UDC: 616-006:577. 21
DOI: 10.52532/2663-4864-2024-3-73-67-74

CHROMIUM-INDUCED CARCINOGENESIS: A LITERATURE REVIEW

Y.M. IZTLEUOV[1], A.B. TULYAEYVA[1], G.M. IZTLEUOVA[1], B.T. BAIZAKOV[1], E.A. KYDYRBAYEVA[1] , A.Zh. KAHHAROV[2]

[1]Marat Ospanov West Kazakhstan Medical University, Aktobe, the Republic of Kazakhstan;
[2]Tashkent State Dental Institute, Tashkent, Uzbekistan

ABSTRACT

Relevance: *According to the International Agency for Research on Cancer (IARC), hexavalent chromium Cr(VI) has been identified as a Group I occupational carcinogen. There is ample evidence that Cr(VI) is associated with lung, nasal, and sinus cancers. A study based on the Baltimore cohort, which consisted of 2357 participants, demonstrated a high positive correlation between cumulative Cr(VI) exposure and lung cancer mortality rates. In the western region of Kazakhstan in the Aktobe region, an anthropogenic stablegenic chromium biochemical province has been formed as a result of many years of activity of the enterprises of TNC Kazchrome JSC (Donskoy GOK, Ferrochrome JSC) and AZKhS JSC, which has an impact on the health of the population of this region. In a survey of workers at a ferroalloy plant in West Kazakhstan over 15 years, the mortality rate from cancer among plant workers was significantly higher than among the general public: the excess among people aged 50-59 years was 3.3 times for men and 7.9 times for women. There is a huge amount of material on the effects of hexavalent chromium on the body, which needs to be streamlined to reveal the role of chromium in carcinogenesis.*

The article aimed to *highlight the role of hexavalent chromium in carcinogenesis.*

Methods: *Data from MEDLINE, Embase, Scopus, PubMed, and Cochrane Central Register of Controlled Trials were analyzed to select and analyze relevant information over the past 10 years using keywords: hexavalent chromium, carcinogenesis, heavy metals, oncogenesis. A total of 173 sources were found, and 50 were included in the analysis, considering the valency of the metal studied.*

Results: *Hexavalent chromium inside the human body can react with cellular agentsБ reducing to form Cr(V), Cr(IV), and, ultimately, Cr(III). The latter can lead to the formation of highly toxic Cr(III) DNA adducts in the cell nucleus. All of these intermediates can cause DNA damage or DNA-protein cross-links. Several mechanisms have been proposed to explain chromium-induced carcinogenicity. Cr-induced carcinogenesis is likely dependent on tissue, cell type, Cr(VI) concentration, exposure time and isoforms of certain heat shock proteins, chromosomal instability, nuclear protein 1 (Nupr) induction, DNA adduction, and free radical formation; reactivity of Cr(V) and Cr(IV) intermediates. Epigenetic gene expression changes are considered a key element of carcinogenesis.*

Conclusions: *Understanding the mechanisms of carcinogenesis is important for preventing and treating Cr(VI)-induced cancer. Strategic developments are needed to prevent oncogenesis in the chromium biogeochemical province.*

Keywords: *hexavalent chromium, carcinogenesis, heavy metals, oncogenesis.*

Introduction: According to the International Agency for Research on Cancer (IARC), hexavalent chromium is recognized as a Group I occupational carcinogen [1]. There is sufficient evidence in the scientific literature linking Cr $^{+6}$ with lung, nasal cavity, and paranasal sinus cancer [2]. A study on the Baltimore Cohort of 2,357 participants demonstrated a high positive correlation between cumulative exposure to Cr(VI) and lung cancer mortality [3]. In the EC assessment of socioeconomic impact on human health, hexavalent chromium and silicon dioxide were strongly associated with cancer death [4]. Exposure to Cr $^{+6}$ occurs in many industries, and workers are often exposed to it through inhalation and skin contact [5]. Hexavalent chromium is contained in car exhaust gases and tobacco products such as traditional electronic cigarettes and hookahs [6]. It is estimated that 66% of existing or former hazardous waste disposal sites included in the list of national priorities also contain Cr [7]. In the Aktobe region of the Republic of Kazakhstan, a stable anthropogenic chromium biochemical province has formed [8] as a result of long-term activities of the enterprises of JSC TNC Kazchrome and JSC AZHS, which affects the health of the population of this region and neighboring regions. A survey of workers of the ferroalloy plant showed that over 15 years, mortality from cancer among plant workers was higher than in the population: among people aged 50-59 years, among men - 3.3 times, among women - 7.9 times. The largest share of all cancer deaths was stomach cancer - 37% and lung cancer - 15.8% [9].

The article aims to highlight the role of hexavalent chromium in carcinogenesis.

Materials and methods: An analysis of MEDLINE, Embase, Scopus, PubMed, and Cochrane Central Register of Controlled Trials data was performed to select and analyze relevant information for the last 10 years using the keywords “hexavalent chromium,” “carcinogenesis,” “heavy metals,” and “oncogenesis.” Of 173 sources found, 50 were included in the analysis, considering the valence of the metal under study.

Results: Cr is a rare element; its most stable forms are trivalent Cr(III) and hexavalent chromium Cr(VI). Due to their stability in water and oxygen, they are considered biologically and ecologically significant. Cr(III) is an essential trace element in the human diet; it supports glucose metabolism and regulates blood glucose levels, which synergizes with insulin. Conversely, Cr(VI) is carcinogenic when inhaled and/or ingested in large quantities. Cytotoxicity of Cr refers to its ability to cause damage to living cells, especially at higher concentrations. In its hexavalent form, Cr exhibits strong cytotoxic effects due to its strong oxidizing properties. Cr(VI) can penetrate cell membranes and convert to Cr(III) inside the cell upon exposure. This conversion produces reactive intermediates and free radicals, leading to oxidative stress and subsequent cellular damage. Cr(VI) interferes with important cellular processes, disrupts DNA repair mechanisms, and causes genotoxicity, which ultimately contributes to cancer development. In addition, Cr(VI) can produce reactive oxygen species, causing lipid peroxidation and protein damage. Elevated levels of reactive oxygen species cause oxidative stress, leading to lipid peroxidation and cellular protein degradation. In addition, Cr(VI) can directly act on DNA, disrupting DNA mismatch repair and, as a result, causing genomic instability [10].

Chromium can exist in three different states: Cr(0), Cr(III), and Cr(VI); only Cr(VI) is a known carcinogen. Environmental and occupational exposure to Cr(VI) via water, air, or landfills has become a major public health concern and is associated with human lung cancer. Changes in signaling pathways and oxidative stress are considered causative factors in response to Cr(VI) exposure. Chromium alters the epigenome; histone modifications and the DNA methylation landscape alter the chromatin state. Recently, dysregulation of microRNAs has been shown to play an important role in Cr(VI)-induced cellular transformation, carcinogenesis, and angiogenesis. Interleukin-8 was induced by Cr(VI) treatment, a major inducer of angiogenesis upregulated by activating the IGF-IR/IRS1 axis and ERK/HIF-1α/NF-κB signaling pathway. This result suggests that miR-143/IL-6/HIF-1α signaling pathway plays a vital role in Cr(VI)-induced malignant cell transformation and carcinogenesis [11].

Ligand-bound Cr(III) enters cells via a phagocytic mechanism or non-specific diffusion. Subcellular Cr(VI) is stored as chromate oxyanion (CrO4), and chromate anions utilize sulfate transporters on the cell surface to enter. Once Cr(VI) enters the cell, it becomes toxic because it is reduced to Cr(III) together with ascorbate and biological thiols such as glutathione (GSH) or because cysteine aminoalkanoic acid residues form reactive oxygen species. Cr(VI) remains a major health problem, contributing to a wide range of cancers: prostate, bone, leukemia, lymphoma, kidney, gastrointestinal, brain, and lung cancers [12].

Occupational exposure and environmental pollution are common routes of exposure to toxic metals. Accumulation of metals in the soil leads to their transfer to flora and fauna. The main source of human exposure to toxic elements is nutrition. There is an assumption about the bioaccumulation of toxic metals in the colon and their involvement in oncology development. A group of 104 patients with various diseases of the colon and rectum was examined, of which 76 were diagnosed with cancer. A significantly higher presence of Cr was observed in tumor biopsies. Molecular data on the effect of Cr on the colon were obtained in both in vivo and in vitro studies. Cr induces centrosome amplification in HCT116 colon cancer cells. It is known that the centrosome plays a role in oncogenesis and invasiveness of cancer cells. The authors found that Cr(VI) can induce centrosomes and promote cancer progression via the ROS-ATF6-PLK4 pathway [13].

Molecular studies have shown that Cr exposure results in decreased expression of p53 and RKIP, while an increase in galectin and c-myc is observed. It should be noted that Cr-induced disruption of p53 expression may significantly affect the development of colorectal cancer. Decreased p53 expression disrupts cell cycle control, leading to uncontrolled tumor proliferation and growth. Impaired p53 function disrupts DNA repair mechanisms, accumulating genetic aberrations and increasing tumor aggressiveness [14].

A meta-analysis of Cr(VI) exposure and gastrointestinal cancer showed an increased risk of gastric cancer in workers exposed to chromium and an increased mortality rate from gastric cancer in chromium-contaminated regions. Exposure to Cr^{+6} increased the risk of brain cancer and malignant lymphoma and mortality from lung, bladder, and pancreatic cancer among tanners.

A meta-analysis based on published epidemiological cohort studies showed that hexavalent chromium causes cancer of the respiratory system, oropharynx, prostate, and stomach and increases the risk of developing cancer of the larynx, bladder, kidney, testicles, thyroid, and bone [15].

Currently, chromium exposure is associated with a wide range of diseases, from cutaneous exposure that causes sensitization to haptens via the mechanism of inflammatory cell activation to carcinogenicity through various exposure modes and mechanisms, including genomic instability or epigenetic changes [16], as well as respiratory, hepatic, renal and reproductive problems and neurological disorders [17]. This brief review summarizes the most relevant results in Cr(VI) carcinogenesis, emphasizing molecular and epigenetic mechanisms.

Epithelial cells can transdifferentiate into motile mesenchymal cells through a dynamic process known as epithelial-mesenchymal transition (EMT). EMT is critical for embryonic development and wound healing but

also contributes to human diseases such as organ fibrosis and cancer progression. Hexavalent chromium has a dual effect on epithelial-mesenchymal transition, sometimes stimulating and sometimes inhibiting the EMT process. [18].

Initially, only inhalation exposure to Cr(VI) was of major concern, but it was subsequently noted that absorption from the gastrointestinal tract can also lead to carcinogenic activity. Although the effects of oral exposure are reduced by chemical reduction of Cr(VI) in the intestine, this phenomenon does not prevent chromium uptake into target tissues, allowing disease to develop [19]. Epidemiological studies conducted in populations consuming contaminated water and meta-analyses of epidemiological cohort studies have shown an increased risk of developing several types of cancer, including gastric, gastrointestinal, renal, genitourinary, bone, leukemia, lymphoma, brain, nose, and lung. Cr(VI) induces a wide range of DNA damage and promotes the induction of neoplasia in several organs other than the respiratory system due to its ability to biotransform in all types of cells [20].

The toxicity and carcinogenicity of Cr(VI) is due to its ability to readily enter cells through isoelectric and isostructural anion transport channels, which are used to transport HPO^{-2}_4 SO^{-2}_4 ions [21]. Although Cr(VI) compounds do not bind directly to DNA, intermediates and byproducts of Cr(VI) metabolism can cause a wide range of damages through DNA adducts and cross-links. Notably, the formation of reactive oxygen species (ROS) through detoxification is mainly responsible for Cr(VI)-induced cellular damages such as DNA damage, cytotoxicity, and tumor development [22]. Cr(III), (IV), (V), and (VI) species are known to produce intracellular ROS. During intracellular reduction of Cr(VI), hydroxyl radicals are generated through Fent-like reactions in the presence of hydrogen peroxide [23]. Endogenous superoxide anions and hydrogen peroxides produce hydroxyl radicals via Haber-Weiss-like reactions in the presence of Cr(VI) [24]. Reactive oxygen species scavengers ascorbic acid and glutathione can detect and reduce Cr^{+6} to Cr^{+3} but produce free radicals, hydroxyl radicals, and DNA-damaging intermediates such as Cr^{+5} and Cr^{+4} [25].

ROS, including hydroxyl radicals, singlet oxygen, peroxides, and superoxides, can be important second messengers and activators of various pathways, including apoptosis, cell signaling, and homeostasis [26]. Cr(VI) has been shown to induce the activation of NF-kB, AP-I, and Nrf 2, which are important in cancer development [27]. Hydroxyl radicals can react with guanine residues to form radical adducts such as 8-hydroxydeoxyguanosine (8-OH-dG), an important marker of oxidative damage in cancer [28]. ROS accumulation can lead to oxidative stress and promote chronic inflammation, metabolic reprogramming, genetic instability, and cancer development [29]. Adducts formed by conjugating Cr and ROS scavengers, including GSH-Cr-DNA, can generate bulky adducts and block proper DNA replication and repair [30]. Hexavalent chromium damages DNA by intracellular reduction as apurinic/apyrimidinic sites and by interacting with proteins, amino acids, or directly with DNA, causing DNA breaks [31]. Upon intracellular reduction, Cr(VI) can form bulky binary Cr(III) adducts (CrIII-DNA) as well as ternary adducts, i.e., Cr(III)-ligand-DNA, the latter being more mutagenic than the binary Cr(III)-DNA analogs and 90% of mutagenic damage occurs in ternary complexes [32]. The literature data on changes in chromatin structure in response to acute and chronic Cr(VI) exposure suggest that the mechanisms governing the transcriptional response induced by Cr(VI) often differ in a dose-dependent manner, and this may influence the molecular mechanisms leading to carcinogenesis, since structural changes in chromatin do not correlate with changes in the global transcriptional response, but do influence gene expression levels in target regions, which vary in a Cr(VI) concentration-dependent manner [33].

Several mechanisms have been proposed to explain chromium-induced carcinogenicity. Cr-induced carcinogenesis probably depends on tissue, cell type, Cr(VI) concentration, exposure time, and isoforms of some heat shock proteins, chromosomal instability, nuclear protein I (Nupr) induction, DNA adduction, and free radical formation; reactivity of Cr(V) and Cr(IV) intermediates [34]. Epigenetic alteration of gene expression is considered a key element in carcinogenesis.

More than the valence stability of chromium, Cr(VI) and Cr(III) are recognized as carcinogens in *vitro experiments* using Cr-induced DNA-protein complexes; *in vivo experiments* did not prove the Cr(III) carcinogenicity [35]. Although the mechanism of chromium carcinogenicity is not fully understood, it is generally accepted that it mainly occurs through DNA damage/genomic instability and ROS generation. Cr(VI) has been shown to alter the epigenetic profile of cells through DNA methylation, histone modification [36], and inhibition of the recruitment of DNA mismatch repair proteins, which facilitates the induction of g-H2AX foci leading to DNA breaks and initiation of p-53 mediated apoptosis [37]. Results such as these suggest a link between chromium-induced epigenetic changes and carcinogenesis [38]. Compared with DNA methylation and histone post-translational modifications, less is known about the effects of Cr(VI) on miRNAs. MiRNAs regulate broad transcriptional pathways; Cr(VI) disrupts specific transcriptional pathways by directly deregulating the miRNA expression profile [39].

Recently [40], it was reported that Cr(VI) induces persistent and heritable chromosome translocations, aneuploidy and polyploidy, centrosome amplification, and

DNA repair defects. The regulatory phenotype favored cancer cell growth due to the imbalance caused by heredity and the persistent nature of chromosomal translocations. In recent years, an increasing number of studies have shown that both short-term and long-term exposure to Cr(VI) causes global changes in epigenetic modifications and non-coding RNA (microRNA) expression in cells, the latter being important regulators of gene expression and have been recognized as important participants in tumor formation, development, and metastasis.

Metabolic reprogramming of key energy metabolism pathways is important for the survival and growth of cancer cells and tumors. All Cr(VI)-transformed cells had no changes in their mitochondrial respiratory functions compared to passenger control cells. However, although mitochondrial dysfunction does not occur during Cr(VI)-induced lung cell transformation, it does occur during tumor development [41].

The carcinogenic effects of Cr(VI) have been mainly studied in lung cancer since the lung is the main target of Cr(VI). Cr(VI) is well known for transforming normal human lung epithelial cells such as BEAS-2B and 16HBE cells; the transformed cells exhibit cancer and cancer stem cell (CSC)-like properties. Multiple mechanisms have been identified that contribute to Cr(VI)-induced lung carcinogenesis, including oxidative stress, DNA damage, abnormal signal transduction, and inflammatory responses. Although Cr(VI)-induced genotoxicity and mutagenicity are considered to be the main mechanisms of Cr(VI) carcinogenesis, an increasing number of studies indicate that altered epigenetic modifications and dysregulation of non-coding RNAs contribute to induced tumorigenesis in the subsequent years [42].

DNA methylation as a major type of epigenetic modification has been extensively studied in the context of Cr(VI) exposure. Fundamental changes in DNA methylation status have been found in blood and lung cancer tissues from Cr(VI)-exposed workers and in Cr(VI)-exposed and transformed lung epithelial cells. Since DNA damage is one of the major genotoxic effects of Cr(VI), some studies have investigated the role of DNA methylation in Cr(VI)-induced DNA damage and dysfunction of the DNA repair system. Cr(VI) exposure causes increased DNA damage and decreased p16INK4a expression in 16HBE cells [43]. Reduced p16INK4a expression and aberrantly increased p16INK4a promoter methylation were also found in workers with lung cancer and long-term (≥15 years) Cr(VI) exposure, suggesting that p16INK4a hypermethylation is involved in Cr(VI) carcinogenesis [44].

Cr(VI) induced gene-specific histone modifications that altered gene expression. Altered global and gene-specific histone modifications and resulting gene expression changes, such as inhibition of the MLH1 tumor suppressor, contribute to Cr(VI) carcinogenesis. Chronic low-dose hexavalent chromium exposure has been shown to transform cells with precancerous cell-like properties. Disruption of the histone DNA modification machinery contributes to the development of genotoxic effects, leading to the onset or progression of the cancer process [45]. Glycolytic shifts and the development of glycolysis play an important role in maintaining the malignant phenotypes of Cr(VI)-transformed cells since reversal of the glycolytic shift by glucose depletion significantly inhibited the growth, tumor-like properties, and tumorigenicity of transformed cells. Involvement of nuclear proto-oncogene-mediated histone hypoacetylation in Cr(VI)-induced lung carcinogenesis [46].

Dysregulation of microRNA expression plays an important role in Cr(VI)-induced cellular transformation, carcinogenesis, and angiogenesis. Cr(VI) exposure altered global microRNA expression in the human bronchial fibroblast cell line WTHBF-6. In silico pathway analysis revealed that these altered microRNAs were enriched in pathways involved in carcinogenesis [47].

Quercetin (antioxidant flavonoid) inhibited Cr(VI)-induced activation of miR-21/PDCD4 pathway in BEAS-2B cells by reducing ROS generation. Quercetin inhibited Cr(VI)-induced malignant transformation and suppressed xenograft tumor growth from Cr(VI)-transformed cells, indicating the preventive and therapeutic role of quercetin in Cr $^{+6-}$ induced lung cancer [36].

Cr(VI) exposure has been shown to induce DNA damage and subsequent activation of DNA repair genes. Exposure of human B lymphoblast HMy2. CIR cells to Cr(VI) induced global changes in miRNA expression. Mechanistic studies showed chronic Cr(VI) exposure increased c-Myc expression by downregulating miR-494. This suggests that inhibition of the miR-494/c-Myc pathway contributes to lung cancer initiation by chronic Cr(VI) exposure. [48].

However, most processes of carcinogenesis remain poorly understood, and an in-depth discussion of these studies is beyond the scope of this review.

Discussion: Chronic Cr(VI) exposure upregulates the expression of the proto-oncogene c-Myc, which significantly contributes to Cr(VI)-induced cell transformation, cancer stem cell (CSC) property, and tumorigenesis. c-Myc is a master regulator of abnormal metabolism in cancer cells, and accumulating evidence suggests that metabolic dysregulation plays an important role in both cancer development and progression. However, little is known about the role of metabolic dysregulation in Cr(VI) carcinogenesis. It was found that Cr(VI)-transformed cells exhibited a glycolytic shift that was dependent on c-Myc activation. The glycolytic shift in Cr(VI)-transformed cells increased acetyl-coenzyme A (acetyl-CoA) production and enhanced histone acetylation. This, in turn, increased the expression of acetyl-CoA, which pro-

duces the key enzyme ATP-citrate lyase, and c-Myc, forming a positive feedback loop between increased c-Myc expression, glycolytic shift, and increased histone acetylation [27].

Glucose depletion reverses the glycolytic shift in Cr(VI)-transformed cells and significantly reduces their growth, tumor-like properties, and tumorigenicity. These data indicate that the glycolytic shift plays an important role in maintaining the malignant phenotypes of Cr(VI)-transformed cells, suggesting that metabolic dysregulation plays a critical role in Cr(VI) carcinogenesis [49].

Although it is well known that Cr(VI) is one of the most common environmental carcinogens causing lung cancer and other cancers, the mechanism of Cr(VI) carcinogenesis is not clearly defined. Studies have shown that metabolic dysregulation plays a critical role in the development and progression of cancer. However, little is known about whether chronic Cr(VI) exposure causes metabolic dysregulation and whether metabolic reprogramming plays an important role in Cr(VI) carcinogenesis [38].

In addition, recent studies have shown that mRNA levels of several genes involved in the glycolytic pathway and lactate production increase in Cr(VI)-transformed cells. Cr(VI)-transformed cells exhibit abnormal metabolism as evidenced by increased glycolysis or glycolytic shift. Subsequent mechanistic studies have determined that the glycolytic shift in Cr(VI)-transformed cells depends on increased c-Myc expression [22, 50].

Importance of the glycolytic shift in Cr(VI) carcinogenesis. Increased glycolysis is thought to support some cancer features. The glycolytic shift is crucial for malignant phenotypes of Cr(VI)-transformed cells, suggesting an important role of the glycolytic shift in Cr(VI) carcinogenesis. However, further studies are needed to determine whether the glycolytic shift occurs early in the course of Cr(VI) exposure and whether it plays a causal role in Cr(VI)-induced malignant cell transformation, tumor-like properties, and tumorigenesis [19, 36].

Cr(VI) exposure also induces epigenetic dysregulation, which may be important in carcinogenesis. The existence of cross-regulation between metabolism and epigenetics suggests that, on the one hand, metabolic dysregulation may lead to epigenetic dysregulation. On the other hand, epigenetic dysregulation, such as increased histone acetylation, may increase the expression levels of key metabolic enzymes, causing metabolic reprogramming [41, 48].

Activation of c-Myc in Cr(VI)-transformed cells promotes a glycolytic shift that increases acetyl-CoA levels and subsequent activation of histone acetylation and non-histone protein acetylation. Upregulation of acetylation increases ACLY and c-Myc expression, forming a positive feedback loop to further promote the glycolytic shift in Cr(VI)-transformed cells. The glycolytic shift in cells explains the epigenetic dysregulation induced by Cr(VI) exposure but also offers additional evidence supporting its important role in carcinogenesis [16, 24].

Conclusion: Thus, it is likely that chronic Cr(VI) exposure induces c-Myc expression, which in turn enhances the expression of several important glycolytic regulatory enzymes, causing a metabolic shift towards glycolysis.

Cells transformed by chronic Cr(VI) exposure exhibit a glycolytic shift. Studies have shown that the glycolytic shift in Cr(VI)-transformed cells depends on the upregulation of the proto-oncogene c-Myc. It was further found that the glycolytic shift in Cr(VI)-transformed cells results in increased acetyl-CoA production and enhanced histone acetylation, which in turn enhances the expression of the key acetyl-CoA-producing enzyme ACLY and c-Myc expression. This results in a positive feedback loop between increased c-Myc expression, glycolytic shift, and histone acetylation. Moreover, glucose depletion reversed the glycolytic shift in Cr(VI)-transformed cells and significantly ameliorated their malignant phenotypes. These data together suggest that metabolic dysregulation plays an important role in Cr(VI) carcinogenesis.

Further animal and human studies are needed to evaluate their role as biomarkers for early diagnosis and to develop prevention methods and treatment options for human cancers induced by carcinogenic chromium in the future. Understanding the mechanisms of carcinogenesis is important for the prevention and treatment of Cr(VI)-induced cancer and the development of appropriate tumor strategies for both prevention and treatment of malignant tumors caused by exposure to various chromium compounds.

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АҢДАТПА

ХРОМ-ИНДУКЦИЯЛАНҒАН КАНЦЕРОГЕНЕЗ: ӘДЕБИЕТКЕ ШОЛУ

Е.М. Изтлеуов[1], А.Б. Туляева[1], Г.М. Изтлеуова[1], Б.Т. Байзаков[1], Э.А. Кыдырбаева[1], А.Ж. Каххаров[2]

[1]«Марат Оспанов атындағы Батыс Қазақстан медицина университеті» КеАҚ, Ақтөбе, Қазақстан Республикасы
[2]Ташкент мемлекеттік стоматологиялық институты, Ташкент, Өзбекстан

Өзектілігі: *Халықаралық қатерлі ісіктерді зерттеу агенттігінің (IARC) мәліметтері бойынша алты валентті хром Cr(VI) I топтағы кәсіптік канцероген ретінде анықталды. Cr(VI) өкпенің, мұрынның және синустың қатерлі ісігімен байланысты екендігі туралы көптеген дәлелдер бар. 2357 қатысушыдан тұратын Балтимор когортына негізделген зерттеу жинақталған Cr(VI) экспозициясы мен өкпе ісігінен болатын өлім-жітім көрсеткіштері арасындағы жоғары оң корреляцияны көрсетті. Қазақстанның батыс өңірінде Ақтөбе облысында «Қазхром» ТҰК» АҚ (Донской ГОК, «Феррохром» АҚ) және «Ақтөбе хром қосындылары зауыты» АҚ кәсіпорындарының көп жылдық қызметінің нәтижесінде тұрақты антропогендік хром биохимиялық провинциясы қалыптасты, бұл өз әсерін тигізуде. осы аймақ тұрғындарының денсаулығы туралы. Батыс өңіріндегі ферроқорытпа зауытының жұмысшылары арасында жүргізілген сауалнама 15 жыл ішінде зауыт жұмысшылары арасында онкологиялық аурулардан болатын өлім-жітім халықтың қалған бөлігімен салыстырғанда айтарлықтай жоғары екенін көрсетті: 50-59 жас аралығындағы адамдар арасында, ерлер арасында – 3,3 есе, әйелдер үшін – 7,9 есе. Алты валентті хромның ағзаға әсері туралы материалдардың үлкен көлемі бар, оны ретке келтіру және соңғысының канцерогенездегі рөлін ашу қажет.*

Зерттеудің мақсаты *– канцерогенездегі алты валентті хромның рөлін көрсету.*

Әдістері: *MEDLINE, Embase, Scopus, PubMed, Cochrane бақыланатын сынақтардың орталық тізілімінен алынған деректер соңғы 10 жылдағы маңызды ақпаратты таңдау және талдау үшін: алты валентті хром, канцерогенез, ауыр металдар, онкогенез сияқты негізгі сөздерді пайдалана отырып талданды. Барлығы 173 дереккөз табылды, оның 50-і зерттелетін металдың валенттілігін ескере отырып талдауға енгізілді.*

Нәтижелері: *алты валентті хром адам ағзасында болған кезде жасушалық тотықсыздандырғыштармен әрекеттесіп, Cr(V), Cr(IV) және, сайып келгенде, Cr(III) түзеді. Соңғысы жасуша ядросында өте уытты Cr(III) ДНҚ қосындыларының түзілуіне әкелуі мүмкін. Осы аралық өнімдердің барлығы ДНҚ зақымдануын немесе ДНҚ-ақуыздың айқаспалы байланыстарын тудыруы мүмкін. Хромның канцерогенділігін түсіндірудің бірнеше механизмдері ұсынылды. Шын мәнінде, Cr-индукцияланған канцерогенез тінге, жасуша түріне, Cr(VI) концентрациясына, әсер ету уақытына және белгілі бір жылу соққысының белоктарының изоформаларына, хромосомалық тұрақсыздыққа, ядролық ақуыз I (Nupr) индукциясы, ДНҚ аддукциясы және бос радикалдардың түзілуіне байланысты болуы мүмкін; Cr(V) және Cr(IV) аралық өнімдерінің реактивтілігі. Ген экспрессиясының эпигенетикалық өзгерістері канцерогенездің негізгі элементі болып саналады.*

Қорытынды: *Канцерогенез механизмдерін түсіну Cr(VI)-индукцияланған қатерлі ісіктің алдын алу және емдеу үшін маңызды. Хром биогеохимиялық провинциясында онкогенездің алдын алу үшін стратегиялық әзірлемелер қажет.*

Түйінді сөздер: *алты валентті хром, канцерогенез, ауыр металдар, онкогенез.*

АННОТАЦИЯ

ХРОМ-ИНДУЦИРОВАННЫЙ КАНЦЕРОГЕНЕЗ: ОБЗОР ЛИТЕРАТУРЫ

Е.М. Изтлеуов[1], А.Б. Туляева[1], Г.М. Изтлеуова[1], Б.Т. Байзаков[1], Э.А. Кыдырбаева[1], А.Ж. Каххаров[2]

[1]НАО «Западно-Казахстанский медицинский университет имени М. Оспанова», Актобе, Республика Казахстан;
[2]Ташкентский государственный стоматологический институт, Ташкент, Узбекистан

Актуальность: *Согласно данным международного агентства по изучению рака (IARC), шестивалентный хром Cr(VI) признан профессиональным канцерогеном I группы. Доказано, что Cr(VI) связан с раком легких, полости носа и околоносовых пазух. Исследование на Балтиморской когорте (2357 человек) продемонстрировало положительную корреляцию между кумулятивным воздействием Cr(VI) и уровнем смертности от рака легких. В западном регионе Казахстана в Актюбинской области сформировалась устойчивая антропотехногенная хромовая биохимическая провинция, в результате многолетней деятельности предприятий АО ТНК «Казхром» и АО «Актюбинский завод хромовых соединений», которая оказывает влияние на здоровье населения данного региона. Обследование рабочих завода ферросплавов (возраст 50-59 лет) показало, что в течение 15 лет смертность среди них была существенно выше,*

чем у остального населения: у мужчин – в 3,3 раза, у женщин – 7,9 раза. Имеется огромный материал по воздействию на организм шестивалентного хрома, который нуждается в упорядочивании и раскрытии роли последнего в канцерогенезе.

***Цель статьи** – освещение роли шестивалентного хрома в канцерогенезе.*

***Методы:** Проведен анализ данных MEDLINE, Embase, Scopus, PubMed, Cochrane Central Register of Controlled Trials для отбора и анализа релевантной информации за последние 10 лет по ключевым словам: шестивалентный хром, канцерогенез, тяжелые металлы, онкогенез. Всего найдено 173 источника, включено в анализ 50.*

***Результаты:** В теле человека Cr(VI) может вступать в реакцию с клеточными восстановителями с образованием Cr(V), Cr(IV) и, в конечном счете, Cr(III). Последнее может привести к образованию высокотоксичных аддуктов Cr(III) ДНК в ядре клетки. Промежуточные соединения могут вызывать повреждения ДНК или перекрестных связей ДНК-белок. Предлагается несколько механизмов канцерогенности хрома. Cr-индуцированный канцерогенез, вероятно, зависит от ткани, типа клеток, концентрации Cr(VI), времени воздействия, хромосомной нестабильности, ядерного белка I индукции, аддукции ДНК и образования свободных радикалов; реакционной способности промежуточных соединений Cr(V) и Cr(IV). Эпигенетическое изменение экспрессии генов рассматривается как ключевой элемент канцерогенеза.*

***Заключение:** Понимание механизмов канцерогенеза важно для профилактики и лечения рака, индуцированного Cr(VI). Необходимы стратегические разработки по профилактике онкогенеза в хромовой биогеохимической провинции.*

***Ключевые слова:** шестивалентный хром, канцерогенез, тяжелые металлы, онкогенез.*

***Transparency of the study:** Authors take full responsibility for the content of this manuscript.*
***Conflict of interest:** The authors declare no conflict of interest.*
***Financing:** The work was carried out within the framework of a scientific project with grant funding from the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan "AP19678225 Prevention of spontaneous oncogenesis in the first generation of rats whose parents were exposed to gamma irradiation and chromium (experiment)" (reg. no. 0123PK00613).*
***Authors' details:** contribution to the concept – Iztleuov E.M., Kahharov A.Zh.; scientific design – Iztleuov E.M.; execution of the declared scientific research – Iztleuov E.M., Tulyaeva A.B.; interpretation of the declared scientific research – Iztleuov E.M., Baizakov B.T.; creation of the scientific article – Iztleuov E.M., Kydyrbaeva E.A.*

Author's data:
Iztleuov E.M. (corresponding author) – Associate Professor, Candidate of Medical Sciences, Head of Radiology Department, Marat Ospanov West Kazakhstan Medical University, Aktobe, the Republic of Kazakhstan, tel. +77756988866, e-mail: ermar80@mail.ru, ORCID ID: 0000-0002-5303-8593;
Tulyaeva A.B. – PhD , Assistant at Oncology Department, Marat Ospanov West Kazakhstan Medical University, Aktobe, the Republic of Kazakhstan, tel. +77016599861, e-mail: ermar80@mail.ru, ORCID ID: 0000-0001-9819-1105;
Iztleuova G.M. – Candidate of Medical Sciences, Head of the Course of Dermatovenerology, Marat Ospanov West Kazakhstan Medical University, Aktobe, the Republic of Kazakhstan, tel. +77078818666; e-mail: ermar80@mail.ru, ORCID ID: 0000-0002-5695-0895;
Baizakov B.T. – Candidate of Medical Sciences, Head of Radiotherapy Department, Marat Ospanov West Kazakhstan Medical University, Aktobe, the Republic of Kazakhstan, tel. +77072177737; e-mail: ermar80@mail.ru, ORCID ID: 0009-0000-3246-2726;
Kydyrbaeva E.A. – PhD student, Marat Ospanov West Kazakhstan Medical University, Aktobe, the Republic of Kazakhstan, tel. +77756988899, e-mail: elay_vip_k@mail.ru, ORCID ID: 0009-0009-4160-1893;
Kahharov A.Zh. – MD, PhD, Associate Professor, Department of Oncology and Medical Radiology, Tashkent State Dental Institute, Tashkent, Uzbekistan, tel. +998977032339, e-mail: alisher1510@mail.ru, ORCID: 0009-0003-1304-3261.

***Address for correspondence:** Iztleuov E.M., Marat Ospanov West Kazakhstan Medical University, Maresyev St. 68, Aktobe 030000, Republic of Kazakhstan.*