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THE EFFECTS OF THE ACTION OF CHROMIUM, ALUMINUM, NICKEL AND IRON ON HUMAN FIBROBLAST AND STEM CELL CULTURES

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Abstract: This review is a collection of general information about chromium, aluminum, nickel and iron. We tried to include not only the data about absorption, metabolism, interactions with other elements and the importance of those microelements in the human body but also their toxic and mutagenic effects. Moreover, we examined their effect on human fibroblast and stem cell cultures which may be important due to abuse of supplementation in the population nowadays.

Keywords: chromium; aluminum; nickel; iron; fibroblast; stem cell

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1. CR – CHROMIUM

Chromium most often occurs in two main oxidation states – trivalent and hexavalent. Chromium in the trivalent form is a trace element necessary for the proper functioning of the body, and is present in food. The hexavalent form is used in industry and is considered as a carcinogen [Pechova and Pavlata 2007, Czarnek and Siwicki 2021a]. Although chromium (III) is considered much safer than chromium (VI), both of these forms, after getting into the body, can change their oxidation levels, and thus affect the oxidative/antioxidant balance in the body and induce oxidative stress (OS) [Sugden and Stearns 2000]. Until recently, trivalent chromium was considered a micronutrient necessary for the proper course of many metabolic pathways in the body, as its trivalent form acts as a cofactor and/or modulator of many enzymatic reactions. Due to the body's low demand for chromium, deficiencies of this element are very rare. The daily, recommended dietary allowances (RDA) of chromium are 50-200 μg. The adequate daily intake (AI) of this element is defined as 25 μg for women and 35 μg for men.

Chromium (VI) is much more easily absorbed than chromium (III). Significant differences in the bioavailability of orally administered organic and inorganic chromium (III) salts have also been demonstrated. Data found in literature shows that the absorption of chromium (III) salts is low, ranging from 0.4 to 2.5%. The presence of other nutrients also affects the bioavailability of chromium. Absorption is increased, for example, by zinc chelating compounds (vitamin C, niacin, amino acids, oxalates. Moreover, iron, manganese, zinc and titanium ions inhibit the absorption of this bio-element. Also, eating foods with a high content of simple sugars and a diet rich in fat contribute to the loss of this element from the body and additionally reduce its absorption [Lukaski et al. 2007]. After being absorbed in the intestines, chromium (III) passes into the blood, where it combines with plasma proteins that transport it to the liver and other organs. However, the mechanism of Cr (III) transport into the body's cells has not been fully understood. Two protein complexes are responsible for chromium binding in vivo: transferrin and oligopeptide – chromodulin. Binding of chromium with transferrin can interact with iron by disturbing its metabolism and storage. Despite the fact that at low concentrations, these metals prefer other binding sites to the transport protein, at higher concentrations they act competitively, which may result in reduced transferrin saturation with iron ions, and in extreme cases anemia [Piotrowska et al. 2018]. Chromium is stored in various organs – in the largest amounts in the kidneys, spleen and testes, and in trace ones – in the heart, lungs, pancreas and brain. The storage capacity of this element does not change significantly with age, but it has been observed that as

a result of the aging of the organism it may decrease and the risk of cardiovascular diseases and type 2 diabetes increases [Costello et al. 2016].

It is known that chromium (III) is necessary for the proper functioning of the body, because it is a component of some enzymes (e.g. trypsin) and has properties that stimulate their action. It is also present in RNA and is responsible for the stabilization of its structure. There are also studies stating that supplementation with chromium (III) compounds has a positive effect on lipid metabolism [Czarnek and Siwicki 2021b], and Cr (III) can be used in the prevention of the development of atherosclerosis and heart disease because it is believed to have the ability to lower the concentration of total cholesterol, LDL cholesterol and triglycerides [Clodfelder et al. 2005]. Due to the properties that sensitize cells to insulin, resulting in accelerated weight loss, Cr (III) has been used as a component of dietary supplements supporting weight loss [Otag et al. 2014]. It is believed that supplementation with chromium (III) may be protective and prevent the development of neurodegenerative diseases [Leszek et al. 2019].

In general, supplementation with chromium (III) is considered safe. However high doses of chromium (III) are likely to limit the absorption of iron and zinc ions, and also affect the metabolism of calcium ions in bone. In recent years, information about the carcinogenic effect of chromium (III) has also appeared. In Poland, two values of the maximum permissible concentration (NDS) have been established for chromium and its compounds: 0.5 mg/m3 for metallic chromium, chromium (II) compounds and chromium (III) compounds converted to chromium, and 0.1 mg/m3 for chromates (VI) and dichromates (VI) converted to chromium (VI). The highest instantaneous concentration (STEL) for these compounds is 0.3 mg/m3.

2. AL – ALUMINUM

Aluminum is one of the most common metals on the planet. In the free state, this metal does not exist, it is very reactive, and its compounds are present in almost all rocks, surface waters and living organisms. The complex chemical properties of aluminum, regulating its mobility and the transition from solid to water phase, determine its important role in the environment. Under natural conditions, aluminum can be found in the form of sparingly soluble minerals – silicates and aluminosilicates. They are not harmful to humans, but different forms of aluminum speciation may have different properties. Some of them may be necessary for the proper functioning of living organisms, while others may show toxic properties. The lower the pH, the higher the aluminum concentration. Acidification of the soil below pH = 4.8 and the release of mobile aluminum into the soil solution results in the release of ionic aluminum into surface waters. The basic

forms of aluminum in waters are hydroxide, fluoride, sulfate and organic complexes. The water pH varies in the range of pH = 5-9, and at such a concentration of hydrogen ions, aluminum compounds are characterized by low solubility. In reservoirs with such a reaction, the aluminum concentration in most cases does not exceed 300 μg/l, and in river waters it does not exceed 64 μg/l on average [Widłak 2011]. Aluminum is also contained in plants, and its main source is soil, atmospheric dust and rainfall. From a dietary and medical point of view, it is important to test and control the content of this element. Plants grown on acidic soils can be characterized by very high concentrations of aluminum. An example of such a plant is tea, which accumulates 500-20,000 ppm of aluminum in its leaves, and spices such as marjoram, thyme and cumin. In animal organisms, aluminum is present in trace amounts. The highest content of this element is noticeable in the hard tissues of marine organisms (70-4500 ppm). The concentration of aluminum in animal organisms depends on its content in feed, water and other foods eaten by animals, and on the ability of tissues to accumulate aluminum [Gromysz-Kałkowska and Szubartowska 1999].

In the body of a healthy adult person, 50 to 150 mg of aluminum is present, 50% of which is in the skeleton, 25% in the lungs, and the rest is contained in soft tissues. The concentration of aluminum in the lungs increases with age. This is due to the deposition of solid and insoluble aluminum compounds that have entered the respiratory system. The amount of aluminum in brain tissue ranges from 0.5 mg/kg of brain weight and is twice as high in gray matter as in white matter. The content of Al3 + (as in the case of plants) increases with age – from 0.2 mg/kg in infants to 0.6-0.7 mg/kg in the elderly. The similarity of the Al3 + ion radius to the biologically active Fe3 + and Mg2 + ions is the reason for their substitution by aluminum and accumulation of this element in the human body. Aluminum metabolism is due to the physical and chemical similarities of iron and aluminum ions. After crossing the mucosal barrier, aluminum competes with iron for a binding site to transferrin – a protein that transports Fe3 + ions. Transferrin regulates the concentration of iron ions in blood plasma and transports them to the tissues. Saturated with iron ions, it binds to the transferrin receptor and through endocytosis, this complex is absorbed into the cell, where iron is released, and free transferrin returns to the cell membrane and to the bloodstream. In the same way, aluminum is transported to various tissues of the body, e.g. brain, liver, spleen, lungs, kidneys, bones. After the aluminum ion passes into the cytoplasm, it forms in the cytosol the so-called labile pool associated with citrates and other chelating agents. The degree of accumulation depends on the chemical form of aluminum, dose, time and type of exposure. Accumulation of aluminum in tissues is accompanied by the occurrence of changes in the concentration of bioelements, ie Ca, Fe, Mg,

Zn, Cu, which may interact with aluminum of a very different nature. The inability to reduce aluminum to a divalent ion prevents it from combining and storing with ferritin and penetrating into the mitochondria. Aluminum ions, on the other hand, can bind to molecules showing a stronger affinity for this metal than the cytosolic pool of chelates, e.g. ATP, GTP, phosphate anions, phosphate groups of cell membranes phospholipids, phosphorized proteins. The effects of these processes may cause disturbances in intracellular transmission, metabolism, secretory functions and cell growth [Fiejka, Długaszek, Alfreda, et al. 2001].

The influence of aluminum on the human body can be clearly described as toxic. Al3 + has been documented to be contributory in the pathogenesis of many diseases in dialysis patients. Donnan diaphragms used in dialysis machines do not eliminate aluminum as effectively as the kidneys, which is a problem for nephrologic patients. Movement coordination disorders, tremors, involuntary movements, myoclonus, dysarthria, and dysphasia are some of the direct symptoms of post-dialysis encephalopathy. The long-term symptom of this disorder is dementia, which has appeared as soon as 15 months after starting dialysis. Significantly elevated levels of aluminum have been found in the brain, muscles and bones of those who died as a result of this disease. The occurrence of sub-dialysis encephalopathy is influenced by the quality of the water used in dialysates and the damage to the blood-brain barrier. Already in the 1980s it was found that aluminum ions from water can diffuse into the blood plasma causing damage to the nervous system, and the penetration of ions through the blood-brain barrier depends on the degree of ionization of the compound, its lipid solubility and particle size. Subsequent studies have shown the great importance of the dynamics of aluminum penetration on brain and kidney function. The half-life of aluminum in blood serum is about 30 minutes, so its accumulation depends on the capacity of the kidneys. The described encephalopathy syndrome may also occur as a result of taking drugs containing aluminum, e.g. anti-acid agents containing Al (OH) 3. As a result of numerous studies and attempts to eliminate aluminum from drugs and dialysates, cases of encephalopathy are relatively rare [Gromysz-Kałkowska and Szubartowska 1999]. Amyotrophic lateral sclerosis and parkinsonism associated with senile dementia are other diseases that are largely considered to be caused by aluminum. The common feature of these diseases is neuronal atrophy, degeneration of neurofibrils, lymphopenia, and T lymphocyte dysfunction. Magnetic resonance imaging studies indicate aluminum accumulation within the hippocampus [Zabłocka 2006]. It is likely that aluminum is also an etiological factor in classical Parkinson's disease. Proponents of this theory argue, *inter alia*, that 30-50% of Parkinsonism sufferers concurrently suffer from Alzheimer's disease, and extrapyramidal disorders occur in 60% of patients with Alzheimer's

dementia. The role of aluminum in Alzheimer's disease has been the subject of much research. It is believed that aluminum may act as an environmental factor in accelerating disease progression. Histological examinations of the brains of people who died as a result of neurodegenerative processes show a higher level of aluminum in places affected by degenerative changes.

3. NI – NICKEL

Nickel is another of the basic elements found as part of the Earth's crust, at an average concentration of about 75 μg/g. It is a metallic element with high electrical and thermal conductivity, resistant to corrosion at ambient temperatures ranging from -20° C to + 30° C, therefore it is often electroplated as a protective coating [Chau and Cordeiro 1995]. Although it has an oxidation state of -1, 0, +1, +2, +3 and +4, it exists mainly in the divalent state (Ni2 +) and is an environmentally stable form. Nickel is an essential element in the organisms of animals, microorganisms, plants, and is an important component of enzymes and proteins. In acetogenic bacteria, the reduction of carbon monoxide to acetate depends on nickel, which is needed for the activation and synthesis of carbon monoxide dehydrogenase [Drake 1982]. Nickel is essential for the active synthesis of urease in plant cells.

High nickel concentrations inhibited the formation of IAA, tryptophan and at the same time promoted the formation of phenolic and terpenoid inhibitors [Tikhomirov, Kuznetsova, and Magina 1987]. S.U. Khan and A. Moheman reported that nickel interacts with iron in hemoglobin and helps in oxygen transport and stimulates metabolism [Khan and Moheman 2006]. Nickel is involved in the transmission of the genetic code (DNA, RNA) and is also present in some enzyme systems that metabolize sugars. Nickel can replace calcium in the process of excitation and binding to membrane ligands such as phospholipid phosphate groups in the process of nerve transmission and muscle contraction [Howard 2003]. Nickel exists in human and rabbit sera in three forms, namely ultrafiltrable ligand-bound nickel, albumin-bound nickel, and macroglobulin-bound nickel. Albumin is the major nickel transport protein in human, rat and bovine serum. A metalloprotein called nickeloplasmin was isolated from the sera of rabbits (α-2 macroglobulin) and humans (α-glycoprotein).[1] Ultrafiltrable nickel-binding ligands play an important role in extracellular transport and in the elimination of nickel in the urine. L-histidine has been identified as a low molecular weight nickel binding component in human serum that has a greater affinity for nickel than serum albumin. The L-histidine-nickel complex was found to be

[1] U. S. Public Health Service (USPHS), Toxicological profile for nickel, U.S. Public health service, Agency for toxic substances and disease registry, Atlanta, Georgia 1993, p. 158.

smaller in molecular size than the albumin-nickel complex which mediates transport across a biological membrane due to the balance between the two nickel molecules. Nickel exchange and transfer between L-histidine and albumin appears to be mediated by the nickel albumin ternary complex L-histidine [Sigel and Sigel 1988]. Nickel is also an essential element for humans [Wintz, Fox, and Vulpe 2002]. H.A. Schnegg and M. Kirchgessner reported that nickel deficiency in rats led to a decrease in organ iron, a decrease in hemoglobin and hematocrit, and anemia [Schnegg and Kirchgessner 1980]. M.M. King, K.K. Lynn, and C.Y. Huang suggested that nickel may serve as a cofactor for the activation of calcineurin, the calmodulin-dependent phosphoprotein phosphatase [King, Lynn, and Huang 1985]. Nickel plays an important role in the action or formation of cGMP, a signaling factor that regulates various physiological processes such as blood pressure control, sperm physiology, sodium metabolism, and cardiovascular health. Nickel is permanently present in RNA and binds to several biological substances such as proteins (keratin, insulin), amino acids and serum albumin. It also activates enzymes such as arginase, trypsin, acetyl coenzyme A, carboxylase, and synthetase [Yokoi, Uthus, and Nielson 2002]. Nickel is an element that occurs naturally in soil, water, air and biological materials. It is a natural component of the earth's crust and is found in igneous rocks [Chauhan, Thakur, and Sharma 2008]. Natural sources of nickel are ashes from volcanic emissions and the weathering of rocks and soils. Inorganic fertilizers, in particular phosphorus fertilizers, are characterized by a variable level of nickel depending on their resources. Some of the atmospheric nickel entering the environment comes from meteorite dust, smoke particles from forest fires, volcanic ash and soil dust [Ross 1994].

Although nickel is ubiquitous and essential for the functioning of many organisms, its concentrations in some areas, due to both anthropogenic release and its naturally varying levels, can be toxic to living organisms [Czarnek, Terpiłowska, and Siwicki 2019]. Wastewater discharged from electroplating, electronics and metal cleaning industries often contains high concentrations of nickel ions and causes various types of acute and chronic environmental disturbances [Akhtar et al. 2004]. In humans, nickel is known to damage the liver, kidneys, spleen, brain and tissues.[2] Nickel causes embryotoxic and nephrotoxic effects, allergic reactions and contact dermatitis.[3] Nickel sensitization also occurs in the general population through exposure to coins, jewelry, watches and clothing. It causes conjunctivitis, eosinophilic pneumonia, asthma, and local or systemic reactions to nickel-containing joint prostheses [Hostynek and Maibach 2002]. Nickel compounds are

[2] International Programme on Chemical Safety (IPCS), Environmental Health Criteria, Nickel, World Health Organization, Geneva 1992, p. 108.

[3] EPA, Nickel and nickel compound. Poll. Prevent. Fact Sheet, 96 (2002), p. 1-2.

carcinogenic to humans.[4] M.M. Matlock, B.S. Howerton, and D.A. Atwood observed the transformation of neoplastic cells, which includes DNA damage resulting from mutations induced by the hydroxyl radical or other oxidizing species [Matlock, Howerton, and Atwood 2002]. Acute exposure of human lungs to nickel causes pathological changes in the lungs, hemorrhages, edema, degeneration of the bronchial epithelium, and pulmonary fibrosis. Nickel compounds have been found to cross the mammalian placental barrier and affect the fetus [Sunderman, Sullivan, and Krieger 2001]. Nickel is a potent animal teratogen. Inhalation of and exposure to nickel carbonyl compounds in rats and hamsters have been found to result in fetal death, reduced weight gain, and eye malformations [Sevin 1980]. In Poland according to the Regulation of the Minister of Agriculture and Rural Development of March 21, 2002, the permissible nickel concentration in light soil is 30 mg/kg dry weight, in medium-heavy soil 50 mg/kg dry weight, and in heavy soil 75 mg/kg dry weight. For drinking water, the standard is 20 μg/l for nickel and it is defined in Council Directive 98/83/EC. The WHO established the Tolerable Daily Intake (TDI) of 11 μg nickel/kg body weight and based on this derived an indicative value of nickel content for drinking water of 70 μg nickel/l. The EFSA Scientific Panel on Dietetic Products, Nutrition and Allergies concluded that it is not possible to establish a tolerable upper limit for the intake of nickel from food.

4. FE − IRON

Iron is the fourth most abundant element that comprises the Earth's crust. Iron, which constitutes less than 0.01% of the total human body weight (about 4 g in an adult male) is an element without which a human being could not live [Ganz and Nemeth 2012]. This metal participates in many biochemical and physiological processes, thanks to which it is possible, among others, to such processes as: oxygen transport, DNA synthesis and electron transport. Iron is a component and is necessary for the synthesis of many proteins involved in these processes. Hemoglobin and myoglobin are proteins involved in the transport and storage of oxygen. They contain a prosthetic heme group, which forms a complex with centrally located iron that can bind or release oxygen. Oxygen transport seems to be one of the most important processes in which iron plays an important regulatory role. However, it is not the only important process in which it participates. Iron is essential for the proper neurological development of infants and

[4] National Academy of Sciences (NAS), Medical and biological effects of environmental pollutants, Nickel, National Research Council, National Academy of Sciences, Washington 1975, p. 277.

children. This element is needed in the processes of myelination of neurons, neurogenesis and differentiation of brain cells, which can affect sensory systems, learning, memory and behavior. In addition, iron is also a cofactor of enzymes that synthesize neurotransmitters in the brain [Iannotti, Tielsch, Black, et al 2006; Beard 2008, Baker, Greer, and The Committee on Nutrition 2010]. Maintaining the correct range of values of stored iron in the body is necessary to maintain the proper functioning of all tissues. For example, both a deficiency and an excess of iron adversely affect the function of the body's immune system. Both innate immunity cells (granulocytes, monocytes, macrophages) and acquired immunity cells (T and B lymphocytes) need adequate iron availability to function properly. Under conditions of deficiency, these processes are impaired and the response to pathogens weakened [Ward, Crichton, Taylor, et al. 2011]. On the other hand, iron is an excellent medium for pathogenic microorganisms, necessary for their multiplication and the development of infection. Therefore, the excess of this element is unfavorable in the fight against the disease [Ganz 2018].

Taking into account the functions described above, iron should be considered as an element favorable to human physiology. The face of iron, however, is ambiguous. Iron excess and its unbound form (ferric ion, Fe2 +) is toxic to many tissues because due to its wide range of redox potentials, it has the ability to form a hydroxyl radical and many others, which in turn can damage proteins, DNA and lipids [Chifman, Laubenbacher, and Torti 2014]. Due to the fact that iron is necessary, and at the same time can be toxic to humans, our body has mechanisms that allow for very strict control of the level of this element. The concentration of iron in the body is subject to very complex and precise regulatory processes, which, unfortunately, sometimes fail, often due to our own fault. Currently, there are two levels of regulation of iron metabolism: at the systemic and intracellular levels. In a well-nourished adult, the iron level in the body fluctuates around 3-5 g, which is about 45 mg Fe/kg body weight in women and 55 mg Fe/kg body weight in men [Milto, Suhodolo, Prokopieva, et al. 2016]. The largest part of the iron (60%) is in the blood bound to hemoglobin – in red blood cells and bone marrow, while 10% is the iron bound to myoglobin in the muscle. The rest of it is concentrated mainly in hepatocytes and macrophages [Chifman, Laubenbacher, and Torti 2014]. The daily iron requirement of man is 20-25 mg. Iron is obtained by humans in two ways: exogenous, through the absorption of dietary iron, and endogenous, as a result of iron reutilization. For example, the process of iron recovery from macrophage phagocytic erythrocytes allows an adult to recover 20-30 mg of iron. This amount is sufficient to ensure the daily needs of the body for the process of erythropoiesis and others [Muckenthaler, Rivella, Hentze, et al. 2017]. Absorbing iron from the diet is not such an efficient process. The diet provides about

10-20 mg of iron daily, of which only about 10% is absorbed. Such a small amount, however, is sufficient to provide a person's daily iron requirement, which compensates for the iron that is lost from the body through sweat, blood, and exfoliating intestinal epithelium. The restriction of excess iron absorption is a very important process, because apart from a small amount of iron that is excreted from the body with sweat or exfoliating epithelium and with blood, in mammals there is no physiological way to remove excess iron from the body. Therefore, disturbances in its metabolism and excessive supply of dietary iron lead to its accumulation and toxicity. The daily recommended dietary allowances (RDA) of iron for all age groups of men and postmenopausal women is 8 mg/day; The RDA for premenopausal women is 18 mg/day.

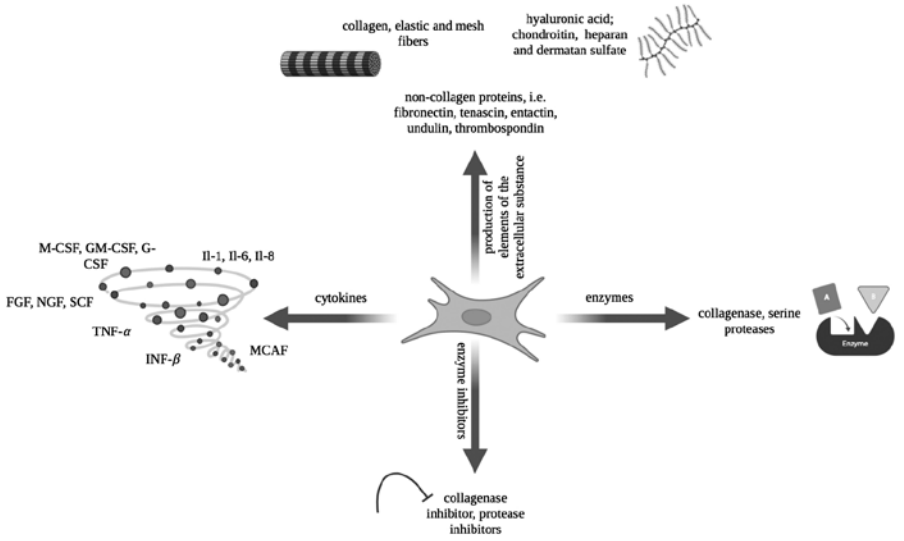
5. THE INFLUENCE OF THE ELEMENTS CR, NI, AL, AND FE ON HUMAN FIBROBLASTS

Fibroblasts are animal cells that originate in the mesoderm i.e., the middle layer of calls in the embryo. They are the most numerous groups of connective tissue cells. They have a round cell nucleus with a well-defined nucleolus. Two forms of fibroblasts can be distinguished: active – the presence of a rough cellular reticulum, and inactive (fibrocytes) – smaller, with a reduced cellular reticulum [Brzezińska-Błaszczyk and Zalewska 1997]. The diversity of fibroblasts is related to a particular organ, but they can also be found within a specific anatomical space. The types and short characteristics of fibroblasts are shown in the Table 1 below.

Tab. 1. Characteristics of different types of human fibroblasts.

Type of fibroblasts	Characteristics	Ref.
Myofibroblasts	Cells arising from mesenchyme; modified fibroblasts having the characteristics of smooth muscle cells (ability to contract); numerous actin filaments are present in the cytoplasm.	[Gabbiani 1992; Hinz et al. 2007]
Fibrocytes	Reduced form of fibroblast with reduced metabolic activity; they have elongated call nuclei and eosinophilic cytoplasm. Fibrocytes are circulating mesenchymal progenitor cells that participate in tissue responses to injury and invasion.	[Sawicki 2008, Herzog and Bucala 2010]
Melanophores	A variety of fibroblasts filled with melanin grains by endocytosis; contain melanin pigment produced by melanocytes of the epidermis.	[Sawicki 2008; Logan et al. 2006; Sugden et al. 2004]

Ryc. 1. Graphic illustration of substances produced by fibroblasts [Brzezińska-Błaszczyk and Zalewska 1997; Marklund 1992; Daghigh et al. 2002; Asp et al. 2011].



Chromium is one of the most debatable transition metals, and its role in the human body is constantly being replenished [Vincent 2010]. Recent publications oscillate around the functions concerning Cr (III) however, it can be regarded as an essential micronutrient, and its action should be largely considered as a pharmacological effect [Piotrowska et al. 2018]. Chromium (III) can cause DNA damage and inhibit the DNA relaxation activity of topoisomerases in bacteria [Fathima and Rao 2018]. However, chromium also exists in another valence state i.e., Cr (VI) which is widely used in various industries [Wang et al. 2017]. Cr (III) salts are used as dietary supplements and are believed to be about 100 times less toxic compared to Cr (VI) [Kumar and Gangwar 2012].

The cytotoxicity of chromium complexes varies by ion and ligand environment. Sharivastava et al. in their study on dermis fibroblasts confirmed that [Cr(en)3]3+, a triple-charged cation inhibits cell proliferation, causes morphological changes (damage to the cell nucleus), and TEM (Transmission Electron Microscopy) analysis showed intracellular damage to fibroblasts in terms of formation of apoptotic bodies and chromatin condensation which is directly related to cell death [Shrivastava et al. 2005]. In an *in vitro* study by Bidermann et al., it was reported that Cr (III) induced anchorage-independent growth in a dose-dependent manner in cultured diploid human fibroblasts [Biedermann and Landolph 1990]. Although it was found that Cr (VI) compounds were significantly more cytotoxic and mutagenic than Cr (III) compounds tested.

Nickel is a transition metal that is characterized by incomplete filling of electro shells. It follows from the above that nickel has catalytic properties i.e., it accelerates certain chemical reactions without being part of the newly formed compound and is additionally able to form complex compounds [Śpiewak and Piętowska 2006]. In addition, nickel is the central atom of ureases (enzymes found in plants, bacteria, mycoplasmas, fungi, yeast), as well as bacterial enzymes such as hydrogenases, coenzyme M methyl reductase involved in methane biogenesis, and carbon monoxide dehydrogenase involved in the formation of the acetate group ibid.].

Studies attempting to determine the effect of nickel on fibroblasts rely heavily on nickel-titanium (NiTi) alloy. This alloy, used in implants, has been studied since the 1980s [Ponsonnet et al. 2002]. It is currently used in orthopedics and orthodontics. More than a dozen in vitro studies of the response of fibroblasts to NiTi application have been conducted. A study by Castleman and Motzkin suggest that NiTi significantly reduces cell growth in human fetal fibroblasts and modifies cell morphology [Castleman and Motzkin 1981]. Another study by Putters et al. contradicts Castelman and Motzkin's reports, as no inhibition of human fibroblast motility by NiTi was observed [Putters, Kaulesar Sukul, de Zeeuw, et al. 1992]. In another study to investigate the effects of nickel and chromium dental alloys on viability and morphology in cultured human gingival fibroblast cell, it was found that metal ions released from all metal alloys (nickel-based alloys, high and low chromium alloys with and without beryllium) completely inhibited G-6-PDH (Glucose-6-phosphate dehydrogenase) activity and reduced ATP levels in cultured cells. The results obtained confirmed the hypothesis that metal ions released from dental nickel-based alloys interfere with cellular energy metabolism [Bumgardner, Doeller, and Lucas 1995]. Exposure to nickel which was associated with changes in fibroblast activation was also investigated. Nickel has been linked to H2S, a compound involved in numerous cellular signal transduction and pathophysiological responses. The above study showed that a lower dose of nickel (200um) induced activation of human fibroblasts, as evidenced by increased cell growth, migration and higher expression of smooth muscle actin and fibronectin. In contrast, a high dose of nickel (1nM) inhibited cell viability [Racine et al. 2018]. In general, nickel decreased intracellular thiol content and stimulated oxidative stress, and inhibited mRNA and cystathionine gamma-lyse protein expression.

Aluminum is one of the most prevalent elements, accounting for about 8% of the total elemental mass [Widłak 2011]. In the human body it usually occurs in trace amounts (50-150 mg), accumulating to the greatest extent in the bones and lungs. The accumulation of aluminum in the human body is low, as it is removed 90% with urine. Nevertheless, it can interfere with metabolic processes i.e., it blocks enzymes activated by calcium and magnesium

ions, hinders cell division, and degrades nerve fibers [Zuziak and Jakubowska 2016].

The concentrations of aluminum (1-25 g/l) found in most sources of drinking water available for human consumption are sufficient to induce up to a significant level of accumulation of this element depending on the level of exposure [Anane and Creppy 2001]. In a study conducted by Anane et al. showed that skin exposure to low doses of aluminum chloride for 18 weeks leads to aluminum accumulation in the brain [Anane et al. 1995]. It was important to study the impact of analyzing biological responses induced in human fibroblasts. In a study conducted by Nowakowska et al. injectable hemostatic agents based on aluminum chloride, aluminum sulfate and iron sulfate on human gingival fibroblasts (HGF), no reduction in fibroblast viability or proliferation or significant cytoskeletal reorganization was observed. Moreover, the injected hemostatic agents showed biocompatibility with HGF suggesting their potential clinical utility in gingival margin retraction [Nowakowska et al. 2021].

Iron is a common element in the environment. In living organism, it occurs mainly in bound form. The main reservoir of iron (4g of iron in the adult body) are erythrocytes i.e., 75% of the mentioned amount in the form of hemoglobin [Górska and Piech 2018]. In addition, iron supports the immune and nervous systems and has antioxidant effects. However, the most important role of iron is to enable heme molecules to bind oxygen and transport it to all cells in the body [Konturek 2000]. As a trace element and transition metal it is essential in many anabolic processes of cell proliferation and differentiation, protein synthesis and post-translational modifications of procollagen necessary to stabilize collagen molecules [Wlaschek et al. 2019].

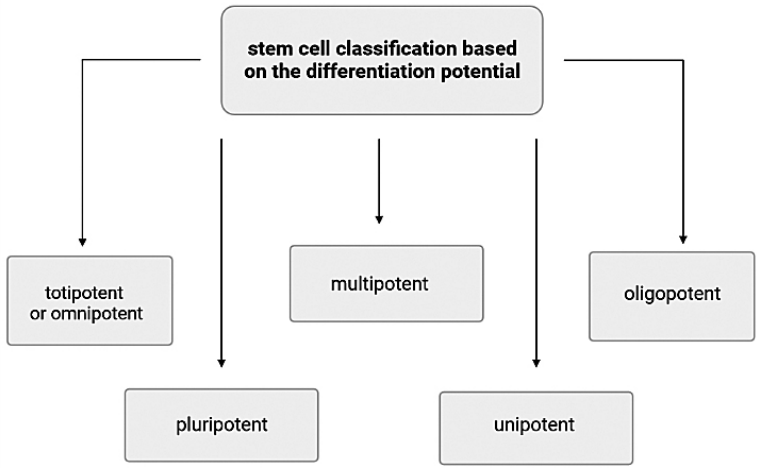
Iron accumulates age-dependently in tissues in vivo and is associated with the pathology of many age-related diseases. The molecular basis of this change may be related to the loss of iron homeostasis at the cellular level. Accordingly, changes in iron content in primary human fibroblasts were studied in vitro as a model of cellular aging. The results shown indicate that iron accumulation occurs during physiological cellular aging in vitro and may contribute to increased oxidative stress and dysfunction in aging cells [Killilea et al. 2003]. Another study examined mouse fibroblasts treated with a pulse of 100 m H2O2 for 1 hour, which proved that the above parameters are sufficient to alter the critical parameters of iron in a time-dependent manner. The applied stimulus inhibits ferritin synthesis for about 8 hours, leading to a decrease in ferritin activity in cells by about 50%. Additionally, treatment with H2O2 induces an increase in mRNA levels, which is associated with a significant increase in cell surface TfR expression, increased

binding to fluorescein-labeled transferritin, and stimulation of iron via transferrin into cells [Caltagirone et al. 2001].

6. THE INFLUENCE OF THE ELEMENTS CR, NI, AL, AND FE ON HUMAN STEM CELLS

Stem cells are defined as undifferentiated cells that are characterized by self-renewal, clonality, and potency. However, these properties may vary between different stem cells [Kolios and Moodley 2013]. As they are able to renew their populations and differentiate into multiple cell lineages, they take part in organ and tissue systems development and regeneration [Weissman 2000]. Based on their differentiation potential, stem cells may be categorized into 5 types which are presented in the graph below [Smith 2006].

Ryc. 2. Graphic illustration of stem cell classification based on their differentiation potential [Smith 2006].



While totipotent or omnipotent cells can differentiate into embryonic and extraembryonic tissues, pluripotent cells can differentiate into any of the three germ layers. In addition, both multipotent and oligopotent stem cells can differentiate only in a closely related family of cells or cell types. Unipotent stem cells may differentiate only into one cell type [Ilic and Polak 2011].

As it comes to their origin, they can be divided into embryonic stem cells (ESCs), fetal and adult stem cells, and induced pluripotent stem cells (iPSCs) [Ilic and Polak 2011; Bongso and Richards 2004]. While ESCs and iPSCs are pluripotent, adult stem cells are usually oligo- or unipotent [Ilic and Polak 2011].

Hexavalent chromium [Cr(VI)], which is the most toxic form, was shown to be cytotoxic and impaired the physiological functions of mouse spermatogonial stem cells (SSCs) and male somatic cells. Due to oxidative stress and subsequent mitochondrial damage, Cr(VI) induced the mitochondria-dependent apoptosis in above-mentioned cells. In addition, disruption in the differentiation and self-renewal mechanisms of SSCs was also observed [Das, Kang, Kim, et al. 2015].

Tet family dioxygenases (Tet1, Tet2, and Tet3) are key enzymes that are responsible for mammalian DNA demethylation [Shen, Song, He, et al. 2014]. Yin et al. showed that nickel(ii) may inhibit the oxidation of DNA 5-methylcytosine (5mC) by 2-oxoglutarate-dependent Tet dioxygenases in somatic cell lines and mouse embryonic stem cells. This inhibition was observed due to the significant decrease in 5-hydroxymethylcytosine which is a critical intermediate that resulted from the 5mC oxidation. In addition, it was suggested that nickel exposure may result in DNA demethylation reduction and cause changes in the methylation status of specific genes [Yin, Mo, Dai, et al. 2018]. Previous studies demonstrated that ascorbic acid enhanced the catalytic activity of Tet dioxygenases for the 5mC oxidation thus promoting DNA demethylation in mammals. Furthermore, its combination with 2i (PD 0325901 and CHIR 99021) appeared to stimulate mouse embryonic stem cells to stay in a naïve or ground pluripotency state [Yin, Mao, Zhao, et al. 2013]. Interestingly, Yin et al. results from 2018 suggested that nickel(II) ions inhibit AA-induced DNA demethylation in these cells [Yin, Mo, Dai, et al. 2018].

Octamer binding protein 4 (OCT4) is a transcription factor responsible for reprogramming somatic cells into pluripotent stem cells [Zhao, Sun, Young, et al. 2013; Takahashi and Yamanaka 2006]. It is also a master regulator of proliferation and self-renewal of embryonic stem cells [Niwa, Miyazaki, and Smith 2000]. Yao et al. examined the nickel effect on the expression of OCT4 cell factor in embryonic Tera-1 cells and stem cells. It was suggested that Ni(II) exposure was associated with the increase in the OCT4 expression due to protein stabilization. Moreover, it was shown that the exposure resulted in ROS production which led to OCT4 stabilization mediated by post-translational modifications [Yao, Lu, Chen, et al. 2014].

Nam et al. investigated aluminum effects on neural stem cells, proliferating cells, differentiating neuroblasts, and mature neurons in the hippocampal dentate gyrus of mice. It was suggested that aluminum plays an inhibitory role in neural stem cells, cell proliferation, and neuroblast differentiation via oxidative stress. However, aluminum exposure did not cause any changes to mature neurons [Nam, Kim, Yoo, et al. 2016].

In addition, aluminum oxide nanoparticles (ANPs) showed dose-dependent cellular toxicity in human mesenchymal stem cells (hMSCs). It

was also mediated through an increase in oxidative stress through the ROS generation. Moreover, ANPs exposure was shown to upregulate stress-related genes expression and downregulate the expression of several antioxidant enzymes. As a result, the enhancement in the production of free radicals in hMSCs was obtained [Alshatwi, Subbarayan, Ramesh, et al. 2013].

Iron-loaded conditions may cause an increase in the generation of reactive oxygen species (ROS) resulting in the intracellular redox homeostasis dysregulation [Mehta, Farnaud and Sharp 2019]. These changes can stimulate signalling pathways leading to mesenchymal stem cells (MSCs) cycle arrest in G0/G1 phase, apoptosis and reduced proliferation of the cells [Zhang, Zhai, Zhao, et al. 2015]. The use of exogenously administered iron chelators and antioxidant protected the iron-loaded MSCs and reversed the negative effects caused by iron excess [ibid.]. Interestingly, iron accumulation was shown to decrease the mineral density of bone due to MSC quantity inhibition in the bone marrow. However, the iron chelator, deferoxamine, rescued the iron-induced suppression of bone marrow MSCs [Yuan, Xu, Cao, et al. 2019].

REFERENCES

Akhtar, Nasreen, et al. 2004. "Removal and recovery of nickel(II) from aqueous solution by loofa sponge-immobilized biomass of Chlorella sorokiniana: characterization studies." *Journal of hazardous materials* 108, no. 1-2:85-94. Doi: 10.1016/j.jhazmat.2004.01.002

Alshatwi, Ali A., Periasamy V. Subbarayan, E. Ramesh, et al. 2013. "Aluminium oxide nanoparticles induce mitochondrial-mediated oxidative stress and alter the expression of antioxidant enzymes in human mesenchymal stem cells." *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*. 30, no. 1:1-10. Doi:10.1080/19440049.2012.729160

Anane, Rachid, et al. 1995. "Bioaccumulation of water-soluble aluminum chloride in the hippocampus after transdermal uptake in mice." *Arch Toxicol*. 69, no. 8:568-71. Doi: 10.1007/s002040050214

Anane, Rachid, and E. E. Creppy. 2001. "Lipid peroxidation as pathway of aluminum cytotoxicity in human skin fibroblast cultures: Prevention by superoxide dismutase+-catalase and vitamins E and C." *Human & Experimental Toxicology* 20:477-81.

Asp, Linnea, et al. 2011. "Effect of pro-inflammatory cytokines on expression of kynurenine pathway enzymes in human dermal fibroblasts." *Journal of Inflammation* 8, no. 25. Doi: 10.1186/1476-9255-8-25

Baker, R. D., F. R. Greer, and The Committee on Nutrition. 2010. "Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age)." *Pediatrics* 126:1040-1050.

Beard, John L. 2008. "Why iron deficiency is important in infant development." *J. Nutr.* 138:2534-536.

Biedermann, K. A. and J. R. Landolph. 1990. "Role of valence state and solubility of chromium compounds on induction of cytotoxicity, mutagenesis, and anchorage independence in diploid human fibroblasts." *Cancer Res.* 50, no. 24:7835-842. PMID: 2253225.

Bongso, Ariff, and Mark Richards. 2004. "History and perspective of stem cell research." *Best Pract Res Clin Obstet Gynaecol.*18, no. 6:827-42. Doi: 10.1016/j.bpobgyn.2004.09.002

Brzezińska-Błaszczyk, Ewa and Anna Zalewska. 1997. "Mastocyty i fibroblasty – obojętni sąsiedzi czy przyjaźni partnerzy?" *Postępy Biologii Komórki* 24, no. 2:127-43.

Bumgardner, J., and J. Doeller, and L. C. Lucas. 1995. "Effect of nickel-based dental casting alloys on fibroblast metabolism and ultrastructural organization." *Journal of Biomedical Materials Research* 29, no. 5:611-17. Doi: 10.1002/jbm.8202900508

Caltagirone, Annie, et al. 2001. "Modulation of cellular iron metabolism by hydrogen peroxide effects of H2O2 in the expression and function of iron – responsive element-containing mRNAs in B6 fibroblasts." *Metabolism and Bioenergetics* 276, no. 23:P19738-19745. Doi: 10.1074/jbc.M100245200

Castleman, L, and S. Motzkin. 1981. *Biocompatibility of clinical implants materials*. Boca Raton, FL: CRC press.

Chau, Y. K. and O. T. R. K. Cordeiro. 1995. „Occurrence of nickel in the Canadian environment." *Environ. Rev.* 3:95-120.

Chauhan, S. S., R. Thakur, and G. D. Sharma. 2008. „Nickel: its availability and reactions in soil." *J. Indl. Polln. Ctrl.* 24, no. 1:57-62.

Chifman J., R. Laubenbacher, and S. V. Torti. 2014. "A systems biology approach to iron metabolism." *Adv. Exp. Med. Biol.* 844:201-25.

Clodfelder, Buffie J., et al. 2005. "Oral administration of the biomimetic [Cr3O(O2C-CH2CH3)6(H2O)3]+ increases insulin sensitivity and improves blood plasma variables in healthy and type 2 diabetic rats." *Journal of biological inorganic chemistry: JBIC: a publication of the Society of Biological Inorganic Chemistry* 10, no. 2:119-30. Doi:10.1007/s00775-004-0618-0

Costello, Rebecca B., et al. 2016. "Chromium supplements for glycemic control in type 2 diabetes: limited evidence of effectiveness." *Nutrition Reviews* 74, no. 7:455-68. Doi:10.1093/nutrit/nuw011

Czarnek, Katarzyna, and Andrzej K. Siwicki. 2021a. "Influence of chromium (III), cobalt (II) and their mixtures on cell metabolic activity." *Current Issues in Pharmacy and Medical Sciences* 34, no. 2:87-93. Doi: 10.2478/cipms-2021-0019

Czarnek, Katarzyna, and Andrzej K. Siwicki. 2021b. "Genotoxicity of chromium (III) and cobalt (II) and interactions between them." *Current Issues in Pharmacy and Medical Sciences* 34, no. 3:142-48. Doi: 10.2478/cipms-2021-0021

Czarnek Katarzyna, Sylwia Terpiłowska, and Andrzej K. Siwicki. 2019. "Genotoxicity and mutagenicity of nickel(II) and iron(III) and interactions between these microelements." *Trace Elements and Electrolytes* 36:17-24. Doi: 10.5414/TEX01545

Daghigh, Farzaneh, et al. 2002. "Human gingival fibroblasts produce nitric oxide in response to proinflammatory cytokines." *Journal of Periodontology* 73, no. 4:392-400. Doi: 10.1902/jop.2002.73.4.392

Das, J., M. H. Kang, E. Kim, et al. 2015. "Hexavalent chromium induces apoptosis in male somatic and spermatogonial stem cells via redox imbalance." *Sci Rep*. 5:13921. Doi:10.1038/srep13921

Drake, Harold L. 1982. "Occurrence of nickel in carbonmonoxide dehydrogenase from Clostridium pasteurianum and Clostridium thermoaceticum." *Journal of Bacteriology* 149, no. 2:561-66.

Fathima, Aafreen, and Jonnalagadda R. Rao. 2018. "Is Cr (III) toxic to bacteria: Toxicity studies using Bacillus subtilis and Escherichia coli as model organism." *Archives of Microbiology* 200:453-62. Doi: 10.1007/s00203-017-1444-4

Fiejka, M, M. Długaszek, G. Alfreda, et al. 2001. *Med. Dośw. Mikrobiol.* 53:102-106.

Gabbiani, Giulio. 1992. "The biology of the myofibroblast." *Kidney International* 41, no. 3:530-32. Doi: 10.1038/ki.1992.75

Ganz, T., and E. Nemeth. 2012. "Iron metabolism: in- teractions with normal and disordered erythro- poiesis." *Cold Spring Harb. Perspect. Med.* 2. Doi: 10.1101/cshperspect.a011668

Ganz, T. 2018. "Iron and infection." *Int. J. Hema- tol.* 107:7-15.

Górska, Anna, and Robert Piech. 2018. "Właściwości i znaczenie żelaza oraz metody jego oznaczania." *Analit* 6:2-9.

Gromysz-Kałkowska, Kazimiera, and Ewa Szubartowska. 1999. *Glin – występowanie w przyrodzie oraz wpływ na organizmy roślin, zwierząt i człowieka*. Lublin: Wydawnictwo UMCS.

Herzog, Erica, and Richard Bucala. 2010. "Fibrocytes in health and disease." *Experimental Hematology* 38, no. 7:548-56. Doi: 10.1016/j.exphem.2010.03.004

Hinz, Boris, et al. 2007. "The myofibroblasts: One function, multiple organs." *The American Journal of Pathology* 170, no. 6:1807-816. Doi: 10.2353/ajpath.2007.070112

Hostynek, J. J., and H. I. Maibach. 2002. *Nickel and the skin*. Boca Raton: CRC Press.

Howard, H. 2003. *The environment and human health*. Ed. Michael Mc. Cually, MIT Press.

Iannotti, L. L., J. M. Tielsch J. M., M. M. Black, et al., 2006. "Iron supplementation in early childhood: health benefits and risks." *Am. J. Clin. Nutr.* 84:1261-276.

Ilic, D., and J.M. Polak. 2011. "Stem cells in regenerative medicine: introduction." *Br Med Bull.* 98:117-26. Doi:10.1093/bmb/ldr012

Khan, Safi U., and Abdul Moheman. 2006. "Effect of heavy metals (cadmium and nickel) on the seed germination, growth and metals uptake by chilli (Capsicum frutescens) and sunflower plants (Helianthus annus)." *Pollution Research* 25, no. 1:99-104.

Killilea, David, et al. 2003. "Iron accumulation during cellular senescence in human fibroblasts in vitro." *Antioxidants and Redox Signaling* 5.5: 507-16.

King, M. M., K.K. Lynn, and C. Y. Huang. 1985. In *Progress in Nickel Toxicology*, edited by S. S. Brown, and F. W. Sunderman Jr., 117-20. Oxford: Blackwell.

Matlock, M.M., B.S. Howerton, and D. A. Atwood, 2002. "Chemical precipitation of heavy metals from acid mine drainage." *Water Res.* 36:4757-764.

Kolios, George, and Yuben Moodley. 2013. "Introduction to stem cells and regenerative medicine." *Respiration*. 85 (1):3-10. doi: 10.1159/000345615

Konturek, Stanisław. 2000. *Fizjologia człowieka, układ trawienny i wydzielanie wewnętrzne*. Kraków: Wydawnictwo Uniwersytetu Jagiellońskiego.

Kumar, Dharmendra, and Satya P. Gangwar. 2012. "Role of antioxidants in detoxification of Cr (VI) toxicity in laboratory rats." *J. Environ Sci Eng.* 54 (3):441-46. PMID: 24749208.

Leszek, Jerzy, et al. 2017. "Type 3 Diabetes Mellitus: A Novel Implication of Alzheimers Disease." *Current topics in medicinal chemistry* 17, no. 12:1331-335. Doi: 10.2174/1568026617666170103163403

Logan, Darren, et al. 2006. "Regulation of pigmentation in zebrafish melanophores." *Pigment Cell Research* 19 (3):206-13. Doi: 10.1111/j.1600-0749.2006.00307.x

Lukaski, Henry C., et al. 2007. "Chromium picolinate supplementation in women: effects on body weight, composition, and iron status." *Nutrition (Burbank, Los Angeles County, Calif.)* 23, no. 3:187-95. Doi: 10.1016/j.nut.2006.12.001

Marklund, Stefan. 1992. "Regulation by cytokines of extracellular superoxide dismutase and other superoxide dismutase isoenzymes in fibroblasts." *Journal of Biological Chemistry* 267 (10):6696-701. Doi: 10.1016/S0021-9258(19)50482-3

Mehta, K.J., S. J. Farnaud, and P. A. Sharp. 2019. "Iron and liver fibrosis: Mechanistic and clinical aspects." *World J Gastroenterol.* 25 (5):521-38. Doi: 10.3748/wjg.v25.i5.521

Milto I. V., I. V. Suhodolo, V. D. Prokopieva, et al. 2016. "Molecular and Cellular Bases of Iron Metabolism in Humans." *Biochemistry* 81:549-64.

Muckenthaler M. U, S. Rivella, M. W. Hentze, et al. 2017. "A Red Carpet for Iron Metabolism." *Cell.* 168 (3):344-61. Doi: 10.1016/j.cell.2016.12.034

Nam, S.M., J. W. Kim, D. Y. Yoo, et al. 2016. "Effects of aluminum on the reduction of neural stem cells, proliferating cells, and differentiating neuroblasts in the dentate gyrus of D-galactose-treated mice via increasing oxidative stress." *J Vet Sci.* 17 (2):127-36. Doi: 10.4142/jvs.2016.17.2.127

Niwa, H., J. Miyazaki, and A. G. Smith. 2000 ."Quantitative expression of Oct-3/4 defines differentiation, dedifferentiation or self-renewal of ES cells." *Nat Genet*. 24 (4):372-76. Doi: 10.1038/74199

Nowakowska, Danuta, et al. 2021. "Biological response induced in primary human gingival fibroblasts upon exposure to various types of injectable astringent retraction agents." *Materials* 14 (8):2081. Doi: 10.3390/ma14082081

Otag, Aynur, et al. 2014. "Responses of trace elements to aerobic maximal exercise in elite sportsmen." *Global journal of health science* 6, no. 3:90-96. Doi: 10.5539/gjhs.v6n3p90

Pechova Alena, and Leos Pavlata. 2007. "Chromium as an essential nutrient: A review." *Veterinarni Medicina* 52(1):1-18. Doi: 10.17221/2010-VETMED

Piotrowska, Anna, et al. 2018. "Biologiczne znaczenie chromu III." *Medycyna Pracy* 69, no. 2:211-23. Doi: 10.13075/mp.5893.00625

Ponsonnet, L, et al. 2002. "Effect of surface topography and chemistry on adhesion, orientation, and growth of fibroblasts on nickel-titanium substrates." *Materials Science and Engineering: C* 21 (1-2):157-65. Doi: 10.1016/S0928-4931(02)00097-8

Putters, J, D. Kaulesar Sukul, G. de Zeeuw, et al. 1992. "Comparative cell culture effects of shape memory metal (Nitinol), Nickel and Titanium: A biocompatibility estimation." *Eur. Surg. Res*. 24:378-82.

Racine, Melanie, et al. 2018. "Reversal of Sp1 transactivation ang TGFb1/SMAD1 signaling by H2S prevent nickel-induced fibroblast activation." *Toxicology and Applied Pharmacology* 356:25-35. Doi: 10.1016/j.taap.2018.07.029

Ross, S. M. 1994. "Sources and forms of potentially toxic metals in soil – plant systems." In *Toxic metals in soil – plant systems*, edited by S M. Ross, 3-25. New York: Wiley and Sons.

Sawicki, Wojciech. 2008. "Tkanka łączna właściwa." In *Histologia*. Warszawa: Wydawnictwo Lekarskie PZWL.

Schnegg, H. A., and M. Kirchgessner. 1980. "Toxic effects of trace elements on the reproduction of mice and rats." *Arch. Environ. Hlth*. 23:102-106.

Sevin, I. F. 1980. *Nickel, Metals in the environment*. London: Academic Press.

Shrivastava, Yamini, et al. 2005. "Cytotoxicity studies of chromium (III) complexes on human dermal fibroblasts." *Free Radic Biol Med.* 38 (1):58-69. Doi: 10.1016/j.freeradbiomed.2004.09.029

Shen, L., C. X. Song, C. He, et al. 2014. "Mechanism and function of oxidative reversal of DNA and RNA methylation." *Annu Rev Biochem*. 83:585-614. Doi: 10.1146/annurev-biochem-060713-035513

Sigel, Helmut, and Astrid Sigel. 1988. *Nickel and its role in biology. Metal ions in biological systems*. New York: Marcel Dekker.

Smith, A. 2006. "A glossary for stem-cell biology." *Nature* 441:1060. Doi: 10.1038/nature04954

Sugden, David, et al. 2004. "Melatonin, melatonin receptors and melanophores: A moving story." *Pigment Cell Research* 17 (5):454-60. Doi: 10.1111/j.1600-0749.2004.00185.x

Sugden, K. D., and D. M. Stearns. 2000. "The role of chromium(V) in the mechanism of chromate-induced oxidative DNA damage and cancer." *Journal of environmental pathology, toxicology and oncology: Official organ of the International Society for Environmental Toxicology and Cancer* 19 (3):215-30. Doi: 10.1016/j.tiv.2004.03.001

Sunderman, F. W., J. B. Sullivan, and G. R. Krieger. 2001. *Nickel in clinical environmental health and toxic exposures*. Baltimore: Williams and Wilkins.

Śpiewak, Radosław, and Justyna Piętowska.. 2006. "Nikiel – alergen wyjątkowy. Od struktury atomu do regulacji prawnych." *Alergologia Immunologia* 3, no. 3-4:58-62.

Takahashi, K., and S. Yamanaka. 2006. "Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors." *Cell*. 126 (4):663-76. Doi: 10.1016/j.cell.2006.07.024

Tikhomirov, F. A., N. N. Kuznetsova, and L. G. Magina. 1987. "Effect of nickel on plants in a sod-podzolic soil." *Agrokhimiya* 8:74-80.

Vincent, John. 2010. "Chromium: Celebrating 50 yers as an essential element?" *Dalton Trans* 39 (16):3787-794. Doi: 10.1039/b920480f

Wang, Yafei, et al. 2017. "Carcinogenicity of chromium and chemoprevention: A brief update." *Onco Targets Ther*. 10:4065-4079. Doi: 10.2147/OTT.S139262

Ward, R. J., R. R. Crichton, D. L. Taylor, et al. 2011. "Iron and the immune system." *J. Neural Transm.* 118:315-28.

Weissman, I. L. 2000. "Stem cells: units of development, units of regeneration, and units in evolution." *Cell*. 100 (1):157-68. Doi: 10.1016/s0092-8674(00)81692-x

Widłak, Małgorzata. 2011. "Toksyczność glinu wyzwaniem środowiskowym (przegląd literatury)." *Rocznik Świętokrzyski. Ser. B – Nauki Przyr*. 32:131-40.

Wintz, M., T. Fox, and C. Vulpe. 2002. "Functional genomics and gene regulation in biometal research." *Bull. Environ. Contam. Toxicol.* 30:765-68.

Wlaschek, Meinhard, et al. 2019. "Iron and iron-dependent reactive oxygen species in the regulation of macrophages and fibroblasts in non-healing chronic wounds." *Free Radical Biology and Medicine* 133:262-75. Doi: 10.1016/j.freeradbiomed.2018.09.036

Yao, Y., Y. Lu, W. C. Chen, et al. 2014. "Cobalt and nickel stabilize stem cell transcription factor OCT4 through modulating its sumoylation and ubiquitination." *PLoS One*. 9 (1):e86620. Doi: 10.1371/journal.pone.0086620

Yin, R., S. Q. Mao, B. Zhao, et al. 2013. "Ascorbic acid enhances Tet-mediated 5-methylcytosine oxidation and promotes DNA demethylation in mammals." *J Am Chem Soc*. 135 (28):10396-10403. Doi: 10.1021/ja4028346

Yin, R., J. Mo, J. Dai, et al. 2018. "Nickel(ii) inhibits the oxidation of DNA 5-methylcytosine in mammalian somatic cells and embryonic stem cells." *Metallomics*. 10 (3):504-12. Doi: 10.1039/c7mt00346c

Yokoi, K., E. O. Uthus, and F. H. Nielson. 2002. "The essential use of nickel affects physiological functions regulated by the cyclic – GMP signal transduction system." Proceedings of the 7th international symposium on metal ions in biology and medicine, St. Petersburg, Russia, 5-9.

Yuan, Ye, Fei Xu, Yan Cao, et al. 2019. "Iron Accumulation Leads to Bone Loss by Inducing Mesenchymal Stem Cell Apoptosis Through the Activation of Caspase3." *Biological Trace Element Research* 187, no. 2:434-41. Doi: 10.1007/s12011-018-1388-9

Zabłocka, Agnieszka. 2006. *Postępy Higieny i Medycyny Doświadczalnej* 60:209-16.

Zhang, Y., W. Zhai, M. Zhao, et al. 2015. "Effects of iron overload on the bone marrow microenvironment in mice." *PLoS One*. 10(3):e0120219. Doi:10.1371/journal.pone.0120219

Zhao, H., N. Sun, S. R. Young, et al. 2013. "Induced pluripotency of human prostatic epithelial cells." *PLoS One*. 8 (5):e64503. Doi:10.1371/journal.pone.0064503

Zuziak, Justyna, and Małgorzata Jakubowska. 2016. "Glin w otoczeniu i jego wpływ na organizmy żywe." *Analit* 2:110-20.