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EXPERIMENTAL RESEARCH

Expression of Endoplasmic Reticulum Stress Related Genes in Blood Cells of Obese Boys with and without Insulin Resistance

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Abstract

Objective: to study the changes in the expression level of the subset of genes, encoding for important cell growth factors and enzymes, which play an important role in the control of cellular growth and apoptosis, in blood cells of obese boys with and without insulin resistance for evaluation of its possible significance in the development of obesity and impaired insulin sensitivity.

Material and Methods: We studied the expression of genes, which are responsible for control of cell growth and survival, in blood cells of obese boys with normal and impaired insulin sensitivity as compared to normal (control) individuals.

Results: It was shown that the expression level of *PLAGL, CYR61, ITGA5*, and *TFPI2* genes is increased, but the *GADD45A* gene is decreased in blood cells of obese children with normal insulin sensitivity as compared to the control group. Insulin resistance in obese boys leads to the up-regulation of *PPP1R15A* and *PLAGL*1 gene expressions as well as to the down-regulation of *TFPI2, GADD45A, ALDH1A2, CYR61*, and *HSPA6* genes in blood cells as compared to obese patients with normal insulin sensitivity.

Conclusion: Results of this study provide evidence that obesity affects the expression of the subset of genes related to the control of cell growth and survival in blood cells and that impaired insulin sensitivity in obesity is associated with changes in the expression level of *PLAGL, CYR61, GADD45A, PPP1R15A, TFPI2, ALDH1A2,* and *HSPA6* genes, which possibly contributes to the development of obesity and its metabolic complications, including insulin resistance.

Keywords*: mRNA expression; CYR61; PLAGL; ITGA5; PPP1R15A; GADD45A; TFPI2; blood; obesity; insulin resistance.*

Introduction

The development of obesity and its metabolic complications, one of the most profound public health problems, is associated with dysregulation of various intrinsic mechanisms, which control the most basic metabolic processes, as well as changes in numerous gene expressions, which contribute to the development of obesity as well as its metabolic complications and possibly reflect some changes in fat and other tissues. Obesity and its metabolic complications are associated with dysregulation of numerous intrinsic mechanisms, which control most of the key metabolic processes, including cellular growth, apoptosis, and insulin sensitivity [1-5]. Moreover, obesity and metabolic syndrome result from interactions between genes and environmental factors and are associated with changes in gene expressions of the regulatory network in adipose tissue as well as in various organs and tissues, including blood cells [5-9]. Adipose tissue growth is a center of obesity, is tightly associated with apoptosis and the cell proliferation processes, and is controlled by different interconnected regulatory factors and enzymes [1,6,8]. Special interest should be given to key regulatory factors and enzymes, which control cell growth and survival, especially *GADD45A, PLAGL1, CYR61, PPP1R15A, TFPI2, HSPA6,* and *ITGA5* [10-17].

The cysteine-rich angiogenic inducer 61 (*CYR61*), also known as CCN family member 1 and insulin-like growth factor-binding protein 10 (*IGFBP10*), is a secreted, cysteine-rich, heparin-binding protein encoded by a growth factor-inducible, immediate-early gene and acting as an extracellular, matrix-associated signaling molecule, which promotes matrix remodeling, cell proliferation, cell migration and adhesion by up-regulating the expression of a number of genes [10-12].

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Moreover, the expression of the *CYR61* gene is regulated by TP53, miRNA-22 and miRNA-100 as well as through activation of the PI3K/Akt signaling [10,18,19]. It is interesting to note that degradome products of this matricellular protein may modulate the pathological angiogenesis in the retina [20]. The *PLAGL1* (pleiomorphic adenoma gene-like 1) gene encodes a C2H2 zinc finger protein, which is a transcriptional regulator with anti-proliferative properties [21,22].

The *ITGA5* (integrin, alpha 5) gene encodes an alpha polypeptide of fibronectin receptor, which interacts with different extracellular matrix proteins, including *CYR61* and vascular endothelial growth factor receptor 2, and participates in cell-surface mediated signaling. Integrins can also activate protein kinases involved in the regulation of cell growth, division, survival, differentiation, migration and apoptosis [13,23]. There are data that *TFPI2* (tissue factor pathway inhibitor 2) can also participate in the control of tumor growth preferentially through inhibition of a variety of serine proteases as well as through the regulation of plasmin-mediated matrix remodeling [14,24,25]. The growth arrest and DNA-damage-inducible, alpha (*GADD45A*) gene plays an important role in cell cycle control as a regulator of some protein kinases and responds to environmental stresses [15,26]. Furthermore, *GADD45A* is associated with growth arrest and apoptosis and has both tumor suppressor and tumor promoter functions, depending on the tissue/cell type and transforming event [15,26]. *PPP1R15A* (protein phosphatase 1, regulatory subunit 15A) is a regulatory subunit of serine/threonine-protein phosphatase PP1, which dephosphorylates the translation initiation factor eIF-2A/EIF2S1, thereby reversing the shut-off of protein synthesis initiated by stress-inducible kinases and facilitating recovery of cells from stress, as well as down-regulating the TGF-beta signaling pathway, and may promote apoptosis by inducing TP53 phosphorylation [16,27]. The aldehyde dehydrogenase 1 family member A2 (*ALDH1A2*) catalyzes the PPARγ-directed synthesis of retinoic acid, the active derivative of vitamin A, which is a hormonal signaling molecule that functions in developing and adult tissues and has a relation to suppression of tumor growth [17,28]. The heat shock 70kDa protein-6 is a stress responsible protein, which mediates the folding of newly translated polypeptides and is associated with childhood leukemia [29].

The 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, including *GADD45A, PLAGL1, CYR61, PPP1R15A, TFPI2, HSPA6,* and *ITGA5,* resulting in peripheral insulin resistance and other obesity complications [1,5,30-32], 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 understand why obesity develops and why only some obese individuals develop secondary metabolic disorders [33]. However, a detailed molecular mechanism of the involvement of different genes of the regulatory network in the development of obesity and its complications is not clear yet and remains to be determined.

The main goal of this study was to clarify the role of the subset of gene expressions, encoding for important cell growth factors and enzymes, which play an important role in the control of cellular growth and apoptosis, in blood cells of obese boys with and without insulin resistance for evaluation of its possible significance in the development of obesity and impaired insulin sensitivity.

Materials and Methods

Fifteen boys participated in this study. They were divided into three equal groups (5 subjects in each group): normal individuals as control, obese patients with insulin resistance, and obese patients without insulin resistance. Written informed consent was obtained from all participants. The study was 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, both with normal insulin sensitivity and with insulin resistance, had a mean age of 14±0.6 and 14±0.4 years, respectively, and mean BMI 31.0±0.40 and 34.2±2.39 kg/m^2, respectively.

Table 1.

Clinical characteristics of the study participants

Variable	Control	Obesity	Obesity + IR
Age at visit (years)	14±0.73	14±0.6	14±0.38
BMI (kg/m^2)	18.7±0.12	31±0.40 *	34.2±2.39 *
HOMA-IR	2.36±0.17	2.70±0.28	8.70±1.41*^
FI (mIU/mL)	13.0±0.95	14.1±1.35	43.4±6.70 *^

*IR – insulin resistance; HOMA-IR - insulin resistance index; FI - fasting insulin; * - P< 0.05 versus the control group; ^ - P<0.05 versus the obese group.*

Thus, BMI, which is a main criterion of obesity, in these last two groups of patients was significantly higher (+66 and +83 %, respectively; P<0.05 in both cases) as compared to the control individuals (Table 1). Moreover, no significant changes were found in insulin resistance index in obese individuals as compared to the control group. In obese patients with impaired insulin sensitivity, versus both the control boys and the obese subjects with normal insulin sensitivity, the insulin resistance index was significantly increased (3.7 and 3.2 fold, respectively; P<0.05 in both cases). 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 the control group.

RNA isolation

Trisol reagent (Invitrogen, USA) was used for RNA extraction from blood of normal (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 cell growth and glucose homeostasis (*PLAGL, CYR61, GADD45A, GADD34(PPP1R15A), ITGA5, TFPI2, ALDH1A2,* and *HSPA6*) were measured in blood cells by a real-time quantitative PCR 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 PCR (Table 2).

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 visualized by 5x-Sight DNA Stain (EUROMEDEA). An analysis of quantitative PCR was performed using special computer program "Differential expression calculator". Statistical analysis was performed as described previously [34]. All values are expressed as mean ± SEM from five independent experiments; P<0.05 was considered as significant difference.

Results and Discussion

We studied the expression of the subset of genes (*CYR61, PLAGL, GADD45A, GADD34 (PPP1R15A), ITGA5, TFPI2, ALDH1A2,* and *HSPA6*), which control cell proliferation and apoptosis, in blood cells of the three groups for evaluation of its possible significance to the development of obesity and insulin resistance. As shown in Fig.1, the levels of *PLAGL1* and *CYR61* mRNA expression are increased (+25 and +69 %, respectively; *P<0.05* and *P<0.01*, respectively) in blood cells of obese boys with normal insulin sensitivity as compared to the control group.

The development of insulin resistance in obese boys is associated with additional up-regulation of *PLAGL1* mRNA expression (+34%; *P<0.05*) in blood cells as compared to the group with obesity and normal insulin sensitivity. At the same time, the expression level of *CYR61* mRNA is decreased (-17%; *P<0.05*) in blood cells of obese children with impaired insulin sensitivity versus the group of obese boys without insulin resistance, but it is significantly higher relative to the control group (+41%; *P<0.05*; Fig. 1).

These data clearly demonstrate that obesity leads to significant dysregulation of *PLAGL1* and *CYR61* genes in blood cells, being more evident for the *CYR61* gene, and that this dysregulation of *PLAGL1* and *CYR61* genes possibly contributes to the development of enhanced cell proliferation, obesity, and insulin resistance. Moreover, we have also shown that development of insulin resistance in obese individuals is associated with down-regulation of *CYR61* and up-regulation of *PLAGL1* gene expressions. These results correlate with data

Table 2.
Characteristics of the primers used for quantitative real-time PCR

Gene symbol	Gene name	Primer's sequence	Nucleotide numbers in sequence	GenBank accession number
PLAGL1	pleiomorphic adenoma gene-like 1	F: 5'- gggaccattgaagaattcca R: 5'- acactcctcacacccaaagg	436–455 716–697	NM_002656
CYR61 (IGFBP10)	cysteine-rich, angiogenic inducer, 61 (insulin-like growth factor binding protein 10)	F: 5'- ctccctgtttttggaatgga R: 5'- tggtcttgctgcatttcttg	852–871 1092–1073	NM_001554
PPP1R15A (GADD34)	protein phosphatase 1, regulatory subunit 15A (growth arrest and DNA-damage-inducible 34)	F: 5'- gaatcaagccacggaggata R: 5'- cagggaggacactcagcttc	953–972 1261–1242	NM_014330
GADD45A (DDIT1)	growth arrest and DNA-damage-inducible 45 alpha (DNA damage-inducible transcript-1)	F: 5'- acgaggacgacgacagagat R: 5'- tcccggcaaaaacaaataag	503–522 764–745	NM_001924
ITGA5	integrin, alpha 5 (fibronectin receptor, alpha polypeptide)	F: 5'- gtggtgctgtctacctctgt R: 5'- tcagtggctccttctctgtg	346–365 576–2557	NM_002205
TFPI2	tissue factor pathway inhibitor 2	F: 5'- gggccctacttctccgttac R: 5'- cacactggtcgtccacactc	212–231 394–375	NM_006528
ALDH1A2 (RALDH2)	aldehyde dehydrogenase 1 family, member A2 (retinal dehydrogenase 2)	F: 5'- c agcccacagtgttttccaac R: 5'- ctgggcatttaaggcattgt	1472–1491 1713–1694	NM_003888
HSPA6	heat shock 70kDa protein 6	F: 5'- ccaagcagacccagactttc R: 5'- gccttacctgtgctcctgtc	1684–1703 1912–1893	NM_002155
ACTB	beta-actin	F: 5'- ggacttcgagcaagagatgg R: 5'- agcactgtgttggcgtacag	747–766 980–961	NM_001101

of other authors that down-regulation of *CYR61* is associated with inhibition of tumor cell proliferation [10,12] and that *PLAGL1* may have a role in tumorigenesis of von Hippel-Lindau-associated central nervous system hemangioblastoma [22].

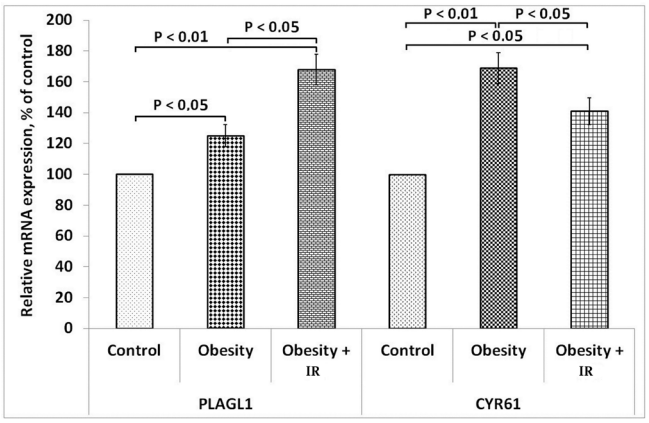

Fig.1. Relative mRNA expression of PLAGL1 and CYR61 in blood cells of normal boys (Control) and obese individuals with normal insulin sensitivity (Obesity) and obese patients with insulin resistance (Obesity + IR). Levels of PLAGL1 and CYR61 mRNA were normalized to the beta-actin mRNA and are represented *as mean ± SEM and* expressed *as a percent of the control (100 %).*

Investigation of the expression level of the growth arrest and DNA-damage-inducible 34 (*GADD34)* gene, also known as regulatory subunit 15A of protein phosphatase 1 (*PPP1R15A)*, in blood cells of obese boys who have normal insulin sensitivity has revealed that obesity does not change significantly the expression of this gene when compared to the control group, but insulin resistance leads to an up-regulation of *GADD34* mRNA expression (+21%; *P<0.05*; Fig. 2) as compared to the group of obese boys with normal insulin sensitivity.

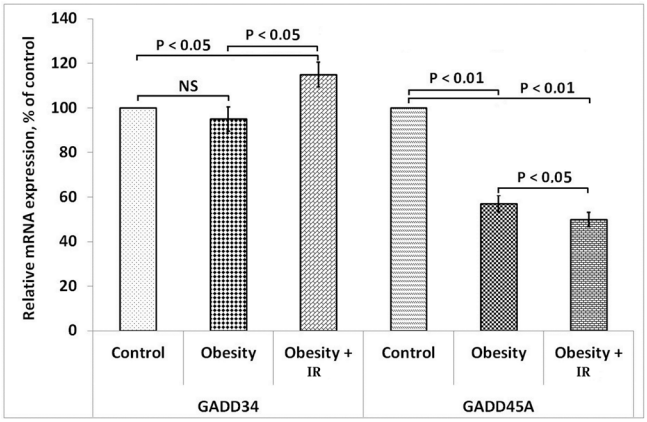

Fig. 2. Relative mRNA expression of GADD34 and GADD45A in blood cells of normal boys (Control) and obese individuals with normal insulin sensitivity (Obesity) and obese patients with insulin resistance (Obesity + IR). Levels of GADD34 and GADD45A mRNA were normalized to the beta-actin mRNA and are represented *as mean ± SEM and* expressed *as a percent of the control (100 %).*

At the same time, another member of the DNA-damage-inducible protein family, DNA-damage-inducible proteins 45 (*GADD45A*), also known as DNA damage-inducible transcript-1 (*DDIT1)*, is significantly decreased in obesity without insulin resistance (almost two fold; *P<0.05*; Fig. 2). Furthermore, development of an insulin resistance induces additional down-regulation of *GADD45A* mRNA expression (-12%; P<0.05). Thus, the expression of both DNA-damage-inducible proteins is decreased in obesity with normal as well as with impaired insulin sensitivity. These results completely correlate with the anti-proliferative properties of both *PPP1R15A* and *GADD45A* [15, 26, 27].

As shown in Fig.3, the expression level of both *ITGA5* and *TFPI2* mRNA is increased (+24 and +18 %, respectively; *P<0.05*) in blood cells of obese boys with normal insulin sensitivity, as compared to control children, but development of insulin resistance in obese individuals is associated with the down-regulation of *TFPI2* mRNA expression (-19%; *P<0.05*) in blood cells, as compared to the group with obesity and normal insulin sensitivity, up to the level in the control boys.

At the same time, the expression level of *ITGA5* mRNA does not change significantly in blood cells of obese children with impaired insulin sensitivity versus the group of obese boys without insulin resistance, and it is significantly higher relative to the control group (+29%; *P<0.05*; Fig. 3).

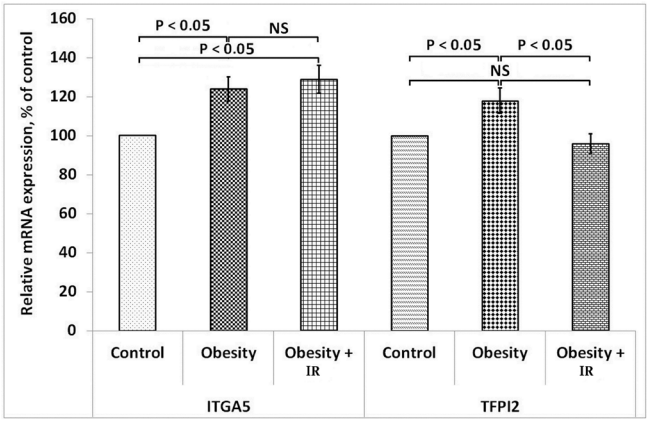

Fig.3. Relative mRNA expression of ITGA5 and TFPI2 in blood cells of normal boys (Control) and obese individuals with normal insulin sensitivity (Obesity) and obese patients with insulin resistance (Obesity + IR). Levels of ITGA5 and TFPI2 mRNA were normalized to the beta-actin mRNA and are represented *as mean ± SEM and* expressed *as a percent of the control (100 %).*

The increased level of *ITGA5* and *TFPI2* mRNA expression agrees with the biological significance of proteins encoded by these genes, because an alpha polypeptide of fibronectin receptor as well as *TFPI2* interacts with different extracellular matrix proteins, including *CYR61* and vascular endothelial growth factor receptor 2, and participates in cell-surface-mediated signaling and is involved in the regulation of cell growth, division, survival, differentiation, migration and apoptosis through activation of some protein kinases [13, 14, 23-25].

We next tested whether obesity also affects the expression of member A2 of the aldehyde dehydrogenase 1 family (*ALDH1A2*), which is a retinal dehydrogenase 2, as well as heat shock 70kDa protein-6 (*HSPA6*) mRNA in blood cells of obese children with normal and impaired insulin sensitivity (Fig. 4).

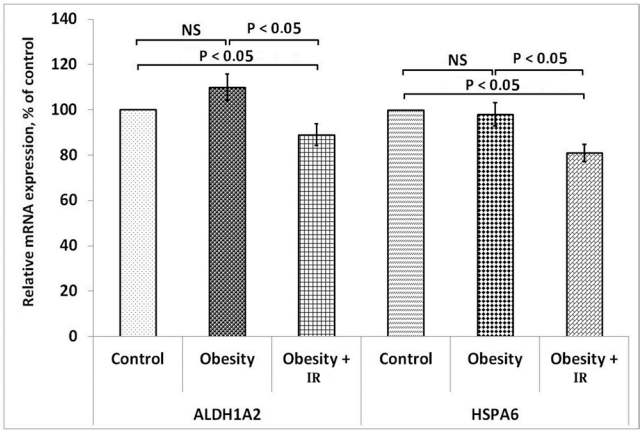

Fig.4. Relative mRNA expression of ALDH1A2 and HSPA6 in blood cells of normal boys (Control) and obese individuals with normal insulin sensitivity (Obesity) and obese patients with insulin resistance (Obesity + IR). Levels of ALDH1A2 and HSPA6 mRNA were normalized to the beta-actin mRNA and are represented *as mean ± SEM and* expressed *as a percent of the control (100 %).*

As shown in Fig.4, no significant changes were observed in the expression level of both *ALDH1A2* and *HSPA6* mRNA in blood cells of obese boys with normal insulin sensitivity, as compared to control children, but development of insulin resistance in obese individuals is associated with down-regulation of both mRNA expressions (-19 and -17%, respectively; *P<0.05*) in blood cells versus the group with obesity and normal insulin sensitivity.

The decreased level of *ALDH1A2* and *HSPA6* gene expressions correlates to data that *ALDH1A2* may control the synthesis of retinoic acid, a hormonal signaling molecule that has a relation to suppression of tumor growth, and that the expression of heat shock protein A6, as a stress-responsible protein, responds to oxidized low density lipoprotein immune complexes [17, 28, 35].

Thus, results of this study provide evidence that obesity affects the expression of the subset of genes related to cellular growth and apoptosis in blood cells and that insulin resistance in obese children is associated with changes in the expression level of *CYR61, PLAGL, GADD45A, PPP1R15A, TFPI2, ALDH1A2,* and *HSPA6* genes, which possibly contribute to the development of obesity and its complications, and reflect some changes in other tissues, including fat tissue.

Conclusions

Obesity (with normal insulin sensitivity) enhances the expression of *CYR61, ITGA5,* and *TFPI2* genes, which control cell growth, and decreases the expression of the *GADD45A* gene, which controls apoptosis, in blood cells, versus the control group. Insulin resistance in obese boys leads to up-regulation of *PLAGL1* and *PPP1R15A* gene expressions and to down-regulation of *CYR61, GADD45A, ALDH1A2, TFPI2,* and *HSPA6* genes in the blood cells versus obese patients with normal insulin sensitivity.

This study has demonstrated that obesity affects the expression of the subset of genes related to the control of cell growth and survival in the blood and that insulin resistance in obesity is associated with changes in the expression level of *CYR61, PLAGL, GADD45A, PPP1R15A, TFPI2, ALDH1A2,* and *HSPA6* genes, which contribute to the development of obesity and its metabolic complications and possibly reflect some changes in other tissues.

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