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Review

Oxidative damage and carcinogenesis

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Oxygen is an essential element to conduct life processes but some of the metabolic byproducts e.g. reactive oxygen species (ROS), are toxic for living organisms. Endogenous ROS are produced e.g. reduction of dioxygen; some exogenous sources of radicals also exist, including nicotine and ionizing radiation. Reactive oxygen species include superoxide anion, hydroxyl radical, singlet oxygen, hydrogen peroxide and hypochlorous acid.

Carcinogenesis is a multistep process. The exact reasons for the development of cancer are still unknown. Many factors contribute to the development of carcinogenesis, one of which is oxidative stress. Oxidative stress is defined as an imbalance between oxidizing agents (pro-oxidants) and antioxidants, agents that protect biomolecules against injury by pro-oxidants. When reactive oxygen species are overproduced it can damage nucleic acids, proteins and lipids. ROS are considered as a significant class of carcinogens participating in cancer initiation, promotion and progression.

Key words: oxidative stress, reactive oxygen species, reactive nitrogen species, oxidative damage, cancer, carcinogenesis.

Oxygen is an essential element to conduct life processes, but its high chemical reactivity is a reason why some of its metabolic by products are toxic for living organisms. These include reactive oxygen species (ROS) and free radicals [1, 2]. Free radicals are atoms or molecules that can exist independently, yet they have one or more unpaired electrons [3]. Free radicals strive to have their electrons paired, that is to get rid of a surplus electron or to bind another one. Therefore they are highly reactive [4]. Reactive oxygen species (ROS) include superoxide anion ($^{\bullet}O_2^-$), hydroxyl radical ($^{\bullet}OH$), singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2) and hypochlorous acid (HOCl). Reactive oxygen species are produced in endogenous reactions, e.g. in reduction of dioxygen but also under the influence of exogenous sources such as cigarette smoke or ionizing radiation [3, 5–9]. Reactive oxygen species are molecules commonly encountered in living organisms, where they participate in numerous physiological processes. They are mediators in many important functions of organic cells, such as regular growth, differentiation, proliferation and apoptosis [10]. They also play an important role as intra- and extracellular conductors and are the response of cells to tissue hypoxia [2, 3, 7, 9, 11–14].

Oxidative stress is defined as lack of equilibrium between oxidizing substances (pro-oxidants) and antioxidants, that is compounds that protect biomolecules against harmful effects of pro-oxidants [6]. If the volume of created ROS exceeds the organism's ability to recycle them, damage occurs to nucleic acids, proteins and lipids which, in turn, results in dysfunction of cells, tissues or organs of the body [2, 15–21].

It was proven that intense oxidative stress contributes to the pathomechanism of numerous diseases, including senile cataract, atherosclerosis, diabetes and neurodegenerative disease [22–27]. Excessive synthesis of reactive oxygen species and insufficiency of antioxidant defence mechanisms are also contributing aetiological factors of neoplastic diseases [2, 6, 9, 28–37].

Apart from ROS, cell oxidants also include reactive nitrogen species (RNS), such as nitric oxide radical ($NO^{\bullet}$) and peroxynitrite ion ($ONOO^-$), also associated with carcinogenesis [7, 13, 38–44].

It is said that RNS are factors that take part in initiation, promotion and progression of carcinogenesis [6, 8, 20, 45–48]. As early as in 1984, Zimmerman and Cerutti [49] proved that exposure of mouse fibroblasts to reactive species of oxygen can lead to carcinogenic transformation of cells. Increased levels of oxidative damage may be a result of: (I) increased production of ROS without further disruption of the antioxidant system, (II) a stable level of ROS with simultaneously a less effective antioxidant system, (III) errors in the system that repairs oxidative damage in the DNA, or (IV) a combination of the above [6, 13, 44, 50].

The conducted research proves that excessive production of ROS and related oxidative stress are features characteristic for neoplastic cells, both *in vivo* and *in vitro* [15, 16, 50–57]. Moreover, the results of the research of Kondo *et al*. [50] showed increased levels of ROS in cases of adenocarcinoma when compared to cases of colorectal cancer. The main causes of increased levels of ROS in neoplastic cells, when compared to the normal tissue surrounding them, is excessive production of ROS related to the 'respiratory (oxidative) burst' of phagocytes, as well as an increasing volume of ROS in the part of the cir-

culatory system which surrounds the neoplastic changes [15, 45]. Moreover, increased metabolic activity of neoplastic cells also intensifies production of superoxide anion radical [58].

Reactive oxygen species are considered to be a pro-neoplastic factor as they stimulate proliferation, invasiveness, angiogenesis and metastasis, and inhibit apoptosis [44, 59, 60]. They are able to stimulate development of a neoplasm in the promotion stage through influencing genes related to apoptosis and proliferation. As a result of 'an attack' of free radicals, the concentration of Ca^{2+} ions increases within the intracellular area, which results in activation of proto-oncogenes such as c-fos, c-jun, c-myc or activated protein kinase C (PKC). That, in turn, intensifies proliferation and speeds up the carcinogenesis [2, 6, 61]. High concentrations of ROS and their derivatives influence activation of transcription factors including NF-κB, which results in induction of cytokine gene expression and of growth factors. That leads to intensified proliferation of cells and occurrence of neoplastic lesions in otherwise healthy tissue [6, 14, 44, 62]. Reactive oxygen species also influence activity of proteins involved in the cell cycle, such as p53 protein [14]. If there is no oxidative stress or after a period of mild stress, p53 activity is related to the antioxidant response of the cell through activation of transcription of MnSOD and GPx1 coding genes [63]. High levels of production of reactive oxygen species may also cause increased activity of p53 protein. However, excessive levels of ROS may inhibit p53 activity, which is related to the inhibition of apoptosis [44, 64]. Moreover, a relationship between ROS and invasiveness or occurrence of metastasis was also proven [65–67]. Oberley *et al*. [68] observed that human cells that originated from metastatic changes in the course of prostate cancer produced more ROS than the original cancer cells. Moreover, the influence of ROS on the development of angiogenesis through an increase in production of vascular endothelial growth factor (VEGF) was also proven [66, 69].

Numerous research studies indicate participation of ROS, which act within cells, as secondary relays in the intracellular signal cascade. They induce and sustain the oncogenic phenotype of neoplastic cells. Moreover, there is an increasing amount of evidence that ROS can induce aging of cells and their apoptosis or necrosis, as well as being able to inhibit the process of angiogenesis, therefore being antineoplastic molecules [2, 6, 44, 70].

The biggest participation in the process of carcinogenesis, especially in the initiation phase, is attributed to the hydroxyl radical [13, 20]. The hydroxyl radical can react with both the deoxyribose molecule and nitrogenous bases which are elements of the DNA. A reaction between the hydroxyl radical and the deoxyribose molecule produces both single and double cracks of the DNA strands [13, 45, 46]. The results of reactions with nitrogenous bases are their adducts. One of the most typical DNA adducts which is an oxidative product of damage done to nucleic acids is 8-hydroxy-2'-deoxyguanosine (8-OHdG) [36, 50, 71–74]. Presence of modified bases can trigger mutational changes which, in turn, may cause inactivation of suppressor genes or activation of proto-oncogenes [6, 8, 13, 45, 75]. The increased levels of 8-OHdG and other modified bases in the DNA are also influenced by possible defects in enzymes that repair oxidative damage in the DNA, which in turn is related to the progression of age-related, increasing incidence of neoplasms [76–78]. Mice without MTH1 enzyme, which hydrolyzes 8OHdGTP, suffered from an increasing incidence of lung, stomach and liver cancer with the progress of age [76, 77].

The superoxide anion radical can inhibit the functions of the mitochondrion through inactivation of the Fe-S centre in the electron transport chain. The ongoing accumulation of damage and inhibition of the mitochondrial activity eventually leads to apoptosis of the cell [2]. It is also assumed that H_2O_2 plays some role in the process of carcinogenesis. Hydrogen peroxide is not a radical itself but can be easily transformed into one as a result of Fenton's reaction, in which iron and copper ions (Fe^{2+}, Cu^{2+}) participate [45]. Occurrence of H_2O_2 in higher concentrations was also observed in human tumour cells [13, 51].

The effects of the influence of ROS include not only damage done to the genetic material but also damage of the cell membrane caused most frequently by free radical oxidation reactions of lipid structures. One of the end products of lipid peroxidation is malondialdehyde (MDA), which can have a mutagenic and carcinogenic influence on a cell [2, 30].

Another negative consequence of the presence of ROS is changes in the spatial structure of proteins resulting in the occurrence of new cross-sectional bonds. Moreover, they may cause aggregation and fragmentation of proteins. Additionally, modifications caused by ROS change proteolytic susceptibility and antigenicity of proteins. Denaturation of some proteins was also observed as ROS can oxidize and, subsequently, break thiol groups and disulfide bridges. Reactive oxygen species may cause inactivation of proteolytic inhibitors, which increases activity of proteolytic enzymes against proteins. What is more, ROS react with proteins and lipids, raising the risk of DNA damage [2, 12, 42, 44].

A similar relationship can also be found between other reactive molecules, such as reactive nitrogen species. These oxidants may appear as a result of inducible nitric oxide synthase (iNOS). The nitric oxide radical ($NO^{\bullet}$) can react with $^{\bullet}O_2^-$ and create $^{\bullet}OH$ and the peroxynitrite anion ($ONOO^-$), which influences the process of lipid peroxidation causing cracks in the DNA and induces transversion-type mutations. They can also disrupt the respiratory chain in the mitochondrion and influence the phosphorylation process of proteins, including p53 type [6, 8, 13, 14, 34, 39, 79]. Moreover, reactive nitrogen species cause inhibition in the activity of caspases, which is related to delays in apoptosis. Additionally, inhibition of cytochrome oxidase slows down formation of mitochondrial ATP, impairing the course of proliferation, which in turn may delay the growth of a tumour [44, 80].

Cells of eukaryote organisms have created defence mechanisms that limit the level of RNS and damage caused by their actions. Such defence mechanisms include antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, glutathione S-transferase and catalase. These enzymes have various isoforms and occur in both intra- and extracellular areas. Their activity forms an integrated antioxidant protection system [2, 6, 7]. As previously mentioned, an increased level of oxidative damage in tumour cells may also be a result of a less efficient antioxidant system. An example of such inefficiency of the antioxidant protection system as a factor which contributes to carcinogenesis can be the

case of mice with turned off CuZnSOD gene, which demonstrated an increased incidence of liver tumour progressing with age [81]. Similarly, heterozygous mice that had 50% of content of the regular mitochondrial MnSOD demonstrated an increased incidence of neoplasms such as leukaemia, adenocarcinomas and pituitary adenomas [82]. Chu *et al.* [83] carried out a study in which they turned off two out of four GPx genes of mice (that is GPx1 and GPx2). This caused the occurrence of colorectal cancer. Moreover, the mice with decreased activity of catalase proved to be more prone to occurrence of breast tumours [84].

Numerous epidemiological research cases prove that an increase in expression of MnSOD in a group of patients with neoplasms correlates with higher invasiveness and aggressiveness of stomach, intestinal, lung and breast cancers [67, 85]. Liu *et al.* [60] proved that MnSOD inhibits the process of apoptosis in the neoplastic cells of the large intestine. They also demonstrated that a selenium deficiency leads to decreased activity of peroxidases and increased risk of the occurrence of neoplastic lesions [86].

Trosko and Upham [87] suggest that oxidative stress not only causes damage of the DNA but also influences epigenetic modification of gene expression that, in turn, is one of the factors of carcinogenesis. Therefore, the influence that epigenetically modified gene expression has on disturbances in proliferation, differentiation and apoptosis of the cell is more and more often emphasized.

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