Краткие сообщения
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ХИМЕРИН УЧАСТВУЕТ В РЕГУЛЯЦИИ КОНТРОЛЯ КАЧЕСТВА МИТОХОНДРИЙ У БОЛЬНЫХ ОЖИРЕНИЕМ

Вульф М.А., Шунькина (Скуратовская) Д.А., Ву Х., Комар А.А., Затолокин П.А., Кириенкова Е.В., Газатова Н.Д., Литвинова Л.С.

ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия

Резюме. У больных ожирением выявлены взаимосвязи содержания химерина в плазме крови с экспрессией генов *TFAM*, *Drp1*, *MFN2*, *SOD*, *BAX*, ответственных за контроль качества митохондрий, в инсулинзависимых тканях (жировая ткань, печень). Установлены тканеспецифические особенности экспрессии генов (*TFAM*, *Drp1*, *MFN2*, *SOD*, *BAX*), числа копий мтДНК в исследуемых депо у больных ожирением. Доказано, что изменение (снижение) числа копий мтДНК в инсулинзависимых тканях может оказывать протекторное действие на митохондрии, в условиях повышенного окислительного стресса.

Выявлено, что у больных без СД 2-го типа повышение продукции химерина способствует активации антиоксидатной системы в висцеральной жировой ткани, но не в печени. Напротив, у всех больных ожирением с СД 2 типа регистрировалось снижение (в сравнении с больными без СД 2 типа) плазменного уровня химерина.

Таким образом, низкое содержание химерина в плазме крови у больных с СД 2-го типа опосредует формирование дисфунции митохондрий в инсулинзависимых тканях (жировая ткань, печень).

Ключевые слова: ожирение, СД 2 типа, митохондрии, химерин, печень, жировая ткань, мтДНК

CHEMERIN AS A POTENTIAL REGULATOR OF MITOCHONDRIAL QUALITY CONTROL IN OBESE PATIENTS

Vulf M.A., Shunkina (Skuratovskaia) D.A., Hung V., Komar A.A., Zatolokin P.A., Kirienkova E.V., Gazatova N.D., Litvinova L.S.

Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation

Abstract. In obese patients, the relationship between the content of chemerin in blood plasma and the expression of genes *TFAM*, *Drp1*, *MFN2*, *SOD*, *BAX*, responsible for quality control of mitochondria, in insulin-dependent tissues (adipose tissue, liver) was revealed. The tissue-specific features of gene expression (*TFAM*, *Drp1*, *MFN2*, *SOD, BAX*), the number of mtDNA copies in the studied depots in obese patients were established. It has been proven that a change (decrease) in the number of mtDNA copies in insulin-dependent

Адрес для переписки:	Address for correspondence:
Вульф Мария Александровна	*Vulf Maria A.*
ФГАОУ ВО «Балтийский федеральный университет имени	*Immanuel Kant Baltic Federal University, Kaliningrad,*
Иммануила Канта», г. Калининград, Россия	*Russian Federation*
236001, Россия, г. Калининград, ул. Гайдара, 6, НТП	*236001, Russian Federation, Kaliningrad, Gaidar str., 6, STP*
«Фабрика».	*"Fabrika".*
Тел.: 8 (911) 489-22-39.	*Phone: 7 (911) 489-22-39.*
E-mail: mary-jean@yandex.ru	*E-mail: mary-jean@yandex.ru*

tissues can have a protective effect on mitochondria under conditions of increased oxidative stress. It was found that in patients without type 2 diabetes, an increase in chemerin production promotes the activation of the antioxidant system in the visceral adipose tissue but not in the liver. On the contrary, all obese patients with type 2 diabetes showed a decrease (compared with patients without type 2 diabetes) in the plasma level of chemerin. Thus, the low content of chemerin in the blood plasma in patients with type 2 diabetes mediates the formation of mitochondrial dysfunction in insulin-dependent tissues (adipose tissue, liver).

Keywords: obesity, T2DM, mitochondria, chemerin, liver, adipose tissue, mtDNA

Introduction

Obesity has been shown to directly or indirectly cause type 2 diabetes mellitus (T2DM), cardiovascular and oncological diseases. Russia poses the fourth and fifth place worldwide in the number of overweight people and patients with type 2 diabetes, respectively. Epidemiological forecasting shows that by 2025, 40% of males and 50% females will be overweight and obese. Abdominal obesity is associated with dysfunction of adipose tissue (AT) and accumulation of free fatty acids (FFA) outside of it; it all leads to development of nonalcoholic fatty liver disease (NAFLD), atherosclerosis, and dysfunction of pancreatic cells.

A high FFA content activates cell oxidative stress and increases reactive oxygen species (ROS). ROS damage mitochondrial DNA (mtDNA), disrupt mitochondrial quality control (MQC) processes (dynamics, biogenesis, mitophagy). Mitochondrial dysfunction in insulin-dependent tissues contributes to insulin resistance (IR).

Chemerin — a cytokine known as tazarotene-induced gene 2 (*TIG2*) or retinoic acid responder receptor 2 (*RARRES2*), is secreted by preadipocytes, adipocytes, hepatocytes and leukocytes [5] and involved in the regulation of angiogenesis, adipogenesis, inflammation, and energy metabolism.

Mitochondria are essential regulators of cellular energy homeostasis. The number of mitochondria in cells depends on the level tissue metabolic activity. Tissue-specific features of mitochondrial quality control in insulin-dependent tissues (AT, liver) are of particular interest. Thus, the study aimed to identify the role of chemerin in regulating mitochondrial quality control processes in insulin-dependent tissues of obese patients.

Materials and methods

There were enrolled 264 obese patients, among which 154 had T2DM (42.90 ± 10.10 years; 42 males and 112 females), and 110 obese patients had no carbohydrate metabolism disorders (41.80 ± 7.00 years; 50 males and 60 females) (Table 1). The control group consisted of 38 apparently healthy donors with normal anthropometric and biochemical parameters (37.50 ± 10.10 years; 20 males and 18 females). All participants provided an informed consent for participation in the study.

AT biopsy samples of various localization (visceral — greater omentum (GO), mesentery of the small intestine (MES), subcutaneous AT (SAT) and liver samples) were obtained during bariatric surgery in obese patients with/without T2DM and during routine laparoscopic operations: right- or left-side inguinal hernia, femoral, diaphragmatic and ventral hernias, nephroptosis in apparently healthy donors (control group).

Total RNA from liver biopsies was isolated using the ExtractRNA reagent (Evrogen, Moscow, Russia). Reverse transcription was performed using the MMLV RT kit (Evrogen, Moscow, Russia).

The level of serum chemerin was determined using an enzyme-linked immunosorbent assay (BIO Vendor, Czech Republic). Statistical data processing was carried out using the IBM SPSS Statistics 20 software (Statistical Package for the Social Sciences), by plotting data with Graphpad Prism 9.0 software.

Results and discussion

Visceral *vs* subcutaneous AT adipocytes have a high lipolysis rate [14] and synthesize more molecules with a proinflammatory profile. Differences in cellular composition, innervation and blood supply suggest opposite roles of fat stores in the pathogenesis of obesity. Excessive accumulation of TG in adipocytes leads to their hypertrophy and subsequent AT dysfunction and inflammation. When adipocytes are unable to store fatty acids, their excessive amount enters the systemic circulation to be deposited in the liver, muscles, heart, leading to ectopic lipid accumulation [10]. Most obese people develop NAFLD. FFAs are the main source of lipid accumulation in the liver. IR occurs as a result of the accumulated lipids both at the organ and body level.

Mitochondria play an important role in regulating whole body energy homeostasis and controlling insulin and glucose metabolism sensitivity. In mitochondria, fatty acid β-oxidation occurs, the pro-

cess of degradation of fatty acids. Mitochondria exert high plasticity, which allows them to provide the cell with energy demands. Mitochondria under stress conditions activate mitochondrial quality control (MQC) processes (biogenesis, dynamics, autophagy/mitophagy). MQC maintains organelle homeostasis, structure and function [6]. Energy-sensitive mediators affect mitochondrial plasticity.

Xie Q. et al. (2015) demonstrated that chemerin is involved in regulating mitochondrial biogenesis and mitophagy in skeletal muscle [13]. Previously, our studies have shown that chemerin in patients with morbid obesity without T2DM has a protective effect on IR development by decreasing the number of mtDNA copies in visceral adipose tissue [9].

White AT is the main source of chemerin; its expression has tissue-specific features [12]. Earlier, we showed that the chemerin level depends on RARRES2 gene expression in GO of obese patients [12]. An increase in chemerin production is positively associated with increased BMI (r = 0.25, p < 0.05) in patients without T2DM, which is quite logical and consistent with other studies [5]. In obese patients with T2DM, the level of serum chemerin, on the contrary, decreased (Table 1). Horn P. et al. (2018) associated a low level of serum chemerin with impaired liver function [8]. Chemerin deficiency is associated with IR in the AT and liver. This leads to increased production of glucose in the liver and blood. Chemerin regulates the β-cell function and plays an essential role in tissue-dependent glucose homeostasis. It was found that the level of glucose and chemerin was positively associated (r = -0.66, p < 0.05) in the control group, whereas in group with obesity lacking type 2 diabetes it showed negative relation (r = -0.47, p < 0.05).

Our studies have shown that in patients with type 2 diabetes in the liver, hepatocyte dystrophy, karyolysis, intracellular cholestasis, lymphocytic infiltration, and liver capsules enlargement were detected [2].

Chemerin is secreted as an inactive precursor to be activated by proteases via C-terminal processing. Thus, different isoforms have distinct biological effects and activities. Moreover, it is extensively discussed about what receptors are more critical for the chimeric biological and pathophysiological effects.

Chemokine-like receptor 1 (CMKLR1 or ChemR23) is the main most examined molecule transducing chimer signals. Studies have shown that obesity increases the expression of mRNA CMKLR1 in AT that rises in obesity; this is associated with macrophage tissue recruitment. The G protein-coupled receptor 1 (GPR1) and Chemokine receptor-like 2 (CCRL2) receptors are less studied.

GPR1 is expressed on the AT stromal vascular cells. In the liver of obese patients, the level of mRNA expression of chemerin and CMKLR1 is positively associated with BMI and concomitant NAFLD [3].

Interestingly, CMKLR1 mRNA is expressed by hepatocytes, hepatic stellate cells, endothelial cells, and Kupffer cells. Another receptor, CCRL2, is expressed by various liver cells, except for hepatocytes, transmitting no signals [11].

Mitochondria are a primary source of energy production in cells. The mtDNA copy number is adapted to the energy requirement, physiological or pathological state. Increased FFAs, ROS, reactive nitrogen species, and lipid peroxidation products can damage mtDNA.

In obese patients without T2DM, mtDNA copy number in AT from diverse sites localization was comparable to the control. In contrast, in obese patients with T2DM, an increased mtDNA copy number in AT was recorded. In the liver of obese patients without T2DM, we found decreased amount of mtDNA copy number compared to the control, while in patients with T2DM, it was higher than control group and patients with T2DM. mtDNA copy number in healthy donor liver was increased compared to that in adipose tissue depots, which is necessary to maintain the liver metabolic processes (Figure 1).

A decrease in the amount of mtDNA copy number may be due to increased oxidative stress. "Mild" uncoupling of mitochondrial processes can stimulate their activity. Mitochondria send alarms to the nucleus to activate processes associated with cellular homeostasis. Along with excess of nutrients and IR, increased mtDNA copy number is necessary to support energy-consuming processes.

In obese patients without T2DM, negative relations were found between chemerin content and mtDNA copy number in the liver (r = -0.59, p < 0.05). Shen W. et al. (2003) showed that chemerin, through the ChemR23 receptor, increases ROS production and activates autophagy in endothelial cells. The activation of this process is considered as an adaptation to stressful conditions. Cultured endothelial cells treated with chemerin had upregulated gene expression responsible for mitochondrial biogenesis (*PGC-1A*) [7]. Similar results were obtained by Xie Q. et al. (2015) on the C2C12 mouse myoblast cell line. The CMKLR1-dependent pathway of chemerin led to increased ROS production and decreased the number of mitochondria through the formation of autophagosomes [13].

On the contrary, in obese patients with T2DM, increased mtDNA copy number in GO negatively correlated with the chemerin level (r = -0.44, p < 0.05). It is possible that in patients with T2DM coupled to AT hypertrophy and increased inflammatory background in AT and liver, the production of chemerin decreases below the level when it is unable to to exert its effects.

We investigated gene expression (*TFAM, SOD1, DRP1*) to characterize mitochondrial quality control (MQC) processes (biogenesis, mitochondrial division
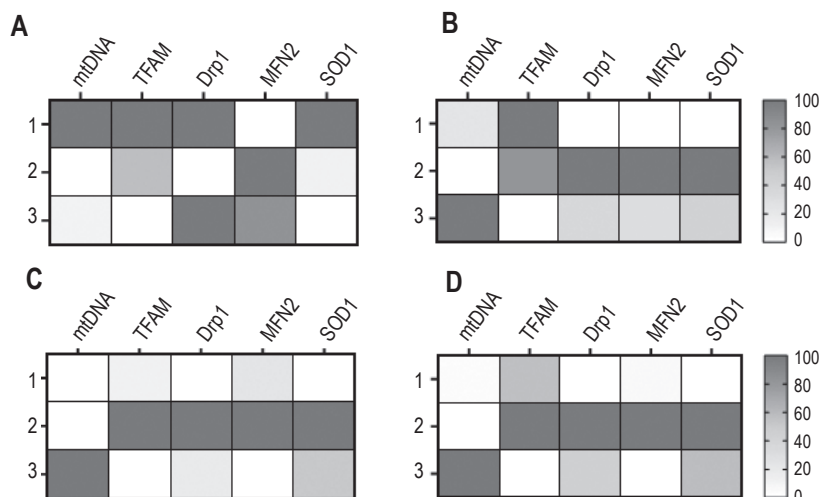
Figure 1. Heat map of the normalized expression levels of liver (A), greater omentum (B), mesentery of the small intestine (C) subcutaneous adipose tissue (D)

Note. 1, control group; 2, obesity without T2DM; 3, obesity with T2DM. Data are presented as a percentage.

TABLE 1. CLINICAL AND BIOCHEMICAL PARAMETERS OF THE STUDIED GROUPS

Indicators	Control group, n = 38	Obesity group without T2DM, n = 110	Obesity group with T2DM, n = 154
No.	1	2	3
BMI, kg/m2	22.20±8.40	41.80±9.20 $p_1 = 0.01^*$	45.10±7.10 $p_1 = 0.01^*$
Insulin, µU/ml	6.61 (5.00-12.48)	14.00 (8.35-23.46)	37.38 (28.60-73.76) $p_1 < 0.001^{**}$ $p_2 = 0.01^*$
Glucose, mmol/l	5.03 (4.67-5.91)	5.41 (4.84-6.15)	6.85 (5.58-8.80) $p_1 < 0.001^{**}$ $p_2 < 0.001^{**}$
Chemerin, ng/ml	141.00 (116.00-157.50)	173.00 (148.5-190.0) $p_1 < 0.001^{**}$	147.00 (133.8-173.5) $p_2 = 0.018^*$

and fusion) in various adipose tissue depots and liver biopsies of obese patients.

Mitochondrial biogenesis (the formation of new mitochondria) is the cooperation of two genomes (cellular and mitochondrial). Mitochondria contain core-encoded proteins (*PGC1α* and β*, NFR-1, 2)* that regulate the transcription of mitochondrial genes.

Mitochondrial transcription factor A (*TFAM*) is a regulator of mtDNA transcription associated with changes in mitochondrial division/fusion and mtDNA replication [1].

In adipocytes of *Tfam*- knockout mice, the activity of proteins in complexes I, III, and IV of the respiratory electron transport chain was reduced, which led to the adipocyte death and AT inflammation.

Jin-Ho Koh et al. (2019) in mice with muscle-specific overexpression of human *TFAM* (hTFAM) showed that *TFAM* increases insulin sensitivity,

suppresses oxidative stress caused by a high-fat diet via enhanced antioxidant protection [4].

The expression level of *TFAM* increased in the SAT of patients without T2DM, which may point at increased mtDNA transcription under conditions of tissue inflammation. In GO and liver, the changes in gene expression were insignificant in study groups. We find no increased intensity of mitochondrial biogenesis in visceral AT and liver, but not in SAT (Figure 1).

ROS play an important role in the maintenance of mitochondrial dynamics. Mitochondrial dynamics are essential for maintaining a healthy mitochondrial population and depend on coordinated cycles of fusion and division. An imbalance in mitochondrial dynamics is associated with the pathophysiology of metabolic diseases such as obesity and T2DM, NAFLD.

Dynamin-related protein 1 (DRP1) regulates mitochondrial division and apoptosis. Mitophagy, a highly selective form of autophagy, utilizes damaged mitochondria. Disruption of mitophagy processes can lead to the accumulation of damaged mitochondrial components. In obese patients without T2DM, an increase in *DRP1* expression relative to control was revealed in all fat stores. On the contrary, in patients with diabetes, the *DRP1* expression was decreased. In liver of all obese patients with/without T2DM, the level of *DRP1* expression decreased compared to control. Strengthening the processes of division is associated with the degradation of mitochondria. In patients without T2DM, a decreased expression of the *DRP1* gene negatively correlated with increased concentration of chemerin (r = -0.40, p < 0.05) and steatosis (r = -0.35, p < 0.05) (Figure 1).

Chemerin can activate autophagy to remove damaged mitochondria. Potentially, liver biopsies from patients without T2DM had undisturbed balance between division and fusion. Fusion allows damaged mitochondria having oxidized lipids, proteins, and mutant mitochondrial DNA to mix with healthy ones that helps to restore mitochondrial function and maintain cellular homeostasis. However, we found no significant changes in *MFN2* expression.

Superoxide dismutase 1 (*SOD1*) regulates ROS levels that are produced by mitochondria in the respiratory chain. Changes in *SOD1* gene expression and its production may indicate the state of activity of the organ antioxidant system. The expression of *SOD1* gene was increased in the GO in obese patients with/ without T2DM. An increase in *SOD1* expression in SAT was observed in patients without T2DM. *SOD1* expression decreased in MES and SAT in patients with T2DM relative to patients without T2DM. In liver biopsies, *SOD1* activity was reduced and negatively correlated with detected steatosis (r = -0.89, p < 0.05). The multidirectional dynamics indicate a different effectiveness of the antioxidant system in liver and adipose tissue. The production of chemerin had a positive relationship with expressed *SOD1* (r = 0.60 p < 0.05) in GO patients without T2DM. In contrast, in patients with T2DM, negative relationships between chemerin and *SOD1* gene expression in MES were recorded (r = -0.46, p < 0.05). Thus, an increased level of chemerin in patients without T2DM can activate the antioxidant system in visceral AT, but not in liver (Figure 1).

Thus, an increased level of chemerin has a positive effect on mitochondrial quality control in patients without T2DM to maintain a balance between mitochondrial division and fusion in the liver. A decreased mtDNA copy number in liver may indicate activation of autophagy paralleled with high levels of chemerin, which leads to removal of damaged mitochondria. A decreased mtDNA copy number can be considered as an adaptation mechanism that protects against vicious cycle of ROS production. In visceral AT, chemerin can maintain the activity of the antioxidant system. In patients with T2DM, mitochondrial dysfunction is recorded, biogenesis processes, dynamics, antioxidant protection are suppressed along with elevated mtDNA copy number in all studied depots. The formation of inflammation and IR of AT and liver leads to decreased chemerin production. We hypothesize that stimulation of the production/administration of exogenous chemerin in T2DM can neutralize the effects of oxidative stress through activated autophagy. Further research is needed to find out how the ratios between different chemerin isoforms change during pathological processes and affect MQC processes in insulin-dependent tissues.

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Медицинская Иммунология
Medical Immunology (Russia)/Meditsinskaya Immunologiya

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Авторы:

Вульф М.А. *— к.б.н., старший научный сотрудник Центра иммунологии и клеточных технологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Шунькина (Скуратовская) Д.А. *— к.б.н., старший научный сотрудник Центра иммунологии и клеточных, биотехнологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Ву Хунг *— аспирант Центра иммунологии и клеточных биотехнологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Комар А.А. *— аспирант Центра иммунологии и клеточных биотехнологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Затолокин П.А. *— к.м.н., старший научный сотрудник Центра иммунологии и клеточных биотехнологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Кириенкова Е.В. *— д.м.н., старший научный сотрудник Центра иммунологии и клеточных биотехнологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Газатова Н.Д. *— к.б.н., старший научный сотрудник Центра иммунологии и клеточных, биотехнологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Литвинова Л.С. *— д.м.н., директор Центра иммунологии и клеточных биотехнологий ФГАОУ ВО «Балтийский федеральный университет имени Иммануила Канта», г. Калининград, Россия*

Authors:

Vulf M.A., *PhD (Biology), Senior Research Associate, Center for Immunology and Cellular Biotechnology at the Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*

Shunkina (Skuratovskaia) D.A., *PhD (Biology), Senior Research Associate, Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University Kaliningrad, Russian Federation*

Vu Hung, *Postgraduate Student, Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*

Komar A.A., *Postgraduate Student, Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*

Zatolokin P.A., *PhD (Medicine), Senior Researcher at the Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*

Kirienkova E.V., *PhD, MD (Medicine), Senior Research Associate, Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*

Gazatova N.D., *PhD (Biology), Senior Research Associate, Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*

Litvinova L.S., *PhD, MD (Medicine), Director, Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, Kaliningrad, Russian Federation*