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The role of sTNFSF14 in the liver mitochondrial dynamics in obese patients

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ABSTRACT

Background. The pathogenesis of nonalcoholic fatty liver disease (NAFLD), which develops in obesity and type 2 diabetes mellitus (T2DM), is associated with the effects of inflammatory factors on the liver parenchyma and liver mitochondrial dysfunction.

Aim. To determine the role of sTNFSF14 in the regulation of liver mitochondrial biogenesis in obese patients with and without T2DM.

Materials and methods. The study included 263 obese patients with and without T2DM and 42 apparently healthy donors. Quantitative determination of cytokines in the blood plasma was performed by fluorescence flow cytometry. The level of relative gene expression in the liver biopsy samples was investigated by real-time PCR. Semi-quantitative determination of proteins in the liver biopsy samples was studied by western blotting.

Results. The study showed that the levels of sTNFSF14, interleukin (IL)-10, gp130 / sIL-6Rb, and sIL-6Ra in the blood plasma of the obese patients without T2DM significantly exceeded the similar values in the control patients and obese patients with T2DM. In the liver biopsy samples of the obese patients with T2DM and a body mass index (BMI) > 40 kg / m^2, the expression level of the dynamin-1-like protein (DRP1 / DNM1L) gene was lower than in the control group, and the expression level of the mitofusin 2 (MFN2) gene tended to be higher. Compared with the control group, an increase in the expression level of the NADH-ubiquinone oxidoreductase chain 4 (MT-ND4) gene was recorded in the liver of all the obese patients. The patients with obesity showed a decrease in the amount of mitochondrial DNA (mtDNA) compared with the control group.

Conclusion. Thus, sTNFSF14, interacting with IL-10 and gp130 / sIL-6Rb in the circulation, positively effects the liver in the obese patients without T2DM. A low level of sTNFSF14 in the blood plasma of the obese patients with T2DM results in decreased mitochondrial division and increased cellular respiration.

Key words: obesity, type 2 diabetes mellitus, sTNFSF14, IL-6, gp130 / sIL-6Rb, sIL-6Ra.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at IKBFU (Protocol No. 2 of 06.03.2017).

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Влияние sTNFSF14 на митохондриальную динамику в печени у пациентов с ожирением

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РЕЗЮМЕ

Актуальность. Патогенез неалкогольной жировой болезни печени, формирующейся при ожирении и сахарном диабете (СД) 2-го типа, опосредован воздействием многочисленных воспалительных факторов на паренхиму этого органа, а также развивающейся митохондриальной дисфункцией гепатоцитов.

Цель – определение роли растворимой формы sTNFSF14 в регуляции биогенеза митохондрий в печени у больных ожирением с сахарным диабетом СД 2-го типа и без него.

Материалы и методы. В исследование включены 263 больных ожирением с СД 2-го типа и без него и 42 условно здоровых донора. Количественное определение цитокинов в плазме крови проводили методом проточной флуориметрии. Уровень относительной экспрессии генов в биоптатах печени исследовали методом полимеразной цепной реакции в реальном времени. Полуколичественное определение белков в биоптатах печени проведено методом иммуноблоттинга.

Результаты. Показано, что уровни sTNFSF14, интерлейкина (IL) 10, gp130/sIL-6Rb и sIL-6Ra в плазме крови у больных ожирением без СД 2-го типа значимо превышали аналогичные значения контроля и больных ожирением с СД 2-го типа. В биоптатах печени, полученных у больных ожирением с СД 2-го типа с индексом массы тела более 40 кг/м^2, уровень экспрессии гена белка, подобного динамину 1 (*DRP1/DNM1L*), был ниже в сравнении с группой контроля, а уровень экспрессии гена митофузина 2 (*MFN2*) имел тенденцию к увеличению. В печени у всех больных ожирением регистрировалось повышение (в сравнении с контролем) уровня экспрессии белка НАДН-убихинона оксидоредуктазы цепи 4 (MT-ND4) и, напротив, снижение количества митохондриальной ДНК (мтДНК).

Заключение. Таким образом, sTNFSF14, взаимодействуя с IL-10 и gp130/sIL-6Rb в циркуляции, оказывает положительное воздействие на печень у больных ожирением без СД 2-го типа. Низкий уровень sTNFSF14 в плазме крови, регистрируемый у больных ожирением с СД 2-го типа, приводит к снижению деления митохондрий и увеличению клеточного дыхания у этой категории больных.

Ключевые слова: ожирение, СД 2-го типа, sTNFSF14, IL-6, gp130/sIL-6Rb, sIL-6Ra.

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INTRODUCTION

Obesity is a multifactorial disease that affects more than one third of the world population [1]. Obesity significantly increases the risk of developing chronic diseases such as type 2 diabetes mellitus (T2DM), cardiovascular diseases (atherosclerosis, hypertension), nonalcoholic fatty liver disease (NAFLD), and some types of cancer [1]. The complications of obesity often lead to disability and death. In 2017, 8% of deaths worldwide were associated with obesity [1]. NAFLD is one of the most common complications of obesity and occupies the leading position in hepatology [2, 3].

Changes in the function and structure of mitochondria are a hallmark in NAFLD formation. The hyperactive tricarboxylic acid cycle overloads the electron transport chain (ETC) in hepatocyte mitochondria, which intensifies production of reactive oxygen species (ROS) [4]. The experimental models of NAFLD (with choline deficiency) showed that mitochondrial compensatory mechanisms were activated at early stages of the disease. However, these reserves become depleted over time [5]. Despite the relevance of the problem and many works on the etiological factors and aspects of the NAFLD pathogenesis, protective factors in the liver steatosis and inflammation in obesity are still poorly studied and understood.

Tumor necrosis factor ligand superfamily member (TNFSF) 14 (also known as LIGHT) has a beneficial effect in treatment of various diseases [6, 7]. For instance, high level of sTNFSF14 in the circulation promotes formation of antitumor immunity in colon [6] and liver cancer [7].

Currently, the role of TNFSF14 in the development of metabolic syndrome is being actively discussed. Studies by J. Bassols et al. (2010) demonstrated a high level of TNFSF14 in the plasma of obese patients compared with healthy controls [8].

The Tnfsf14 -/- mice receiving a diet high in fat develop obesity, glucose intolerance, and impaired insulin sensitivity [9]. Besides, TNFSF14 deficiency in the experimental animals led to dysregulation of mitochondrial respiration in the liver, which contributed to increased oxygen consumption by the respiratory ETC in the mitochondria [9]. Given that the mitochondria play an important role in NAFLD development in obesity [4], changes in the mitochondrial dynamics (fission and fusion) and biogenesis may significantly contribute to the progression of steatosis in obese patients.

Thus, the study was aimed at determining the role of sTNFSF14 in the regulation of mitochondrial biogenesis in the liver of obese patients with and without T2DM.

MATERIALS AND METHODS

The study included 263 patients suffering from alimentary-constitutional obesity with abdominal localization hypertrophic in morphology. Among them, there were 44 obese patients without T2DM with a body mass index (BMI) < 40 kg / m^2 (group 2), 88 obese patients without T2DM with a BMI > 40 kg / m^2 (group 3). Groups 4 and 5 included obese patients with T2DM – 42 patients with a BMI < 40 kg / m^2 and 89 patients with a BMI > 40 kg / m^2, respectively (Table).

Table

The main clinical parameters of the studied groups

Parameters	Group 1	Group 2	Group 3	Group 4	Group 5
Males / Females	17/25	11/33	18/70	18/24	21/68
Age, years, M ± SD	38.69 ± 7.57	41.59 ± 8.72	44.19 ± 9.11	45.1 ± 9.13	48.47 ± 8.17
BMI, kg / m^2, M ± SD	23.11 ± 3.33	35.69 ± 2.62	48.38 ± 7.31	36.1 ± 2.73	49.53 ± 7.59

Plasma factors (TNFSF14 / LIGHT, IL-6, gp130 / sIL-6Rb, sIL6-Ra, and IL-10) were evaluated in the venous blood taken in the fasted state in the morning into vacuum tubes Vacuette (Greiner Bio-One, Austria) with EDTA (BD Vacutainer, Russia). The expression levels of gene mRNA, absolute mitochondrial DNA copy number (mtDNA-CN), and protein production levels were analyzed in the liver biopsy samples (1 ml each) obtained during elective laparoscopic surgeries.

According to the data that we published earlier, the histological analysis revealed steatosis in 72.7% of the obese patients without T2DM and in 93.3% of the obese patients with T2DM. Morphological manifestations of steatohepatitis were found in 63.6% of the patients without T2DM and in 86.6% of the patients with T2DM [10].

The control group (group 1) consisted of 42 apparently healthy donors with normal anthropometric and biochemical parameters. The main clinical character-

istics of the studied groups are presented in the table. These groups were comparable in terms of age and gender characteristics.

The quantitative determination of TNFSF14 / LIGHT, IL-6, gp130 / sIL-6Rb, sIL6-Ra, and IL-10 in the blood plasma was carried out by fluorescence flow cytometry using commercial test systems (Bio-Plex Pro Human Inflammation Panel 1, 37-Plex, Bio-Rad, USA) on a dual-laser automated analyzer (Bio-Plex 200 Systems, Bio-Rad, USA) and Bio-PlexManager software (Bio-Rad, USA).

Isolation of total RNA from the liver biopsy samples was carried out using the ExtractRNA reagent (Evrogen, Russia). Isolation of mitochondria for the analysis of the NADH-ubiquinone oxidoreductase chain 4 (MT-ND4) protein gene was carried out in a buffer containing sucrose and was followed by centrifugation. To determine the relative gene expression level of dynamin-1-like protein (DRP1 / DNM1L), mitofusin 2 (MFN2), and MT-ND4, quantitative PCR was performed. To do that, qPCR mix-HS reagents (Evrogen, Russia) and a CFX96 detection system (Bio-Rad, USA) were used.

Isolation of protein molecules from the liver biopsy samples was carried out using the RIPA buffer (RIPA Buffer, Thermo Fisher Scientific, USA), followed by measuring the protein concentration with the help of the Bradford protein assay (BCA Protein Assay Kit, Thermo Fisher Scientific, USA). To confirm the gene expression results, semi-quantitative analysis of protein production in the liver biopsy samples was performed by western blotting. It was carried out using specific monoclonal antibodies: DNM1L (Invitrogen, USA), MFN2 (Invitrogen, USA), GAPDH (Thermo Fisher Scientific, USA) and blotting systems (Mini-PROTEAN Tetra Systems, Trans-Blot Turbo, Bio-Rad, USA). The target proteins were detected by a ChemiDoc MP Imaging System (Bio-Rad, USA).

To better investigate the mitochondrial biogenesis in the liver samples, the analysis of the absolute mitochondrial DNA copy number (mtDNA-CN) was carried out. The Droplet Digital PCR (ddPCR) method and a QX200 Droplet Digital PCR System (Bio-Rad, USA) were used.

The data were analyzed for normal distribution using the Kolmogorov – Smirnov test. For normal distribution, the differences were assessed using the Student's t-test (two groups, a parametric test). For non-normal distribution, the Mann – Whitney test was used (two groups, a non-parametric test). Quantitative variables were presented as the mean and standard deviation (M ± SD) and the median and the interquartile range Me (Q_{25}–Q_{75}). The relationship between the two variables was analyzed using the Spearman's correlation coefficient. The results were considered significant at $p < 0.05$.

RESULTS

The level of pro- and anti-inflammatory cytokines in the blood plasma. In the obese patients without T2DM with a BMI > 40 kg/m^2, the values of sLIGHT / TNFSF14 in the blood plasma significantly exceeded the same parameters in the control and obese patients without T2DM with a BMI < 40 kg / m^2 ($p = 0.0408$), obese patients with T2DM with a BMI < 40 kg / m^2 ($p = 0.0017$), and obese patients with T2DM with a BMI > 40 kg / m^2 ($p < 0.0001$). The level of sLIGHT / TNFSF14 in the blood plasma was lower in the obese patients with T2DM with a BMI > 40 kg / m^2 than in the controls ($p = 0.0003$) and in the group of the obese patients without T2DM with a BMI < 40 kg / m^2 ($p < 0.0001$) (Fig. 1, a).

In the obese patients with T2DM with a BMI > 40 kg / m^2, the level of IL-10 in the blood plasma was significantly higher than in the controls ($p = 0.0002$) and lower than in the obese patients without T2DM with a BMI < 40 kg / m^2 ($p < 0.0001$) and a BMI > 40 kg / m^2 ($p < 0.0001$). In the obese patients with T2DM with a BMI < 40 kg / m^2, the level of IL-10 in the plasma was significantly lower in comparison with the obese patients without carbohydrate metabolism disorders with a BMI < 40 kg / m^2 ($p = 0.0019$) and with a BMI > 40 kg / m^2 ($p = 0.0003$). The plasma levels of IL-10 in both groups of the obese patients without T2DM significantly exceeded those in the control group ($p < 0.0001$) (Fig. 1, b).

In all the studied groups, the plasma levels of IL-6 were higher than in the control group ($p < 0.05$). In the obese patients with T2DM with a BMI > 40 kg / m^2, the levels of IL-6 in the blood plasma decreased significantly, compared with the group of the obese patients without carbohydrate metabolism disorders with a BMI < 40 kg / m^2 ($p = 0.0416$) (Fig. 1, c).

The plasma values of gp130 / sIL-6Rb in all the studied groups differed from the control group significantly. Thus, in both groups of the obese patients without T2DM, the level of gp130 / sIL-6Rb in the plasma was remarkably higher than in the control group ($p = 0.0079$ and $p < 0.0001$, respectively). Both groups of the obese patients with T2DM showed lower plasma levels of gp130 / sIL-6Rb in contrast to the control group ($p < 0.0001$) (Fig. 1, d).

The groups with and without T2DM demonstrated different gp130 / sIL-6Rb levels. Plasma gp130 / sIL-6Rb levels were significantly lower in the obese patients with T2DM with a BMI < 40 kg / m^2 than in the obese patients without T2DM ($p < 0.0001$). Similar differences were found in the obese patients with T2DM with a BMI > 40 kg / m^2 in contrast to the obese patients without T2DM ($p < 0.0001$) (Fig. 1, *d*).

In the obese patients without T2DM with a BMI < 40 kg / m^2 and a BMI > 40 kg / m^2, the plasma sIL-6Ra level exceeded similar values in the control group ($p = 0.0026$ and $p = 0.0002$, respectively). However, the obese patients with T2DM with a BMI > 40 kg / m^2 had lower sIL-6Ra level than the control group ($p = 0.0024$) as well as both groups of the obese patients without T2DM with a BMI < 40 kg / m^2 ($p < 0.0001$) and with a BMI > 40 kg / m^2 ($p < 0.0001$). In the obese patients with T2DM with a BMI < 40 kg / m^2, the plasma sIL-6Ra levels were significantly lower than in the obese patients without T2DM with a BMI < 40 kg / m^2 ($p = 0.0005$) and with a BMI > 40 kg / m^2 ($p < 0.0001$) (Fig. 1, *e*).

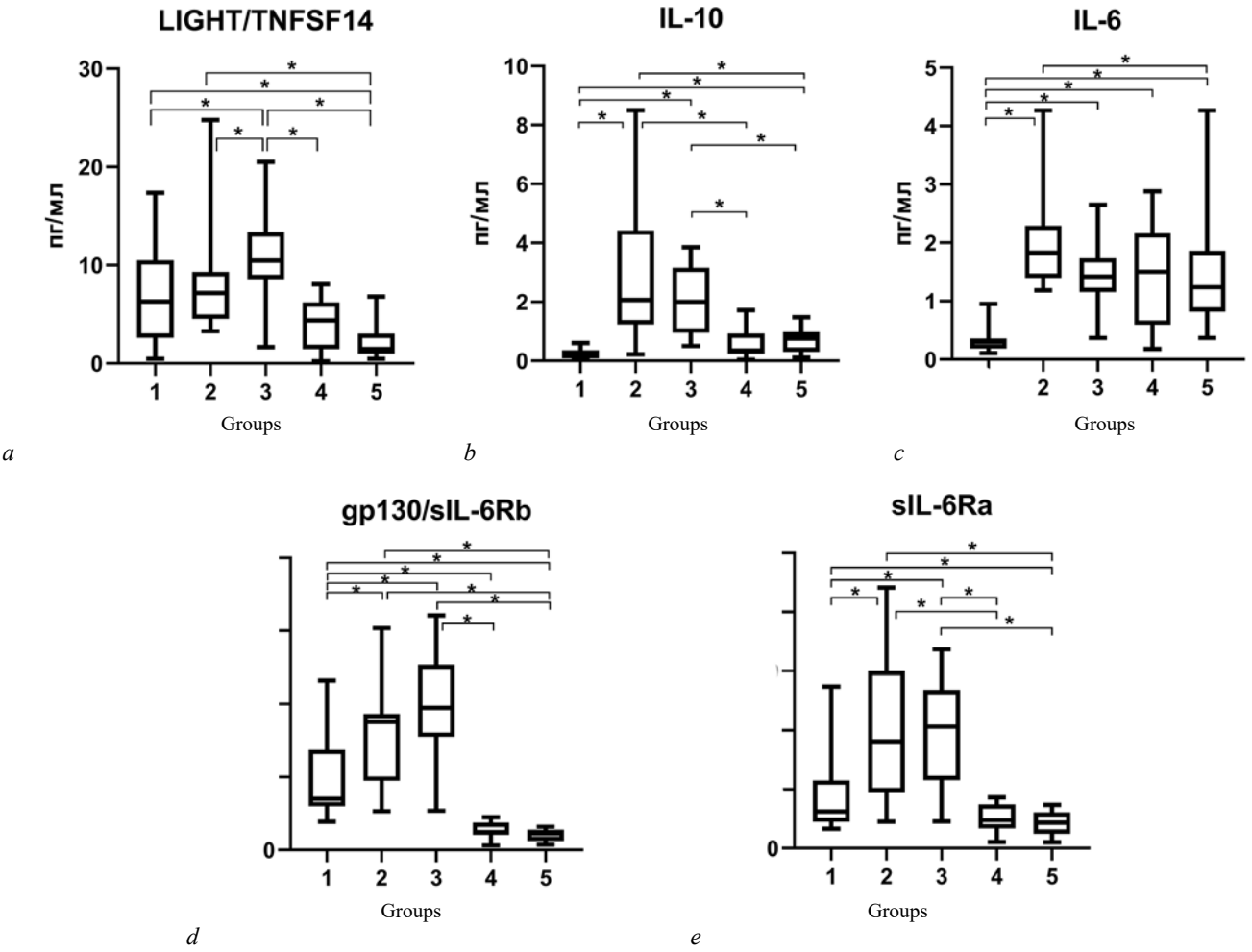

Fig. 1. Changes in the levels of pro- and anti-inflammatory cytokines in the blood plasma. *1* – control group; group of the obese patients: *2* – without T2DM with a BMI < 40 kg / m^2; *3* – without T2DM with a BMI > 40 kg / m^2; 4 – with T2DM with a BMI < 40 kg / m^2; *5* – with T2DM with a BMI > 40 kg / m^2. The level in the blood plasma: *a* – of sLIGHT / TNFSF14; *b* – IL-6; *c* – gp13 / sIL-6Rb; *d* – sIL-6Ra; *e* – IL-10. Here and in Fig. 2: * significant differences between the groups ($p < 0.05$)

Production of components of mitochondrial dynamics and biogenesis in the liver biopsy samples. In the obese patients with T2DM with a BMI > 40 kg / m^2, a decrease in the DRP1 gene expression in the liver was noted, compared with the controls ($p = 0.04$) (Fig. 2, *a*). The relative amount of staining of the DNM1L protein was measured using densitometry and was equal to 0.47 relative units (r.u.) in the control group; in the obese patients without T2DM, it was 0.2 r.u., in the obese patients with T2DM – 0.14 r.u.

The groups demonstrated no significant differences in the MFN2 gene expression in the liver biopsy samples. Despite this fact, the MFN2 gene expression tended to be higher in the liver biopsy samples of the obese patients with and without T2DM with a BMI < 40 kg / m^2 than in the controls (Fig. 2, *c*). The relative amount of staining of the MFN2 protein in the control group was 0.18 r.u.; in the obese patients without T2DM – 0.23 r.u..; in the obese patients with T2DM – 0.35 r.u. (Fig. 2, *d*).

The MT-ND4 gene expression in the liver biopsy samples in all the groups significantly exceeded similar control parameters ($p = 0.0094$; $p < 0.0001$; $p = 0.0001$; $p = 0.0023$) (Fig. 2, *e*). The amounts of mtDNA in the liver biopsy samples of the obese patients without carbohydrate metabolism disorders with a BMI > 40 kg / m^2 was significantly lower than in the control group and in the obese patients with T2DM with a BMI < 40 kg / m^2 ($p = 0.0045$) and with a BMI > 40 kg / m^2 ($p = 0.0007$) (Fig. 2, *f*).

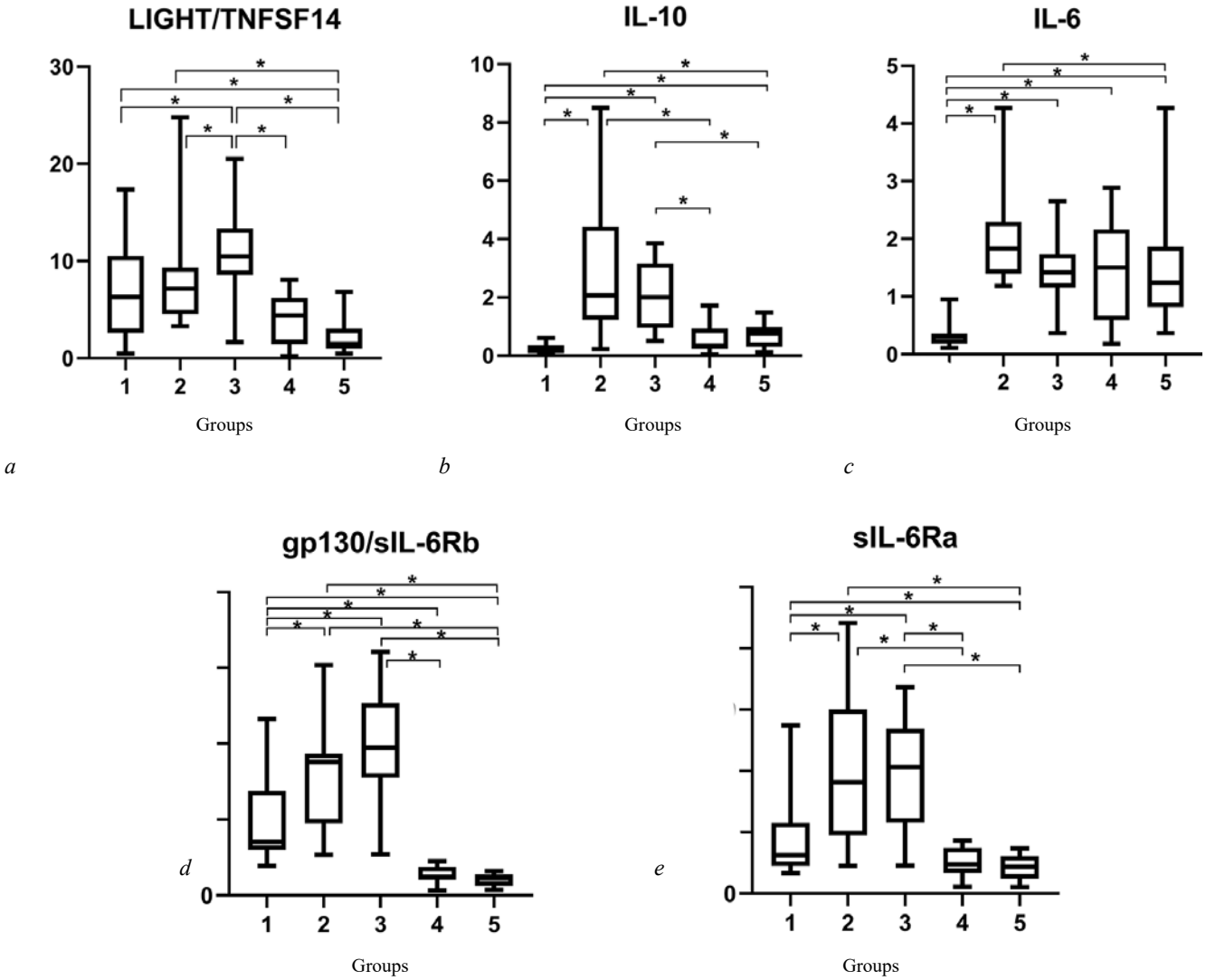

Fig. 2. Changes in the expression levels of the genes and corresponding proteins of liver mitochondrial dynamics and bioenergetics: *a* – the expression level of the DRP1 gene; *b* – an image of chemiluminescence of the DNM1L protein with respect to the reference GAPDH protein; *c* – the expression level of the MFN2 gene; *d* – the MFN2 protein; *e* – the expression level of the MT-ND4 gene; *f* – the amount of mitochondrial DNA. *a, c, e, f*: *1* – control group; group of the obese patients: *2* – without T2DM with a BMI < 40 kg / m^2; *3* – without T2DM with a BMI > 40 kg / m^2; *4* – with T2DM with a BMI < 40 kg / m^2; *5* – with T2DM with a BMI > 40 kg / m^2; *b*, *d*: *1* – control group; group of the obese patients: *2* – without T2DM; *3* – with T2DM

DISCUSSION

In obesity, an excessive amount of triglycerides enter the liver, which results in steatosis [11]. Progression of the latter is facilitated by an increase in the secretion of proinflammatory cytokines (TNFα, IL-1 α and β) by immune cells [12]. Once in the hepatic portal vein, proinflammatory cytokines can aggravate the already existing high level of ROS in hepatocytes [4]. Increased β-oxidation in the mitochondria leads to accumulation of toxic lipid intermediates (ceramides and diacylglycerol) [4].

These toxins and high ROS levels trigger production of proinflammatory cytokines by immune cells in the liver [4, 12]. Chronic liver inflammation aggravates the progression of NAFLD and leads to fibrosis and cirrhosis [4]. In this regard, the search for protective molecules aimed at reducing liver inflammation and preventing complications of steatosis is becoming more relevant.

As it was mentioned earlier, some secreted factors are involved in the pathogenesis of obesity and insulin resistance [4, 11, 12]. One of these factors is LIGHT / TNFSF14. Our data on the increase in the plasma level of sTNFSF14 in all the obese patients without T2DM in contrast to the parameters in the apparently healthy donors and patients with obesity and T2DM are consistent with other studies [8].

However, the reason for an increase in sLIGHT / TNFSF14 levels in obesity has not been found. It is known that many immune cells, including resting and activated T cells, B cells, monocytes and macrophages, produce TNFSF14 [13]. TNFSF14 transmits a signal through the receptors – lymphotoxin-β (LTβR) and herpes virus entry mediator (HVEM). The latter is highly expressed in visceral adipose tissue and, along with LTβR, in β-cells of the pancreas [13].

The study by G. Tiller et al. (2011) on 3T3-L1 preadipocyte cell lines and primary human preadipocytes demonstrated that LIGHT / TNFSF14 prevents the differentiation of preadipocytes into adipocytes in mice and humans without changing their metabolic functions [14]. There are assumptions that sTNFSF14 may potentially contribute to the pathogenesis of complications in obesity.

It was previously shown that the effects of sTNFSF14 could be mediated by its interaction with other cytokines, in particular, IL-6 and IL-10. It was found that IL-10 helps to suppress inflammation by inhibiting synthesis and effect of proinflammatory cytokines, including TNFα, IL-1β, and IL-6, as well as by reducing activation of macrophages [15]. B.M. Saunders et al. (2018) showed that the Tnfsf14 -/- mice receiving a diet high in fat developed insulin resistance. Moreover, the IL-10 production in the liver of such mice sharply increased in comparison with the wild-type mice [9]. The authors considered this increase in the mediator as a compensatory mechanism to reduce inflammation in the liver tissue.

In support of the above-mentioned, the study found a significant increase in plasma IL-10 in the obese patients without T2DM and, on the contrary, its significant decrease in the obese patients with T2DM (Fig. 1, *b*). Furthermore, the study revealed a positive relationship between sTNFSF14 and IL-10 in the obese patients without and with T2DM ($r = 0.43$ and $r = 0.4$, respectively). Probably, the decrease in TNFSF14 and IL-10 in the blood plasma of the obese patients with T2DM plays a crucial role in the progression of complications in obesity.

Cytokines of the IL-6 family regulate liver damage / regeneration and maintain a balance between regulatory and effector T cells [16]. IL-6 is one of the main factors in chronic subclinical inflammation, as it promotes insulin resistance and impairs glucose homeostasis [16]. In our study, an increase in plasma IL-6 was detected in all the obese patients compared with the group of apparently healthy donors. The obese patients with T2DM showed a positive relationship between IL-6 and sTNFSF14 ($r = 0.43$).

It is known that IL-6 on the cell surface binds to the receptor complex, which contains two subunits of the gp130 signaling receptor [17]. We found a significant increase in the amount of sIL-6Ra and gp130 / sIL-6Rb in the plasma of the obese patients without T2DM compared with the control group and obese patients with T2DM.

Hepatocytes and immune cells are the main sources of sIL-6R [16]. Having bound to IL-6R or sIL-6R, IL-6 initiates subsequent signaling through interaction with gp130 [17]. The IL-6 / sIL-6R complex acts as an agonist of the gp130-mediated IL-6 signaling and is called trans-signaling [17]. This type of signaling broadens the array of potential IL-6 targets for any cell type due to the ubiquitous expression of gp130. However, gp130 can also be in a soluble form; because of this, the IL-6 signaling is inhibited while the classical type of signaling is not affected [17]. Soluble gp130 (sgp130) is found in the bloodstream of healthy donors, inhibiting the systemic response to circulating IL-6 [17]. IL-6R can be in the soluble form of sIL-6Ra and form a complex with IL-6.

The complex of IL-6 and sIL-6Ra implements trans-signaling effects by binding to surface gp130

receptors [15, 16]. gp130 activates the yes-associated protein 1 (YAP) and Notch pathways and controls tissue growth and regeneration independently of the signal transducer and activator of transcription 3 (STAT3) protein [18]. A positive relationship was found between sIL-6Ra and gp130 / sIL-6Rb in the groups of the obese patients without T2DM (r = 0.88) and with T2DM (r = 0.94). It may indicate a protective role of these receptors regarding complications in obesity. Plasma sTNFSF14 in both groups of the obese patients with and without T2DM, regardless of their BMI, positively correlated with sIL-6Ra (r = 0.34 and r = 43, respectively) and gp130 / sIL-6Rb (r = 0.37 and r = 0.44, respectively). It should be noted that in the patients with obesity and T2DM, a positive correlation was found between gp130 / sIL-6Rb and IL-10 (r = 0.3).

Several studies demonstrated that TNFSF14 directly induces IL-6 [16], which supports the hypothesis that IL-6 production is regulated by TNFSF14. Thus, the Tnfsf14 -/- mice had a low level of IL-6 production in the liver, compared with the wild-type mice [9]. Therefore, it can be assumed that a decrease in the production of sTNFSF14 and IL-6 may be one of the key factors involved in the progression of NAFLD in obesity.

Hepatic mitochondria control energy metabolism through ATP synthesis and fatty acid oxidation [4]. It was previously shown that insulin resistance is associated with mitochondrial dysfunction in the liver [4]. Thus, TNFSF14 deficiency in the mice that received a diet rich in fat contributed to a significant increase in liver oxygen consumption with the use of substrates for complexes I, II, and III, compared with the wild-type mice [9].

The conducted study of liver mitochondrial dynamics in obesity, depending on the absence / presence of T2DM, revealed the following patterns. The expression of the DRP1 gene responsible for mitochondrial fission was significantly lower in the obese patients with T2DM than in the control group. Regarding the MFN2 gene responsible for the mitochondrial fusion, the groups demonstrated no differences. However, this parameter tended to be higher in the obese patients with T2DM than in the control group. This is consistent with the data of quantitative determination of mtDNA: a decrease (compared with the control group) in the mtDNA level in the liver of the obese patients with and without T2DM with a BMI < 40 kg / m^2. However, such a rise in the mtDNA level increases respiration in the hepatocyte mitochondria, thus making ROS production higher.

Consequently, the liver biopsy samples from the obese patients with and without T2DM demonstrated a high (compared with the control group) expression level of the MT-ND4 gene encoding the subunit of the respiratory chain complex I. Complex I is responsible for the first step in electron transfer from nicotinamide adenine dinucleotide (NADH) to ubiquinone. The electrons are then transferred from ubiquinone through complexes II, III, and IV to provide energy during ATP synthesis. A negative relationship between the level of sTNFSF14 in the blood plasma and the expression of the MT-ND4 gene (r = –0.3) in the liver was found in the obese patients without T2DM. Thus, the level of sTNFSF14 in the blood plasma can influence the liver mitochondrial biogenesis through interaction with the genes of fission (DRP1), fusion (MFN2), and mitochondrial respiration (MT-ND4).

CONCLUSION

The following conclusions can be made.

A high sTNFSF14 level in the plasma of the obese patients without T2DM (compared with the controls and obese patients with T2DM) has a protective effect on the liver through the interaction of gp130 / sIL-6Rb and IL-10.

A unidirectional decrease in the levels of sTNFSF14 and IL-6 in the plasma of the obese patients with T2DM is one of the key factors involved in the NAFLD progression in obesity.

In the obese patients with T2DM, a reduced (compared with the controls and obese patients without T2DM) sTNFSF14 level in the plasma mediates a decrease in the DRP1 gene expression in the liver, and, on the contrary, an increase in the MT-ND4 gene expression, which leads to a decrease in mitochondrial fission and a compensatory increase in mitochondrial respiration.

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Komar A.A., Darinskas A. – analysis and interpretation of data, conception and design. Skuratovskaia D.A., Vulf M.A., Gazatova N.D. – substantiation of the manuscript, analysis and interpretation of data. Todosenko N.M., Vu H.K. – analysis of data. Zatolokin P.A. – provision of materials for the study. Kirienkova E.V. – critical revision of the manuscript for important intellectual content. Litvinova L.S. – conception and design, final approval of the manuscript for publication.

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