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INSULIN RESISTANCE AFFECTS THE EXPRESSION OF GENES RELATED TO THE CONTROL OF CELL GROWTH AND SURVIVING IN BLOOD CELLS OF OBESE BOYS

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The development of obesity and its metabolic complications is associated with dysregulation of numerous intrinsic mechanisms, which control most key metabolic processes, including insulin sensitivity as well as cell growth and surviving. We studied the expression of genes, which responsible for control of cell growth and surviving, in the blood cells of obese boys with normal and impaired insulin sensitivity as compared to the group of normal individuals (control). It was shown that the expression level of DUSP1, LOX, and HSD17B10 genes is decreased in blood cells of obese boys with normal insulin sensitivity as compared to control group. Insulin resistance in obese boys leads to down-regulation of DUSP1, LOX, KRT18, HSD17B2, and HSD17B10 gene expressions in blood cells as compared to obese patients with normal insulin sensitivity. Results of this study provide evidence that obesity affects the expression of the subset of genes related to cell growth and surviving in blood cells and that impaired insulin sensitivity in obesity is associated with changes in the expression level of DUSP1, LOX, KRT18, HSD17B2, and HSD17B10 genes, which contribute to the development of obesity and glucose intolerance and possibly reflect the changes in fat and other tissues.

Key words: mRNA expression, LOX, DUSP1, KRT18, HSD17B2, HSD17B10, blood, obesity, insulin resistance.

Introduction. The development of obesity as well as its metabolic complications, the most profound public health problems, is associated with dysregulation of numerous intrinsic mechanisms, which control basic metabolic processes, including cell growth, surviving and insulin sensitivity (Bray and Young, 2009; Bray and Young, 2011; Huang et al., 2011; Kovac et al., 2009). Moreover, obesity as well as metabolic syndrome results from interactions between genes and environmental factors and is associated with changes in regulatory network preferentially in adipose tissue (Duong et al., 2011; Ruderman et al., 2013; Shimba et al., 2011). Adipose tissue growth is tightly associated with obesity and controlled by different regulatory factors as well as interconnected with various organs and tissues including blood (Lee and Ozcan, 2014; Ozcan et al., 2004). Obesity is a well-known risk factor for the development of secondary complications such as type 2 diabetes; however, only a part of the obese population develops secondary metabolic disorders (Meissburger et al., 2011).

The obesity and its metabolic complications have been linked to cell growth, insulin resistance, and glucose in tolerance through changing of numerous gene expressions, which control basic metabolic processes (Bashta et al., 2014; Minchenko et al., 2013; Oberauer et al., 2010; Ratushna et al., 2012). Special interest represents protein phosphatases including a family of dual specificity phosphatases (DUSP), which play an important role in the regulation a wide array of different physiological events, including cellular growth and proliferation, mitochondrial function and biogenesis, and activity of numerous factors and enzymes (Bray and Young, 2011; Cagnol and Rivard, 2013; Groschl et al., 2013; Piya et al., 2012). These phosphatases participate in the control of cell cycle progression and cell proliferationas well as apoptosis by very precisely changing a multitude of enzymatic reactions among which protein dephosphorylation both the phosphoserine/threonine and phosphotyrosine residues their target proteins, especially kinases, which are tightly associated with cellular proliferation (Bray and Young, 2011; Cagnol and Rivard, 2013; Groschl et al., 2013; Piya et al., 2012). Thus, protein phosphatase DUSP1 is essential for the prevention of apoptosis induced by deoxynivalenol in the epithelial cell line HepG2 (Cagnol and Rivard, 2013). It is interesting that DUSP6, as a novel transcriptional target of TP53, regulates TP53-mediated apoptosis by modulating

expression levels of BCL2 family proteins (Piya et al., 2012).

Lysyl oxidase (LOX) plays an important role in the regulation of cell proliferation and death, because LKB1 loss of function promotes lung cancer malignancy through remodeling of extracellular matrix microenvironment (Gao et al., 2010). Keratin 18 (KRT18), also known as cell proliferation-inducing gene 46 protein, is a multifunctional protein and controls both cell proliferation and apoptosis and is a potential cell death biomarker (John et al., 2013; Koruk et al., 2012). The hydroxysteroid (17-beta) dehydrogenase 10 (HSD17B10) also known as mitochondrial ribonuclease P protein 2 (MRPP2) as well as HSD17B2 is a multifunctional protein, which catalyzes the oxidation of a wide variety of fatty acids, alcohols, and steroids as well as participates in cleavage of tRNA molecules in their 5'-ends and is required for mitochondrial integrity and cell survival (Rauschenberger et al., 2010).

Endoplasmic reticulum stress is also recognized as an important determinant of obesity, insulin resistance, and impaired glucose tolerance and contributes to the expression profile of many regulatory genes resulting in peripheral insulin resistance and other obesity complications (Lee and Ozcan, 2014; Minchenko et al., 2014; Ozcan et al., 2004; Wang and Kaufman, 2012; Yuzefovych et al., 2013), although detailed molecular mechanisms cannot be ruled out.

It is possible that identification of real mechanisms of metabolic abnormalities in obesity as well as its complications at molecular and cellular levels helps to better understanding why obesity develops and why only a part of the obese individuals develops secondary metabolic disorders. However, a detailed molecular mechanism of the involvement of different genes of regulatory network in the development of obesity and its complications are not clear yet and remains to be determined.

The main goal of this work was to clarify the role of the subset of gene expressions, encoding for important cell growth and surviving factors and enzymes, in blood cells of obese boys for evaluation of its possible significance to development of obesity and insulin resistance.

Materials and Methods. The 15 boys participate in this study. They were divided into three equal groups (5 subjects in each group): normal individuals as control and patients with obesity and with or without insulin resistance. All participants gave written informed consent and the studies were approved by the local research ethics committees of Institute of Children and Adolescent Health Care of the National Academy of Medical Science of Ukraine.

Clinical characteristics of the study participants are shown in Table 1. The normal (control) participants were individuals with mean age 14 ± 0.7 years and mean body mass index (BMI) 18.7 ± 0.12 kg/m^2. The obese participants with normal insulin sensitivity as well as the patients with insulin resistance were individuals with mean age (14 ± 0.6 and 14 ± 0.4 years, correspondingly) and mean BMI (31.0 ± 0.40 and 34.2 ± 2.39 kg/m^2, correspondingly).

Table 1.

Characteristics of the study participants

Variable	***Control***	***Obesity***	***Obesity + IR***
Age at visit (years) (*n*)	14 ± 0.73 (5)	14 ± 0.6 (5)	14 ± 0.38 (5)
Body mass index (BMI) (kg/m^2) (*n*)	18.7 ± 0.12 (5)	31 ± 0.40 * (5)	34.2 ± 2.39 * (5)
Insulin resistance index (HOMA) (*n*)	2.36 ± 0.17 (5)	2.70 ± 0.28 (5)	8.70 ± 1.41*^ (5)
Fasting insulin μIU/ml) (*n*)	13.0 ± 0.95 (5)	14.1 ± 1.35 (5)	43.4 ± 6.70 *^ (5)

*Note: Data are means ± SEM; IR – insulin resistance; * - P < 0.05 versus control group; ^ - P < 0.05 versus obese group.*

Thus, BMI, which is a main criteria of obesity, in these last two groups of patients was significantly higher (+66 and +83 %, correspondingly; P<0.05 in both cases) as compared to control individuals (Table 1). Moreover, no significant changes were found in insulin resistance index in obese individuals as compared to control group, but in obese patients with impaired insulin sensitivity, versus control boys as well as obese subjects with normal insulin sensitivity, the insulin resistance index is significantly increased (3.7 and 3.2 fold, correspondingly; P<0.05 in both cases), but decreased (almost two fold; P<0.05) (Table 1). Similar results were observed in the fasting insulin levels: no significant changes in obese individuals and strong increase in obese children with insulin resistance (3.3 fold; P<0.05) as compared to control group.

RNA isolation. Trisol reagent (Invitrogen, USA) was used for RNA extraction from blood of lean (control) and obese individuals with or without insulin resistance.

Reverse transcription and quantitative real-time polymerase chain reaction analysis. The expression levels of genes related to regulation of an angiogenesis (*DUSP1, LOX, KRT18, HSD17B2,* and *HSD17B10*) were measured in blood cells by real-

time quantitative polymerase chain reaction of complementary DNA (cDNA). QuaniTect Reverse Transcription Kit (QIAGEN, Germany) was used for cDNA synthesis. The 7900 HT Fast Real-Time PCR System (Applied Biosystems), Absolute QPCR SYBRGreen Mix (Thermo Scientific, UK) and pair of primers specific for each studied gene (Sigma/Aldrich, USA) were used for quantitative polymerase chain reaction.

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For amplification the cDNA for DUSP1 (dual specificity phosphatase 1), which also known as MKP1 (mitogen-activated protein kinase phosphatase 1), we used next primers: forward 5'– ctgccttgatcaacgtctca –3' and reverse 5'– acccttcctccagcattctt –3'. The nucleotide sequences of these primers correspond to sequences 850 – 869 and 1009 – 990 of human DUSP1 cDNA (GenBank accession number NM_004417). The size of amplified fragment is 160 bp.

The amplification of cDNA for LOX (lysyl oxidase) was performed using forward primer (5'– cagaggagagtggctgaagg –3') and reverse primer (5'– ccaggtagctggggtttaca –3'). These oligonucleotides correspond to sequences 1309 – 1328 and 1531 – 1512 of human LOX cDNA (GenBank accession number NM_002317). The size of amplified fragment is 223 bp.

For amplification the cDNA for KRT18 (keratin 18) also known as cell proliferation-inducing gene 46 protein was used next oligonucleotide primers: forward – 5'– t –3' and reverse – 5'– c –3'. The nucleotide sequences of these primers correspond to sequences 5 – 585 and 8 – 595 of human KRT18 cDNA (GenBank accession number NM_000224). The size of amplified fragment is 2 bp.

The amplification of cDNA for HSD17B2 (hydroxysteroid (17-beta) dehydrogenase 2) was performed using forward primer (5'– agtctgcctgctcatcctgT –3') and reverse primer (5'– ttatctgcactggcttcgtg –3'). These oligonucleotides correspond to sequences 310 – 329 and 608 – 589 of human HSD17B2 cDNA (GenBank accession number NM_002153). The size of amplified fragment is 299 bp.

For amplification of cDNA for HSD17B10 (hydroxysteroid (17-beta) dehydrogenase 10) also known as mitochondrial ribonuclease P protein 2 (MRPP2) we used forward 5'– ccagcgagttcttgatgtga –3' and reverse 5'– catcacccggatacctatgg –3' primers. The nucleotide sequences of these primers correspond to sequences 373 – 392 and 613 – 594 of human HSD17B10 cDNA (GenBank accession number NM_004493). The size of amplified fragment is 241 bp.

The amplification of beta-actin (ACTB) cDNA was performed using forward - 5'– ggacttcgagcaagagatgg –3' and reverse - 5'– agcactgtgttggcgtacag –3' primers. These primers nucleotide sequences correspond to 747 – 766 and 980 – 961 of human ACTB cDNA (GenBank accession number NM_001101). The size of amplified fragment is 234 bp. The expression of beta-actin mRNA was used as control of analyzed RNA quantity. The primers were received from "Sigma" (USA).

The expression of beta-actin mRNA was used as control of analyzed RNA quantity. The amplified DNA fragments were analyzed on a 2 % agarose gel and that visualized by 5x Sight DNA Stain (EUROMEDEA). An analysis of quantitative PCR was performed using special computer program "Differential expression calculator".

Statistical analyses were performed according to Student's *t*-test using OriginPro 7.5 software. All values are expressed as mean ± SEM from four independent experiments; $P < 0.05$ was considered as significant difference.

Results and Discussion. We studied the expression of *DUSP1, LOX, KRT18, HSD17B2,* and *HSD17B10* genes, which preferentially responsible for control of cell growth and surviving, in the blood cells of obese boys with normal as well as impaired insulin sensitivity and compared to control lean individuals. As shown in Fig. 1, the expression level of *DUSP1* gene is decreased (-14 %; $P < 0.05$) in blood cells of obese boys with normal insulin sensitivity as compared to control group. Insulin resistance in obese boys leads to down-regulation of *DUSP1* gene expression (more than in 2 fold; $P < 0.05$) in blood cells as compared to obese patients with normal insulin sensitivity. These data correlates with previous result concerning *DUSP1* gene expression in fat tissue of obese men with normal glucose tolerance (Bashta et al., 2014), because in subcutaneous fat tissue as well as in blood cells obesity decreases the expression level of *DUSP1* gene.

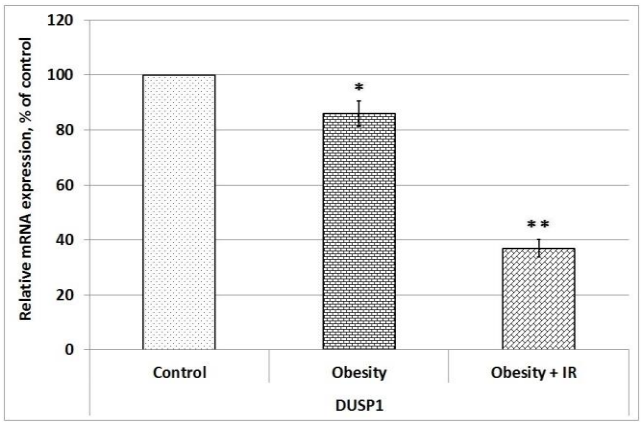

Fig. 1. Relative expression level of dual specificity phosphatase 1 (DUSP1) mRNA in blood cells of lean boys (control) and obese individuals without (obesity) and with insulin resistance (obesity + IR). The values of DUSP1 mRNA expression were normalized to the beta-actin mRNA and are expressed as mean ± SEM and represented as a percent of control (100 %); n = 4; * - P < 0.05 vs group of control individuals; ** - P < 0.05 vs group with obesity and normal insulin sensitivity.

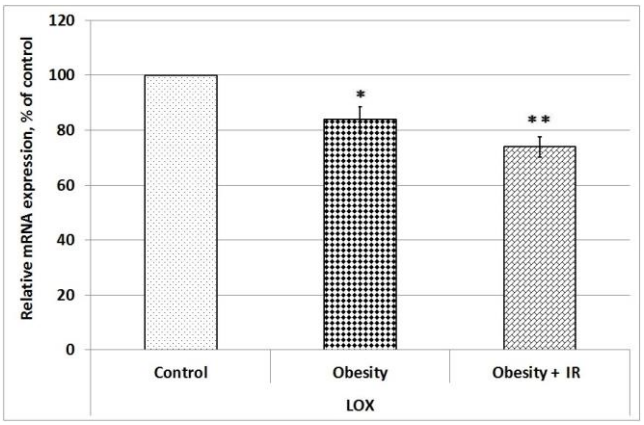

Fig. 2. Relative expression level of lysyl oxidase (LOX) mRNA in blood cells of lean boys (control) and obese individuals with and without insulin resistance (obesity + IR). The values of LOX mRNA expression were normalized to the beta-actin mRNA and are expressed as mean ± SEM and represented as a percent of control (100 %); n = 4; * - P < 0.05 vs group of control individuals; ** - P < 0.05 vs group with obesity and normal insulin sensitivity.

It is possible that decreased expression of *DUSP1* gene in obesity contributes to fat tissue growth through control of cell cycle and apoptosis (Cagnol and Rivard, 2013) as well as to insulin resistance, because in obese children with insulin resistance we observed additional two-fold down-regulation of this gene expression. Results of LOX gene expression is presented in Fig. 2. The expression level of *LOX* gene is also decreased (-16 %; $P < 0.05$) in blood cells of obese boys with normal insulin sensitivity as compared to control patients. Moreover, in obese boys with insulin resistance we observed additional down-regulation of *LOX* gene expression (-12 %; $P < 0.05$) in blood cells as compared to obese patients with normal insulin sensitivity (Fig. 2).

Decreased expression of lysyl oxidase gene, that plays an important role in the regulation of cell proliferation and death, also agrees to data of other researcher, which have been shown increased lung cancer malignancy through remodeling of extracellular matrix microenvironment in case of LKB1 loss of function (Gao et al., 2010). Thus, our results demonstrate that down-regulation of LOX expression may contribute to development of obesity and possibly to impairment insulin sensitivity, because insulin resistance is associated with additional decreasing of this gene expression.

As shown in Fig. 3, the expression level of *KRT18* gene does not change significantly in blood cells of obese individuals with normal insulin sensitivity as compared to control group.

At the same time, development of insulin resistance in obese boys leads to down-regulation of *KRT18* gene expression (-20 %; $P < 0.05$) in blood cells as compared to obese children with normal insulin sensitivity. Decreased expression of multifunctional protein keratin 18, which controls apoptosis and is a potential cell death biomarker, possibly also reflects its contribution to obesity through down-regulation of cell apoptosis (John et al., 2013).

We also studied the expression of *HSD17B2* gene in blood cells of obese boys with normal insulin sensitivity and compared this data to control group (Fig. 4). As shown in Fig. 4, the expression level of *HSD17B2* gene does not change significantly in blood cells of obese boys with normal insulin sensitivity as compared to control group, but insulin resistance in obese boys leads to down-regulation of *HSD17B2* gene expression (-22 %; $P < 0.05$) in blood cells as compared to obese patients with normal insulin sensitivity.

As shown in Fig. 5, the expression level of *HSD17B10* gene is also decreased (-14 %; $P < 0.05$) in blood cells of obese boys with normal insulin sensitivity as compared to group of control children. Furthermore, impaired glucose tolerance in obese individuals induces additional suppression of *HSD17B10* gene expression (-37 %; $P < 0.05$) in blood cells as compared to obese patients with normal insulin sensitivity.

Decreased expression level of *HSD17B2* and *HSD17B10* genes in obesity with impaired insulin sensitivity possibly reflects dysregulation of numerous metabolic processes at this disease including mitochondrial dysfunction as a result of endoplasmic reticulum stress (Casteel et al., 2010; Duong et al., 2011; Rauschenberger et al., 2010; Wang and Kaufman, 2012).

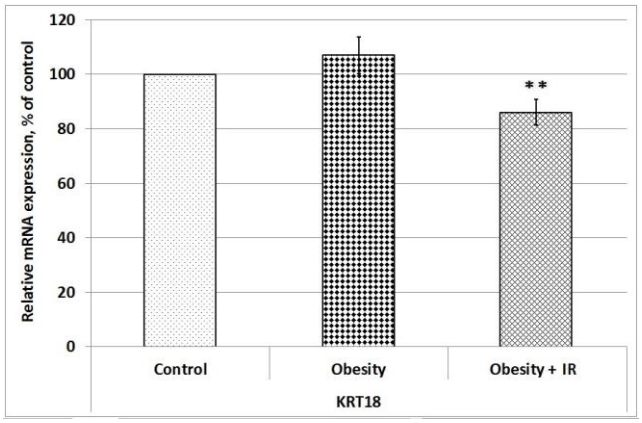

*Fig. 3. Relative expression level of keratin 18 (KRT18), also known as cell proliferation-inducing gene 46 protein, mRNA in blood cells of lean boys (control) and obese individuals with and without insulin resistance (obesity + IR). The values of KRT18 mRNA expression were normalized to the beta-actin mRNA and are expressed as mean ± SEM and represented as a percent of control (100 %); n = 4; * - P < 0.05 vs group of control individuals; ** - P < 0.05 vs group with obesity and normal insulin sensitivity.*

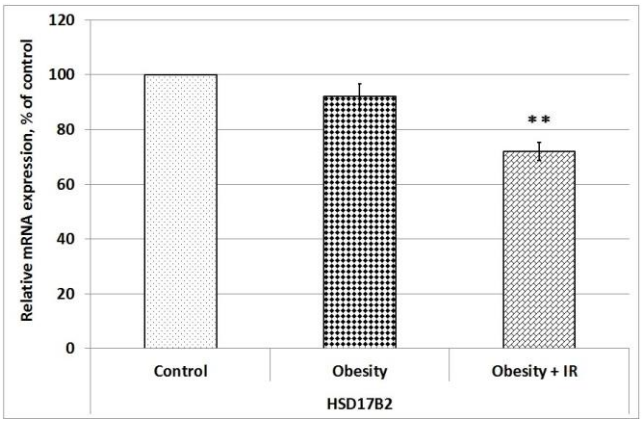

*Fig. 4. Relative expression level of hydroxysteroid (17-beta) dehydrogenase 2 (HSD17B2) mRNA in blood cells of lean boys (control) and obese individuals with and without insulin resistance (obesity + IR). The values of HSD17B2 mRNA expression were normalized to the beta-actin mRNA and are expressed as mean ± SEM and represented as a percent of control (100 %); n = 4; * - P < 0.05 vs group of control individuals; ** - P < 0.05 vs group with obesity and normal insulin sensitivity.*

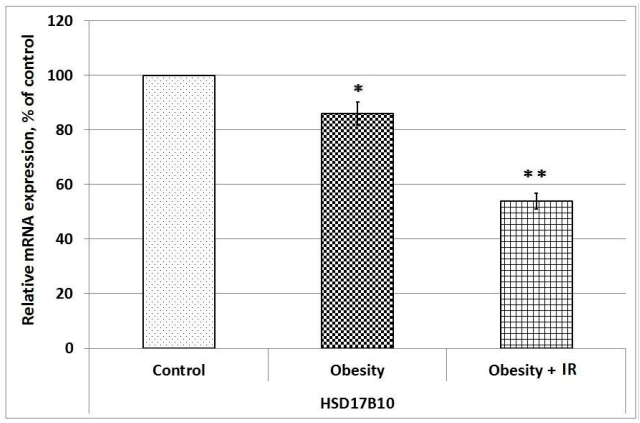

*Fig. 5. Relative expression level of hydroxysteroid (17-beta) dehydrogenase 10 (HSD17B10), also known as mitochondrial ribonuclease P protein 2 (MRPP2), mRNA in blood cells of lean boys (control) and obese individuals with and without insulin resistance (obesity + IR). The values of HSD17B10 mRNA expression were normalized to the beta-actin mRNA and are expressed as mean ± SEM and represented as a percent of control (100 %); n = 4; * - P < 0.05 vs group of control individuals; ** - P < 0.05 vs group with obesity and normal insulin sensitivity.*

Moreover, the development of endoplasmic reticulum stress in obesity and its metabolic complication as well as changes in the expression level of genes, which control cell growth and apoptosis, have some similarity with that in cancer initiates hypothesis that obesity is a major risk factor for cancer (De Pergola and Silvestris, 2013).

Thus, insulin resistance in obese boys leads to down-regulation of gene expressions in blood cells as compared to obese patients with normal insulin sensitivity. Results of this study provide evidence that obesity affects the expression of the subset of genes related to cell growth and surviving in blood cells and that insulin resistance in obesity is associated with changes in the expression level of *DUSP1, LOX, KRT18, HSD17B2*, and *HSD17B10* genes, which contribute to the development of obesity and glucose intolerance and possibly reflect the changes in fat and other tissues.

Conclusions. 1. It was shown that the expression level of DUSP1, LOX, and HSD17B10 genes is decreased in blood cells of obese boys with normal insulin sensitivity as compared to control group.

2. Glucose intolerance in obese boys leads to down-regulation of DUSP1, LOX, KRT18, HSD17B2, and HSD17B10 gene expressions in blood cells as compared to obese patients with normal insulin sensitivity.

3. Results of this study provide evidence that obesity affects the expression of the subset of genes related to cell growth and surviving in blood cells and that insulin resistance in obesity is associated with changes in the expression level of DUSP1, LOX, KRT18, HSD17B2, and HSD17B10 genes, which contribute to the development of obesity and glucose intolerance.

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РЕЗИСТЕНТНІСТЬ ДО ІНСУЛІНУ ЗМІНЮЄ ЕКСПРЕСІЮ ГЕНІВ, ЩО КОНТРОЛЮЮТЬ РІСТ ТА ВИЖИВАННЯ КЛІТИН, У КЛІТИНАХ КРОВІ ДІТЕЙ ЧОЛОВІЧОЇ СТАТІ ЗА УМОВ ОЖИРІННЯ

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Розвиток ожиріння та його метаболічних ускладнень асоціюється з дисрегуляцією численних важливих механізмів, що контролюють більшість ключових метаболічних процесів, включаючи чутливість до інсуліну та ріст і виживання клітин. Ми вивчали експресію генів, що відповідають за контроль процесів росту і виживання клітин, у клітинах крові у дітей чоловічої статі з ожирінням і нормальною або порушеною чутливістю до інсуліну у порівнянні з дітьми без ожиріння (контроль). Встановлено, що рівень експресії генів DUSP1, LOX та HSD17B10 зменшується у клітинах крові дітей з ожирінням з нормальною чутливістю до інсуліну порівняно з контрольною групою. Резистентність до інсуліну у дітей з ожирінням призводить до пригнічення експресії генів DUSP1, LOX, KRT18, HSD17B2, та HSD17B10 у клітинах крові при порівнянні з дітьми, що мали ожиріння і нормальну чутливість до інсуліну. Результати цього дослідження продемонстрували, що ожиріння порушує експресію групи генів, які контролюють процеси росту і виживання клітин і що резистентність до інсуліну асоціюється зі змінами в рівні експресії генів DUSP1, LOX, KRT18, HSD17B2 та HSD17B10, які задіяні у розвитку ожиріння та резистентності до інсуліну і можливо віддзеркалюють зміни у жировій та інших тканинах.

Ключові слова: експресія мРНК, LOX, DUSP1, KRT18, HSD17B2, HSD17B10, кров, ожиріння, резистентність до інсуліну.

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