EXPERIMENTAL WORKS

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EFFECT OF CHROMIUM DISILICIDE AND TITANIUM NITRIDE NANOPARTICLES ON THE EXPRESSION OF *NAMPT*, *E2F8*, *FAS*, *TBX3*, *IL13RA2*, AND *UPS7* GENES IN MOUSE LIVER

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We have studied the effect of chromium disilicide and titanium nitride nanoparticles on the expression level of genes encoding important regulatory enzymes and factors (NAMPT, UPS7, E2F8, FAS/TNFSF6, TBX3, and IL13RA2) in mouse liver for evaluation of possible toxic effects of these nanoparticles. It was shown that treatment of mice by titanium nitride nanoparticles (20 nm; 20 mg with food every working day for 2 months) led to up-regulation of the expression of NAMPT, FAS, TBX3, and IL13RA2 genes and to down-regulation of USP7 and E2F8 genes in the liver tissue. Changes for TBX3 and IL13RA2 genes were more significant than for other genes. Furthermore, treatment of mice by chromium disilicide nanoparticles (45 nm; 20 mg with food every working day for 2 months) led to more significant changes in the expression of USP7, E2F8, FAS, and TBX3 genes in comparison to the effect of titanium nitride nanoparticles. At the same time, effect of titanium nitride nanoparticles on the expression of NAMPT gene in the liver tissue was stronger as compared to chromium disilicide nanoparticles. Additionally, treatment of mice by chromium disilicide nanoparticles did not change significantly the expression of IL13RA2 gene in the liver. The present study demonstrates that chromium disilicide and titanium nitride nanoparticles had variable effects on the expression of most studied genes in a gene specific manner, which possibly reflect genotoxic activities of studied nanoparticles, but molecular mechanisms of observed changes in gene expressions warrant further investigation.

K e y w o r d s: mRNA expression, NAMPT, UPS7, E2F8, TBX3, FAS, IL13RA2, chromium disilicide nanoparticles, titanium nitride nanoparticles, mouse liver.

A rapid development of nanoscience and nanotechnologies has given a rise to wide range applications of man-made nanomaterials in specific biomedicine fields for treating, diagnosing, monitoring, controlling, and repairing biological systems at the molecular level. Titanium dioxide nanoparticles belong to the most widely manufactured nanoparticles (NPs) on a global scale because of their photocatalytic properties and the related surface effects. Ultrafine titanium dioxide nanoparticles is widely used in the number of applications, including white pigment in paint, ceramics, food packaging material, food additive, cosmetic creams, toothpastes, and component of surgical implants [1]. However, long-term exposure to titanium dioxide nanoparticles led to accumulation of these nanoparticles in brain, oxidative stress, over-proliferation of all glial cells, tissue necrosis as well as hippocampal cell apoptosis, resulted in neurogenic disease states in mice [2]. Significant

changes in brain gene expressions were also founded: significant increases in collagen A1 (COL1A1), serine/threonine-protein kinase 1 (AKT1), catenin β1 (CTNNB1), cysteine and serine rich nuclear protein 1 (CSRNP1), DDIT4 (DNA Damage Inducible Transcript 4), cytochrome P450 family 2 subfamily E member 1 (CYP2E1), and Krev interaction trapped protein 1 (KRIT1) expressions and great decreases in dopamine receptor D2 (DRD2), neuraminidase 1 (NEU1), Fc receptor-like A (FCRLA), and 7-dehydrocholesterol reductase (DHCR7) expressions [2]. Furthermore, recently was shown that oral administration of titanium dioxide nanoparticles disrupts hepatic metabolic functions in a mouse model [3]. Titanium nitride nanoparticles have favorable properties and are used for the coating of orthopedic implant, coronary stents, and syringe needles as well as for improving long-term implants in dental medicine [4-7]. At the same time, very little is known about the toxicity including genotoxicity induced by titanium nitride nanoparticles and the effect of these nanoparticles on liver gene expressed profile has not been reported. There is data that chromium oxide nanoparticles had significant cytotoxic effects on murine fibrosarcoma cells [8], but the toxicity of chromium disilicide nanoparticles has not been studied yet.

Nicotinamide phosphoribosyltransferase (NAMPT), also known as PBEF (pre-B-cell colony enhancing factor 1) or visfatin, is thought to be involved in many important biological processes, including metabolism, stress response and aging. NAMPT mediated NAD biosynthesis regulates the function of Sir2α and plays an important role in controlling various biological events including apoptosis, cell proliferation, insulin sensitivity and cancer growth [9-11]. FAS (FAS cell surface death receptor), also known as apoptosis signaling receptor FAS or TNF receptor superfamily member 6 (TNFSF6), plays a central role in the physiological regulation of programmed cell death, cell proliferation and has been implicated in the pathogenesis of various malignancies and diseases of the immune system [12-14]. It is possible that FAS and TNFR/TNFα pathways may have roles in coordinating signaling activities between proliferation and apoptosis [12]. Furthermore, FAS can participate in regulation of cardiac angiogenesis by pigment epithelial-derived factor (PEDF) [13]. There is data that organic extraction from drinking water impairs liver function with the involvement of death receptor FAS and mitochondria-mediated apoptosis in rats [14]. Interleukin 13 receptor, α2 (IL13RA2) has high affinity to interleukin-13 and highly expressed in colorectal cancer, glioblastoma and other malignant tumors, is associated with invasion and liver metastasis [15, 16]. Moreover, low-dose cadmium has growth-promoting effects on NPrEC cells and induces transient overexpression of genes with oncogenic and immunomodulation functions, including *TNF* and *IL13RA2* [17]. Ubiquitin specific peptidase 7 (USP7), also known as herpes virus-associated ubiquitin-specific protease (HAUSP), is hydrolase that deubiquitinates target proteins such as FOXO4, p53/TP53, MDM2, PTEN, PPARG, and other and thus participate in control of cell growth repression and apoptosis [18-20]. There is data that early adipogenesis is regulated through USP7-mediated deubiquitination of the histone acetyltransferase TIP60 [21]. Transcription factors play an important role in the regulation various metabolic pathways as well as proliferation and apoptosis. The evolutionarily conserved T-box family of transcription factors has critical and well-established roles in embryonic development and also gained increasing prominence in the field of cancer biology, where a wide range of cancers exhibit deregulated expression of T-box factors that possess tumor suppressor and/or tumor promoter functions [22-24]. Transcription factor E2F8 has preferentially pro-proliferative properties, could bind to regulatory elements of cyclin D1 and VEGFA, regulating transcription of these genes and promoting proliferation and angiogenesis [24-27]. Moreover, transcription factors E2F8 and TBX3 as well as IL13RA2 are stress responsible and inhibition of IRE1 strongly affects these genes expression [28, 29].

Before, we have shown that C_{60} fullerene and cerium dioxide nanoparticles affect the expression of some endoplasmic reticulum stress response genes, which are linked to cell proliferation, cell surviving and death processes [28, 29]. Multiple studies have clarified the link between endoplasmic reticulum stress, which controls numerous processes including cell proliferation and surviving and various diseases including cancer and metabolic diseases [30-33]. It is possible that long-term treatment of mice to chromium disilicide and titanium dioxide nanoparticles also led to endoplasmic reticulum stress and altered expression of stress related genes, which are integrated into the unfolded protein response signaling pathways and regulate cell proliferation and apoptosis.

The main goal of this study was investigation of the effect of chromium disilicide and titanium nitride nanoparticles on the expression of key regulatory genes (*NAMPT*, *UPS7*, *E2F8*, *TBX3*, *FAS*, and *IL13RA2*) in mouse liver for evaluation of possible genotoxic effects of these nanoparticles.

Materials and Methods

Nanoparticles and Treatment Conditions. Titanium nitride and chromium disilicide nanoparticles were produced by prof. A. V. Ragulya at I. M. Frantsevich Institute for Problems of Materials Science of the National Academy of Sciences of Ukraine. Titanium nitride nanoparticles have medium size 20 nm and can create conglomerates (Fig. 1 and 2). Chromium disilicide nanoparticles have medium size 45 nm and can create conglomerates (Fig. 1 and 2).

Age-matched male mice, which were kept in the animal facilities of Bohomolets National Medical University and housed in a quiet, temperature controlled room, and were provided with water and dry food pellets ad libitum, were used. Before removing the liver, mice were sacrificed by cervical dislocation. All procedures conformed to the guidelines of the Bohomolets National Medical University. For treatment of mice by nanoparticles animals received 20 mg of titanium nitride or chromium disilicide nanoparticles with food every working day for 2 months. Before using both titanium nitride and chromium disilicide nanoparticles were treated by special procedure for disruption of conglomerates.

RNA isolation. Liver tissue (100 mg) was homogenized into 0.4 ml of Trizol reagent (Invitrogen, USA) and total RNA was extracted according to manufacturer protocol as described previously [36]. The RNA pellets were washed with 75% ethanol and dissolved in nuclease-free water. For additional purification, RNA samples were re-precipitated with 95% ethanol and re-dissolved again in nuclease-free water. RNA concentration and spectral characteristics were measured using NanoDrop Spectrophotometer ND1000 (PEQLAB, Biotechnologie GmbH).

Reverse transcription and quantitative PCR analysis. Thermo Scientific Verso cDNA Synthesis Kit (Lithuania) was used for cDNA synthesis according to manufacturer's protocol. The expression levels of UPS7, NAMPT, E2F8, TBX3, FAS, and IL13RA2 mRNAs as well as ACTB mRNA were measured in liver tissue by real-time quantitative polymerase chain reaction using "7500 HT Fast

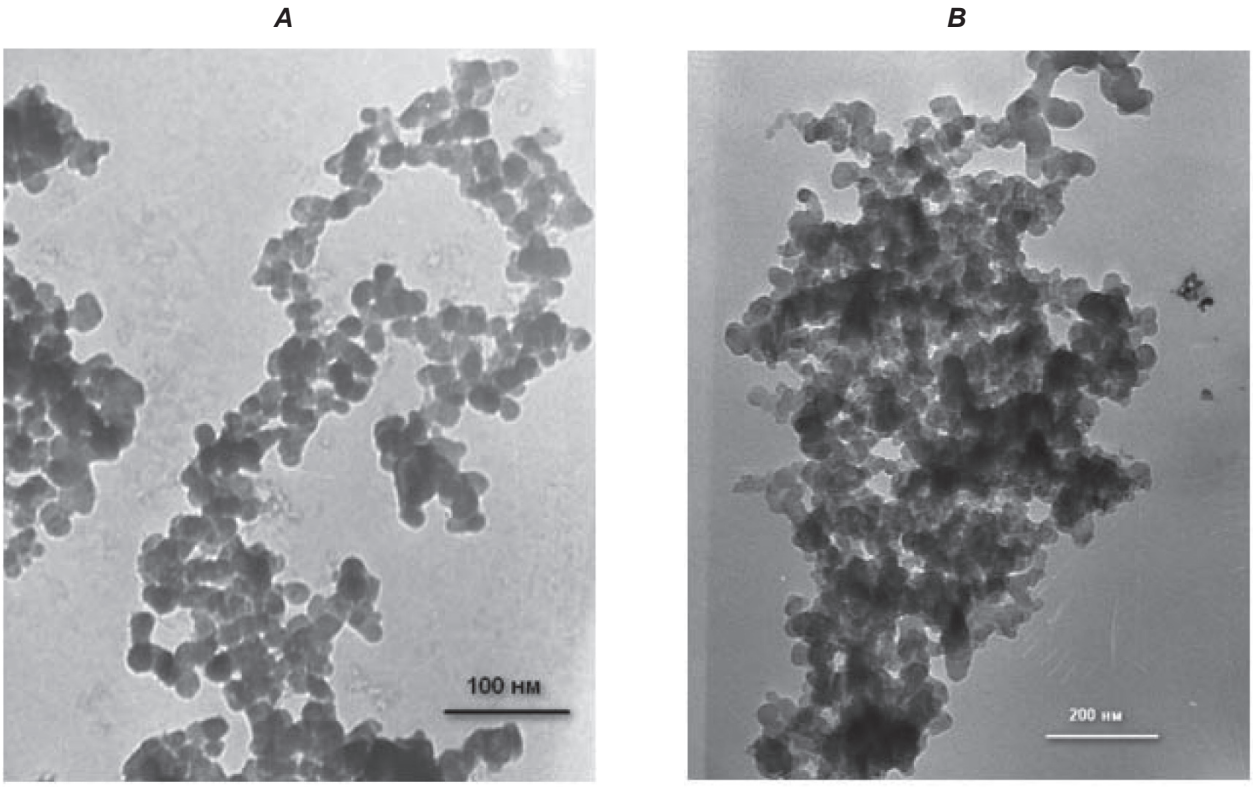

*Fig. 1. The scanning electron microscopy images of titanium nitride (**A**) and chromium disilicide (**B**) nanoparticles*

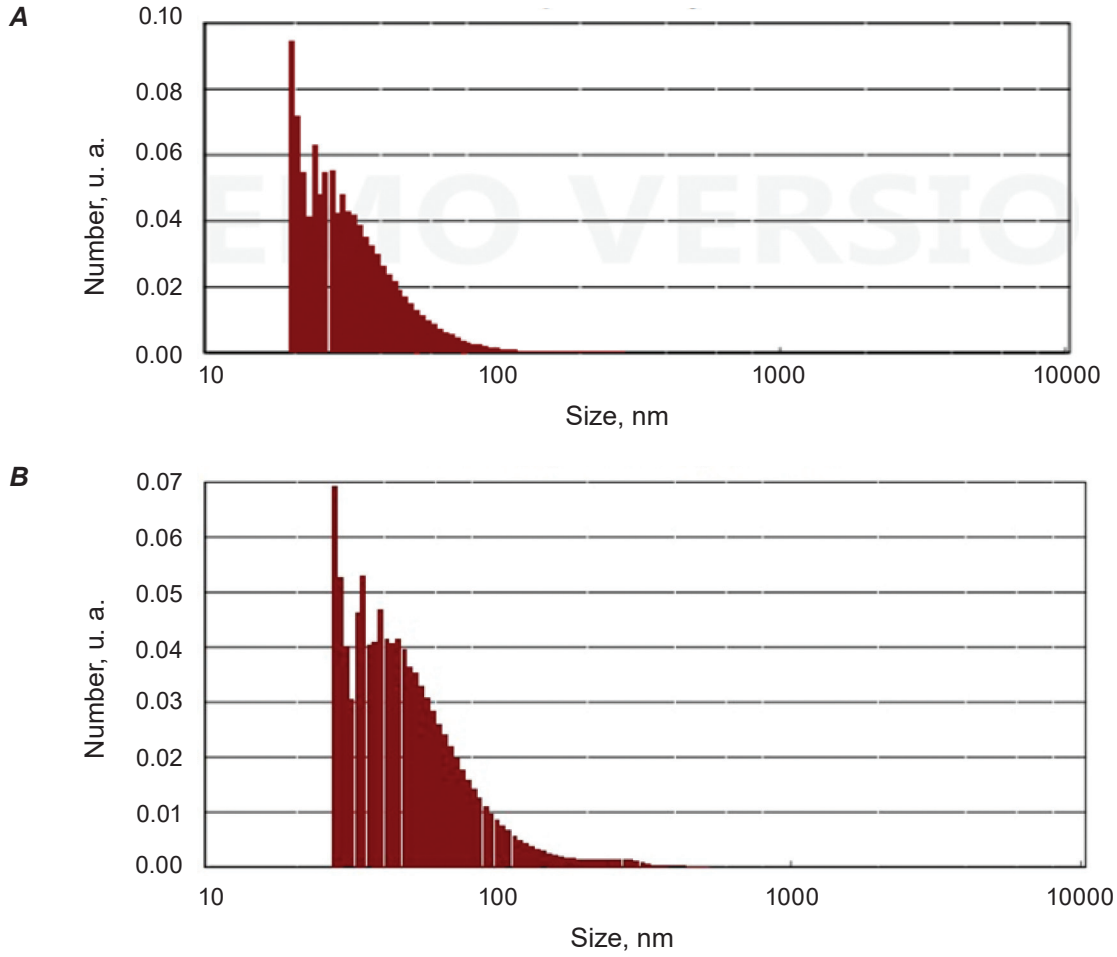

*Fig. 2. The size dispersion by the number of titanium nitride (**A**) and chromium disilicide (**B**) nanoparticles*

Real-Time PCR System" (Applied Biosystems, USA) and Maxima SYBR Green/ROX qPCR Master Mix (Thermo Fisher Scientific, USA). Polymerase chain reaction was performed in triplicate using specific pair of primers, which were received from Metabion (Germany), and Sigma-Aldrich (USA).

For amplification of USP7 (ubiquitin specific peptidase 7; EC_number="3.4.19.12") cDNA we used forward (5′–GTGTCCGGGACCTGTTAGAA–3′ and reverse (5′–TGTGGAAATGTGCCACTGTG–3′) primers. The nucleotide sequences of these primers correspond to sequences 2810–2829 and 3049–3030 of mouse USP7 cDNA (GenBank accession number NM_001003918). The size of amplified fragment is 240 bp.

For amplification of NAMPT (nicotinamide phosphoribosyltransferase; EC_number="2.4.2.12"), also known as PBEF (pre-B-cell colony-enhancing factor 1 homolog) or visfatin, cDNA we were used forward (5′–CGAGAAGTACAGAGGCACCA–3′ and reverse (5′–CCACGCCATCTCCTTGAATG–3′) primers. The nucleotide sequences of these primers correspond to sequences 1137–1156 and 1304–1285 of human *NAMPT* cDNA (GenBank accession number NM_021524). The size of amplified fragment is 168 bp.

The amplification of E2F8 (E2F transcription factor 8) cDNA for real time RCR analysis was performed using two oligonucleotides primers: forward – 5′–ATGGTGTTGGCTGAGATCCA–3′ and reverse – 5′–ACTCGGCTGGGATTTCTCAA–3′. The nucleotide sequences of these primers correspond to sequences 578–597 and 826–807 of mouse E2F8 cDNA (GenBank accession number NM_001013368). The size of amplified fragment is 249 bp.

For amplification of transcription factor TBX3 (T-box 3) cDNA we used forward (5′–GGCATCCCTTTCTCATCCCT–3′ and reverse (5′–CATTCGCCTTCCTGACTTCG–3′) primers. The nucleotide sequences of these primers correspond to sequences

1006–1025 and 1179–1160 of mouse TBX3 cDNA (GenBank accession number NM_011535). The size of amplified fragment is 174 bp.

The amplification of FAS (FAS cell surface death receptor), also known as TNFSF6 (TNF receptor superfamily member 6), apoptosis signaling receptor FAS, and CD95 antigen, cDNA for real time RCR analysis was performed using two oligonucleotides primers: forward – 5′–GTTTTCCCTTGCTGCAGACA–3′ and reverse (5′–TTGACAGCAAAATGGGCCTC–3′). The nucleotide sequences of these primers correspond to sequences 38–57 and 227–208 cDNA of mouse FAS (GenBank accession number NM_007987). The size of amplified fragment is 190 bp.

For amplification of IL13RA2 (interleukin 13 receptor, α2) cDNA we used forward (5′–CGTACGCATTTGTCAGAGCA–3′ and reverse (5′–AGGTTTCCAAGAGCAGACCA–3′) primers. The nucleotide sequences of these primers correspond to sequences 1282–1301 and 1443–1424 of mouse IL13RA2 cDNA (GenBank accession number NM_001306059). The size of amplified fragment is 162 bp.

The amplification of β-actin (ACTB) cDNA was performed using forward – 5′–CCTCTATGCCAACACAGTGC–3′ and reverse – 5′–CCTGCTTGCTGATCCACATC–3′ primers. These primer nucleotide sequences correspond to 985–1004 and 1190–1171 of mouse ACTB cDNA (NM_007393). The size of amplified fragment is 206 bp. The expression of β-actin mRNA was used as control of analyzed RNA quantity. The primers were received from Sigma-Aldrich (USA) and Metabion (Germany).

Quantitative PCR analysis was performed using "Differential expression calculator" software. The values of *UPS7*, *NAMPT*, *E2F8*, *TBX3*, *FAS*, and *IL13RA2* gene expressions were normalized to the expression of β-actin mRNA and represented as percent of control (100%). All values are expressed as mean ± SEM from triplicate measurements performed in 4 independent experiments. The amplified DNA fragments were also analyzed on a 2% agarose gel and visualized by SYBR* Safe DNA Gel Stain (Life Technologies, USA).

Statistical analysis. Statistical analysis was performed according to Student's *t*-test using Excel program as described previously [37]. All values are expressed as mean ± SEM from triplicate measurements performed in 4 independent experiments.

Results and Discussion

To determine if prolonged treatment of mice by chromium disilicide or titanium nitride nanoparticles have genotoxic effects, we studied the expression level of a subset of genes encoding important regulatory enzymes and factors, such as NAMPT, UPS7, FAS, E2F8, TBX3, and IL13RA2, in the liver. It was shown that treatment of mice by titanium nitride nanoparticles led to up-regulation of the expression of *NAMPT/PBEF* gene (+47%) and that chromium disilicide nanoparticles have smaller but statistically significant effect (+15%) on this gene expression in the liver tissue (Fig. 3).

At the same time, titanium nitride and chromium disilicide nanoparticles also enhance the expression of *FAS* (Fas cell surface death receptor) gene, also known as apoptosis signaling receptor FAS and TNF receptor superfamily ember 6 (TNFSF6), but

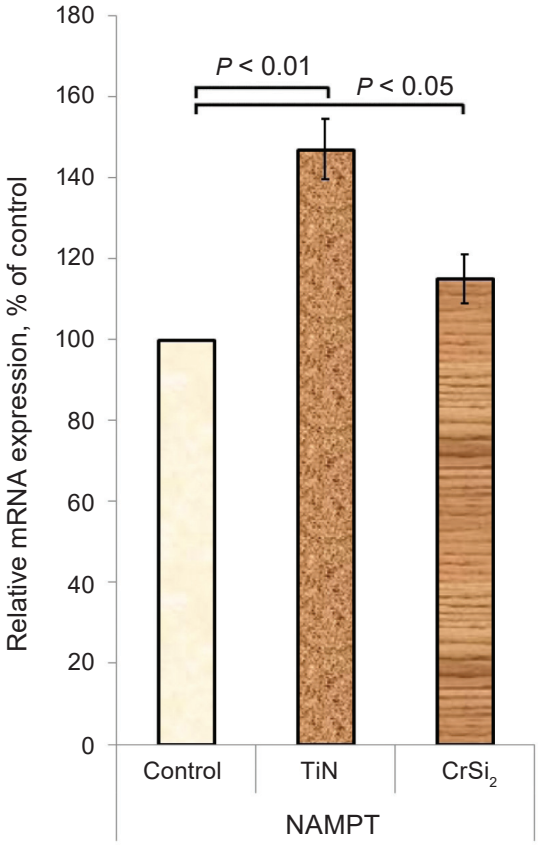

Fig. 3. Effect of prolonged treatment of mice (2 months) by titanium nitride (TiN) and chromium disilicide ($CrSi_2$) nanoparticles on the expression of NAMPT mRNA measured by qPCR. The values of NAMPT mRNA expression were normalized to β-actin mRNA level and presented as percent of control (100%); mean ± SEM, n = 4

this gene expression is more sensitive to chromium disilicide nanoparticles as compared to titanium nitride nanoparticles (Fig. 4). Thus, the treatment of mice by titanium nitride nanoparticles led to +24% up-regulation of the expression of FAS mRNA in the liver and much stronger increase was observed in mice treated by chromium disilicide nanoparticles (+63% versus control).

We also investigated the effect of titanium nitride and chromium disilicide nanoparticles on the expression of IL13RA2 mRNA in the liver tissue. As shown in Fig. 5, the expression of this gene is significantly up-regulated by titanium nitride (+140% versus control) but is resistant to chromium disilicide nanoparticles. More strong changes were obtained for the expression of gene encoding transcription factor TBX3. As shown in Fig. 6, the expression of TBX3 mRNA was strongly up-regulated in both groups of mice treated by nanoparticles, being more significant for animals treated by chromium disilicide nanoparticles. Thus, titanium nitride nanoparticles increased the expression of IL13RA2 mRNA in the liver up to 219% as compared to control mice and chromium disilicide nanoparticles – up to 372% (Fig. 6).

We next investigated the effect of both titanium nitride and chromium disilicide nanoparticles on the expression of transcription factor E2F8 mRNA in mouse liver tissue. As shown in Fig. 7, the expression of this transcription factor gene is significantly down-regulated by chromium disilicide nanoparticles (-38% versus control animals). At the same time, sensitivity of this gene expression to titanium nitride nanoparticles was much lesser but statistically significant (-15% versus to control group of mice). Simi-

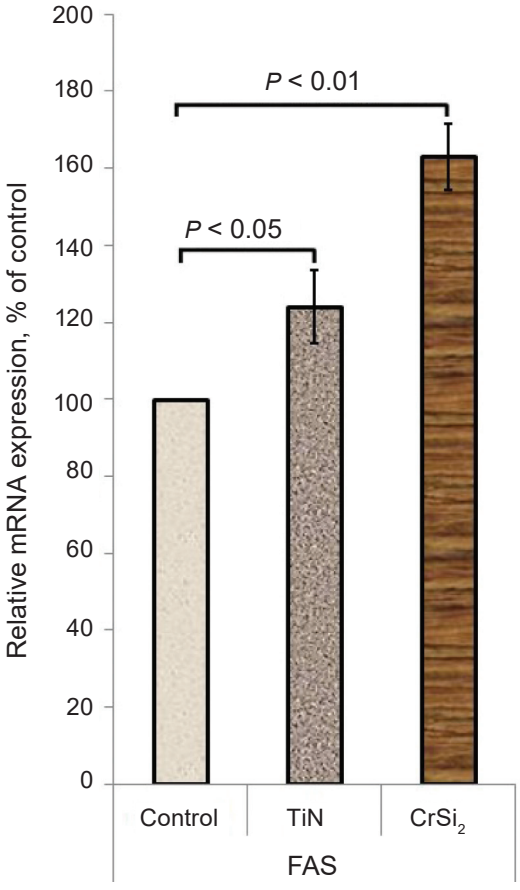

Fig. 4. Effect of prolonged treatment of mice (2 months) by titanium nitride (TiN) and chromium disilicide ($CrSi_2$) nanoparticles on the expression of FAS/TNFSF6 mRNA measured by qPCR. The values of FAS mRNA expression were normalized to β-actin mRNA level and presented as percent of control (100%); mean ± SEM, n = 4

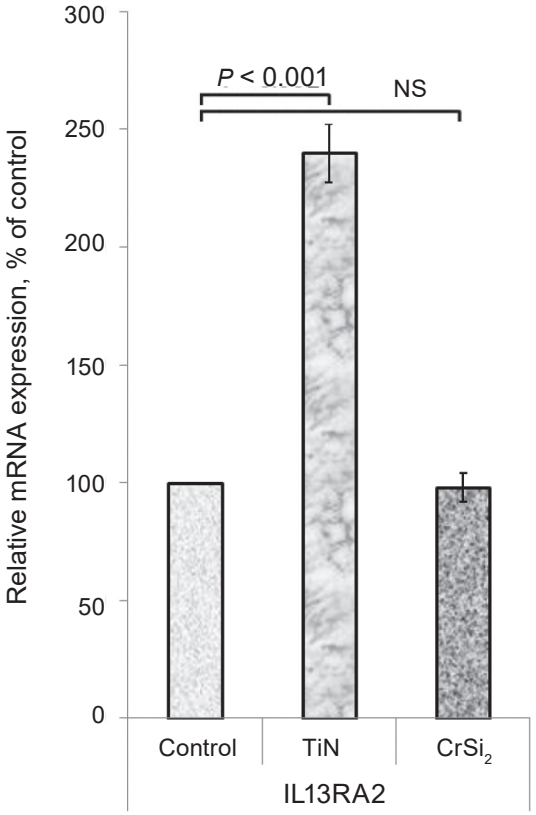

Fig. 5. Effect of prolonged treatment of mice (2 months) by titanium nitride (TiN) and chromium disilicide ($CrSi_2$) nanoparticles on the expression of IL13RA2 mRNA measured by qPCR. The values of IL13RA2 mRNA expression were normalized to β-actin mRNA level and presented as percent of control (100%); mean ± SEM, NS – no significant changes, n = 4

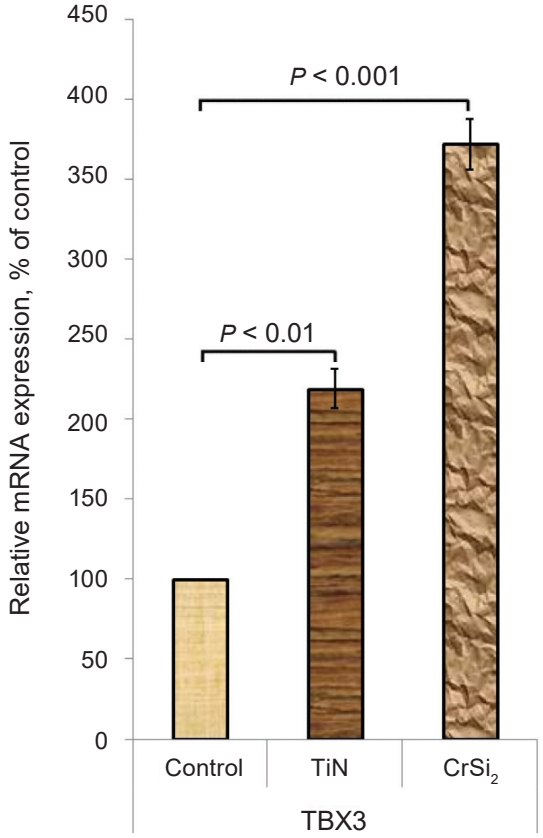

Fig. 6. Effect of prolonged treatment of mice (2 months) by titanium nitride (TiN) and chromium disilicide ($CrSi_2$) nanoparticles on the expression of TBX3 mRNA measured by qPCR. The values of this mRNA expression were normalized to β-actin mRNA level and presented as percent of control (100%); mean ± SEM, n = 4

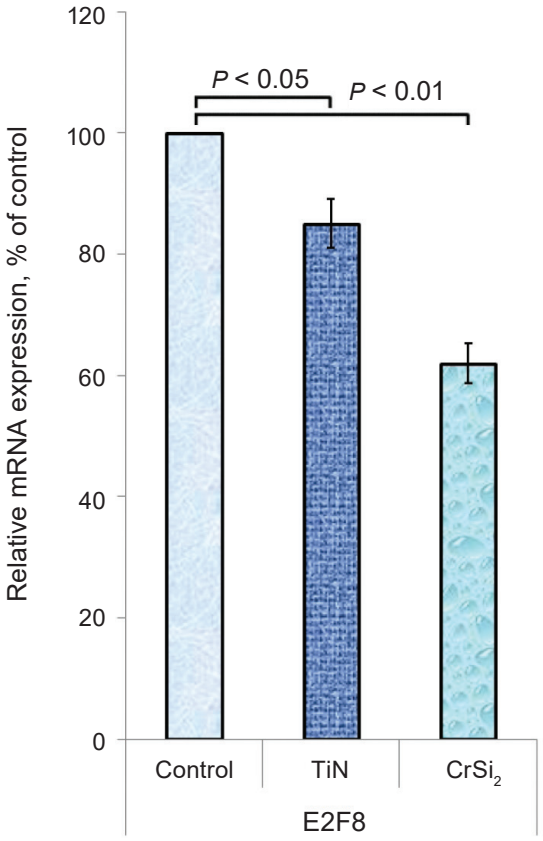

Fig. 7. Effect of prolonged treatment of mice (2 months) by titanium nitride (TiN) and chromium disilicide ($CrSi_2$) nanoparticles on the expression of E2F8 mRNA measured by qPCR. The values of E2F8 mRNA expression were normalized to β-actin mRNA level and presented as percent of control (100%); mean ± SEM, n = 4

lar changes were obtained for the expression of gene encoding ubiquitin specific peptidase 7 (USP7). It was shown that the expression of this mRNA was slightly decreased in the liver of mice treated by titanium nitride nanoparticles and that more significant changes were observed in the group of animals treated by chromium disilicide nanoparticles (-37%) as compared to control animals (Fig. 8).

Therefore, our data clearly demonstrated that treatment of mice by titanium nitride and chromium disilicide nanoparticles (20 mg with food every working day for 2 months) led to up-regulation of the expression of *NAMPT*, *FAS*, and *TBX3* genes and to down-regulation of *USP7* and *E2F8* genes in the liver tissue. The expression of *IL13RA2* gene is up-regulated by titanium nitride nanoparticles only.

In this work, we studied the effect of titanium nitride and chromium disilicide nanoparticles on the expression of a subset of genes encoding different regulatory enzymes, receptors and transcription factors, which play an important role in various metabolic pathways and thus control proliferation and apoptosis [9, 12, 14, 15, 18, 22, 25]. For titanium dioxide nanoparticles, which are widely used in the number of applications, including cosmetic creams, toothpastes, and component of surgical implants, it was shown that long-term exposure to these nanoparticles led to accumulation of these nanoparticles in brain, over-proliferation of glial cells and significant changes in brain gene expressions as well as to neurogenic disease states in mice [1, 2]. At the same time, the genotoxicity of titanium nitride nanoparticles, which have favorable properties and used for coronary stents, syringe needles, and the coating of orthopedic implant as well as in dental medicine for improving long-term implants [4-7], did not studied

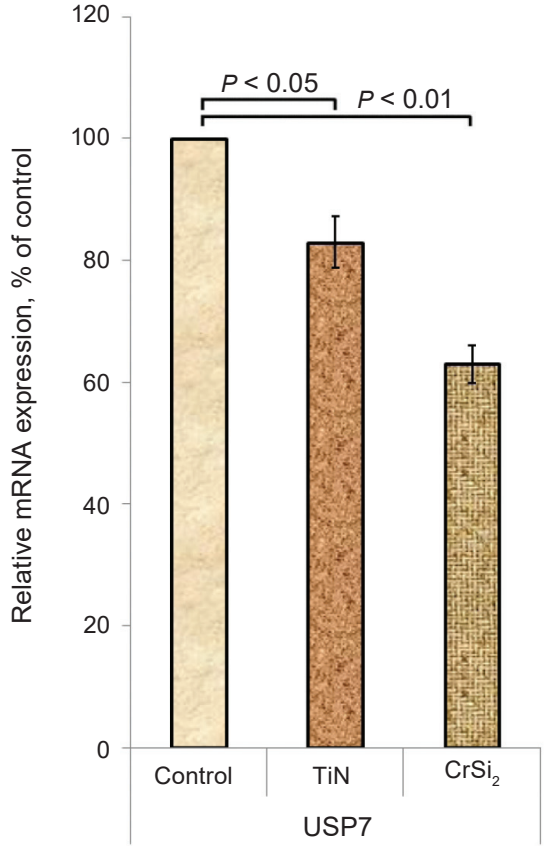

Fig. 8. Effect of prolonged treatment of mice (2 months) by titanium nitride (TiN) and chromium disilicide ($CrSi_2$) nanoparticles on the expression of USP7 mRNA measured by qPCR. The values of USP7 mRNA expression were normalized to β-actin mRNA level and presented as percent of control (100%); mean ± SEM, n = 4

yet. At the same time, very little is known about the toxicity of chromium containing nanoparticles [8]. In this study, we have shown that titanium nitride as well as chromium disilicide nanoparticles affects the expression of a subset of genes encoding important regulatory enzymes and factors in mouse liver in gene-specific manner (Fig. 9).

Therefore, long term treatment of mice by titanium nitride nanoparticles led to increased expression of *NAMPT*, *FAS*, *TBX3*, and *IL13RA2* genes in the liver with more significant changes for *TBX3* and *IL13RA2* genes. It is well known that proteins encoded by all these genes play an important role in controlling apoptosis, cell proliferation, and cancer growth [9, 12, 15, 22]. As shown in Fig. 9, the treatment of mice by chromium disilicide nanoparticles is also led to increased expression of NAMPT, FAS, and TBX3, but does not affect the expression of *IL13RA2* gene. We have also shown that both titanium nitride and chromium disilicide nanoparticles suppress the expression of *E2F8* and *USP7* genes in the liver and that the effect of chromium disilicide nanoparticles on these gene expressions was more significant in comparison to the effect of titanium nitride nanoparticles. It is well known that proteins encoding by *E2F8* and *USP7* genes have variable properties and can contribute to regulation of cell proliferation and apoptosis [18, 25, 26]. It is possible that our results can reflect the genotoxic effect of titanium nitride and chromium disilicide nanoparticles and are mostly consistent with data Ze et al. [2] and Alarifi et al. [8] as well as with our previous data [28, 29].

Therefore, present study demonstrates that chromium disilicide and titanium nitride nanoparticles had variable effects on the expression of most studied genes in a gene specific manner, which possibly reflect genotoxic activities of studied nanoparticles and their effect on important regulatory mechanisms controlling cell proliferation and survival processes. Moreover, our results suggest more cautions needed in biomedical applications of both chromium disilicide and titanium nitride nanoparticles. However, the detailed molecular mechanisms of observed changes in the expression of studied genes warrant further investigation.

ВПЛИВ НАНОЧАСТИНОК ДИСИЛІЦИДУ ХРОМУ І НІТРИДУ ТИТАНУ НА ЕКСПРЕСІЮ ГЕНІВ *NAMPT*, *E2F8*, *FAS*, *TBX3*, *IL13RA2* ТА *UPS7* У ПЕЧІНЦІ МИШЕЙ

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Вивчено ефект наночастинок дисиліциду хрому та нітриду титану на рівень експресії генів, що кодують важливі регуляторні ензими та фактори (NAMPT, UPS7, E2F8, FAS/TNFSF6, TBX3 та IL13RA2) в печінці мишей для виявлення можливого токсичного впливу цих наночастинок. Встановлено, що за дії на мишей наночастинок нітриду титану (20 нм; 20 мг з їжею кожен

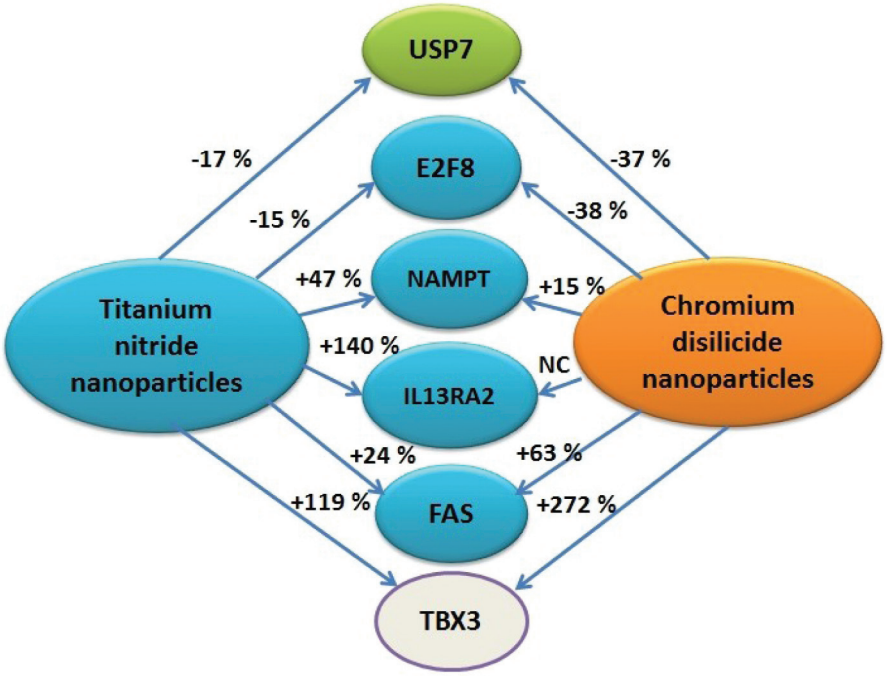

Fig. 9. Schematic representation of genotoxic effect of titanium nitride and chromium disilicide nanoparticles on the expression of genes encoding important regulatory enzymes and factors, such as NAMPT, UPS7, FAS, E2F8, TBX3, and IL13RA2, in the liver of mice treated by these nanoparticles for 2 months; NC – nonsignificant changes

день, крім суботи і неділі, протягом 2 місяців) у клітинах печінки посилювалась експресія генів *NAMPT*, *FAS*, *TBX3* та *IL13RA2* і знижувалась – *USP7* та *E2F8*, причому вираженіші зміни виявлено для генів *TBX3* та *IL13RA2*. За дії на мишей наночастинок дисиліциду хрому (45 нм; 20 мг з їжею кожен день, крім суботи і неділі, протягом 2 місяців) спостерігалися більш виражені зміни в експресії генів *USP7*, *E2F8*, *FAS* та *TBX3* порівняно з ефектом наночастинок нітриду титану. В той самий час вплив наночастинок нітриду титану на експресію гена *NAMPT* у тканині печінки був вираженішим порівняно з дією наночастинок дисиліциду хрому. Проте експресія гена *IL13RA2* істотно не змінювалася в печінці мишей за дії на них наночастинок дисиліциду хрому. Показано, що наночастинки дисиліциду хрому та нітриду титану проявляли різні ефекти на експресію більшості досліджених генів геноспецифічно, які відображають можливу генотоксичну активність досліджених наночастинок, але молекулярні механізми цих змін в експресії генів потребують подальшого вивчення.

Ключові слова: експресія мРНК, *NAMPT*, *UPS7*, *E2F8*, *TBX3*, *FAS*, *IL13RA2*, наночастинки дисиліциду хрому, наночастинки нітриду титану, печінка мишей.

ВЛИЯНИЕ НАНОЧАСТИЦ ДИСИЛИЦИДА ХРОМА И НИТРИДА ТИТАНА НА ЭКСПРЕССИЮ ГЕНОВ *NAMPT*, *E2F8*, *FAS*, *TBX3*, *IL13RA2* И *UPS7* В ПЕЧЕНИ МЫШЕЙ

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Изучен эффект наночастиц дисилицида хрома и нитрида титана на уровень экспрессии генов, которые кодируют важные регуляторные энзимы и факторы (NAMPT, UPS7, E2F8, FAS/TNFSF6, TBX3 и IL13RA2) в печени мышей для выявления возможного токсического влияния этих наночастиц. Установлено, что при действии на мышей наночастиц нитрида титана (20 нм; 20 мг с едой каждый день, кроме субботы и воскресенья, в течение 2 месяцев) в клетках печени усиливалась экспрессия генов *NAMPT*, *FAS*, *TBX3* и *IL13RA2* и снижалась – *USP7* и *E2F8*, причем более выраженные изменения выявлены для генов *TBX3* и *IL13RA2*. При действии на мышей наночастиц дисилицида хрома (45 нм; 20 мг с едой каждый день, кроме субботы и воскресенья, в течение 2 месяцев) наблюдались более выраженные изменения в экспрессии генов *USP7*, *E2F8*, *FAS* и *TBX3* по сравнению с эффектом наночастиц нитрида титана. В то же время влияние наночастиц нитрида титана на экспрессию гена *NAMPT* в ткани печени был более выраженным по сравнению с действием наночастиц дисилицида хрома. Однако, экспрессия гена *IL13RA2* существенно не изменялась в печени мышей при действии на них наночастиц дисилицида хрома. Показано, что наночастицы дисилицида хрома и нитрида титана проявляли различные эффекты на экспрессию большинства исследованных генов геноспецифически, которые отражают возможную генотоксическую активность исследованных наночастиц, но молекулярные механизмы этих изменений в экспрессии генов нуждаются в дальнейшем изучении.

Ключевые слова: экспрессия мРНК, *NAMPT*, *UPS7*, *E2F8*, *TBX3*, *FAS*, *IL13RA2*, наночастицы дисилицида хрома, наночастицы нитрида титана, печень мышей.

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