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Selenium, selenoproteins and cancer of the thyroid

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Abstract: Selenium is an essential mineral element with important biological functions for the whole body through incorporation into selenoproteins. This element is highly concentrated in the thyroid gland. Selenoproteins provide antioxidant protection for this tissue against the oxidative stress caused by free radicals and contribute, via iodothyronine deiodinases, to the metabolism of thyroid hormones. It is known that oxidative stress plays a major role in carcinogenesis and that in recent decades there has been an increase in the incidence of thyroid cancer. The anti-carcinogenic action of selenium, although not fully understood, is mainly attributable to selenoproteins antioxidant properties, and to the ability to modulate cell proliferation (cell cycle and apoptosis), energy metabolism, and cellular immune response, significantly altered

during tumorigenesis. Researchers have suggested that different forms of selenium supplementation may be beneficial in the prevention and treatment of thyroid cancer; however, the studies have several methodological limitations. This review is a summary of the current knowledge on how selenium and selenoproteins related to thyroid cancer.

Keywords: selenium; selenoproteins; thyroid cancer; oxidative stress; supplementation

1. Introduction

Selenium (Se) is a critical microelement that was discovered and isolated for the first time in 1817 by Swedish chemist Jöns Jacob Berzelius [1]. While not an essential nutrient for plants, it is an essential nutrient for humans and many other life forms [2, 3]. In tissues, Se forms part of the amino acids selenomethionine and selenocysteine, with the latter being responsible for the main known biological activity of selenoproteins [4].

The thyroid gland is the organ in the human body with the highest Se content per unit of tissue [5,6]. In it, selenoproteins play a crucial role in the cellular defence system against hydrogen peroxide (H_2O_2) and other reactive oxygen species (ROS) [7,8]. The overproduction of free radicals, which triggers oxidative stress (OS), has been associated with several diseases and with cancer in particular [9-11].

Thyroid cancer is the most prevalent malignant neoplasm of the endocrine system and its incidence has increased worldwide over the last four decades [12]. Histologically, there are three main types of thyroid cancer: differentiated thyroid carcinoma, anaplastic thyroid carcinoma and medullary thyroid carcinoma. Differentiated thyroid carcinoma accounts for about 95% of thyroid cancers and it originates from follicular thyroid cells, which are responsible for hormone production. This cancer can be subdivided into papillary, follicular and Hurthle cell carcinoma. The first of these is the most common and has the best prognosis [13]. Papillary thyroid cancer invades the lymph nodes, spreading to the cervical lymph nodes and also, less frequently, to other distant sites such as the lungs [14]. This pattern of dissemination is important and can be a presenting symptom of papillary carcinoma because the primary tumour is very small in some cases. When they are less than 1 cm they are often referred to as microcarcinomas [15]. Conversely, in the follicular form, haematogenous metastases are more frequent, mainly affecting the lungs and bones [14]. Hurthle cell carcinoma is follicular in origin, with at least 75% of the cells being Hurthle cells and having capsular and/or vascular invasion [16]. The Hurthle cell is characterized cytologically as a large cell with abundant eosinophilic, granular cytoplasm, and a large hyperchromatic nucleus with a prominent nucleolus. Cytoplasmic granularity is due to the presence of numerous mitochondria [17]. Hurthle cell carcinoma is poorly avid to radioiodine and poorly responsive to chemotherapy and radiation [18]. Hurthle cell carcinoma is believed to be more aggressive than common follicular carcinoma [16].

Since the thyroid is specially high in Se, and it plays an important role in this gland, the relationship of Se with the incidence of thyroid cancer has been extensively studied [11,19,20, 21, 22]. Thus, this review primarily aims to outline the current knowledge on the association between Se, selenoproteins and thyroid cancer.

2. Selenium, selenoproteins and thyroid homeostasis

Adequate Se nutrition supports the synthesis and metabolism of thyroids hormones (THs) and protects the thyroid gland from damage from overexposure to iodide which increases OS [23]. Se is thus considered to be the second most important element in thyroid metabolism after iodine, which plays a beneficial role by forming part of different antioxidant selenoproteins [19].

There are 25 different selenoproteins in the human body with at least one selenocysteine (Sec) amino acid in their structure [24,25]. Their difference in Sec incorporation efficiency leads to a "selenoprotein hierarchy" under selenium deficiency: proteins with higher Sec incorporation efficiency exploit more charged Sec-specific (Sec-tRNASec) and are more rapidly synthesized [26]. The well-studied selenoproteins have antioxidant properties (such as the glutathione peroxidase (GPx) family), are involved in redox regulation (such as the thioredoxin reductases (TXNRD) family), or transport the serum Se to tissues as selenoprotein P (SELENOP). But they also have other biological functions, being regulators of growth, development, and cell differentiation, quality control of protein biosynthesis, inhibitors of non-specific immune responses, neutralizers of inflammatory responses, or antiapoptotic function [25, 27]. Many of these selenoproteins are expressed in the thyroid gland and are involved in different processes, such as the formation and regulation of THs (the iodothyronine deiodinases (DIO) family) and redox processes linked to gland protection (GPx and TXNRD) (GPx and TXNRD) [24]. These selenoproteins are necessary for the correct functioning of the thyrotropin-releasing hormone (TRH) and thyroid stimulating hormone (TSH). TSH is the major regulator of THs biosynthesis, since it activates a complex signaling network across the TSH-receptor in thyrocytes and ends up forming T3 and T4 hormones (Figure 1) [28]. In addition, TSH is involved in the selenoproteins regulation since, through its receptor, it clearly increases the expression of GPx1, GPx3 and TXNRD1[29]. This signaling pathway also stimulate the expression of DIO1 (and DIO2 in human) inside the thyrocytes as well as H_2O_2 production [29,30,31].

THs mediate important physiological processes such as development, growth, thermogenesis, and energy metabolism, as well as regulate fatty acid, cholesterol, and carbohydrate homeostasis [32,33]. The synthesis of THs is a complex, multistep process that encompasses several redox reactions that need H_2O_2 as an oxidative agent. THs synthesis requires the oxidative iodination of specific tyrosine residues of thyroglobulin. This process is catalyzed by the enzyme thyroid peroxidase (TPO), which requires an appropriate amount of H_2O_2 for oxidation in the colloid (Figure 1). Therefore THs synthesis needs H_2O_2 production. However, this is a disadvantage for thyrocyte, as this large amount of H_2O_2 in the colloid could cross the apical membrane of the thyrocyte and accumulate inside the cell, leading to OS-damage.

As it was mentioned, GPxs protect thyroid follicles from excess H_2O_2 that is produced during the synthesis of THs [34]. Cytotoxic ROS are mainly produced in thyroid follicles following activation of TPO as a result of the interaction between H_2O_2, iodide and heme iron [35]. It has been demonstrated that the role of these selenoproteins, in relation to H_2O_2, is fundamental to the thyroid, since in severe Se deficiency the lack of GPx activity causes oxidative damage to the thyroid gland, leading to thyroid damage

and fibrosis [36, 37]. It has also been shown that pre-incubation of human thyroid follicles with Se (sodium selenite), even at low doses (10 nM) increases GPx activity and decreases cell death induced by high doses of H_2O_2, iodide or TGF-β [38, 39].

The TXNRDs also play an important role in thyroid metabolism and, together with thioredoxin (Trx) and NADPH, form the thioredoxin system, common to nearly all living cells [40]. This system functions in thiol-dependent thiol-disulfide exchange reactions, crucial for controlling the reduced intracellular redox environment, cell proliferation and growth, defence against oxidative stress or control of apoptosis. Moreover, this system participates in the synthesis of deoxyribonucleotides for DNA synthesis and is involved in cancer protection [40]. The two main thioredoxin reductases are thioredoxin reductase 1 (TXNRD1), a cytosolic and nuclear form, and thioredoxin reductase 2 (TXNRD2), which is found only as a mitochondrial form [41]. TXNRDs are highly expressed in thyroid cells [8].

Specifically, type 1 and 2 deiodinases (DIO1 and DIO2) activate THs, while type 3 deiodinases (DIO3) inactivate both tetraiodothyronine (T4) and 3,5,3′-triiodothyronine (T3) [42]. DIO1 is mainly found in the liver, kidneys and thyroid [43]. In humans, most of the circulating T3 is derived from the conversion of T4 to T3 by the actions of DIO1 [44]. Unlike DIO1, the primary function of DIO2 is believed to be the supply of T3 to the nucleus so as to meet intracellular needs, as it is a subcellularly located selenoprotein that appears in muscle, brain, heart, bone and brown adipose tissue [45]. DIO2 is important in determining T3 content in developing tissues and the adult brain, and in promoting the process of adaptive thermogenesis in brown adipose tissue. In particular, DIO2 plays a primary role in T4-mediated negative feedback in the pituitary gland and hypothalamus, in which T4 inhibits the expression of thyroid stimulating hormone (TSH) and thyrotropin-releasing hormone (TRH), respectively [33]. DIO3 is the physiological inactivator of THs, which acts by catalysing the deiodination of T4 into reverse triiodothyronine (rT3) and converts T3 into 3,3`diiodothyronine (T2) [46]. This enzyme controls the local homeostasis of THs and protects tissues from their excess [47]. Deiodinases appear to occupy a special place in the hierarchy in cases of selenium deficiencies thanks to the existence of a selenium accumulation and/or redistribution system in the thyroid gland [39]. Initial cell culture and animal experimental studies indicated that adequate nutritional selenium supply appears to limit expression of functional deiodinases during development and in the adult organism. However, the deiodinative turnover of thyroid hormones requires only minimal amounts of active enzymes, in contrast to enzymatic pathways acting on abundant metabolic intermediates (e.g. carbohydrate, fatty acid, aminoacido or proteins). This might be one of the reasons why inadequate intake of the essential trace element selenium does not initially manifest as impaired deiodinase activity, but rather affects those metabolic pathways, which are catalyzed by more abundant selenoenzymes acting at higher substrate concentrations. These include GPxs and TXNRD involved in celular redox control, several endoplasmatic reticulum-associated selenoproteins as well as selenoprotein N (SELENON), all of which contribute to protein biosynthesis or represente structural componentes of cells and tissues [6]. Although small amounts of Se are required for the activity of DIOs, a deficiency of this nutrient decreases THs synthesis and has a major impact on thyroid function [48]. Decreased production of THs

leads to stimulation of the TRH-TSH-THs axis, due to lack of control of negative feedback, increasing the production of TSH [36].

Finally, other selenoproteins, including selenoprotein P, K, S (SELENOP, SELENOK, and SELENOS, respectively) as well as SELENON are actively secreted in the thyrocytes. SELENOP is actively secreted together with GPx3 to protect thyrocytes from H_2O_2 at the colloid in absence of TSH, while the rest of the selenoproteins, within the endoplasmatic reticulum, take part in the quality control pathways [28, 49, 50]. The biosynthesis of these protective selenoproteins is mainly affected by genotype, Se availability, and inflammatory cytokines [28, 49].

3. Selenium and thyroid cancer

Se is recognised as a nutrient with many health benefits in humans and other mammals such as decreasing the incidence of cancer [51]. Although the specific mechanisms are not fully understood, the chemopreventive effects of Se result from its protective role on cell membranes against OS, its stabilising effect on DNA and its enhancement of cellular immune response [52]. This element also inhibits the proliferation of tumor cells by acting on the expression of the Bcl-2 apoptosis-suppressor gene and p53 tumor suppressor gene, which plays an important role in the processes of control and regulation of cell lifecycle and DNA replication. Furthermore, in vitro and in vivo studies have revealed that both Se compounds and selenoproteins act as anti-metastatic agents, inhibiting cell motility, migration and invasion, and reducing angiogenic factors [53]. Nevertheless, it is important to mention that some selenoproteins, like TXNRD1, SELENOF and GPx2 exhibit a split role in preventing and promoting cancer [51]. In addition, Se may exhibits a U-shape relation with cancer risk [54, 55].

Various studies have been carried out to examine the relationship between Se and the development of thyroid cancer (Table 1). Overall, the findings suggest a potential association between lower Se concentrations and the development of thyroid cancer.

Kucharzewski et al. [56] found that whole blood Se concentrations in a group of patients (n=21) with thyroid cancer were significantly lower (0.57 µg/g) than in a control group (0.71 µg/g, $p < 0.01$). There is no information as to the histological types of cancer included in the research. Moncayo et al. [57], in a study of patients with benign and malignant thyroid pathologies taking thyroid medication found that serum Se levels were lower in patients with papillary (n=73) (0.080 ± 0.020 µg/ml) and follicular (n=42) (0.077 ± 0.021 µg/ml) carcinoma than in the control group (0.091 ± 0.021 µg/ml), $p = 0.015$ and $p = 0.031$ respectively). On the other hand, Przybylik-Mazurek et al. [58] found no significant changes in Se levels in the serum of patients with papillary carcinoma (n=25) and in that of patients with follicular carcinoma (n=13) compared with a control group. The same finding was noted for glutathione peroxidase 3 (GPx3) activity. The tumours were diagnosed histologically on routine basis, after surgery. The lag time between surgery and this study examination ranged between 8 and 120 months, with mean ± SD of 42.9 ± 25.3 months. Patients with carcinomas were receiving thyroid medication. Subsequently, in 2013, Jonklaas et al. [59] conducted a study involving a group of euthyroid patients with indication for thyroidectomy for suspected thyroid cancer or nodular disease. Of the cohort, 48 patients had differentiated thyroid carcinoma and 17 had benign thyroid pathology. 33 of patients with

Authors, year	Study design	Description of participants	Blood Se levels	Main results	Reference

differentiated thyroid carcinoma had papillary carcinoma. Blood samples were obtained two to four weeks before thyroidectomy. In the final analysis, although Se concentrations were not significantly lower in thyroid cancer patients, they were inversely correlated with disease stage ($p = 0.011$).

Kucharzewski et al., 2003	- Cross - sectional study	- Thyroid cancer (n=21) - Control (n= 50)	- Whole blood (TXRF) - 0.57 ± 0.12 (µg/g) - 0.71 ± 0.06 (µg/g)	- Whole blood Se levels were significantly lower in the group of patients with thyroid cancer vs. control group ($p < 0.01$)	[56]
Moncayo et al., 2008	- Cross - sectional study	- Papillary carcinoma (n=73) - Follicular carcinoma (n= 42) - Control (n= 554)	- Serum (AAS) - 0.080 ± 0.020 (µg/ml) - 0.077 ± 0.021 (µg/ml) - 0.091 ± 0.021 (µg/ml)	- Serum Se levels were significantly lower in patients with papillary and and folicular carcinoma vs. control group ($p = 0.015$ and $p = 0.031$ respectively)	[57]
Przybylik-Mazurek et al., 2011	- Cross - sectional study	- Papillary carcinoma (n=25) - Follicular carcinoma (n= 13) - Control (n=20)	- Serum (AAS) - 0.78 ± 0.12 (µM/L) - 0.80 ± 0.14 (µM/L) - 0.76 ± 0.12 (µM/L)	- No significant differences among the groups in serum Se levels	[58]
Jonklaas et al., 2013	- Cross - sectional study	- Differentiated thyroid carcinoma (n=48) - Benign thyroid disease (n= 17)	- Serum (AAS) - 0.116 ± 0.014 (µg/ml) - 0.117 ± 0.010 (µg/ml)	- No significant differences among the groups in serum Se levels - Serum Se levels were inversely correlated with thyroid cancer stage ($p=0.011$)	[59]
Baltaci et al., 2017	- Cross - sectional study	- Group 1: male thyroid cancer patients group (n = 15) - Group 2: female thyroid cancer patients group - (n = 15); - Group 3: male control group (n = 10) - Group 4: female control group (n = 10).	- Serum (ICP-AES) Pre-operative (µg/dl) - Group 1: 52.4 ± 5.6 - Group 2: 50.5 ± 4.8 - Group 3: 70.1 ± 6.9 - Group 4: 66.9 ± 7.3 Post- operative (µg/dl) - Group 1: 54.6 ± 5.5 - Group 2: 51.7 ± 5.2 - Group 3: 69.5 ± 7.1 - Group 4: 67.6 ± 5.9 15 days after the operation (µg/dl) - Group 1: 70.6 ± 5.9 - Group 2: 70.2 ± 5.5 - Group 3: 72.5 ± 6.5 - Group 4: 68.6 ± 8.0	- Pre- and postoperative serum Se concentrations in patients with thyroid cancer were significantly lower in serum vs. control groups ($p < 0.05$) - 15 days after the operation, insignificant differences were detected in serum Se concentrations among the groups	[60]
Mehl et al., 2020	- Cross - sectional study	- Thyroid patients (n=323) - Control (n=200)	- Serum (TXRF) - 76.9 ±18.8 (µg/L) - 85.1 ± 17.4 (µg/L)	- A high fraction of patients (37.5%) was classified as Se-deficient (serum Se concentrations <70 µg/L), in particular the patients with thyroid malignancy (59%)	[61]

Table 1. Summary of the most important clinical trials examining the relation between blood Se levels and thyroid cancer. TXRF- total-reflection X-ray fluorescence, AAS- atomic absorption spectrometry, ICP-AES- inductively coupled plasma - atomic emission spectrometry.

In 2017, Baltaci et al. [60] conducted a study to examine the changes in serum Se levels before, immediately after and fifteen days after thyroidectomy in patients (n=30) with

thyroid cancer (papillary carcinoma). In addition, thyroid tissue samples were taken from all subjects in the postoperative period. Serum Se levels were significantly decreased ($p < 0.05$) before and immediately after surgery compared with the controls. Fifteen days later Se levels were similar to those found in the control group. Thyroid Se levels postoperatively were significantly higher ($p < 0.05$) than those of the controls. The fact that the same patients have less Se in their serum indicates, according to the authors, that Se is retained excessively in the thyroid and that changes in the levels of this mineral could be related to the pathogenesis of thyroid cancer. Very recently, Mehl et al. [61] carried out a study to assess the levels of trace elements (iodine, Se, copper and zinc) in patients with thyroid pathologies in a European metropolis. The authors found that patient serum Se values were lower than those in control group participants ($p < 0.0001$) More importantly, it was found that it was in the group of patients with thyroid malignancy (n= 17) that a higher fraction of Se deficient patients were found (59%).

It is not yet clear whether the decrease in serum Se levels detected in most studies on thyroid cancer is a consequence or a cause of the disease or if it is simply associated with related pro-inflammatory conditions that alter the expression and secretion of hepatic selenoprotein P, the main contributor to the Se content in serum [6]. A decrease in this protein may be a phenomenon secondary to negative regulation triggered by inflammatory mediators such as tumour necrosis factor α (TNF-α), interleukin 1 β (IL-1 β) and interferon γ (IFN- γ) [62, 63].

4. Selenoproteins and thyroid cancer

Se is co-translationally inserted in protein as the 21st amino acid, Sec and accounts for a vast majority of the biological activities of Se [64]. Twenty-five selenoproteins have been identified in the human proteome and twenty-four in rat and mouse proteome [65]. The share of selenium in the metabolic pathways associated with the protection of cells against oxidative stress causes changes in the activity of selenoproteins. Selenoprotein expression is regulated by the concentration of this element [66, 67]. However, there are differences in protein expression. These differences are the result of changes in mRNA translation or the reduction of its stability (increased degradation) [67].

There have also been several studies relating the activity and expression of seleno-proteins with thyroid cancer, the most studied being the DIO1 and DIO2 implicated in the control of THs turnover, and GPx1, GPx3 and TXNRD1, which protect thyroid from OS-damage [11, 21, 68, 69, 70, 71, 72, 73, 74].

4.a. Selenoproteins implicated in the control of THs turnover

Deiodinase expression patterns in thyroid cancers vary and depend on the type and differentiation of the tumour stage. T3 is known to regulate the expression and/or activity of tumour suppressors genes and oncogenes. Thus, local alterations in the expression and activity of DIOs may have the potential to influence carcinogenesis [75].

Different studies in papillary and follicular carcinomas support this fact. In 2005, Arnaldi et al. [68] found that DIO1 and DIO2 were underexpressed in papillary carcinoma following evaluation using cDNA analysis of three thyroid cancer cell lines. In the same year, Ambroziak et al. [69] identified significantly decreased levels of DIO1

and DIO2 expression ($p = 0.017$ and $p = 0.012$, respectively) in papillary carcinoma samples compared to control group samples (thyroid tissue from a non-cancer affected part in human patients) and Meyer et al. [70] found in human patients that DIO1 expression and activity were decreased in papillary carcinoma samples compared to surrounding normal tissue (0.25 ± 0.24 vs. 1.09 ± 0.54 arbitrary units (AU), $p < 0.001$ and 0.08 ± 0.07 vs. 0.24 ± 0.15 pmol T4/min/mg protein, $p = 0.045$, respectively). However, in the latter study, the authors found a significant increase in DIO1 expression and activity in tissue samples with follicular carcinoma (1.2 ± 0.46 vs. 0.67 ± 0.18 AU, $p = 0.038$ and 1.20 ± 0.58 vs. 0.20 ± 0.10 pmol T4/min/mg protein, $p < 0{\cdot}001$, respectively). They also detected an increase in DIO2 activity in tissue samples with metastatic follicular carcinoma (5.20 ± 0.81 vs. 0.30 ± 0.27 fmol T4/min/mg protein, $p < 0.001$) Subsequently, Romitti et al. [76] analysed the expression and activity of DIO3 in papillary carcinoma human samples. The researchers observed that the augmentations in D3 activity were paralleled by increased DIO3 mRNA levels (approximately fivefold). They also found a positive correlation between tumour size and DIO3 activity ($r=0.68$, $p=0.003$). Finally, they found that an increase in DIO3 activity in tumour samples was associated with more advanced disease at diagnosis.

Taken together, one could posit that the changes found in the expressions of DIOs in papillary carcinoma samples could cause a decrease in intracellular hormones and favour tumour proliferation. Increased DIO3 and decreased DIO1 and DIO2, leading to decreased T3 concentrations, could provide an advantage for tumour cell proliferation, as THs can block oncogenic Ras-mediated proliferation, which specifically interferes with the activity of the mitogen-activated protein kinase (MAPK) signalling pathway [71]. This pathway has previously been implicated in DIO3 overregulation in other pathological changes [77,78]. Genetic alterations leading to the activation of this pathway are a distinguishing marker of papillary thyroid carcinoma [76]. It is known that DIO3 is upregulated in the papillary thyroid carcinoma-derived cell line, K1, by transforming growth factor β 1 (TGF β 1). Furthermore, it is known that treatment with the inhibitors U0126 (ERK pathway) and SB203580 (p38 pathway) leads to blocking of the MAPK pathway and subsequent decrease of DIO3 and inhibition of transcriptional induction of DIO3 through TGF β 1, which clearly suggests that DIO3 is positively regulated through the MAPK signalling pathway [76,79]. In the development of this carcinoma, the BRAF gene is one of those principally affected, with the BRAFV 600 E mutation occurring frequently, through substitution of a valine for a glutamic acid at position 600 [80]. In the study described above, Romitti et al. [76] found that the samples in which this mutation was present were those in which there was greater DIO3 activity. Subsequently, Romitti et al. [81] found that activation of the sonic hedgehog (SHH) pathway could also be involved in DIO3 upregulation through a signalling cooperation with the MAPK pathway. SHH signalling is critical for embryogenesis and other cellular processes such as proliferation and differentiation. Disruption of SHH signalling leads to several human diseases and appears to contribute to the development of neoplastic processes. Reactivation of SHH occurs in about 25% of human tumours and has been associated with the induction of DIO3 [81-83].

Interestingly, retinoic acid (RA) has been shown to induce DIO1 activity in human thyroid carcinoma cell lines. RA transcriptionally increased the abundance of the p27 subunit of DIO1. RA stimulated DIO1 activity to a greater extent in follicular thyroid

carcinoma-133 cells than in follicular thyroid carcinoma-238 cells and had no effect in anaplastic thyroid carcinoma. Retinoid induction of DIO1 may thus serve as a parameter of functional differentiation of thyroid follicular carcinoma cells [84].

The higher DIO2 activity, in metastatic follicular carcinoma, without significant changes in DIO2 mRNA levels, suggests that DIO2 uprregulation occurs mainly via post-transcriptional regulatory mechanisms [71]. The expression pattern of DIO2 reveals that this selenoprotein is encoded by an cAMP-sensitive gene, so its expression increases in tumoural contexts, such as follicular carcinoma, in which there is an overstimulation of the cAMP pathway [45].

4.b. Selenoproteins which protect thyroid from OS-damage

OS plays an important role in carcinogenesis by inducing DNA damage and its effects on intracellular signal transduction pathways. ROS can induce almost all forms of DNA damage that have been described in the dysfunction of genes involved in cancer genesis and play a key role in cancer development by originating and maintaining oncogenic phenotypes [65].

In the thyroid gland, high amounts of H_2O_2 are produced, which triggers high OS, during synthesis of thyroid hormones in follicular cells. On the other hand, as mentioned above, Se deficiency, regardless of the cause, diminished expression and activity of selenoproteins with antioxidant functions such as GPx and TXNRDs. Thus, these selenoproteins cannot fight properly ROS generated during cellular metabolism, increasing OS and cancer genesis [85]. Moreover, thyroid cancer itself can induce OS through inflammation, which is one of its significant features, and this in turn is a classic source of ROS. As a consequence of OS, instability in DNA can be produced and maintained, which are believed to be neoplasia-preceding events in thyroid cells [86].

There are also two ‘professional’ ROS-generating systems in thyroid gland, the NADPH oxidases DUOX1 and NOX4, which cause DNA damage that may promote chromosomal instability, tumourigenesis and anaplasia. Ionising radiation and mutation of oncogenes such as RAS and BRAF positively regulate these NADPH oxidases, playing a key role in thyroid carcinogenesis [87]. In turn, ROS can stimulate MAPK, phosphatidylinositol-3-kinase (PI3K) and NFκB pathways, forming a vicious circle that spurs carcinogenesis [86].

In this context, Young et al. [88] evaluated the levels of DNA damage and lipid peroxidation, measured 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG) and the 4-HNE respectively, in patients with follicular thyroid adenoma (n = 71), papillary thyroid carcinoma (n = 45) and follicular thyroid carcinoma (n = 17). They established that the cytoplasmic expression of 8-oxo-dG and 4-HNE was significantly higher in thyroid tissue samples from patients with follicular adenoma, follicular carcinoma and papillary carcinoma compared to their normal tissue (all p values < 0.001). Similarly, increased nuclear levels of 8-oxo-dG were found in thyroid tissue samples from patients with follicular adenoma, follicular carcinoma and papillary carcinoma compared to their normal tissue (p values < 0.07, $p < 0.001$ and $p < 0.001$, respectively).

Since a correct oxidative balance plays an important role in thyroid carcinogenesis, the main antioxidant selenoproteins expressed in thyroid have been analysed in this context.

GPx1 is distributed throughout the human body and its main activity is antioxidant [1]. It catalyses the reduction of H_2O_2, using reduced glutathione (GSH), transforming it into water. During this process, glutathione is oxidised, subsequently returning to its original state through the action of the enzyme glutathione reductase (GR), so as to maintain GSH levels [89]. GPx1 is one of the selenoproteins that is most sensitive to Se alterations in the body, exhibiting dramatic reductions when this microelement is depleted [90].

Zagrodzki et al. [21] detected decreased GPx1 activity in anaplastic carcinoma samples compared to normal tissue samples from surrounding parts of the gland. Previously, Hasegawa et al. [72] found decreased expression of this enzyme in the same type of thyroid cancer. More recently, Metere et al. [11] analysed the expression of GPx1 and TXNRD1 in tissue samples with papillary carcinoma. The researchers found a reduction in the expression of these enzymes compared to that observed in healthy tissue samples taken from the same patients.

Several studies show a decrease in GPx1 expression in different tumours and suggest a protective role for GPx1 [91]. GPx1 can limit oxidant-induced cell mutagenesis, as well as the inflammatory responses that promote certain cancers. Loss of GPx1 in the early stages of carcinogenesis may contribute to cancer initiation and, in later stages, its deficiency may induce proliferative responses [92].

With respect to GPx3, this selenoenzyme is the only extracellular enzyme of the GPx family [65]. It has an important extracellular antioxidant role and affords protection to the thyroid against H_2O_2 [36]. It is one of the most highly expressed selenoproteins in follicular cells and, as a result, contributes to the high Se levels of the thyroid [39, 93].

In situ hybridization revealed to Menth et al. [73] reduced levels of GPx3 in Hurthle cell carcinoma. Subsequently, Schmutzler et al. [94] also used in situ hybridization to study the localization of various selenoproteins within the thyroid gland using goiter, autoimmune thyroiditis or thyroid tumor samples. The researchers found that the strongest hybridization signals were obtained from GPx3 mRNA. In thyroid carcinomas, the follicular structure of the normal thyroid was disrupted and GPx3 signals were evenly dispersed over the whole sample areas or parts of it without any of the thyroid-specific differential distribution patterns observed, e.g., in goiter. More recently, Zhao et al. [74] investigated the expression of GPx3 in patients with primary papillary carcinoma. They found that its expression was often reduced/absent in the carcinoma samples compared to surrounding healthy tissue samples. In addition, they found that GPx3 was frequently methylated in the carcinoma samples. These authors also found that the reduced/absent expression was related to hypermethylation of the promoter region and that carcinoma metastasis was suppressed by GPx3 through inhibition of the Wnt / β-catenin signalling pathway. In this context, gene hypermethylation has also been indicated as a cause of down-regulation in various tumour tissues [95-97]. Decreased GPx3 expression has been associated with tumour initiation, proliferation and migration as a consequence of increased oxidative stress and pro-

tumourigenic redox signalling. It is currently unclear whether loss of GPx3 leads to compensatory increases in other antioxidant enzymes in tumour cells [98].

GPx7 is mainly involved in maintaining the redox homeostasis of the body [99]. In functional terms, GPx7 is not selenocysteine-containing peroxidase due to the lack of a GSH-binding domain, but rather a protein disulfide isomerase peroxidase. It is located in the lumen of the endoplasmic reticulum, where it uses the H_2O_2 produced by endoplasmic reticulum oxidoreductase 1 alpha to oxidize protein disulfide isomerase [100]. Recently, Li-Dan Liu et al. [99] investigated the expression of GPx7 in papillary thyroid carcinoma tissues. In this study, GPx7 was found to be expressed at higher levels in papillary thyroid carcinoma tissues and papillary thyroid carcinoma cell lines than in other thyroid tissues and related to the size of papillary thyroid tumors. GPx7 was successfully knocked down in K1 cells, and knockdown of GPx7 inhibited cell proliferation and clone formation as well as increased apoptosis and caspase 3/7 activity in K1 cells. According to the authors, these results demonstrated that GPx7 promotes the growth of papillary thyroid carcinoma but the mechanisms underlying of action of GPx7 on proliferation and apoptosis are still unclear.

Overexpression and hyperactivation of TXNRD1 have been described in several cancers [101]. Moreover, the high expression and activity of TXNRD1 has been directly related to cellular protection against oxidative stress induced by 4-hydroxynonenal (4- HNE), one of the end products of lipid peroxidation [102].

Metere et al. [11] suggest that the reduction in TXNRD1 and GPx1 expression seen in their study may result from hyperproduction of free radicals, which were not adequately counteracted by the altered antioxidant system in cancer cells, possibly due to increased consumption of antioxidants. Furthermore, the authors detected a significant increase in free radical production in all thyroid tumour tissue samples, compared with healthy tissue from the same patients.

Finally, it is important to bear in mind that not just selenoproteins protect thyroid from OS-damage. For instance, J. Maier et al. [103] detected a higher mRNA expression for superoxide dismutase (SOD)-3 isoform and increased total SOD enzyme activity in the thyroid exposed to iodine deficiency compared to normal diet. Especially increased SOD-3 expression, which is the extra cellular SOD isoform, could detoxify superoxide in the follicular lumen and might act as an effective shield against oxidative stress induced by ROS in response to luminal H_2O_2. Catalase, as well as the peroxiredoxins (PRDX), also protect thyroid cells against H_2O_2 [104, 105].

5. Selenium supplementation and thyroid cancer

Due to growing evidence suggesting the vulnerability of cancer cells to oxidative stress, the idea of targeting the antioxidant capacity of tumour cells has grown as a therapeutic strategy, leading to the rational design of new anticancer agents. Accordingly, Se has stood out as a redox modulator of cancer cells among compounds with great anti-cancer potential [106]. Different forms of Se have anti-cancer effects on different cancers, such as hepatocarcinoma, breast cancer, oesophageal cancer, prostate cancer and ovarian cancer, among others [25]. However, several studies have shown that Se has a tumor-promoting effect. The NPC trial, for example, found that selenium supplementation (as

selenized yeast; 200 μg/day) significantly increased the risk of non-melanoma skin cancer and squamous-cell carcinoma [107]. Another study was conducted on the population of the Reggio Emilia municipality in Italy, who were exposed to 7–9 μg/liter of selenate in tap water from 1975 to 1985. Melanoma incidence was 3.9 times higher in selenium-exposed people than in non-selenium exposed people, according to the findings of this study [108]. More recently, Tsuji et al. [109] detected that the deficiency in the 15 kDa selenoprotein inhibits human colon cancer cell growth. Because Sep15 expression depends on the selenium status, these results are important in regards to differential intake of, and response to, dietary selenium and potential cancer risk.

The anti-cancer activity of different forms of Se depends on many factors, such as chemical form, dose, acute vs. long-term nutrition, preventive or pharmacological application, type of cancer cell, bioavailability, and stage of disease [110]. Selenium exhibits chemopreventive activity when used at higher than optimal concentrations or applied for cancer treatment in combination with chemotherapy and radiation [111]. Also, the greatest anticarcinogenic Se effect has been obtained when it is administered before or at an early stage of disease development. It is important to bear in mind that one of the marginal problems of Se use is its narrow range between the toxic dose and the dose necessary for the proper functioning of living organisms [112]. In recent years, due to both their reduced toxicity and their selectivity, Se nanoparticles are considered to be more effective in cancer treatment than other Se compounds. These nanoparticles are prepared by chemical, physical or biological methods, and contain a main inorganic therapeutic core of elemental Se, which presents better antitumor properties than the Se salts [113]. Based on this, Kuršvietienė et al. [110], studying the role of Se and the selenoproteins in maintaining cellular redox balance and anticancerogenic function, suggested that nanoparticles are taken up by cancer cells via endocytosis. In these cells, Se nanoparticles act as prooxidants producing endoplasmic reticulum stress, mitochondrial membrane cleavage, apoptosis, DNA fragmentation, and cell cycle arrest. Besides, Khurana et al. [114] trying to understand the various pharmacological activities of Se nanoparticles as well reduction in toxicity of Se upon nanoparticlization, proposed that Se nanoparticles act as antioxidants against high ROS generated by cancer cells. Moreover, their low toxicity, their high bioavailability and biocompatibility are some of the properties that also make Se nanoparticles an attractive drug delivery vehicle, reducing the systemic toxicities associated with conventional chemotherapeutic drugs and working synergistically to improve their efficacy [115]. Very recently, beneficial in vivo results have been obtained using a tumor model of mice preinoculated with K1 cells and treated with a combination of drugs including Se nanoparticles for the treatment of thyroid cancer [116]. However, additional and independent studies are needed to confirm these results in animals. On the other hand, in order to apply the anticancer benefits of Se nanoparticle in clinical studies, extensive studies on its safety and synergistic activities with other therapeutic compounds are still needed.

Even though Se supplementation may combat the development of thyroid cancer, the data that exist so far are not conclusive. The question of whether a Se deficit is a consequence of thyroid cancer or a predisposing risk factor remains unresolved [20]. Access to mostly retrospective data, relatively small patient groups and short observation periods are significant limitations of the studies performed [117].

Recent studies have shown beneficial effects of Se supplementation. Nettore et al. [7] conducted a study to characterise the molecular effects determined by Se supplementation (10 nM sodium selenite) on thyroid follicular cells, using the rat thyroid follicular cell line FRTL5 as a model. They examined the effect of Se on cell growth, mortality and proliferation, and modulation of pro- and anti-apoptotic pathways, concluding that Se supplementation improved the growth rate of FRTL5. Furthermore, they found that Se reduced cell death and was associated with a downregulation of the proapoptotic genes p53 and Bim and an upregulation of the antiapoptotic genes NF-kB and Bcl2. More recently, Ruggeri et al. [118] investigated the effects of Se on oxidative damage in human thyroid follicular cells and thyroid fibroblasts in vitro. Primary cultures were exposed to H_2O_2 in the presence or absence of Se, in the form of selenomethionine or selenite. Administration of increasing concentrations of Se, from 0.05 to 20 μM, significantly prevented the genotoxic and cytotoxic effects of H_2O_2 by increasing cell viability, reducing morphological abnormalities, improving cellular DNA integrity and decreasing lipid peroxidation. H_2O_2-induced apoptosis was reduced and almost eliminated, as evidenced by reduced caspase-3 activity and modulation of the expression of the antiapoptotic Bcl2/proapoptotic Bax genes. Furthermore, both selenomethione and selenite induce an increase in GPx activity which, according to the authors, suggests that these protective effects may be, in part, mediated by these selenoproteins.

Animal and human studies have suggested that supplementation with different forms of Se at concentrations higher than those required to maximise selenoprotein expression decreases the incidence of cancer [119]. However, a recent meta-analysis that took as one of its research questions "describe the efficacy of Se supplementation for cancer prevention in humans" found no evidence to suggest that increasing Se intake, through diet or by supplementation, prevents cancer in humans [120]. All observational studies and randomised trials appear to be highly conditioned by population characteristics with regard to covariates and confounding factors, which include initial Se intake levels, antioxidants cosupplemented, age, gender, diet, lifestyle [65].

6. Conclusions and future perspectives

Se and selenoproteins play a significant role in the development of thyroid cancer. It is generally agreed that oxidative stress plays an important role in cancer genesis and tumour progression. Most studies indicate an association between Se deficiency and the development of thyroid cancer, as well as significant changes in the expression and activity of various selenoproteins in different types of thyroid cancer. The mechanisms underlying these changes are not yet fully understood. Although Se supplementation is theoretically beneficial for cancer, in practice the studies are not conclusive, mainly due to methodological limitations. In this respect, and specifically for thyroid cancer, the literature is also very scarce. Nevertheless, Se components have already become part of the therapeutic strategy to fight thyroid cancer. It is expected that in the near future there will be a greater knowledge of these components' mechanisms of action, in order to improve their use in the prevention and treatment of thyroid cancer.

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