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Significance of reactive oxygen species and oxidative stress in carcinogenesis

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Summary

Introduction and aim. Reactive oxygen species and increased oxidative stress cause a series of disorders in the metabolism of the cell. Initiate adverse changes to the structure of DNA, lipids and proteins. The purpose of this article is to introduce the concept of oxidative stress and reactive oxygen species and to present their contribution to the formation and development of precancerous and cancerous.

Description of knowledge. The process of oxidation damage of DNA molecules nitrogen bases, contributes to the rupture of DNA strands and the formation of adducts. Lipid peroxidation cause damage to membranes of cytoplasmic and mitochondrial which causes unfavorable changes in their physical properties. The end products of this process show mutagenic and carcinogenic. Oxidation of proteins leading to changes in their structure and the presence of structurally abnormal protein, which is the main regulator of the cell can cause the

initiation of the neoplastic process. The emergence of mutations in the DNA is a critical point in the process of carcinogenesis.

Conclusions. Oxidative stress and the effects of reactive oxygen species is one of the reasons for the initiation and development of cancer. Permanent changes in the structure of DNA, lipids and proteins leading to the loss of their biological functions and following the development of lesions.

Keywords: Reactive oxygen species, oxidative stress, process of carcinogenesis

Introduction

There are a number of biological, chemical and physical, which initiate the process of carcinogenesis. They cause a cell to malfunction of transcription factors, abnormal regulation of its cycle of continuous stimulation of growth, loss of replication control and inhibition of its death [1]. Accumulation of genetic and epigenetic changes in a cell is mainly mediated by two types of genes- proto-oncogenes and tumor suppressor genes (antyonkogenów). The former encode proteins responsible for controlling the progress of DNA replication, cell division and differentiation. Currently, there are about identified three types. Damaged proto-oncogenes by mutations are called oncogenes. The second group of genes responsible for DNA stabilization and regulation of cell division. Act as a brake on cell growth, currently known, there are about 50, although the biological functions of many products of these genes are still undefined. The best-known of this group of genes are genes TP53 and RB1. Imbalance between proto-oncogenes and tumor suppressor genes as well as mutations occurring therein may be the cause of neoplastic transformation [2,3,4,5].

Process tumor proceeds in four steps. These include: preinitiation, promotion and progression. The first one comprises prolonged exposure of carcinogenic agents on normal cells, resulting in damage to and modifications in the structure of DNA. Initiation step is characterized by the appearance of permanent changes in the genetic material of the cell, which leads to the transformation of normal cells in a tumor cell. It obtains unlimited ability to divide. The next stage is associated with the activation of oncogenes and the synthesis thereof, which are intended to cause the growth and multiplication of cells. However, in progression, cancer cells acquire the ability to metastasize. They are developing their phenotypic features of

malignancy. Intensifies the process of neoangiogenesis also designed to generate new vascular connection to the tumor was better fed [5,6,7,8]. It should be noted that tumor cells are also characterized by genetic instability, lack of sensitivity factors antywzrostowe and impaired energy metabolism [9].

One white of the main factors present at each stage of carcinogenesis are oxygen reactive - ROS (reactive oxygen species) which adversely affect the integrity and proper functioning of the cells [10].

The aim of work is to bring the concept of oxidative stress and reactive oxygen species and to present their contribution to the formation and development of precancerous and cancerous.

Oxidative stress and reactive oxygen species and their source

Free radicals are molecules, atoms, or ions which are capable of independent existence. They have an unpaired electron valence orbitals. This characteristic gives these compounds the properties of the para-magnetic and very high chemical reactivity, which enables them to attack the cells and tissues of living organisms. Oxygen free radicals are reactive oxygen species (ROS), which include hydroxyl radical, superoxide anion radical, wodoronadtlenkowy radical, an alkoxy radical and peroxide. In contrast, precursors ROS are peroxynitrite, hypochlorous acid, hydrogen peroxide, singlet oxygen and ozone [11,12]. RFT They are generated by factors exogenous and endogenous origin. The first of them include primarily environmental pollution, exercise, smoking, drinking alcohol, ultraviolet and ionizing radiation and improper diet. Whereas for the second factors include all biochemical processes running in physiological conditions, such as inter alia breathing and inflammation. The most free radical formed in the respiratory chain in mitochondria and Fenton reactions and Haber-Weiss [13,14,15].

Under conditions of homeostasis, ROS within safe cell concentrations. They fulfill the role of mediators and then controls many processes in cells. RFT, among others, stimulate glucose transport into cells, transmit signals from cell to cell and within the effect on the differentiation and apoptosis of cells, inactivate nitric oxide. In addition, they participate in the secretion of hormones, removing drugs from the body and muscle spasms. Also they play an important role in the proper functioning of the immune system by, among others, stimulation of T lymphocytes and increasing the permeability of the capillary walls, which in turn leads to a proper course of the inflammatory response in the body. Inflammations in the body cause so. "Respiratory burst," that is to a sharp increase in oxygen consumption by phagocytic cells [16,17].

Oxidative stress is defined as a disturbed equilibrium oxidation-antioxidant. This is in contrast overproduction of ROS with respect to the concentration and activity of antioxidants. As a result, the oxidation reaction occurs. Excessive amounts of ROS in the human body leads to a number of adverse effects, such as inter alia hemoglobin oxidation, inactivation of transport proteins, and various enzymes, disorders of intracellular calcium ions, the peroxidation of lipid membranes and DNA damage, which leads to neoplastic transformation of the cell [12,18].

Oxidative DNA damage

The genetic material is exposed to the influence of both endogenous and exogenous, which damage its structure. Identifying and addressing any irregularities in the genome is done through a system of DNA repair (*DNA repair*pathways). The correct DNA replication and maintenance of the integrity and stability of the genome is essential for the proper functioning of the cells [19]. Reactive oxygen species are those agents which act on the nuclear and mitochondrial (mtDNA) genetic material causes some of the most dangerous forms of damage at the cellular level , which include, among others, should be Single and double strand breaks of DNA modifications, single base nitrogen and the formation of irregular cross-linking of DNA strands or between DNA and proteins. The effect of this transformation is the occurrence of errors in the replication process, and instability of the genome [20]. Particularly susceptible to oxidative damage mtDNA is because it is adjacent to the chain oxygen and does not have a histone proteins, which serve protective functions. MtDNA damage leading to oxidative stress potentiation by some influence signaling cascades, causing dysfunction of the respiratory chain as well as increase production of the hydroxyl radical, which is one of the most reactive oxidants [21,22]. It reacts with nitrogenous bases as a result, which comes to the induction of point mutations in the protoonkogenach and antyonkogenach. It also causes dehydration deoxyribose molecules. As a result of the reaction of the hydroxyl radical and the deoxyribose ring may be a single (single stand SSB- break) and the DNA double-strand breaks (DSB - double strand breaks). No recovery in the first case is a possibility of appearance of changes in the structure of DNA molecules in the second case there is a high probability of cell death. The effect of these changes is also the appearance of products that accumulating in the cellular DNA leading to initiation of carcinogenesis and mutagenesis [19,23]. Preparation of ROS in the vicinity of the chromatin causes cross-linking between DNA and proteins. The main contributor to this type of damage is also a hydroxyl radical, which oxidation of a nitrogen base and sugar moieties of the nucleic acids. This enables the formation of bonds between them. As a result, it is causing inhibition of polymerase activity, which in the course of replication or DNA repair catalyzes

DNA synthesis [24]. Crosslinks serve as biomarkers length of exposure to a mutagen, since the longer the dwell time factor causing changes in the structure of the genome of the more forms bonds other hand, DNA-protein crosslinks between DNA strands are formed by merging nucleotides that are on one DNA strand with two groups of reactive alkylating agent. These compounds result from the transfer of an alkyl group from one compound to another. They may be attached to any oxygen or nitrogen, which is substantially nitrogen. Causes include the formation of AP sites that are devoid of nitrogen base. Is lost purine or pyrimidine (*APyrimidinic /APurinic site*). AP occurrence DNA chain may lead to chromosomal aberrations, DNA strand breaks, abnormal transcription and point mutations [19].

Oxidative damage nitrogen bases leads to the production of certain modified products. These include, among others, 5,6-dihydroxy-5,6-dihydrotymina (thymine glycol,Tg) and 8-hydroksydeoksyguanozyna (8-OHdG). The first one has the ability to block replication of just one nucleotide before or after the damage. The second one is potentially mutogenny. Can affect the binding of transcription factors. In the region of AP-1 may stop its binding with the effect of blocking transcription. It is considered a biological marker of oxidative stress. It should be noted that the presence of modified bases may initiate the process of carcinogenesis, and the subsequent conversion steps affect the change in benign and malignant increases the potential of metastasis (metastatic process) [25,26,27].

RFT also has a stimulating effect on the increase in the concentration of calcium ions which reach more of the cell and are released from the specialized cellular compartments. As a result of this process there is an activation of ions endonucleases that cause DNA damage. In addition, direct cytosolic ions of the element leads to the induction of some proto-oncogenes [21,28]

Oxidative damage of proteins and lipid membranes

The basic building blocks of biological membranes are phospholipids, which include among others of polyunsaturated fatty acids, which are mostly at risk of the oxidation process. Oxidative stress leads to lipid peroxidation, which occurs as a result of numerous cytoplasmic membrane damage and mitochondrial and their depolarization, i.e. reduction in the electric potential difference between the extracellular medium and the interior of the cell. Lipid peroxidation is a multistep process in which there are three main phases. These are the initiation, propagation and termination. In the first phase of ROS cause abstraction of hydrogen atom from the molecule or polyunsaturated fatty acid residues of the acid, which is a component of the phospholipid. The next stage involves reacting the free alkyl radicals of oxygen which results

in superoxide. Their presence causes further detachment of a hydrogen atom of the molecules of unsaturated fatty acids. The end result of these reactions is the formation of a further alkyl radical peroxide and fatty acid. In the last phase reactions occur between free radicals as a result of which the formed dimer fatty acids, and oxo and hydroxy. Are damaged and modified lipid molecules [29,30]. The most mutagenic and carcinogenic process end products of lipid peroxidation are malondialdehyde (MDA), trans-4-hydroxy-2-nonenal (4HNE), 4-hydroksyheksenal (4HHE), which can be the cause of damage to nucleic acids and proteins. These products are capable of forming five-and six-adducts with DNA, causing genetic instability and the formation of replication errors. In addition, changing the physical properties of cell membranes. This leads to asymmetry of their disorder, inhibiting the activity of enzymes and membrane transport proteins. They are also impaired their integrity. MDA is the most mutagenic, which is a factor genotoxic. RTF increased production increases the concentration of MDA in the tissues. 4HNE while characterized by high toxicity and the possibility of influencing the rate of mutation and inhibition of DNA synthesis [24,31]. Lipid peroxidation products may contribute to the induction of expression cyclooxygenase-2 (COX-2). It is an enzyme that is involved in the development and progression of cancer. Its high activity effect on the inhibition of apoptosis through the activation of the serotonin-threonine kinase and the increase in the activity of anti-apoptotic proteins (Bcl-2). Furthermore, the overexpression of this enzyme is important in the process of angiogenesis. COX-2 affects the formation and growth of new vessels. Indirectly increases the expression and activity of the vascular endothelial growth factor (VEGF) and MMP-2 and MMP-9 that are involved in the process of metastasis formation is significant. VEGF stimulates angiogenesis necessary for tumor growth. While MMP-2 (gelatinase A) and MMP-9 (gelatinase B), cause the destruction of collagen IV, which is the basement membrane of the timber. As a result, the tumor cells moving through the vascular system have the ability to populate in other organs [32,33].

By the action of ROS and oxidative stress appear as modifications of proteins, which play a significant role in the pathogenesis of cancer. Their oxidation of peroxides implies the proteins and amino acids. Oxidative damage of proteins and interfere with their biological functions and to cause a plurality of changes in the structure. The main culprits of these transformations is the hydroxyl radical, superoxide anion and hydrogen peroxide. Oxidation chain polypeptide is initiated by the hydroxyl radical. This leads to oxidation of the amino acid residues. The greatest sensitivity to oxidation exhibit tyrosine, cysteine, methionine and typtofan. As a result of the oxidation process there is a risk breakage of the chain, dimer formation, and the formation of protein aggregates modification of amino acid residues. Protein

aggregates are resistant to degradation, which leads to the accumulation of altered proteins in cells thereby interfering with their biological and physiological functions [34,35,36]. Oxidative changes occurring in the proteins are one of the causes of disturbances in the redox balance of the cell. It is necessary for the proper functioning of certain enzymes, which contain metal ions. Damage caused by oxidation of these enzymes lead to a reduction in ability to eliminate the hydrogen peroxide, thereby leading to increased oxidative stress in a cell. It should also be noted that the redox potential of cells affected, among others, transcription factors such as AP-1 and NF-KB (*nuclear factor kappa B*), which govern the expression of genes responsible for growth, differentiation and apoptosis [26]. The expression of NF-KB may occur in the course of inflammation and is one of the indicators of activity neoplastic tissue. The best known is the factor NF-KB p65 /p50, which is composed of two proteins. It is present in every cell functioning properly. Mutations in the genes encoding NF-KB or genes which regulate the activity of this factor may result in activation of NF-KB p65 /p50. Consequently, this is one of the causes of tumor development through the increase in cell proliferation, angiogenesis and inhibition of apoptosis. Research shows that in the process of carcinogenesis and tumor aggressiveness level plays a significant role abnormal transcriptional regulation NF-KB p65 / p50 [37,38].

Summary:

As a result of external factors, and cellular metabolism followed by production of free radicals and reactive oxygen species. Disturbed redox balance leads to oxidative stress, which is considered one of the reasons for initiating the process of carcinogenesis. ROS and oxidative stress directly damage DNA and cause inhibition of repair. In addition, they activate oncogenes and inactivate tumor suppressor genes, which affect the course of all stages of carcinogenesis. They act as a brake on the apoptosis, which is one of the major defense mechanisms against cancer. ROS can also cause pathological activation of the transcription factors causing adverse effects in the proper functioning of cells. The accumulation of mutations in the genetic material results in a loss of control over the processes of differentiation and growth resulting in the malignant transformation. In the later stages of tumorigenesis oxidative stress may enhance the metastasis process, as with the number of oxidative DNA damage occurs increasing metastatic potential.

List of references:

1. Deptała A. Podstawy epidemiologii nowotworów. Środowiskowe i genetyczne uwarunkowania rozwoju nowotworów (w:) Deptała A (red.). Onkologia w praktyce. Wydawnictwo Lekarskie PZWL, Warszawa; 2015: 32-45.

2. Kiełczewski T, Dylewska M, Kurek B, Jarosz A, Falkiewicz B. Dostęp pacjentów onkologicznych do terapii lekowych w Polsce na tle aktualnej wiedzy medycznej. PEX Pharma Sequence, Warszawa; 2017: 9.

3. Gackowska M. Interpretacja wyników badań laboratoryjnych w praktyce dietetyka, część IV- markery nowotworowe, genetyczne podstawy onkogenezy, dieta w prewencji chorób nowotworowych. Food Forum. 2016; 4(14): 39-46.

4.Kozłowska J, Łaczmańska I. Niestabiloność genetyczna – jej znaczenie w procesie powstawania nowotworów oraz diagnostyka laboratoryjna. NOWOTWORY Journal of Oncology. 2010; 6(10): 548-553.

5.Siedlecki AJ. Biologia molekularna nowotworów (w:) Meder J (red.). Podstawy onkologii klinicznej. Centrum Medyczne Kształcenia Podyplomowego, Warszawa; 2011. s. 41-46.

6. Klauning EJ, Kamendulis ML. Kancerogeneza chemiczna (w:) Zielińska-Psuja B, Sapota A (red.). Podstawy toksykologii. Casarett & Doull, Wrocław; 2014: 151-165.

7. Mesri EA, Feitelson MA, Munger K. Human viral oncogenesis: a cancer hallmarks analysis. Cell Host Microbe. 2014; 5(3): 266–282.

8. Drewa G, Ferenc T. Genetyka medyczna. Elsevier Urban& Partner, Wrocław; 2011: 581-625.

9. Krok D. W poszukiwaniu znaczenia choroby nowotworowej. Uniwersytet Opolski, Opole; 2017: 17.

10. Guyton KZ, Kensler TW. Oxidative mechanisms in carcinogenesis. Brit Med Bull. 1993; 49: 523–544.

11. Białek M, Czauderna M. Budowa chemiczna oraz funkcje fizjologiczne wybranych antyoksydantów. Instytut Fizjologii i Żywienia Zwierząt im. Jana Kielanowskiego Polskiej Akademii Nauk, Jabłonna; 2016: 8.

12. Kulczyński B. Znaczenie stresu oksydacyjnego i wolnych rodników w rozwoju chorób cywilizacyjnych. Food Forum 2017; 3(19): 100-104.

13. Czajka A. Wolne rodniki tlenowe a mechanizmy obronne organizmu. Now Lek. 2006; 75(6): 582-586.

14. Piekarska-Matyska E, Łuszczewski A, Łącki J, Wawer I. Rola stresu oksydacyjnego w etiopatogenezie reumatoidalnego zapalenia stawów. Post Hig Med Dosw. 2006; 60: 617-623.

15. Pawliczak R. Rola wolnych rodników tlenowych w zapaleniu. Pol Merk Lek 2003; 14: 493–6
16. Jopkiewicz S. Stres oksydacyjny. Część I. Stres oksydacyjny jako czynniki rozwoju chorób cywilizacyjnych. Med Środow. 2018; 21(2): 48-52. DOI: 10.19243/2018207.
17. Zabłocka A, Janusz M. Dwa oblicza wolnych rodników tlenowych. Post Hig Med Dosw. 2008; 62: 118-124.
18. Cacciapuoti F. Oxidative Stress as „Mother" of Many Human Diseases at Strong Clinical Impact. J Cardiovasc Med Cardiol. 2016; 3(1): 001-006.
19. Mol A, Stolarek M. Indukowane mutagenami uszkodzenia DNA i mechanizmy ich powstawania. Post Biol Komórki. 2011; 38(3): 491-505.
20. Federico A, Morgillo F, Tuccillo C, Ciardiello F, Loguercio C. Chronic inflammation and oxidative stress in human carcinogenesis. Int J Cancer. 2007; 121: 2381-2386.
21. Ścibior-Bentkowska D, Czeczot H. Komórki nowotworowe a stres oksydacyjny. Post Hig Med Dośw. 2009; 63: 58-72.
22. Ulatowski K, Sobieszczuk P, Kuźmińska A, Ciach T. Badanie cytotoksyczności dyspersji nanopęcherzyków tlenu w wodzie. Acta Sci. Pol., Biotechnologia . 2018; 17(2): 51-57.
23. Piotrowska A, Bartnik E. Rola reaktywnych form tlenu i mitochondriów w starzeniu. Post Bioch. 2014; 60(2): 240-247.
24. Grosicka-Maciąg E. Biologiczne skutki stresu oksydacyjnego wywołanego działaniem pestycydów. Post Hig Med Dosw. 2011; 65: 357-366.
25. Przybyszewski MW, Kasperczyk J, Stokłosa K, Bkhiyan A. Uszkodzenia DNA powodowane przez produkty peroksydacji lipidów. Post Hig Med Dosw. 2005; 59: 75-81.
26. Sawicka E, Lisowska A, Kowal P, Długosz A. Rola stresu oksydacyjnego w raku pęcherza moczowego. Post Med Dosw. 2015; 69: 744-752.
27. Zaręba T, Oliński R. Oksydacyjne uszkodzenia DNA- ich analiza oraz znaczenie kliniczne, Post Bioch. 2010; 56(2): 124-138.
28. Radzikowska A. Cytotoksyczność. W: Maśliński W, Kontny E. Podstawy immunologii dla reumatologów. Narodowy Instytut Geriatrii, Reumatologii i Rehabilitacji, Warszawa; 2015: 125.
29. Gutowi M. Wpływ reaktywnych form tlenu na ośrodkowy układ nerwowy. Post Med Dosw 2011; 65: 104-113.
30. Dąbrowska M, Zielińska A, Nowak I. Produkty utleniania lipidów jako potencjalny problem zdrowotny oraz analityczny. Chemik. 2015; 69(2): 89-94.

31.Jędrzejczak-Pośpiech K, Błaszczyk J. Wpływ suplementacji luteiną na procesy peroksydacji lipidów we krwi u ludzi zdrowych. Probl Hig Epidemiol. 2015; 93(3): 677-680.
32. Leahy MK, Koki TA, Masferrer LJ. Role of cyclooxygenases in angiogenesis. Curr Med Chem. 2000; 7(11): 1163–1170.
33. Somiari BS, Shriver DC, Heckman C, Olsen C, Hu H, Jordan R, et al. Plasma concentration and activity of matrix metalloproteinase 2 and 9 in patients with breast disease, breast cancer and at risk of developing breast cancer. Cancer Lett. 2006; 23(1): 98–107. DOI:10.1016/j.canlet.2005.03.003.
34. Ognik K, Cholewińska E. Biomarkery wykorzystywane w ocenie oksydacyjnych uszkodzeń białek. Probl Nauk Biol KOSMOS. 2018; 67(2): 347-359.
35. Gębicki MJ, Bartosz G. Rola białek jako przekaźników uszkodzeń indukowanych przez reaktywne formy tlenu *in vitro*, Post Biochem. 2010; 56(2): 115-123.
36. Guenther I, Kędzierska-Mieszkowska S. System kontroli białek w cytoplazmie- rola białek opiekuńczych w biologii chorób neurodegeneracyjnych. Post Biochem. 2011; 57(3): 274-282.
37. Sung B, Prasad S, Yadav VR. Cancer cel signaling pathways targeted by spice-derived nutraceuticals. Nutr Cancer. 2012; 64(2): 173-197.
38. Lerebours F, Vacher S, Andrieu C, Espie M, Marty M, Lidereau R, et al. NF-kappa B genes have a major role in inflammatory breast cancer. BMC Cancer. 2008; 8: 41. DOI: 10.1186/1471-2407-8-41.