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DETERMINATION OF MOLECULAR MECHANISMS OF CELLULAR PLASTICITY AND PANCREAS TISSUE REMODELING UNDER CONDITIONS OF EXPERIMENTAL DIABETES

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Abstract

The pancreas functions as a highly integrated system , in which endocrine islets closely interact with exocrine tissue and vascular-stromal-immune microenvironment. Under conditions of experimental diabetes, chronic hyperglycemia, dyslipidemia, oxidative-inflammatory signals and impaired proteostasis initiate prolonged tissue remodeling, the central mechanism of which is cellular plasticity, namely the restructuring of transcriptional-

epigenetic programs and secretory competence of endocrine cells. Identification of key molecular nodes of this response using a panel analysis of expression ($2^{-}\Delta\Delta Ct$) is necessary to distinguish adaptive and maladaptive remodeling scenarios and to substantiate potential targets for the correction of diabetes-associated disfunction.

The aim of the work: to determine the molecular mechanisms of cellular plasticity and remodeling of the pancreas under conditions of experimental diabetes mellitus by analyzing the expression profile of key genes.

Materials and methods. For the analysis of gene expression, the real-time reverse transcription polymerase chain reaction method was used using the PARN-405Z RT² Profiler™ PCR Array Rat Stem Cell kit (QIAGEN, Germany), where the pancreas was the object of the study in experimental animals.

Results. In the pancreas of rats under conditions of experimental diabetes mellitus, an increase in the expression of 7 genes (Aldh1a1, Bmp1, Btrc, Cd8a, Cdc42, Dtx2, Myc) was detected relative to the control using the $2^{-}\Delta\Delta Ct$ method. The most pronounced was the increase in Cdc42 (11.49 times). Also an increase in Bmp1 (7.13), Myc (5.21), Btrc (5.16), Dtx2 (3.19), Aldh1a1 (2.94), and Cd8a (2.24) fold noted was, reflecting a combination of cytoskeletal-secretory adaptation, matrix remodeling, rearrangement of ubiquitin-dependent and Notch-context signaling and a possible immune contribution.

Conclusions: 1. In the pancreas of rats under conditions of experimental diabetes, a limited but distinct profile of increased gene expression (Aldh1a1, Bmp1, Btrc, Cd8a, Cdc42, Dtx2, Myc) was detected by the $2^{-}\Delta\Delta Ct$ method, reflecting a holistic tissue response to chronic metabolic stress. 2. The dominant increase in Cdc42 (+11.49) is consistent with the predominant activation of the cytoskeletal-secretory module and can be interpreted as a compensatory reconfiguration of regulated exocytosis of endocrinocytes in a diabetes-associated stress context. 3. The increase in Bmp1 (+7.13) together with the increase in Btrc (+5.16) and Dtx2 (+3.19) indicates the involvement of stromal-matrix remodeling and ubiquitin-dependent and signaling rearrangements that shape the islet microenvironment and modify plasticity trajectories. 4. The combination of increases in Cd8a (+2.24), Aldh1a1 (+2.94) and Myc (+5.21) highlights the contribution of immune-stress and detoxification-adaptive programs in unfractionated tissue, which requires further cell-specific validation to clarify the source of the signals and their functional consequences.

Keywords: Wistar rats; pancreas; genes; experimental diabetes mellitus; endocrinocytes; cellular plasticity; tissue remodeling.

Introduction. The pancreas is an organ with high structural and functional integration, where the endocrine apparatus (pancreatic islets) functions in close connection with the exocrine tissue, vascular bed, nervous influences and stromal-immune microenvironment. Under conditions of experimental diabetes mellitus (EDM), this system is subjected to multicomponent chronic stress, which includes persistent hyperglycemia, dyslipidemia, oxidative stress, pro-inflammatory signals and impaired proteostasis. The combination of these factors forms an environment,in which tissue remodeling becomes not an episodic reaction, but a long-term process, that determines the trajectory of dysfunction progression or, conversely, the implementation of compensatory mechanisms [1-2].

A key biological substrate of remodeling in diabetes is cellular plasticity, namely the ability of cell populations to change transcriptional and epigenetic programs in response to stress with modification of metabolic architecture, secretory competence, intercellular contacts and dependence on trophic signals. In modern concepts, the plasticity of the endocrine apparatus is not limited to cell loss due to death, but scenarios of functional exhaustion and changes in the identity of endocrinocytes, which can be potentially reversible at certain stages, are considered significant [3-4].

It is important, that the tissue phenotype in EDM is formed not only by intraendocrine mechanisms. Inflammation (local and systemic) can affect the survival and function of endocrine cells, the state of microcirculation and stromal remodeling, and therefore indirectly change both the cellular composition and the transcriptional profile of the tissue. Within the concept of diabetes as an inflammatory disease, it is pro-inflammatory mediators and immune cells that are considered as factors that maintain chronic stress load and can modify plasticity trajectories [2, 5].

An additional critical node in the pathogenesis and remodeling of EDC is endoplasmic reticulum stress and impaired response to misfolded proteins. For β-cells, which are specialized for insulin synthesis and secretion, prolonged imbalance in proteostasis can transition from an adaptive stage to a dysfunctional stage, accompanied by changes in regulatory gene expression, decreased secretory efficiency, and increased vulnerability to death [6-7].

Remodeling in EDM also has a distinct microenvironmental dimension: extracellular matrix remodeling, changes in adhesion and mechanotransduction can affect islet architecture, signal diffusion, trophism and cellular sensitivity to stress. In a number of organs in diabetes, matrix remodeling and fibrosis are considered typical responses to chronic metabolic stress.

In the pancreas, these processes may define the boundaries within which endocrine cell plasticity is realized [8-9].

At the molecular level, plasticity and remodeling are realized through the interaction of several regulatory blocks: epigenetic mechanisms of stabilization and reconfiguration of the transcriptional landscape, stress-induced signaling cascades, developmental modules, as well as nodes of the cell cycle and cytoskeletal-secretory regulation. A separate role is played by epigenetic control, which determines the accessibility of chromatin for key factors and, accordingly, the limits of allowed plasticity in the postnatal period [10].

Given the multifactorial nature of remodeling processes, a panel phenotype-oriented approach to assessing gene expression is practically significant, which allows simultaneously covering several functional axes (stress response, epigenetics, signaling modules, matrix, proliferative and reparative circuits) and comparing them with the experimental model. Quantification of expression changes using the $2^{-}\Delta\Delta Ct$ method is a standardized basis for such analysis, ensuring a correct comparison with the control, provided that it is properly normalized to reference genes [11].

In conclusion, determining the molecular mechanisms of cellular plasticity and remodeling of pancreatic tissue under conditions of EDM is necessary for: distinguishing adaptive and maladaptive restructuring scenarios; identifying key regulatory nodes that control the phenotype of the model; substantiating targets for the correction of diabetes-associated disfunction of the endocrine system.

The aim of the work: to determine the molecular mechanisms of cellular plasticity and pancreatic remodeling under conditions of experimental diabetes by analyzing the expression profile of key genes.

Materials and methods of the study. The study was conducted on 10 white Wistar rats, which were divided into 2 groups (5 animals in each). Animals of group 1 were included in the control group. Animals of group 2 were administered a single intraperitoneal injection of 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. For the purity of the experiment and laboratory confirmation of the development of diabetes mellitus in rats of the second group, 2 weeks after the administration of streptozotocin, the concentration of glucose in the blood was determined in all experimental animals using a GlucoCard-II glucometer (Japan). After decapitation of experimental animals under thiopental anesthesia (50 mg/kg), the pancreas was harvested, fixed in Buena's solution (20 hours) and after standard histological processing was embedded in paraplast (MkCormick, USA).

For gene expression analysis, real-time reverse transcription polymerase chain reaction was used using the PARN-405Z RT² Profiler™ PCR Array Rat Stem Cell kit (QIAGEN, Germany), where the pancreas was the object of study in experimental animals. Polymerase chain reaction data analysis was performed using PCR GeneGlobe software (QIAGEN, Germany) using the $2^{-}\Delta\Delta Ct$ method [11].

Results. The PARN-405Z RT² Profiler™ PCR Array Rat Stem Cell gene panel, which covers 84 genes, associated with cellular plasticity and self-maintenance programs, cell fate signaling pathways, and phenotype maintenance mechanisms. The results obtained reflect changes in the expression of the corresponding genes in the pancreatic tissue as a whole, and therefore characterize the molecular features of cellular plasticity of the endocrine cell population as a functionally heterogeneous system.

According to the results of PCR studies of genes in pancreatic samples of control animals and animals with EDM, the activity of genes in the PCR panel was systematized according to the direction of expression changes as follows: genes with high expression compared to the control group of animals; genes with low expression compared to the control group of animals; genes in which no changes were detected in the samples compared to the control group of animals and genes whose expression was not detected (Table 1).

Table 1 – Characteristics of gene activity of the PARN-405Z RT² Profiler™ PCR Array Rat Stem Cell PCR panel in animals under EDM conditions compared to the control group (analysis by the $2^{-}\Delta\Delta Ct$ method)

	1	2	3	4	5	6	7	8	9	10	11	12
A	*Abcg2*	*Acan*	*Actc1*	*Adar*	*Aldh1a1*	*Aldh2*	*Alpi*	*Apc*	*Ascl2*	*Axin1*	*Bglap*	*Bmp1*
B	*Bmp2*	*Bmp3*	*Btrc*	*Catna1*	*Ccna2*	*Ccnd1*	*Ccnd2*	*Ccne1*	*Cd19*	*Cd3d*	*Cd3e*	*Cd4*
C	*Cd44*	*Cd8a*	*Cd8b*	*Cdc42*	*Cdh1*	*Cdh2*	*Cdk1*	*Col1a1*	*Col2a1*	*Col9a1*	*Cxcl12*	*Dhh*
D	*Dll1*	*Dll3*	*Dtx2*	*Dvl1*	*Ep300*	*Fgf1*	*Fgf2*	*Fgf3*	*Fgf4*	*Fgfr1*	*Foxa2*	*Fzd1*
E	*Gdf3*	*Gja1*	*Gjb1*	*Hdac1*	*Hdac2*	*Hspa9*	*Igf1*	*Ihh*	*Isl1*	*Jag1*	*Kat2a*	*Krt15*
F	*LOC683469*	*Mme*	*Msx1*	*Myc*	*Myod1*	*Kat8*	*Kat7*	*Ncam1*	*Neurog2*	*Notch1*	*Notch2*	*Numb*
G	*Pard6a*	*Pdx1*	*Ppard*	*Pparg*	*Rb1*	*S100b*	*Sigmar1*	*Sox2*	*Tbxt*	*Tert*	*Tubb3*	*Wnt1*

Notes: 1. Green indicates genes with increased expression. Red indicates genes with decreased expression. Yellow indicates genes with no changes in expression (≈1).Gray indicates genes with undetected expression (for the listed genes, expression was not detected either in the control group or in the group of animals under EDM conditions. The threshold

cycle values were at the sensitivity limit of the RT-qPCR method (Ct ≈ 40), which indicates the absence of detected transcriptional activity in the experimental conditions studied).

2. Data are presented as average values (AVG) normalized to reference genes according to the PCR Array algorithm.

Discussion. In this article, we will focus on the mRNA expression characteristics of genes that demonstrated high expression activity (Table 2).

Table 2 - Genes with increased expression relative to the control group of animals according to the results of analysis using the $2^{-}\Delta\Delta Ct$ method

Hole	Gene	Average Amplification Cycle Threshold (Avg Ct) Control	Average Amplification Cycle Threshold (Avg Ct) EDM	The mean value is the test gene/reference gene (ΔCt). Control	The mean value is the test gene/reference gene (ΔCt). EDM	Normalized relative expression level of the studied gene ($2^{-}\Delta Ct$). Control	Normalized relative expression level of the studied gene ($2^{-}\Delta Ct$). EDM	Fold change in expression
A05	*Aldh1a1*	40.00	39.01	3.80	2.24	0.0719	0.2112	2.94
A12	*Bmp1*	34.06	31.80	-2.14	-4.97	4.4041	31.3923	7.13
B03	*Btrc*	39.09	37.29	2.89	0.52	0.1353	0.6986	5.16
C02	*Cd8a*	40.00	39.41	3.80	2.64	0.0719	0.1607	2.24
C04	*Cdc42*	40.00	37.04	3.80	0.28	0.0719	0.8260	11.49
D03	*Dtx2*	37.41	36.30	1.21	-0.47	0.4333	1.3809	3.19
F04	*Myc*	40.00	38.18	3.80	1.42	0.0719	0.3750	5.21

Note: Data are presented as average values (AVG) normalized to reference genes according to the PCR Array algorithm.

In pancreatic samples from rats with EDM, increased expression of 7 genes was detected - Aldh1a1, Bmp1, Btrc, Cd8a, Cdc42, Dtx2, Myc (see Table 2).

The most pronounced increased transcript in the EDM group is Cdc42, the expression of which was increased 11.49 fold ($2^{-}\Delta\Delta Ct$ method). Cdc42 is a key regulator of the actin cytoskeleton and the stages of regulated exocytosis in β-cells, in particular through the reorganization of cortical actin and ensuring the mobilization of secretory granules. In the

development of EDM, this is reasonable to interpret as a compensatory signal to maintain the secretory readiness of endocrinocytes against the background of diabetes-associated stress.

Cdc42 is a key coordinator of cytoskeletal remodeling and exocytosis efficiency, so its increase can be observed in various experimental models as an element of adaptation of the secretory apparatus. At the same time, the biological context and functional consequences of such a change in EDC may reflect mainly stress-compensatory activation with the risk of approaching exhaustion. The accompanying expression pattern of other genes and the state of the tissue microenvironment are decisive for interpretation [12].

In the development of EDM, the Bmp1 gene is upregulated 7.13-fold ($2^{-}\Delta\Delta Ct$ method). Bmp1 is a metalloproteinase known as procollagen-C proteinase, which is involved in the maturation of fibrillar collagens and remodeling of the extracellular matrix. Therefore, the shown increase in Bmp1 in the pancreas in EDM is consistent with the model of stromal-matrix reorganization, which affects the islet microenvironment, tissue mechanical properties and intercellular signaling. The role of extracellular matrix components as determinants of β-cell survival and function and islet stability is discussed in detail in recent reviews [13].

In rats with EDM, a 5.16-fold increase in Btrc expression was detected ($2^{-}\Delta\Delta Ct$ method). The Btrc protein is a component of the ubiquitin ligase complex that tags phosphorylated proteins for proteasomal degradation. Accordingly, Btrc is able to modulate the cell cycle and the function of key signaling cascades, in particular the inflammatory stress pathway and the pathway associated with the regulation of growth and differentiation [14]. In the context of the development of EDM, such an increase probably reflects the increased protein quality control and signaling rewiring characteristic of prolonged metabolic and inflammatory stress.

In parallel, a 3.19-fold increase in Dtx2 was shown ($2^{-}\Delta\Delta Ct$ method). Deltex proteins (DTX family, including Dtx2) are E3 ubiquitin ligases and modulators associated with Notch-dependent networks and receptor endocytosis and trafficking, and are able to influence the process of further cell specialization and parameters of its plasticity [15].

In EDM, a 2.24-fold increase in Cd8a expression ($2^{-}\Delta\Delta Ct$ method) was recorded. Given, that the PCR analysis was performed on unfractionated pancreatic samples, this increase most likely reflects the activation of $CD8^{+}$ T cells and other immune cells in the tissue, rather than changes in Cd8a expression in endocrine cells. This composite signal is consistent with the notion of the involvement of T-cell mechanisms in inflammation and islet damage in diabetes-associated conditions [16].

In EDM, Aldh1a1 expression is increased 2.94 fold ($2^{-}\Delta\Delta Ct$ method). Since Aldh1a1 is involved in aldehyde detoxification and retinoid metabolism, the increase in its transcripts in the pancreas may reflect the activation of stress-adaptive (detoxification) and reparative programs. At the same time, given the analysis of unfractionated tissue, such a signal may also be a consequence of a change in the cellular composition of the sample, i.e. an increase in the proportion of non-endocrine and epithelial components, which should be taken into account when interpreting indicators related to regenerative potential at the level of the whole organ [17].

In general, the profile of increased expression in the pancreas of rats under conditions of EDM (Aldh1a1, Bmp1, Btrc, Cd8a, Cdc42, Dtx2, Myc) reflects a multicomponent tissue response to chronic metabolic stress, which combines: adaptive reconfiguration of the secretory apparatus and cytoskeletal dynamics; activation of stromal-matrix remodeling with potential changes in the islet microenvironment; enhancement of proteostatic and ubiquitin-dependent control and signaling rearrangement; indicators of the inflammatory-immune component; stress-adaptive and detoxification and reparative shifts with the possible participation of high-voltage transcriptional programs. Such a configuration is more consistent with the scenario of compensatory remodeling with simultaneous involvement of the microenvironment and the immune component,than with an isolated endocrine reaction. Accordingly, the ultimate functional consequences of these changes will be determined by the balance between maintaining secretory competence and the risk of progressive exhaustion and dysfunction under conditions of prolonged diabetes-associated stress.

Conclusions: 1. In the pancreas of rats under conditions of experimental diabetes, a limited but distinct profile of increased gene expression (Aldh1a1, Bmp1, Btrc, Cd8a, Cdc42, Dtx2, Myc) was detected by the $2^{-}\Delta\Delta Ct$ method, which reflects the holistic tissue response to chronic metabolic load.

2. The dominant increase in Cdc42 (+11.49) is consistent with the predominant activation of the cytoskeletal-secretory module and can be interpreted as a compensatory reconfiguration of regulated exocytosis of endocrinocytes in the diabetes-associated stress context.

3. The increase in Bmp1 (+7.13) together with the increase in Btrc (+5.16) and Dtx2 (+3.19) indicates the involvement of stromal-matrix remodeling and ubiquitin-dependent and signaling rearrangements that shape the islet microenvironment and modify plasticity trajectories.

4. The combination of increases in Cd8a (+2.24), Aldh1a1 (+2.94), and Myc (+5.21) highlight the contribution of immune-stress and detoxification-adaptive programs in unfractionated tissue, which requires further cell-specific validation to clarify the source of the signals and their functional consequences.

Conflicts of Interest: authors has no conflict of interest to declare.

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