Journal of Trace Elements in Medicine and Biology 39 (2017) 76–85

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

Review

Contribution of mammalian selenocysteine-containing proteins to carcinogenesis

Elena Gennadyevna Varlamova[a,*], Irina Valentinovna Cheremushkina[b]

[a] Federal State Institution of Science Institute of Cell Biophysics, Russian Academy of Sciences, Moscow Region, Institutskaya st. 3, 142290, Pushchino, Russia
[b] Federal State Educational Institution of Higher Education Voronezh State University of Engineering Technology, Prospect revolution st. 19, 394000, Voronezh, Russia

ARTICLE INFO

Article history:
Received 25 May 2016
Received in revised form 28 July 2016
Accepted 9 August 2016

Keywords:
Selenium
Mammalian selenoproteins
Carcinogenesis

ABSTRACT

Oxidative stress caused by a sharp growth of free radicals in the organism is a major cause underlying the occurrence of all kinds of malignant formations. Selenium is an important essential trace element found in selenoproteins in the form of selenocysteine, an amino acid differing from cysteine for the presence of selenium instead of sulfur and making such proteins highly active. To date the role of selenium has been extensively investigated through studying the functions of selenoproteins in carcinogenesis. Analysis of the obtained results clearly demonstrates that selenoproteins can act as oncosuppressors, but can also, on the contrary, favor the formation of malignant tumors.

Contents

1. Introduction

Selenium is an essential trace element and a key component in 25 selenoproteins essential to health [1–11]. In recent years more and more data on the role of selenium-containing mammalian proteins in carcinogenic processes have been obtained, and the crucial role belongs to microelement selenium. It is known that oxidative stress due to the growth of free radicals in the organism contributes to origination of malignant tumors. Additionally, certain chemotherapeutic drugs, radiotherapy and ionizing radiation result in the formation of free radicals, which considerably induce cytotoxicity [12,13]. For instance, excessive ROS change the mitochondrial potential and initiate signaling pathways that lead to mitochondria-dependent apoptosis [14]. In this regard, studying the role of selenium through effects of selenoproteins as antioxidants is of great interest.

To date 25 selenocysteine-containing proteins are known in mammals, and for nearly half of them the functions are unknown. However, a great number of studies have been devoted to elucidating the action of these proteins in carcinogenesis, and it becomes quite clear that the mechanisms of their regulation are ambiguous, requiring large-scale detailed analyses. Reduction of expression of selenoprotein-coding genes in cancerous cell lines produced a dual effect on oncologic neoplasms: oncologic transformation was either inhibited or, conversely, cells again obtained oncologic phenotype.

* Corresponding author.
E-mail addresses: 1928lv@mail.ru (E.G. Varlamova), irinacher2010@yandex.ru (I.V. Cheremushkina).

http://dx.doi.org/10.1016/j.jtemb.2016.08.004
0946-672X/

2. Glutathione peroxidases

The expression of glutathione peroxidase 1 (GPx1) gene is largely dependent from selenium concentration in the organism. The main function of GPx1 consists in the protection of cells from oxidative damage by reduction of hydrogen peroxide and a variety of organic peroxides. The cytoplasmic form of GPx-1 belongs to the family of selenium-dependent peroxidases, which also includes GPx-2, GPx-3, GPx-4, human GPx-6 [15,16]. It was shown that mice knockout for the gpx-1 gene had a normal phenotype but exhibited high sensitivity against oxidative stress [17]. The gpx-1 gene is located in chromosome 3p21, and a genetic polymorphism was determined in codon 198 of human gpx-1, encoding either proline (Pro) or leucine (Leu) (SNP 1050450). Substitution of Pro for Leu results in a reduction of the activity of GPx-1. Moreover, a number of works testified the interrelation of this polymorphism with breast [18,19], lung [20–22], bladder [23] cancers. There are also evidences that substitution of Pro-198 in the human gpx-1 gene can result in prostate cancer [24], though the risk is insignificant. However, when studying the influence of this polymorphism on the onset of prostate cancer in two groups of men (smokers and asbestos exposed), Choi and coauthors did not confirm such relation [25]. Which is more, Arsova-Sarafinovska and colleagues [26,27] revealed a protective effect of substitution of Pro(198) Leu substitution in human gpx-1 человека against prostate cancer development. It was also demonstrated that GPx-1 acts as a suppressor of brain tumor growth [28,29]. Real-time PCR indicated that gpx-1 expression in intestinal cancer cells is 2-fold higher in comparison to normal cells [30].

It was reported that human transcription factor NF-kB, when bound with the promoter region of the GPx-1 gene, could be and upstream regulator of GPx-1 expression and function [31]. The same phenomenon was observed using a specific inhibitor of NF-kB- BAY 11-7082 [32], and it was also demonstrated that vitamin D, which inhibits NF-kB, causes suppression of GPx-1 synthesis and, thus, reduces the grade of esophageal cancer [33–35]. It was also reported that, in esophageal cancer cell lines EC109 and EC9706, enhanced GPX1 activity can lead to the capability of invasion and migration changes through enzymes MMP2(matrix metalloprotease-2) and uPA (urokinase type plasminogen activator), which are crucial for tumor formation and metastasis [36].

GPx-2 is a selenium-dependent glutathione peroxidase with anti-inflammatory activity, which reduces the level of hydrogen peroxide and alkyl hydroperoxides [37]. This enzyme was confirmed to be involved in the regulation of various malignant tumors. For example, overexpression of the gpx-2 gene was observed in rectal adenoma cells, Barrett's mucosa of the esophagus, hepatic cancer cells [38–42]. Inactivation of GPx-2 was identified in patients with squamous cell skin carcinoma caused by UV irradiation [43]. The use of immunohistochemical methods testified that in breast cancer the expression of the gene encoding GPx-2, which is involved in the co-regulation of this tumor type along with protein p53, is increased. It is known that in 20–35% cases the onset of breast cancer is induced by the presence of a mutated from of p53 [44]. Suppression of GPx-2 synthesis resulted in inhibition of human and rat breast cancer cells proliferation only under normal functioning of p53, but not in the case of its mutant form [45–47]. The study of the role of GPx-2 in castration-resistant prostate cancer (CRPC) determined that this enzyme is highly expressed in tumor cells PC3 (castration-resistant cell line), as compared to androgen-depended cell line (LNCaP). GPx-2 is mainly formed in the cytoplasm of basal cells in normal prostate glands and prostate tumor cells [48]. GPx-2 as an enzyme that is required to protect colon cancer cells against a variety of stress sources (H_2O_2, loss of cell–cell adhesion, and chemotherapeutic drugs). Thus, by maintaining redox homeostasis, GPx-2 controls the balance between survival, proliferation, and differentiation colon cancer cells [49]. In cytokine-treated colorectal cancer cells, endogenous GPx-2 expression and GPx-2 promoter activity were enhanced by anti-inflammatory mediators 15d-PGJ2 (15-deoxy-Δ12,14-prostaglandin J2) and IL-22 (interleukin-22), while it was unaffected by classical proinflammatory cytokines like IL-1β. IL-22 activates transcription factors of the signal transducers and activators of transcription (STAT) family. It has been suggested that GPx2 is a novel target of STAT transcription factors, and the upregulation of GPx-2 by IL-22 indicates that GPx-2 might be important for the resolution of inflammation [50].

Enzyme GPx-3 is a secretory protein, holding 20% of the total blood plasma selenium [51]. The kidneys are the main source of GPx-3 in the blood plasma, with the enzyme being secreted by epithelial cells of the proximal tubules and parietal cells of the Bowman's capsule and released into the blood [52]. Deletions or hypermethylation in the promoter region of gpx-3, leading to a significant reduction of expression, were demonstrated in different types of cancer cells: prostate, Barrett's mucosa of the esophagus, gaster, bladder, different myelomas, cancers of the colon, muscle stem cells, uterine cervix etc. [53–59]. Contrariwise, overproduction of GPx-3 restrains tumor growth and metastasis [60,61]. Moreover, this enzyme takes part in the regulation of sensitivity of ovary adenocarcinoma cells against cisplatin [62]. The critical role of GPx3 was also established for the regulation of defensive mechanisms against prostate cancer; this glutathione peroxidase inhibits tumor progression and invasion. Additionally, an interrelation was established between the regulation of expression of GPx3 and tyrosine kinase receptor c-Met: the expression of c-met in prostate cancer cells was inhibited under increased expression of gpx3 [63,64].

Glutathionee peroxidase 4 (GPx-4), also called phospholipid hydroperoxide glutathionee peroxidase (PHGPx), is a monomer protein by its quaternary structure, containing Sec in its active center. This glutathionee peroxidase is capable of reducing a wide range of hydroperoxides: from hydrogen peroxide to hydroperoxy groups of complex lipids of biological membranes [65], evidencing for antioxidant properties of this glutathionee peroxidase. Real-time PCR and immunohistochemical staining revealed that GPx-4 is co-overexpressed with GPx-7 in cancerous hepatic tissues, correlating with an increase of tumor grade [66].

Currently available information about GPx-6 is scarce. It is only known that mRNA of this protein is synthesized exclusively in the olfactory epithelium [16], and the protein itself has nucleocytoplasmic localization and is not found in mitochondria [67]. Unfortunately, no data are available regarding the involvement of this protein in carcinogenesis. We have previously shown that the gpx-6 gene is not expressed in the following human cancer cell lines: *HT-1080* (fibrosarcoma), *HepG2* (hepatic carcinoma), *MCF7* (mammary adenocarcinoma), *A-172* (glioblastoma), *Hela* (cervical adenocarcinoma) and *DU-145* (prostate carcinoma) [68].

3. Thioredoxin reductases

Animal thioredoxin reductases are NADPH-dependent, FAD-containing pyridine nucleotide-disulphide oxidoreductase family protein [69,70]. Mammals have three thioredoxin reductases.

Thioredoxin reductase 1 (TXNRD1) is a key regulator of the redox balance in mammalian cells, being involved in the protection of normal and cancerous cells from oxidative stress [71–74]. Thioredoxin reductase activity in lung cancer cells was approximately the same as in normal cells and cancerous cells of the liver was lower than in normal cells. Furthermore the TXNRD activity was 25% higher in normal lung compared to normal liver tissue. The differences in the amounts of TXNRD1 protein as assessed