertensive SHR rats. The imbalance between the synthesis of proapoptotic and antiapoptotic factors may be one of the possible causes of disturbed formation of the endocrinocyte population in the pancreas.

The aim of the research was to study the parameters of Bcl2 and p53 proteins synthesis in pancreatic islets in normotensive and hypertensive rats in the streptozotocin-induced diabetes mellitus development.

Materials and methods. The study was performed on 30 normotensive male Wistar rats (systolic BP = 105.0 ± 1.1 mm Hg) and 25 hypertensive SHR rats (systolic BP = 155.7 ± 0.9 mm Hg) with fasting normoglycemia (4.73 ± 0.10 mmol/l). Bcl2 and p53 proteins were detected in histological pancreas sections by immunofluorescence method. The relative area of Bcl2- and p53-immunopositive material, concentration of proteins in endocrinocytes, their content in the islets and apoptosis index p53/Bcl2 were analyzed in pancreatic islands.

Results. The area of relative immunofluorescence to the Bcl2 protein was 2 times less, and the protein content was 3 times lower in pancreatic islets of hypertensive rats (SHR) compared with normotensive Wistar rats. At the same time, no statistical differences in the area of the immunopositive material to the p53 protein and its content in the islets between the experimental groups were revealed. The development of streptozotocin-induced diabetes in Wistar rats was accompanied by approximately 2-fold decrease in the Bcl2 protein expression in pancreatic islets, a significant increase in the specific content of p53 protein and a 3.8-fold increase in the apoptosis index of p53/Bcl2. In pancreatic islets of SHR rats, diabetes mellitus development was accompanied by 2-fold increase in the specific content of the proapoptotic protein p53 without the reduction of the antiapoptotic protein Bcl2 synthesis. At the same time, the p53/Bcl2 apoptosis index in SHR rats remained statistically higher than in Wistar rats.

Conclusions. Endocrine cells of pancreatic islets of SHR rats are characterized by the prevalence of proapoptotic protein p53 expression as compared with Wistar line normotensive rats. The development of streptozotocin diabetes in Wistar rats leads to a significant decrease in the number of endocrinocytes synthesizing the antiapoptotic protein Bcl2. At the same time, an increase in the synthesis of the proapoptotic protein p53 in endocrinocytes in diabetes is observed both in normotensive and hypertensive rats.

Key words: essential hypertension, diabetes mellitus, pancreatic islets, apoptosis.
Essential hypertension is one of the most common chronic diseases, the incidence of which ranges from 29.0 % in adults to 64.9 % in people over 60 years [1]. Patients with arterial hypertension present the majority of the cardiological group of patients; type 2 diabetes mellitus accompanies from 20 % in the USA to 30 % of cases in Italy [2]. The combination of essential hypertension and diabetes mellitus in patients is known as a metabolic syndrome that increases the clinical severity of single chronic diseases, the incidence of which ranges from 5.5 mmol/L in 2/3 of the SHR rats with hereditary arterial hypertension [4]. Nevertheless, the signs of pancreatic islet cytoarchitectonics can be affected not only by β-cytopathic factors, such as streptozotocin, antibodies to intra-islet antigens, hypoxia, but also the level of intracellular expression of proapoptotic and antiapoptotic factors, such as p53 and Bcl2 proteins [13,14].

The aim of the research was to study the parameters of Bcl2 and p53 proteins synthesis in pancreatic islets in normotensive and hypertensive rats subjected to streptozotocin-induced diabetes mellitus development.

Materials and methods

The research was carried out on 30 normotensive male rats of Wistar line (systolic BP = 105.0 ± 1.1 mm Hg) and 25 hypertensive SHR rats (systolic BP = 155.7 ± 0.9 mm Hg). The aim was to study the parameters of β-cells death in the pancreas under normal and pathological conditions.
and 25 hypertensive rats of SHR line (systolic BP = 155.7 ± 0.9 mm Hg) with fasting normoglycemia (4.73 ± 0.10 mmol/L). The animals were kept in standard vivarium conditions under natural light without restriction of access to water and food. The studies were conducted in accordance with the requirements of international principles of the European Convention (Strasbourg, 1985). Diabetes mellitus was modeled in 15 Wistar rats and 10 SHR rats by a single intraperitoneal injection of streptozotocin (SIGMA Chemical, USA) in a dose of 50 mg/kg dissolved in 0.5 ml of 0.1 M citrate buffer (pH = 4.5). 3 weeks after, the concentration of glucose in the blood was measured in animals with the help of GlucoCard-II glucometer (Japan), and systolic blood pressure was measured with the help of BP-2000 non-invasive pressure control system (Visitech Systems, USA).

The pancreas was extracted after decapitation of experimental animals under thiopental anesthesia (50 mg/kg), fixed in Bouin solution (20 hours) and poured into paraplast (McCormick, USA) after standard histological processing. Serial histological slices of the pancreas 5 μm thick were dewaxed and unmasked in a citrate buffer solution (pH = 9.0) in the PT-module (Thermo Scientific, USA). Bcl2 and p53 proteins in pancreatic islets were detected by immunofluorescence method using antibodies produced by Santa Cruz Biotechnology (USA). Primary antibodies were incubated in dilution 1:200 (wet chamber, T = +4 °C, 24 hours), secondary antibodies conjugated with FITC were incubated in dilution 1:64 (wet chamber, T = +37 °C, 45 min).

The slices were washed in phosphate buffer and then enclosed in a mixture of glycerin/phosphate buffer (9:1). Specificity of antibody binding was controlled in similar way, except for incubation with primary antibodies. Immunofluorescence reaction was studied using the Axiosmager-M2 fluorescence microscope (Carl Zeiss, Germany) with the digital camera AxioCam-HRM (Carl Zeiss, Germany) and with the use of the high-emission 38HE filter (λ_{ex} = 470/40 nm, λ_{em} = 525/50 nm) (Carl Zeiss, Germany). Quantitative analysis of the immunofluorescence reaction was carried out with the help of AxioVision-4.8.2 digital image analysis system (Carl Zeiss, Germany). At least 75 pancreatic islets were examined in each series and the following parameters were measured and calculated:

1) the relative area of the immunopositive material (the percentage of the immunopositive material in the islet area);
2) the concentration of proteins in endocrinocytes (the module of the logarithm of the background fluorescence to the fluorescence of immunopositive material ratio, expressed in relative units of fluorescence – \( U_p \));
3) the protein content in pancreatic islets (calculated as the product of the specific concentration of proteins and immunopositive material area in 1 cm² of the area of the islets, expressed in \( U_p \) cm²);
4) apoptosis index (the ratio of p53 protein content to Bcl2 protein content in pancreatic islets).

Experimental data were processed with Excel 2003 (Microsoft Corp.) statistical analysis software package. The reliability of the differences between the experimental groups was assessed using the Student's criterion, considering the differences to be reliable at \( P < 0.05 \).

**Results**

The development of streptozotocin diabetes led to the formation of hyperglycemia both in normotensive Wistar rats (17.69 ± 1.10 mmol/L) and in SHR rats with hereditary hypertension (11.45 ± 0.89 mmol/L). Earlier, we attributed this to significant reduction of the α-endocrinocyte pool in the pancreas of hypertensive rats, which does not lead to excessive glucagon synthesis, which is observed in Wistar rats along with of intensive α-cells proliferation [9].

The area of relative immunofluorescence to the Bcl2 protein was 2 times less in pancreatic islets, in hypertensive rats than in normotensive animals, while the area of p53 protein immunopositive material was almost the same (Table 1).

Despite the fact that the parameters of protein concentration in the cells in normo- and hypertensive rats did not statistically differ, their ratio indicated the predominance of pro-apoptotic p53 protein expression in the endocrinocytes in SHR rats (Table 2).

Calculation of the Bcl2 protein content in pancreatic islets demonstrated its 3-fold decrease in hypertensive rats in comparison with normotensive animals (Table 3). The p53 protein content in the islets of both animal lines did not statistically differ. It is possible that low indices of Bcl2 antiapoptotic protein expression in pancreatic endocrinocytes in SHR line rats may be one of the reasons for the decrease in the β-cell population in these animals [5,6].

The development of experimental diabetes in normotensive rats led to a 2-fold decrease in the area of Bcl2 immunopositive material in pancreatic islets accompanied with an increase in the area of immunoreactivity to p53 protein by 55%. In contrast, there was an increase in immunoreactivity both to Bcl2 and p53 protein by more than 50% in pancreatic islets of hypertensive animals (Table 1).

The development of diabetes led to an increase in the concentration of p53 protein in endocrinocytes in normotensive animals and in hypertensive rats by 24% and 31%, respectively. At the same time, the development of diabetes in normotensive animals did not affect the concentration of Bcl2 protein in the cells, while in hypertensive animals a decrease in the concentration of Bcl2 protein by 33% was observed (Table 2). This resulted in the fact that the index of apoptosis – Bcl2/p53 in endocrinocytes in normotensive animals with diabetes decreased only by 12% (\( P < 0.02 \)), and in hypertensive rats – by 40% (\( P < 0.001 \)).

Changes in the parameters of Bcl2 and p53 proteins immunoreactivity in the diabetes mellitus development in normotensive rats resulted in a 40% decrease in the specific content of the antiapoptotic Bcl2 protein in pancreatic islets, combined with a 2.3-fold increase in the specific content of the proapoptotic p53 protein (Table 3). Whereas, the development of diabetes in hypertensive rats of resulted only in 2-fold increase in the specific content of the p53 protein in the pancreatic islets as compared with the control group. Moreover, the development of diabetes in normotensive animals resulted in the increase of the apoptosis index by 3.84 times, while in hypertensive

**Table 1**

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<tr>
<th>Parameter</th>
<th>Normotensive</th>
<th>Hypertensive</th>
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</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.73 ± 0.10</td>
<td>17.69 ± 1.10</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area (cm²)</td>
<td>50%</td>
<td>25%</td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>24%</td>
<td>31%</td>
</tr>
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</table>

**Table 4**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index</td>
<td>12%</td>
<td>40%</td>
</tr>
</tbody>
</table>
Table 1. Relative area (%) of immunopositive material in pancreatic islets (M ± m)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensive rats</th>
<th>Hypertensive rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control, n = 91</td>
<td>Diabetes, n = 76</td>
</tr>
<tr>
<td>Bcl2</td>
<td>4.966 ± 0.728*</td>
<td>2.706 ± 0.164*</td>
</tr>
<tr>
<td>p53</td>
<td>2.157 ± 0.199</td>
<td>3.344 ± 0.258**</td>
</tr>
<tr>
<td>Bcl2 / p53</td>
<td>2.302 ± 0.063*</td>
<td>0.836 ± 0.074**</td>
</tr>
</tbody>
</table>

Reliability P < 0.05 of differences in comparison with normotensive (*) and hypertensive (**) rats without diabetes; n: the number of pancreatic islets that were examined.

Table 2. Protein concentration (U/mg) in endocrinocytes (M ± m)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensive rats</th>
<th>Hypertensive rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control, n = 91</td>
<td>Diabetes, n = 76</td>
</tr>
<tr>
<td>Bcl2</td>
<td>0.611 ± 0.079</td>
<td>0.664 ± 0.040*</td>
</tr>
<tr>
<td>p53</td>
<td>0.449 ± 0.017</td>
<td>0.556 ± 0.042**</td>
</tr>
<tr>
<td>Bcl2 / p53</td>
<td>1.360 ± 0.050</td>
<td>1.194 ± 0.048*</td>
</tr>
</tbody>
</table>

Significance (P < 0.05) of differences in comparison with normotensive (*) and hypertensive (**) rats without diabetes; n: the number of pancreatic islets that were examined.

Table 3. Protein content (U/cm²) in pancreatic islets (M ± m)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensive rats</th>
<th>Hypertensive rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control, n = 91</td>
<td>Diabetes, n = 76</td>
</tr>
<tr>
<td>Bcl2</td>
<td>3.570 ± 0.203*</td>
<td>2.118 ± 0.285**</td>
</tr>
<tr>
<td>p53</td>
<td>0.984±0.102</td>
<td>2.242 ± 0.372**</td>
</tr>
<tr>
<td>apoptosis index p53/Bcl2</td>
<td>0.275 ± 0.059*</td>
<td>1.058 ± 0.077**</td>
</tr>
</tbody>
</table>

Significance (P < 0.05) of differences in comparison with normotensive (*) and hypertensive (**) rats without diabetes; n: the number of pancreatic islets that were examined.

Rats with diabetes, the apoptosis index in pancreatic islets was still significantly higher (P < 0.05) than in normotensive rats.

**Discussion**

The data obtained in the current research indicate that the development of experimental diabetes mellitus leads to a significant decrease in quantity of the endocrinocytes that synthesize the anti-apoptotic protein Bcl2 only in normotensive rats. At the same time, an increase of pro-apoptotic p53 protein synthesis in endocrinocytes in diabetes is observed both in normotensive and hypertensive rats.

It is known that Bcl-2 family of proteins include proteins both with anti-apoptotic and pro-apoptotic activity. Such proteins as Bcl2-protein (Bcl2), B-cell lymphoma-extra-large (Bcl-xL), Bcl-2-like protein 2 (Bcl-w), Bcl-2-like protein 10 (Bcl-B), myeloid cell leukemia 1 (MCL-1) and Bcl-2 related gene A1 (A1) prevent apoptosis [15]. They realize their anti-apoptotic effect at the mitochondrial level, and also block the activity of caspasases and proapoptotic proteins Bcl-2 family members in the cell [16]. Other proteins of Bcl-2 family such as Bcl-2-associated X protein (Bax) and Bcl-2 antagonist killer 1 (Bak), in contrast, have a proapoptotic influence [15,16]. It is believed that the balance between pro- and anti-apoptotic proteins of the Bcl-2 family is a key parameter that determines the choice between life and death for a cell [17]. It has been established that in type 1 and type 2 diabetes Bcl2 production increases in β-cells along with other molecular regulators of apoptosis, [16], that might have a protective value and to some extent reflect the compensatory potential of β-endocrinocytes in diabetes.

It was noted that apoptosis of β-cells in diabetes, caused by overproduction of pro-inflammatory cytokines and a decrease in the mitochondrial transmembrane potential in endocrinocytes is inhibited by stimulation of Bcl2 expression [18].

A product of the TP53 gene (tumor suppressor gene) activity – p53 protein is an important regulator of apoptosis in cells along with the Bcl-2 family proteins [17]. Being a kind of “guardian of the genome”, the p53 protein initiates apoptosis in DNA damage caused by radiation, chemical agents, reactive oxygen species, hypoxia, and other injuring factors. Furthermore, the p53 protein realizes its proapoptotic potential by inducing pro-apoptotic proteins of the Bcl-2 family: Bax, PUMA (p53 upregulated modulator of apoptosis) and Noxa (phorbol-12-myristate-13-acetate-induced protein 1) [17,19]. It is proved that p53 protein can trigger β-cell dysfunction and suppress insulin secretion in them [19]. At the same time, inhibition of p53 activity or knockout of the TP53 gene in mice preclude apoptosis of β-endocrinocytes and prevent insulin resistance development in adipocytes [19].

Therefore, the estimation of the balance between the synthesis of anti- and proapoptotic factors in pancreatic endocrinocytes can be a prognostic factor for assessing the resistance of β-endocrinocytes to the action of pathogenic factors, as well as for assessment the risk of diabetes mellitus development. In the present study, we revealed a deficiency of anti-apoptotic potential caused by a decrease in the Bcl2 protein synthesis in pancreatic islets that led to an increase in the endocrinocyte apoptosis index in normoglycemic hypertensive SHR rats to the level typical to normotensive Wistar rats with streptozotocin-induced diabetes. This fact to some extent explains the low specific density of the β-endocrinocyte population in spontaneously hypertensive rats compared with normotensive Wistar animals [5,6]. In addition to that, adaptive hypobaric hypoxic training of Wistar rats with streptozotocin-induced diabetes increases the anti-apop-


Conclusions

1. The endocrineocytes of pancreatic islets in normotensive Wistar rats demonstrate higher level of the anti-apoptotic protein Bcl2 synthesis than hypertensive rats of the SHR line, while the level of the pro-apoptotic protein p53 expression is almost the same.

2. Experimental diabetes mellitus development in normotensive Wistar rats is accompanied by 2-fold increase in the expression of Bcl2 protein in pancreatic islets, a significant increase in the specific content of p53 protein, and an increase in the p53/Bcl2 apoptosis index by 3.8 times.

3. The development of diabetes in SHR rats is accompanied by 2-fold increase in the specific content of the pro-apoptotic protein p53 in the pancreatic islets without reduction of anti-apoptotic protein Bcl2 synthesis. At the same time, the p53/Bcl2 apoptosis index in SHR rats remains statistically higher than in Wistar rats.

Prospects for further research. Further study of the mechanisms of endocrinecyte death in diabetes, due to the interaction of key molecular regulators of apoptosis β-cells such as Bcl2, Bcl-xL, Bax, Bak, and MST1 proteins are proposed.

Conflicts of interest: authors have no conflict of interest to declare.

References