

Assessment of Mitochondrial Gene Activity in Dopaminergic Neuron Cultures Derived from Induced Pluripotent Stem Cells Obtained from Parkinson's Disease Patients

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Abstract

Introduction. Induced pluripotent stem cells (iPSCs) culturing allows modelling of neurodegenerative diseases in vitro and discovering its early biomarkers.

Our objective was to evaluate the activity of genes involved in mitochondrial dynamics and functions in genetic forms of Parkinson's disease (PD) using cultures of dopaminergic neurons derived from iPSCs.

Materials and methods. Dopaminergic neuron cultures were derived by reprogramming of the cells obtained from PD patients with SNCA and LRRK2 gene mutations, as well as from a healthy donor for control. Expression levels of 112 genes regulating mitochondrial structure, dynamics, and functions were assessed by multiplex gene expression profiling using NanoString nCounter custom mitochondrial gene expression panel.

Results. When comparing the characteristics of the neurons from patients with genetic forms of PD to those of the control, we observed variations in the gene activity associated with the mitochondrial respiratory chain, the tricarboxylic acid cycle enzyme activities, biosynthesis of amino acids, oxidation of fatty acids, steroid metabolism, calcium homeostasis, and free radical quenching. Several genes in the cell cultures with SNCA and LRRK2 gene mutations exhibited differential expression. Moreover, these genes regulate mitophagy, mitochondrial DNA synthesis, redox reactions, cellular detoxification, apoptosis, as well as metabolism of proteins and nucleotides.

Conclusions. The changes in gene network expression found in this pilot study confirm the role of disrupted mitochondrial homeostasis in the molecular pathogenesis of PD. These findings may contribute to the development of biomarkers and to the search for new therapeutic targets for the treatment of SNCA- and LRRK2-associated forms of the disease.

Keywords: Parkinson's disease; SNCA; LRRK2; induced pluripotent stem cells; dopaminergic neurons; transcriptomics; mitochondria

Ethics approval. Authors confirm compliance with institutional and national standards for the use of laboratory animals in accordance with «Consensus Author Guidelines for Animal Use» (IAVES, 23 July 2010). The research protocol was approved by the Local Ethics Committee of the Research Center of Neurology (protocol No. 5-5/22, June 1, 2022).

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Оценка активности митохондриальных генов в культурах дофаминергических нейронов, полученных из индуцированных плюрипотентных стволовых клеток от пациентов с болезнью Паркинсона

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Аннотация

Введение. Технологии культивирования индуцированных плюрипотентных стволовых клеток (ИПСК) предоставляют возможность для моделирования нейродегенеративных заболеваний in vitro и поиска их ранних биомаркеров.

Цель исследования — оценить активность генов, вовлечённых в функционирование митохондрий, на культурах дофаминергических нейронов — производных ИПСК — при генетических формах болезни Паркинсона (БП).

Материалы и методы. Культуры дофаминергических нейронов были получены путём клеточного репрограммирования от пациентов с БП, являющихся носителями мутаций в генах *SNCA* и *LRRK2*, а также от здорового донора (контроль). С помощью технологии мультиплексного профилирования геной экспрессии на платформе «NanoString» оценивали экспрессию 112 генов, участвующих в структурно-функциональной организации митохондрий и собранных в специальную «митохондриальную» панель.

Результаты. При сравнении характеристик нейронов, полученных от пациентов с генетическими формами БП и в контроле, выявлены различия в активности генов, продукты которых связаны с работой митохондриального дыхательного комплекса, ферментами цикла трикарбоновых кислот, биосинтезом аминокислот, окислением жирных кислот, метаболизмом стероидов, гомеостазом кальция в клетке, утилизацией свободных радикалов. Ряд генов показал также дифференцированную экспрессию в культурах с мутациями *SNCA* и *LRRK2*; в дополнение к указанным выше функциям данные гены контролируют митофагию, синтез митохондриальной ДНК, окислительные реакции, процессы детоксикации клетки и апоптоз, метаболизм белков и нуклеотидов.

Заключение. Выявленные в настоящем пилотном исследовании изменения экспрессии генов сетей подтверждают роль нарушений митохондриального гомеостаза в молекулярном патогенезе БП и могут способствовать разработке биомаркеров и поиску новых терапевтических мишеней при *SNCA*- и *LRRK2*-ассоциированных формах заболевания.

Ключевые слова: болезнь Паркинсона; *SNCA*; *LRRK2*; индуцированные плюрипотентные стволовые клетки; дофаминергические нейроны; транскриптомика; митохондрии

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Introduction

Parkinson's disease (PD) is a common age-related neurodegenerative disorder that primarily affects the dopaminergic neurons in the substantia nigra pars compacta (SNpc), resulting in a complex combination of motor and non-motor symptoms. By 2040, the number of people with PD is expected to reach 12.9 million [1]. All current PD treatments are symptomatic and do not stop the disease from progressing. The first motor symptoms occur when the dopaminergic neurons in the SNpc have already degenerated by about 60 %, which is why therapy is initiated too late [2]. Current technologies allow to culture induced pluripotent stem cells (iPSCs) obtained from the PD patients, thus providing new opportunities to study the pathogenesis of neurodegenerative disorders. The *in vitro* PD models and neurons derived from the iPSCs of PD patients with mutations in PD-causing genes appeared to be highly informative for identifying molecular drivers of the neurodegenerative process [3]. It is important to mention that iPSC-based models would help to identify the earliest morphological and functional changes in neurons and to detect the developing disease at its earliest presymptomatic stages.

Rapid advances in molecular technologies allowing efficient and powerful qualitative and quantitative

assessment of various genetic characteristics have brought the studies in the field of disease progression markers to a new level. These include the NanoString nCounter technology developed by NanoString Technologies, which enables targeted multiplex analysis of hundreds of genes in a single run [4, 5]. The advantages of this technology over traditional gene expression analysis are walk-away automation of the workflow, robust performance, and reproducibility of the results. The sensitivity of the method is comparable to the one of a real-time PCR [6]. The method is based on molecular barcoding, in which the studied targets are tagged with target-specific color-coded probe pairs that enable further detection of the captured targets [7]. As the preliminary steps of reverse transcription and amplification often leading to biased data are excluded from the workflow [8], this method demonstrates high level of accuracy and sensitivity with low concentrations and small volumes of the source material [4, 5].

Current studies of the mechanisms involved in the development of PD focus primarily on mitochondrial dynamics [9, 10]. In our research we used bar-coding multiplex gene expression profiling on the NanoString platform to assess the activity of genes involved in mitochondrial dynamics in the cultures of dopaminergic neurons derived from iPSCs of the patients with genetic forms of PD.

Materials and methods

Cell line culturing

Skin biopsy specimen were obtained from two patients with known genetic forms of PD and one healthy donor. One of the PD patients had a heterozygous duplication of exons 2–7 of the *SNCA* gene and the second had the heterozygous *G2019S* point mutation in the *LRRK2* gene. All patients were familiarized with the conditions of the study and signed an informed consent form. The study was approved by the local ethics committee of the Research Center of Neurology (protocol No. 11/12 dated 12 September 2012).

The cells from the primary homogeneous dermal fibroblast culture were reprogrammed into iPSCs. To reprogram the fibroblasts, we used Sendai virus because its reprogramming factors and DNA do not integrate into the genome of the cells studied. All the iPSC lines were cultured in the mTeSR medium (STEMCELL Technologies) on Matrigel-coated substrates. Fibroblast reprogramming and iPSC differentiation into neural progenitor cells and further into neuronal cell cultures enriched by dopaminergic neurons were performed as previously described [11].

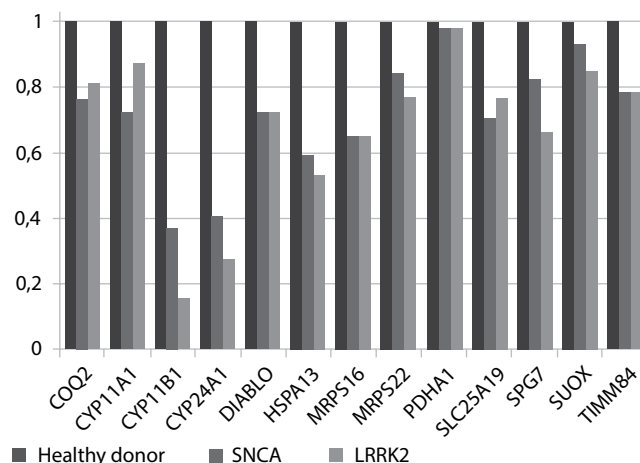
RNA isolation from the neuronal cell culture

Total RNA from the mature neuronal lines of the PD patients and the healthy donor was isolated using Total RNA purification kit (Norgen) according to the manufacturer's instructions. The RNA quantification was made using a Nanodrop 2000 spectrophotometer (ThermoScientific). The RNA isolate was used immediately or stored at -80°C until used in the experiments.

Gene expression analysis

Gene expression was analyzed using NanoString technology (NanoString Technologies). The analysis used the custom gene expression panel containing 12 gene networks associated with dynamics and functions of mitochondria. The panel includes 112 genes, which were selected based on existing scientific data on their involvement in the regulation of mitochondrial structure and dynamics. The panel also includes 5 house-keeping genes as the controls. After hybridization of total RNA (100 ng) with the target-specific fluorescent tags, the samples were loaded into the prep station of the nCounter Analysis System (NanoString Technologies) for further digital analysis according to the manufacturer's protocols.

The data obtained were analyzed using nSolver v. 4.0 software. Source data were normalized using the house-keeping control genes included in the panel: β -actin (NM_001101.2), GAPDH (NM_002046.3), HPRT1



Decreased expression of some genes associated with mitochondrial dynamics and functions in neurons derived from patients with genetic form of PD.

(NM_000194.1), RPL19 (NM_000981.3), and β -tubulin (NM_178014.2). The data obtained with the nCounter system are expressed in the units reflecting concentration of target RNA molecules in the sample.

Results

For the iPSCs obtained from the PD patients and the healthy donor all necessary tests required by international standards were performed, namely the assessment of pluripotency marker expression, pluripotent cell gene expression, and karyotyping to confirm the normal karyotype of the cells and their ability to form embryoid bodies and derivatives of the three germ layers. The differentiation of the iPSCs from the PD patients and the healthy donor into neuronal progenitor cells was initiated simultaneously. The selection of iPSC lines was based on the results of the tests performed. The iPSC lines that showed a tendency towards preferential formation of neural derivatives in the spontaneous *in vitro* differentiation assay, were used first. Terminal differentiation into dopaminergic neurons was performed in two steps according to the previously used protocol [12].

Further, changes in mitochondrial gene expression profiles in three neuronal cell cultures derived from iPSCs were analyzed using the NanoString platform. We assessed expression levels of 112 genes from the custom NanoString Human mitochondrial panel. Comparative analysis revealed unidirectional changes (decreases) in the expression levels of 13 genes in the cell cultures from both patients with genetic forms of PD compared with those in the control neuron cell culture (see the Figure). In the known genetic forms of PD, a decrease in expression appeared to be typical for the genes associated with oxidative phosphorylation, the tricarboxylic acid cycle, amino acid biosynthesis, fatty acid oxidation, steroid metabolism, calcium homeostasis, and free radical quenching [13–15].

Table 1. Gene expression changes in the neurons with the *LRRK2* gene mutation

Metabolic pathway	Gene	Gene expression level
Mitochondrial respiratory chain	<i>SDHA</i>	Increased
	<i>CYCS, ATP5E, ATPAF2, NDUFA1, NDUFB9, NDUFS4</i>	Decreased
Transmembrane transport of substrates	<i>SLC25A12, SLC25A13, SLC25A FXN, TMLHE</i>	Increased
Tricarboxylic acid cycle	<i>FH</i>	Increased
Metabolism of the proteins, nucleotides, and vitamins	<i>AMT, PCCA, TMLH</i>	Increased
	<i>GATM, GCDH, PCCB, HADHA</i>	Decreased
Heat shock proteins	<i>HSPA1A, HSPA4L, HSPA6, HSPB1</i>	Decreased
Mitophagy	<i>PINK1</i>	Decreased
Protein translation	<i>TSMF</i>	Decreased

Table 2. Gene expression changes in the neurons with the *SNCA* gene mutation

Metabolic pathway	Gene	Gene expression level
Mitochondrial respiratory chain	<i>COX15, COX6B1, CYP11B2, CYP27A1, ETFA, MT-ATP6, MT-ATP8, MT-CO1, MT-CO2, MT-CO3, MT-CYB, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND4L, MT-ND5, MT-ND6, NDUFA10, NDUFA11, NDUFB3, NDUFS2, NDUFS3, NDUFS6, NDUFV1, SDHB, SDHC, SDHD</i>	Increased
	<i>UQCRB, COX10</i>	Decreased
Transmembrane transport of substrates	<i>ABCB6, CPT1A, SLC25A20, SLC25A4, TIMM44</i>	Increased
	<i>SLC25A15, SLC25A22, SLC9A6</i>	Decreased
Tricarboxylic acid cycle	<i>SUCLA2, PDHB, PDHX</i>	Increased
Mitophagy	<i>GSR</i>	Increased
	<i>HIF-1α, Mfn2, OPA1</i>	Decreased
Amino acid metabolism	<i>HADHB</i>	Increased
	<i>ALDH18A1, NDUFV2, SARDH</i>	Decreased
Heat shock proteins	<i>HSPA9</i>	Increased
	<i>HSPA14</i>	Decreased
Replication and repair of mitochondrial DNA	<i>DGUOK, POLG, C10orf2</i>	Decreased
Protein translation	<i>TUFM, MRPL3</i>	Decreased
Gem synthesis	<i>PPOX</i>	Decreased

Decreased expression of some genes associated with mitochondrial dynamics and functions in neurons derived from patients with genetic form of PD.

Several genes showed a differential expression in the neurons cultured from the PD patient cells with mutations in the *LRRK2* and *SNCA* genes. In the neurons with the *LRRK2* gene mutation 10 genes showed an increase in expression and 16 genes showed a decrease in expression compared to the control neuron cell culture and the culture of neurons with the *SNCA* gene mutation (Table 1). The products of these differentially expressed genes are involved in the mitochondrial respiratory chain, the tricarboxylic acid cycle, mitophagy, protein processing and metabolism of the proteins, nucleotides and vitamins in a cell, transmembrane transport of iron and other substrates [16, 17].

In the neurons derived from the cells with the *SNCA* gene mutation 44 genes showed increased expression levels and 21 genes showed decreased expression levels compared to the control and to the neurons with the *LRRK2* gene mutation (Table 2). Increased expression was observed in genes involved in oxidative phosphorylation, mitophagy, replication and repair of mitochondrial DNA, the tricarboxylic acid cycle, protein processing, lipid and protein metabolism, redox control, apoptosis, and protection against neurotoxicity. The detected genes with decreased expression are mainly involved into protein sorting and accumulation, and protein and nucleotide metabolism [18–23].

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Discussion

Mitochondria play a key role in regulating cellular bioenergetics. Involved in numerous signaling pathways, they contribute to the development, plasticity, and differentiation of neurons, including the activation of cell apoptosis [24].

In our pilot study, we assessed the expression levels of more than 100 genes associated with mitochondrial dynamics and functions using the NanoString platform. Comparative analysis of the characteristics of the neurons obtained from the patients with genetic forms of PD and a healthy donor, allowed us to identify the differences in the expression of genes regulating oxidative phosphorylation activity, the tricarboxylic acid cycle, amino acid biosynthesis, fatty acid oxidation, steroid metabolism, calcium homeostasis, and free radical quenching. Several genes showed a differential expression in the cell cultures with the *SNCA* and *LRRK2* gene mutations. These genes, in addition to the functions mentioned above, regulate mitophagy, mitochondrial DNA synthesis, redox reactions, cellular detoxification and apoptosis, and lipid and protein metabolism.

The identified changes in gene network expression confirm the role of disrupted mitochondrial homeostasis in the molecular pathogenesis of PD. These findings may contribute to the development of new biomarkers and to the search for new therapeutic targets for the treatment of *SNCA*- and *LRRK2*-associated forms of the disease.

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