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DETERMINATION OF THE MOLECULAR-GENETIC MECHANISMS OF CELLULAR PLASTICITY AND PANCREATIC TISSUE REMODELING IN SHR RATS

T. Ivanenko

Zaporizhzhia State Medical and Pharmaceutical University, Ukraine

Information about the authors:
Ivanenko T. V., MD, PhD, Associate Professor, Department of Pathological Physiology with Course of Normal Physiology, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine. ORCID ID:0000-0001-6617-5178
E-mail: ivanenkotv@zsmu.edu.ua tel. +38061 2337334

Abstract

Essential arterial hypertension is accompanied by systemic neurohumoral and microcirculatory disturbances, oxidative stress, and metabolic alterations that may affect the endocrine compartment of the pancreas and promote its remodelling. A key component of these changes is endocrine cell plasticity, which is mediated by reprogramming of transcriptional networks and may contribute to the development of islet dysfunction. In spontaneously hypertensive rats, a model relevant to essential arterial hypertension, the molecular and genetic mechanisms underlying these processes remain insufficiently defined, which justifies analysing the expression profile of key genes associated with cellular plasticity and pancreatic tissue remodelling.

The aim of the work: To determine the molecular mechanisms of cellular plasticity and pancreatic remodelling under conditions of essential arterial hypertension by analysing 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 rats SHR, pancreatic gene expression demonstrates coordinated suppression of regulators of epigenetic and transcriptional control and endocrine cell maturity (*Hdac1* 12.25-fold; *Foxa2* 2.12-fold; *Sox2* 3.11-fold; *Neurog2* 14.37-fold; $2^{-}\Delta\Delta Ct$), together with reduced mitochondrial proteostasis (*Hspa9* 14.87-fold) and trophic fibroblast growth factor signalling (*Fgfr1* 11.51-fold; *Fgf1* 4.91-fold). Concomitant downregulation of Notch and Wnt pathway components (*Dtx2* 7.26-fold; *Numb* 4.17-fold; *Axin1* 3.60-fold) and adhesion and matrix-related genes (*Cdh1* 2.39-fold; *Catna1* 3.44-fold; *Col2a1* 2.12-fold), along with decreased cell-cycle regulators (*Ccne1* 9.06-fold; *Ccnd2* 2.47-fold), indicates microenvironmental disorganisation and limited compensatory renewal. Overall, this profile supports a mechanistic shift toward reduced regenerative reserves, metabolic vulnerability, and functional exhaustion of the endocrine compartment under chronic hypertensive stress.

Conclusions: 1. In SHR rats, the pancreatic transcriptional profile is characterised by a predominant decrease in gene expression, reflecting dysregulatory remodelling of the endocrine compartment under chronic hypertensive stress.

2. Suppression of key regulators of epigenetic and transcriptional control and endocrine cell maturity (*Hdac1, Foxa2, Sox2, Neurog2*) is observed, which is consistent with reduced plasticity and diminished functional reserve of the endocrine compartment.

3. The most pronounced shifts involve mitochondrial resilience and trophic support (*Hspa9; Fgfr1, Fgf1*), indicating energy and trophic insufficiency as major components of the SHR phenotype.

4. Downregulation of Notch and Wnt components and adhesion and matrix-related genes (*Dtx2, Numb, Axin1; Cdh1, Catna1, Col2a1*), together with reduced cell-cycle reserves (*Ccne1, Ccnd2*), supports microenvironmental disorganisation and limited compensatory renewal, thereby favouring functional exhaustion of the endocrine compartment.

Keywords: SHR rats; pancreas; genes; essential arterial hypertension; endocrine cells; cellular plasticity; tissue remodelling.

Introduction. Essential arterial hypertension should be viewed not only as a haemodynamic syndrome, but also as a systemic chronic condition accompanied by neurohumoral activation, endothelial dysfunction, oxidative stress, and microcirculatory disturbances that extend far beyond an isolated increase in arterial pressure [1]. Importantly, essential arterial hypertension is closely associated with insulin resistance and metabolic dysregulation, and the relationship between arterial hypertension and insulin resistance is considered a key pathogenic node within the cardiometabolic continuum [1, 2]. In this context, the pancreas-particularly its endocrine compartment-represents a potential target of prolonged vascular and metabolic stress.

The endocrine compartment of the pancreas is a dynamic system capable of adapting to changes in hormonal demand through structural and functional remodelling of the islets of Langerhans. Alongside compensatory responses (changes in islet size, cellular proliferation and replication, and secretory reserve), long-lasting stress exposures may trigger maladaptive trajectories, including imbalance of endocrine cell populations, impairment of proinsulin and insulin biosynthesis, and disruption of regulatory circuits [3, 4]. The microvascular component is of particular importance: adequate blood flow and vasomotor regulation are critical for islet function, and experimental models of arterial hypertension have demonstrated disturbances of microvascular vasomotion and perfusion within islet tissue [4, 5]. Therefore, remodelling of the endocrine compartment under conditions of essential arterial hypertension may have both a cellular and a vascular dimension.

A conceptual framework for these alterations is cellular plasticity, defined as the ability of differentiated cells to change phenotype and functional state in response to damaging stimuli. In the pancreas, cellular plasticity encompasses dedifferentiation, transdifferentiation, and reprogramming of transcriptional programs, which may involve loss of specialised features and emergence of stress-associated or development-like expression profiles [6-8]. From the standpoint of contemporary endocrinology, shifts in regulatory programs-rather than cell death alone-may represent an important mechanism of endocrine cell dysfunction and progression of disturbances in glucose homeostasis [8, 9]. Accordingly, analysis of molecular and genetic regulators that determine cellular plasticity and tissue remodelling is a methodologically grounded approach to explaining the morphofunctional changes of the endocrine pancreas.

The experimental model of spontaneous hypertension in spontaneously hypertensive rats is relevant for reproducing key features of essential arterial hypertension and its systemic consequences. In spontaneously hypertensive rats, changes in the islet apparatus have been

described, including enlargement of islets and increased cellular replication accompanied by reduced proinsulin and insulin biosynthesis and disturbances of islet blood flow [3], as well as changes in the distribution and organisation of islets within the pancreas [10]. At the same time, evidence regarding the molecular and genetic mechanisms that coordinate cellular plasticity and remodelling of pancreatic tissue under conditions of essential arterial hypertension remains fragmented and requires systematic profiling of the expression of key genes.

The aim of the work: To determine the molecular mechanisms of cellular plasticity and pancreatic remodelling under conditions of essential arterial hypertension by analysing the expression profile of key genes.

Materials and methods of the study. The study was conducted on 10 white rats, which were divided into two groups (5 animals in each group). Animals in Group 1 constituted the control group (normotensive Wistar rats). Animals in Group 2 constituted the experimental group-SHR rats (spontaneously hypertensive rats), which served as a model of essential arterial hypertension.

After decapitation of the experimental animals under thiopental anaesthesia (50 mg/kg), the pancreas was collected, fixed in Buena's solution (20 hours), and, after standard histological processing, embedded in Paraplast (McCormick, USA).

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

Results. The PARN-405Z RT² Profiler™ PCR Array Rat Stem Cell gene panel, which includes 84 genes associated with cellular plasticity and self-renewal programs, cell-fate regulatory signalling pathways, and mechanisms maintaining cellular phenotype, was used to provide a molecular characterisation of pancreatic changes under conditions of essential arterial hypertension. The obtained results reflect changes in the expression of the respective genes in pancreatic tissue as a whole and therefore describe the molecular features of cellular plasticity within the endocrine cell population as a functionally heterogeneous system in SHR rats.

Based on the gene expression analysis in pancreatic samples from control animals and hypertensive SHR rats, the activity of the genes included in the polymerase chain reaction panel was systematised according to the direction of expression changes as follows: genes

with increased expression compared with the control group; genes with decreased expression compared with the control group; genes with no detectable changes in expression relative to the control group; and genes whose expression was not detected (Table 1).

Table 1 - Gene expression profile of the PARN-405Z RT² Profiler™ PCR Array Rat Stem Cell panel in SHR rats compared with the control group ($2^{-}\Delta\Delta Ct$ 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	*LOC 683469*	*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 focus on the characteristics of messenger ribonucleic acid expression of genes that demonstrated low expression activity (Table 2).

In rats with hereditary arterial hypertension, the most pronounced downregulation involves nodes that govern the stability of the differentiated state, transcriptional and epigenetic control, and regenerative potential. *Hdac1* is decreased 12.25-fold ($2^{-}\Delta\Delta Ct$ method). *Hdac1* is a key component of chromatin-remodelling machinery, and its persistent suppression can be interpreted as evidence of restricted transcriptional control under a chronic stress background that includes a vascular component. *Foxa2* is decreased 2.12-fold ($2^{-}\Delta\Delta Ct$ method). *Foxa2* contributes to the maintenance of endocrine cell maturity programs and regulates cascades associated with *Pdx1* [12].

Table 2 - Genes with decreased expression relative to the control group, based on analysis using the $2^{-}\Delta\Delta Ct$ method

Hole	Gene	Average Amplification Cycle Threshold (Avg Ct) Control	Average Amplification Cycle Threshold (Avg Ct) SHR	The mean value is the test gene/reference gene (ΔCt). Control	The mean value is the test gene/reference gene (ΔCt). SHR	Normalized relative expression level of the studied gene ($2^{-}\Delta Ct$). Control	Normalized relative expression level of the studied gene ($2^{-}\Delta Ct$). SHR	Fold change in expression
A10	*Axin1*	38.45	40.00	2.25	4.10	0.2100	0.0583	-3,60
A12	*Bmp1*	34.06	34.96	-2.14	-0.94	4.4041	1.9219	-2,29
B03	*Btrc*	39.09	40.00	2.89	4.10	0.1353	0.0583	-2,32
B04	*Catna1*	37.52	39.00	1.32	3.11	0.4001	0.1162	-3,44
B07	*Ccnd2*	39.00	40.00	2.80	4.10	0.1439	0.0583	-2,47
B08	*Ccne1*	37.12	40.00	0.92	4.10	0.5281	0.0583	-9,06
B09	*Cd19*	35.07	36.07	-1.13	0.17	2.1921	0.8882	-2,47
C05	*Cdh1*	39.05	40.00	2.85	4.10	0.1390	0.0583	-2,39
C09	*Col2a1*	39.22	40.00	3.02	4.10	0.1234	0.0583	-2,12
D03	*Dtx2*	37.41	39.96	1.21	4.07	0.4333	0.0597	-7,26
D06	*Fgf1*	38.01	40.00	1.81	4.10	0.2860	0.0583	-4,91
D10	*Fgfr1*	36.78	40.00	0.58	4.10	0.6708	0.0583	-11,51
D11	*Foxa2*	37.25	38.03	1.05	2.13	0.4831	0.2280	-2,12
E04	*Hdac1*	36.02	39.33	-0.18	3.43	1.1367	0.0928	-12,25
E06	*Hspa9*	36.41	40.00	0.21	4.10	0.8665	0.0583	-14,87
F01	*LOC683469*	36.78	40.00	0.57	4.10	0.6714	0.0583	-11,52
F09	*Neurog2*	36.46	40.00	0.26	4.10	0.8371	0.0583	-14,37
F12	*Numb*	38.24	40.00	2.04	4.10	0.2429	0.0583	-4,17
G03	*Ppard*	35.57	38.13	-0.63	2.23	1.5513	0.2128	-7,29
G08	*Sox2*	38.67	40.00	2.46	4.10	0.1812	0.0583	-3,11

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

Sox2 is decreased 3.11-fold ($2^{-}\Delta\Delta$Ct method), which, at the tissue level, is more consistent with overall suppression of regenerative and progenitor circuits than with their activation. *Neurog2* is decreased 14.37-fold ($2^{-}\Delta\Delta$Ct method); together with *Foxa2* and *Sox2*, this establishes a profile in which transcriptional axes related to differentiation and plasticity are predominantly suppressed. Conceptually, this is consistent with reduced reserve capacity of the endocrine compartment under hypertensive stress, as described in Section 4 of this dissertation.

Because *Hdac1* is decreased across all three experimental models, this should not be interpreted as a contradiction between them. Rather, the unidirectional change suggests that epigenetic reprogramming and partial restraint of plasticity programs and cell-cycle activity may represent a shared tissue response to chronic load [13]. At the same time, the model-specific phenotype is shaped not by *Hdac1* suppression per se, but by the context of accompanying changes, including the nature of trophic signalling, extracellular matrix remodelling, the status of the Notch and Wnt axes, and other microenvironmental components that determine whether repair programs shift toward adaptation or dysregulation.

The strongest suppression in rats with hereditary arterial hypertension is observed for *Hspa9*, decreased 14.87-fold ($2^{-}\Delta\Delta$Ct method). *Hspa9* is a mitochondrial proteostasis protein that is critical for protein quality control and mitochondrial stress resilience [14].

The fibroblast growth factor axis is also markedly suppressed, with direct relevance to islet cell survival and function. *Fgfr1* is decreased 11.51-fold ($2^{-}\Delta\Delta$Ct method) and is considered an important pathway supporting normal beta-cell function and interactions with the microenvironment in the pancreas [15]. *Fgf1* is decreased 4.91-fold ($2^{-}\Delta\Delta$Ct method), *Fgf1* can modulate beta-cell and islet function and survival in experimental models [16]. Taken together, these findings indicate a clear trophic deficit in the transcriptional profile of rats with hereditary arterial hypertension, which provides a plausible explanation for the tendency toward reduced regenerative potential under hereditary hypertension.

In parallel, suppression is observed in components that shape tissue structural organisation and the controllability of remodelling. *Dtx2* is decreased 7.26-fold, and *Numb* is decreased 4.17-fold ($2^{-}\Delta\Delta$Ct method). Both genes are functionally linked to Notch-dependent networks involved in controlling subsequent cellular specialisation and maintaining homeostasis [17]. *Axin1* is decreased 3.60-fold ($2^{-}\Delta\Delta$Ct method) as a regulator of the Wnt and beta-catenin circuit. Wnt signalling is critical for pancreatic development and homeostasis and for programs of cellular identity and plasticity [18]. *Cdh1* is decreased 2.39-fold, *Catna1* is decreased 3.44-fold, and *Col2a1* is decreased 2.12-fold ($2^{-}\Delta\Delta$Ct method), which is consistent

with the concept that, under chronic hypertension, microenvironment remodelling may have a disorganising component-rather than an adaptive pattern as observed under controlled exogenous hypoxia-thereby worsening islet architecture.

Additionally, suppression of *Ccne1* by 9.06-fold and *Ccnd2* by 2.47-fold is observed ($2^{-}\Delta\Delta$Ct method), consistent with inhibition of cell-cycle reserves and, consequently, reduced capacity for compensatory renewal. *Cd19* is decreased 2.47-fold ($2^{-}\Delta\Delta$Ct method), which may reflect the contribution of immune and stromal components to the overall tissue profile. *Ppard* is decreased 7.29-fold ($2^{-}\Delta\Delta$Ct method). Peroxisome proliferator-activated receptor beta and delta is involved in regulating metabolic programs in the pancreas and influences parameters of insulin secretion and beta-cell function [19].

Overall, the transcriptional profile in rats with hereditary arterial hypertension is characterised by coordinated downregulation of epigenetic and transcriptional control (*Hdac1*), endocrine maturity and developmental regulators (*Foxa2, Sox2, Neurog2*), mitochondrial proteostasis (*Hspa9*), trophic fibroblast growth factor signalling (*Fgfr1, Fgf1*), Notch and Wnt network components (*Dtx2, Numb, Axin1*), adhesion and matrix-related genes (*Cdh1, Catna1, Col2a1*), and cell-cycle regulators (*Ccne1, Ccnd2*). This configuration supports a mechanistic model in which chronic hypertensive stress shifts pancreatic tissue toward reduced regenerative reserves, impaired microenvironmental organisation, and metabolic vulnerability, thereby favouring functional exhaustion of the endocrine compartment rather than adaptive plasticity.

Conclusions: 1. In SHR rats, the pancreatic transcriptional profile is characterised by a predominant decrease in gene expression, reflecting dysregulatory remodelling of the endocrine compartment under chronic hypertensive stress.

2. Suppression of key regulators of epigenetic and transcriptional control and endocrine cell maturity (*Hdac1, Foxa2, Sox2, Neurog2*) is observed, which is consistent with reduced plasticity and diminished functional reserve of the endocrine compartment.

3. The most pronounced shifts involve mitochondrial resilience and trophic support (*Hspa9; Fgfr1, Fgf1*), indicating energy and trophic insufficiency as major components of the SHR phenotype.

4. Downregulation of *Notch* and *Wnt* components and adhesion and matrix-related genes (*Dtx2, Numb, Axin1; Cdh1, Catna1, Col2a1*), together with reduced cell-cycle reserves (*Ccne1, Ccnd2*), supports microenvironmental disorganisation and limited compensatory renewal, thereby favouring functional exhaustion of the endocrine compartment.

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