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Oxidative DNA damage and repair in thyroid gland

Oksydacyjne uszkodzenia DNA i ich naprawa w gruczole tarczycy

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S u m m a r y

Reactive oxygen species (ROS) are formed as a consequence of cell metabolism but can also get into cells from external sources. Hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$) and hydroxyl radical ($^{\bullet}OH$) are produced in many physiological processes such as respiration in the mitochondria and oxidation in the peroxisomes. In thyroid H_2O_2 participate in hormone synthesis. ROS induce DNA damages that are implied in mutagenesis, tumorigenesis and other human diseases. Among these DNA lesions 8-oxoG is one of the most mutagenic. The main pathway to repair 8-oxoG and other oxidized bases is base excision repair (BER). The efficiency of BER when it comes to eliminating oxidative DNA lesions may be a risk factor for thyroid cancer and other diseases development. Molecular mechanisms responsible for impaired DNA repair have been widely studied and include polymorphisms of repair genes, their transcriptional activation/down-regulation, post-translational modifications and possibly other factors. The data presented here and literature reports demonstrate that increased oxidative stress, DNA damage and somatic mutation rates are contributing factors to the development of thyroid cancers. Moreover, alterations in DNA repair mechanisms, including polymorphisms of repair genes (OGG1, APE1 and XRCC1) may be linked to the risk of thyroid malignant transformation.

Key words: thyroid gland, oxidative stress, oxidative damages, 8-oxo-7,8-dihydroguanine (8-oxoG); DNA repair, gene polymorphism, XRCC1, OGG1

S t r e s z c z e n i e

Reaktywne formy tlenu (ROS) powstają endogennie, w wyniku metabolizmu komórkowego, jak również dostają się do komórki ze środowiska zewnętrznego (źródła egzogenne). Nadtlenek wodoru (H_2O_2), tlen singletowy ($^1O_2$) czy rodnik hydroksylowy ($^{\bullet}OH$) powstają w wielu procesach fizjologicznych, takich jak oddychanie w mitochondriach czy utlenianie w peroksysomach. W tarczycy H_2O_2 uczestniczy w syntezie hormonów. ROS powodują powstawanie modyfikacji DNA, wśród których 8-oxoG jest najbardziej mutagenną. Uszkodzenia DNA odgrywają istotną rolę w mutagenezie, kancerogenezie i rozwoju innych chorób u ludzi. Główną drogą naprawy utlenionych zasad, w tym 8-oxoG, jest naprawa przez wycinanie zasad (ang. *Base Excision Repair* – BER). Zaburzenia w naprawie DNA mogą być czynnikiem ryzyka rozwoju wielu chorób, w tym raka tarczycy. Badania nad molekularnymi mechanizmami odpowiedzialnymi za zaburzenia naprawy DNA obejmują polimorfizmy genów naprawy, regulację ich transkrypcji, modyfikacje potranslacyjne oraz inne czynniki. Dane literaturowe wskazują, że stres oksydacyjny, uszkodzenia DNA oraz zwiększona częstotliwość mutacji mogą być czynnikami przyczyniającymi się do rozwoju raka tarczycy. Ponadto, zmiany w systemach naprawy DNA, w tym występowanie polimorfizmów genów naprawczych (OGG1, APE1 i XRCC1) może również wiązać się z ryzykiem transformacji nowotworowej w tarczycy.

Słowa kluczowe: tarczyca, stres oksydacyjny, uszkodzenia oksydacyjne, 8-oksy-7,8-dihydroguanina (8-oxoG), naprawa DNA, polimorfizm genu, XRCC1, OGG1

OXIDATIVE STRESS AND REACTIVE OXYGEN SPECIES

Most organisms living on Earth are entirely dependent on the presence of oxygen in the atmosphere. However, the by-products of oxygen metabolism are toxic to living organisms. Reactive oxygen species (ROS) in the cell are produced both during normal cellular metabolism or inflammatory reactions and under the influence of external factors like γ, X and UV radiation, biotransformation of dietary chemicals and some diet components, e.g. transient metal ions (1). Normal cellular metabolism seems to be the primary source of endogenous ROS. An imbalance between the formation of ROS and antioxidant defense leads to increased reactive oxygen species generation and oxidative stress development (2). ROS are radical molecules

containing oxygen, for example superoxide ($O_2^{\bullet -}$) and hydroxyl radical ($^{\bullet}OH$), or non-radical molecules, such as hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$), which may be converted into radical forms. The most reactive ROS, hydroxyl radicals, are responsible for oxidation and fragmentation of nucleic acids, proteins and lipids. They are produced in the metal-catalysed Haber-Weiss and Fenton reactions mediated by the transition metal ions such as iron and the copper (3). Iron is a cofactor for many biological reactions and is an important component of metabolism in various tissues and organs, including the thyroid. Iron deficiency may affect thyroid hormone synthesis by decreasing the activity of the heme-dependent thyroid peroxidase (TPO). In addition, low iron levels reduce deiodinase activity, i.e. it slows down the conversion of T4 to T3, and also causes a raise in circulating concentrations of thyroid stimulating hormone (TSH) (4). With higher levels of TSH and low free T4 and T3 levels hypothyroidism occurs. Iron overload, on the other hand, may promote the persistence of harmful labile iron, which can catalyze the generation of potentially carcinogenic DNA adducts in the cell (5).

THE ROLE OF H_2O_2 IN THE THYROID

H_2O_2 production was found in vivo in many intracellular structures e.g. mitochondria, endoplasmic reticulum and peroxisomes. A high concentration of hydrogen peroxide was also observed in activated phagocytes, spermatozoids, bacteria and even in exhaled air (6). In the thyroid gland H_2O_2 is produced by one or two NADPH oxidases (Duox1/2) at the apical membrane of thyrocytes and it participates in hormone biosynthesis. To synthesize T3 and T4 hormones, the thyroid takes up iodine and incorporates it into the precursor of the hormones – thyroglobulin. Iodination of thyrosyl residues on thyroglobulin requires high concentrations of H_2O_2 as well as oxidized iodine, which is generated by the thyroid peroxidase (TPO) (7). For the TPO function properly H_2O_2 is necessary. It helps to stabilize the enzyme by autocatalytic covalent heme binding to the TPO molecule, which positively affects TPO activity (8). On the other hand, an excess of H_2O_2 may inhibit TPO activity and consequently inhibit thyroid hormone synthesis (9). Because H_2O_2 and iodine are co-substrates in hormone synthesis, changes of iodine concentrations affect the concentration of H_2O_2. *In vitro* and in vivo studies demonstrated that iodide inhibits the generation of H_2O_2 in the thyroid (10, 11). Production of H_2O_2 is moreover stimulated through the cAMP cascade by the thyrotropin (TSH), which increases the expression of genes important for hormone synthesis (e.g. TPO) (12).

H_2O_2 has various effects in the cell and it may enhance cell metabolism through diverse mechanisms. Besides that H_2O_2 acts as an oxidant, and also induces oxidative stress and apoptosis (13) working as an intracellular messenger (14). ROS-derived signals regulate growth, proliferation, differentiation and death of the cell (15-17). It has been demonstrated that in thyroid H_2O_2-mediated cytotoxicity appears at low H_2O_2 concentrations and leads to cell apoptosis or less frequently to necrosis (15). Moreover *in vivo* studies suggest that cytotoxic reaction to oxidative stress may depend on the functional state of the thyroid gland (18).

Despite the fact that hydrogen peroxide does not react directly with components of DNA, it is a precursor to highly reactive hydroxyl radical ($^{\bullet}OH$), hypochlorite (ClO^-) and singlet oxygen ($^1O_2$). Therefore H_2O_2 may facilitate a mutagenic process and DNA modification leading to cancer development (19). A thyrocyte which generates a great amount of H_2O_2 is a long-lived cell and that allows it to accumulate mutations in DNA (20). Consequently, oxidative stress has been suggested to contribute to the pathogenesis of thyroid cancer (21, 22).

DEFENSE AGAINST THE ACTION AND EFFECTS OF ROS

An antioxidative defense systems, that protect from the formation and effects of reactive oxygen species, function in all living organisms. In the cell the defense against the destructive effects of ROS works on the three levels.

The first level of the system prevents the formation of excessive quantities of ROS. The main component of this level are proteins that bind transition metal ions which thus inhibits Fenton reactions. Iron ions are bound by ferritin, transferrin and lactoferrin, copper ions by ceruloplasmin. Metallothioneins bind a number of different metal ions, as well as albumin, which non-specifically, is capable of binding many metal ions (23).

The second defense level neutralizes ROS. This system includes antioxidant enzymes such as superoxide dismutase (SOD), glutathione and ascorbate peroxidases (GPX, APX1), and glutathione transferase. The other elements of this protection level are small molecule antioxidants that work as direct or indirect free radical scavengers: glutathione, ascorbic acid, cysteine, tocopherols (vitamin E), retinoids (vitamin A analogs), uric acid, carotenoids, bilirubin, ubiquinol, and even glucose and pyruvate (3, 24). The above antioxidative protectors have been found in thyroid gland, e.g. GPX and TPO and are upregulated during the synthesis of thyroid hormones (25). There is also evidence that GPX3 which affects the H_2O_2 concentration directly interferes with hormone synthesis (26).

The third level of the defense is the elimination of ROS harmful effects on the most important cellular macromolecule – DNA. Oxidative DNA adducts are repaired by enzymes of excision repair systems, which will be described in subsequent chapters.

DNA DAMAGE CAUSED BY OXYGEN FREE RADICALS ATTACK

ROS reactions with DNA cause the most dangerous consequences for multicellular organisms. The $^{\bullet}OH$ radical molecule is one of the ROS that is extremely reactive in the oxidation of cellular constituents such

as nucleic acids, proteins and lipids. •OH interactions with DNA may lead to considerable damage, such as oxidized bases, base and sugar lesions, abasic sites, DNA-DNA intrastrand adducts, single or double strand breaks and DNA-protein cross-links (2, 27-29).

Among modified DNA products generated by the free radicals a significant part are pyrimidine- and purine-derived lesions (30). Some of these modified DNA bases have considerable potential to affect the integrity of the genome (31). The main products of oxidatively damaged DNA include 8-oxo-7,8-dihydroadenine (8-oxoA); 8-oxo-7,8-dihydroguanine (8-oxoG) and its deoxynucleoside equivalent, 8-oxodG; 5,6-dihydroxy-5,6-dihydrothymine (thymine glycol, Tg) and ringopened lesions: 4,6-diamino-5-formamidopyrimidine (FapyA) and 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG) (32-34).

MUTAGENIC 8-OXOG AND CARCINOGENESIS

Guanine in the cellular nucleotide pool and also as a component of the nucleoside, nucleotide or polynucleotide (DNA, RNA) is especially susceptible to oxidation by ROS. Its oxidation results in the formation of the modified base known as 8-oxo-7,8-dihydroguanine (8-oxoG). 8-oxoG is the most widely studied DNA lesion and the best marker of oxidative DNA damage due to its mutagenic nature and its high sensitivity to immunological detection. The presence of 8-oxoG residues in DNA leads to G > T transversions (35-37) and one of the consequences could be point mutations. Several model studies confirmed that external oxidative factors such as induce G > T transversions in DNA and the overall frequency of point mutations correlate with the level of 8-oxoG (38, 39). Studies on 8-oxoG are focused on finding a link between the presence of mutations in the DNA molecule and malignant transformation of the cell. Elevated levels of 8-oxoG in the DNA were detected in cancer tissues of different origins (40, 41). Moreover experimental data suggests that 8-oxoG occurrence reflects the early changes in the process of carcinogenesis. The significant role of 8-oxoG in carcinogenesis may also be supported by the fact that in tumor tissues G > T transversions are the most common point mutation within the p53 tumor suppressor gene and other genes associated with tumor development (42).

In thyroid tissues, an antibody of 8-oxoG showed the strongest staining near the lumen of thyrocytes where H_2O_2 is produced and the staining in the follicular thyroid cells was stronger than in spleen, lung and liver cells (43). That might indicate a higher load of oxidatively modified DNA in thyroids, possibly caused by high H_2O_2 concentrations. Indeed the rate of spontaneous mutations found in the thyroid gland was 8-10-fold higher compared to liver and stands out from many other tissues (43, 44). Moreover, human thyroid carcinomas demonstrate hypermutability compared with tumors in general (45). In addition among the spectrum of somatic mutations in thyroid tumors one of the most common is G > T transversion induced by oxidative factors. That may suggests the contribution of oxidative stress and oxidative base adducts in thyroid cancer development (46).

REPAIR OF OXIDATIVE DNA DAMAGE

Eukaryotic organisms have a number of repair mechanisms, which are specialized in the removal of various types of DNA damage. These include direct repair, excision repair and the recombination repair system (47). An excision repair consists of three pathways: base excision repair (BER), nucleotide excision repair (NER) and mismatch repair (MMR).

The main mechanism repairing oxidized DNA bases is BER, which can be divided into five steps. The first step is an excision of the damaged base by the specific DNA glycosylase and formation of an apurinic/apyrimidinic (AP) site. In humans the enzyme that initiates the BER pathway is 8-oxoguanine DNA glycosylase – OGG1. The second step is a cleavage of the phosphodiester bond at the AP site by AP-endonuclease (APE1) or AP-lyase. In the next phase chemical groups interfering with gap filling and ligation are removed. The last two steps are gap filling and ligation (48).

BER consists of two distinct pathways: the short and the long path. In the short path BER only one nucleotide is excised, while in the long patch 2-8 nucleotides are removed along with the damaged nucleotide (48).

The excision rate of oxidative DNA lesions may be affected by proteins engaged in the repair mechanism e.g. APE1, XRCC1 or PARP1 (ADPRT). The first step of the BER pathway, recognition and excision of the damaged catalyzed by OGG1, may be greatly influenced by the second BER pathway enzyme, APE1 (AP endonuclease). *In vitro* APE1 stimulates excision of 8-oxoG up to 400 fold by increasing enzyme turnover of damaged DNA (49). The next protein XRCC1 (X-ray cross-complementing group 1), which is a platform protein recruited to the site of damage by several DNA glycosylases and stays until ligation, regulates consecutive stages of the BER. PARP1 (polyADP ribose polymerase), which binds to free DNA ends and protects them against degradation, participates in chromatin relaxation and modulates binding of repair proteins to the site of damage by interaction with poly(ADP-ribose) chains (50).

It is postulated that the efficiency of BER in eliminating oxidative DNA lesions may be a risk factor for the development of cancer and other diseases. The molecular mechanisms responsible for impaired DNA repair are widely studied and include polymorphisms of repair genes, their transcriptional activation/down-regulation, post-translational modifications and possibly other factors (34).

POLYMORPHISMS OF BER GENES AND THYROID DISORDER

Several polymorphisms of DNA repair genes responsible for excision of 8-oxoG are known. Their presence

in the human genome has been linked to the risk of developing specific types of cancers, thyroid included (51). It has been suggested that polymorphisms in repair genes may be associated with differences in the repair efficiency of DNA damage (51).

A number of polymorphic changes have been described in the OGG1 gene, which encodes DNA-glycosylase excising a damaged base from DNA. The major OGG1 polymorphism is the C to G transversion in the exon 7, which results in Ser to Cys change in codon 326 in the protein (52, 53). It has been reported that polymorphic OGG1-Cys326 protein has a lower enzymatic activity in comparison to common OGG1-Ser326 protein. This findings suggest that individuals homozygous for Cys326 might accumulate more mutations under conditions of oxidative stress (53-55). Moreover, the OGG1-Cys326 allele was suggested to be associated with increased risk of lung, stomach, prostate, nasopharyngeal, esophageal and cervical cancers (51, 56-61), although not for breast and colon cancers (62, 63). This OGG1-Cys326 variant was also detected in differentiated thyroid tumors, however there was no significant difference between the control group and the cancer patient group (64). Whether the linkage of the *OGG1* Ser326Cys polymorphism to increased/ /decreased cancer risk is due to decreased enzyme activity remains to be elucidated. The contradictory results concerning the correlation between *OGG1* polymorphism and 8-oxoG incision activity in human leukocytes have been published (65, 66). The less frequent *OGG1* polymorphic variants: Gly12Glu, Arg46Gln, Ala85Ser, Arg131Gln, Arg154His, Arg169Gln, Ser232Thr and Gly308Glu were found in human lung, kidney and gastric tumors (67, 68). However due to the rare occurrence of these alterations in the population their relation to thyroid cancers has not been established. Among these polymorphisms only two OGG1-46Gln and OGG1-154His were demonstrated to possess defective catalytic capacities (69).

The *OGG1* gene has been mapped to chromosome 3p26.2 (70), a region showing loss of heterozygosity (LOH) in various human cancers (58, 71, 72). In both Hashimoto thyroiditis (HT) and papillary thyroid carcinoma (PTC) a high incidence of *OGG1* LOH has been reported. On the contrary there was no *OGG1* LOH in benign goiter specimens. These findings may suggest that PTC and longstanding chronic inflammation in HT could result from altered repairs to oxidative DNA damage (73). The excision activity of OGG1 glycosylase may depend on several protein interactions among partners of the BER pathway, e.g. XRCC1 and APE1, therefore further studies are needed to determine whether the polymorphisms of OGG1 is a significant risk factor for cancer development.

The second enzyme in the BER system is AP endonuclease (APE1). Several sequence variants of the *APE1* gene were identified. The most frequently studied are Gln51His, Ile64Val and Asp148Glu. The presence of Ile64Val was associated with decreased lung cancer risk (74). Asp148Glu polymorphism was related with hypersensitivity to ionizing radiation (76). No association, however, between occurrence of the Asp148Glu polymorphism and thyroid or other cancer development has been demonstrated (76).

The X-ray cross-complementing group 1 (XRCC1) gene is located on chromosome 19q13.2 and encodes a scaffold protein which interacts with a complex of DNA repair enzymes. Three polymorphisms at the conserved sequences in the *XRCC1* gene have been identified: Arg194Trp, Arg280His and Arg399Gln (77). These polymorphisms, involving an amino acid change at evolutionarily conserved regions, which interact with the OGG1 and APE1 (78), could alter the XRCC1 function. Although the importance of XRCC1 protein for the effectiveness of BER was demonstrated in model studies (79), no information is available on the *XRCC1* polymorphisms and 8-oxoG incision rate in humans. It was demonstrated that the presence of XRCC1 polymorphisms are associated with the development and progression of differentiated thyroid cancers (DTC), however the data is inconsistent (80-83).

Replacement C>T in the exon 6 causes Arg to Trp amino acids substitution at codon 194 in protein. Both heterozygous Arg194Trp and homozygous Trp194Trp polymorphic genotypes are showed to increase susceptibility to DTC (80). Furthermore, the XRCC1-194Trp variant may interact with polymorphic ADPRT-762Ala variant (polyADP ribose polymerase, PARP1), which also participates in the BER pathway. Simultaneous occurrence of these polymorphisms is reported to further enhance susceptibility to DTC and regional lymph node (LN) metastasis (81). On the other hand, the polymorphic XRCC1-Trp194 variant was linked with a decreased risk of thyroid nodules and the common XRCC1-Arg194 variant was associated with the occurrence of thyroid nodules and nodules related to radiation exposure of the thyroid gland (82).

The XRCC1 Arg399Gln and Arg280His variants have been widely investigated for their function and involvement in tumorigenesis. The results, however, are controversial rather than conclusive (84). Arg280His polymorphism result from G>A substitution in exon 9 and Arg399Gln is generated from the replacement of G>A in exon 10 of *XRCC1* gene. Existing data on the association of *XRCC1* Arg280His polymorphism occurrence with differentiated thyroid cancer development are contradictory. No associations were observed in populations from Taiwan, Russia and Belorussia (82, 83) in contrast with Spanish data which showed a slight increase of DTC risk for carriers of His280 allele (64). The results of the Arg399Gln polymorphism vary in different cancers for populations with different ethnicities. It has been reported that XRCC1-Gln399 variant may affects the DTC development. Cases with Gln399 allele demonstrated decreased risk of DTC among the patients from Chernobyl and survivors of Hodgkin disease with radiotherapy-related malignancies (80, 85). On the contrary no association between Arg399Gln

polymorphisms and thyroid tumors occurrence was observed in Taiwan and Spain, as is in the populations not exposed to high doses of ionizing irradiation (64, 81). These results suggest that the *XRCC1* polymorphisms, in particular Arg399Gln, may modify the effects of environmental exposure and consequently influence the risk of DTC.

An extensive search for single nucleotide polymorphisms revealed that cancer risk may be increased in individuals bearing multiple genes polymorphisms. These alterations if present separately have no or little effect on the frequency of cancer development. For example the simultaneous presence of *XRCC1* Arg194Trp and *ADPRT* (*PARP1*) Val762Ala polymorphisms increase the risk of thyroid cancer and regional LN metastasis (81).

In summary, ROS may act at several stages of malignant transformation by the induction of permanent DNA sequence changes. The presented data suggest that increased oxidative stress, DNA damage, and somatic mutation rates are contributing factors to the development of human cancers including thyroid. Moreover, alterations in DNA repair mechanisms, such as polymorphisms of repair genes, may be associated with the risk of thyroid malignant transformation.

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