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Review

Selenoproteins that function in cancer prevention and promotion

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ABSTRACT

Of the many health benefits attributed to selenium, the one that has received the most attention is its role in cancer prevention. Selenium-containing proteins (selenoproteins) have been shown in recent years to have roles in cancer prevention. However, selenoproteins have diverse functions and their view as antioxidants is oversimplified. Some selenoproteins appear to have a split personality in having roles both in preventing and promoting cancer. The contrasting roles of one selenoprotein, thioredoxin reductase 1, in cancer are discussed in detail, but as also noted, at least one other selenoprotein may also have such a dual function. In addition, we discuss examples of inhibition of cancer development by selenoprotein deficiency in mouse models. These studies highlight the complex nature of selenium in relation to cancer.

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1. Introduction

Among the many health benefits attributed to selenium that include roles in cancer prevention, inhibiting viral expression, delaying the progression of AIDS in HIV-infected patients, preventing heart disease and other cardiovascular and muscle disorders, slowing the aging process, and having roles in mammalian development, male reproduction and immune function [1], the one that has received the most attention is its role as a cancer chemopreventive agent.

The manner in which this element acts in preventing cancer is poorly understood; and there has been considerable debate in the field whether selenium-containing proteins (selenoproteins) or low molecular weight (non-protein) selenocompounds, or both, are effective in preventing cancer [e.g., see [2–11]. Investigators favoring the proposal that selenocompounds have more influence have argued that the effectiveness of selenium in cancer prevention is seen only following supplementation of the diet with amounts of selenium that are significantly higher than the normal dietary intake [12] and these higher amounts do not increase selenoprotein levels in circulating blood [13,14]. Although substantial experimental data have been obtained supporting the selenocompound proposal [e.g., see [2–5,7,11], many of these studies were carried out in mice supplemented with selenocompounds at levels that could not be used in humans for safety reasons and at the time when an in-depth understanding of only a limited number of selenoproteins was available. We now know that humans have 25 selenoprotein genes and rodents 24 [15].

Our knowledge about the roles of several selenoproteins in cancer is rapidly developing from different approaches that include biochemical, genetic and animal studies. These studies have provided strong evidence that selenoproteins play a major role in cancer prevention and other health benefits in a number of settings and model systems [e.g., see [1,6,8–11,16–19]. For example, two recent studies involving mouse models have shown a direct role of selenoproteins in colon [20] and prostate [21] cancers. Interestingly, one of these studies demonstrated that low molecular selenocompounds also had a role in cancer prevention [20].

Several excellent articles in this special issue on "Selenoprotein expression and function" cover related topics on the roles of selenoproteins in cancer. In the present review, we highlight the complexity of the roles of selenium in cancer and discuss selenoproteins that appear to have roles in both preventing and promoting cancer. We have used thioredoxin reductase 1 (TR1) as a model example to examine the possible molecular mechanisms of how a single protein can have such opposing functions. Finally, in contrast to the well-established role of selenium in preventing cancer, we discuss incidences where selenium deficiency may inhibit tumorigenesis.

2. Selenoproteins harboring a split personality in their roles in cancer

It is becoming more and more apparent that some selenoproteins can serve roles as both a cancer preventing agent and, once the malignancy is initiated, as a cancer promoting agent [e.g., see [22] and references therein]. We will focus on one such selenoprotein, TR1, and also consider another selenoprotein, the 15 kDa selenoprotein (Sep15).

3. Thioredoxin reductase 1 (TR1)

TR1 is among the most investigated selenoproteins due to its essential role in the thioredoxin system as the enzyme that controls the redox state and therefore the function of thioredoxin by keeping this protein in the reduced state [23]. TR1 is considered as one of the major redox regulators in mammalian cells [24,25] with roles in cell proliferation, transcription, DNA repair and angiogenesis [26–29]. It also contributes to antioxidant defense and acts as a redox regulator of cell signaling [24–29]. In mammals, TR1 is an essential enzyme that plays a major role in embryogenesis [30]. It is expressed in all cell types and organs and its Sec moiety, which is the C-terminal penultimate residue [31], is required for catalytic activity [e.g., see [32,33]]. Since TR1 acts by reducing Trx1 and other redox regulators in cells [23–25], and since oxidative stress is one of the principal characteristics of cancer cells [26–29], this selenoenzyme most certainly serves as a cancer preventive protein [34]. The observations that TR1 activates the p53 tumor suppressor, manifests other tumor suppressor activities [35], and is specifically targeted by carcinogenic electrophilic compounds [36] also suggest that TR1 plays a major role in cancer prevention. On the other hand, TR1 has a role in promoting cancer. Its over-expression in many cancer cell lines and cancers [26–29], targeting by a number of anti-cancer drugs and potent inhibitors that alter cancer-related properties of malignant cells [26–29,37,38] and its deficiency that reverses cell morphology and other cancer characteristics [22,39] all point to a role of TR1 in cancer promotion. These observations have led to the proposal that TR1 is a target for cancer therapy [22,26–29,34,37–39].

Whether the cancer promoting or cancer preventing properties of TR1 have greater influence on the fate of a cell may be difficult to predict. An elucidation of how TR1 exerts such contrasting effects, however, may lead to a better means of utilizing these properties in cancer prevention and/or cancer therapy.

To examine how TR1 functions metabolically in preventing cancer and then switching its role to promoting cancer, we initially knocked down this protein in a mouse lung cancer cell line, LLC1 [39]. Many of the cell's malignant properties were reversed including morphology, anchorage-independent growth and expression of two cancer-related mRNAs, Hfg and Opn1. Interestingly, mice injected with the knocked down TR1 cells manifested a pronounced reduction in tumor progression and metastasis compared to mice injected with control, malignant cells as shown in the Figure. Furthermore, tumors arising in mice injected with TR1 knockdown cells were much smaller in size than the tumors from mice injected with control, malignant cells, and most importantly, they had lost their targeting construct (Fig. 1). Clearly, over-expression of TR1 in these cancer cells is required to maintain their tumorigenic properties and TR1 appears to be a major driver in this cancer model. In addition, examination of a number of human and mouse cancer cell lines showed that they had elevated levels of TR1, but not other selenoproteins, and knockdown of TR1 in these cells disrupted characteristics of malignancy, albeit to varying degrees ([22]; and Yoo, M.-H., Carlson, B.A., Gladyshev, V.N., and Hatfield, D.L., unpublished data). The latter data demonstrate that interference with TR1 function in cancer cells may disrupt the malignancy process and further substantiate TR1 as a pro-cancer protein and a target for cancer therapy.

Although the above studies show a direct connection between enriched TR1 levels in cancer cells and the malignancy process, they did not elucidate the molecular basis for the role of this protein in promoting malignancy. One limitation of these studies is that they did not have a parental, normal cell line for comparison. To overcome this limitation, the consequences of targeting the knockdown of TR1 in an oncogenic *k-ras* cell line were compared to the parental (normal) cell line, and it was found that the resulting morphological changes in the knockdown cells were more characteristic of the parental, normal cells [22]. The *k-ras*, TR1 knockdown cells, when grown in serum-deficient medium, lost their self-sufficiency growth properties and manifested a defective progression in their S growth phase. Furthermore, they had a decreased expression of DNA polymerase α which is an enzyme important in DNA replication. The results demonstrate that over-expression of TR1 has a direct role in many of the requirements governing the malignancy process and suggest avenues for the inhibition of cancer [e.g., see [22]].

4. Selenoprotein 15 (Sep15)

Sep15 was discovered in the late 1990s in human T-cells as a 15 kDa selenoprotein [40]. It was found to exist in a complex with UDP-glucose:glycoprotein glucosyltransferase (UGTR), a protein that is involved in the quality control of protein folding [41], and to be localized in the endoplasmic reticulum of mammalian cells [42]. Recent data show that Sep15 may play a role in the reduction or isomerization of disulfide bonds of glycoprotein substrates of UGTR [43]. The gene for Sep15 consists of five exons and four introns and is localized on chromosome 1p31 that is a locus often deleted or mutated in human cancers [44]. The highest levels of Sep15 were found in human and mouse liver, kidney, prostate, brain and testes, but its levels were reduced in hepatocarcinoma and a cancer prostate cell line [44]. Interestingly, two polymorphic sites occur in the human Sep15 gene at nucleotide positions 811 (C/T) and 1125 (A/G) in the 3′UTR and one of these, an A^{1125}/G^{1125} polymorphism, is present in the Sep15 selenocysteine insertion sequence (SECIS) element [40]. These polymorphisms manifest different responses to selenium supplementation and efficiency of Sec incorporation into protein [44,45], as well as differences in allele frequencies among different ethnic groups and among breast or head and neck tumors within African Americans [45]. In addition, Sep15 was found to be down-regulated more than 50% in malignant mesothelioma cells and, although growth was inhibited and apoptosis induced in response to selenium in a dose-dependent manner in malignant cells, those cancerous cells carrying a knockdown of Sep15 were less responsive to selenium [46]. Furthermore, malignant mesothelioma cells carrying the Sep15 A^{1125} variant were less responsive to the effects of selenium than the corresponding cells expressing the other polymorphic form. Among smokers, an increase in lung cancer risk was observed in individuals with a GG or GA^{1125} genotype compared to those individuals with an AA^{1125} genotype [47].

Many of these studies suggested a role of Sep15 in cancer development and/or risk that included its chromosomal location, its variation in expression patterns with the different polymorphic forms wherein they responded differently to selenium levels and protein incorporation, and in its expression patterns in normal and malignant tissues and cells. In spite of these observations suggesting a role of Sep15 in cancer protection, it was recently observed that Sep15 knockdown in a colon cancer cell line reversed many of the cancer characteristics suggesting that it has a dual personality in colon cancer ([48]; and Irons, R., Tsuji, P., Ouyang, P., Yoo, M.-H., Xu, X.-M., Carlson, B.A., Hatfield, D.L., Gladyshev, V.N., and Davis, C.D., unpublished data).

5. Implication of selenoprotein deficiency in preventing tumorigenesis

An additional issue relevant to the contrasting roles of selenium/selenoproteins in cancer is the role of selenium deficiency in this process. On the surface, the possibility that selenium deficiency has anti-cancer effects is contrary to the dominant views on the role of selenium in cancer prevention, but there is emerging evidence that this may be the case in some cancers. One study involved an examination of the progression of peritoneal plasmacytoma (PCT) in selenium-deficient mice [49]. The development of PCT in mice was dependent on chronic peritoneal inflammation wherein PCT was
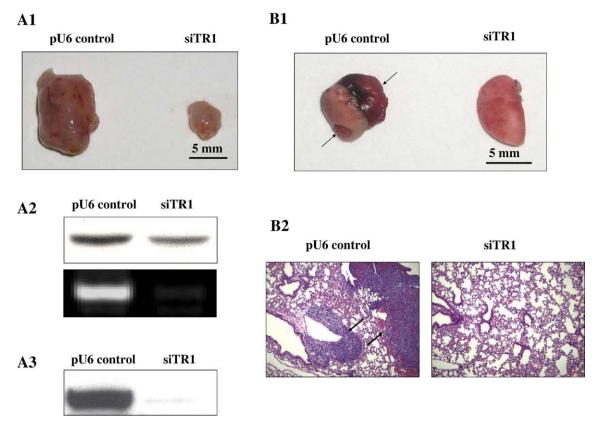
Fig. 1. Tumorigenicity and metastasis of TR1 knockdown LLC1 cells. Mice were injected in either (A) the flank or (B) a tail vein with LLC1 cells expressing a control vector (designated control in the figure) or the same vector, but encoding the TR1 knockdown sequence (see Ref. [39] for details). In A1, tumor formation was monitored over a two week period and mice were euthanized and tumors weighed. In A2, Western blot analysis of TR1 levels in the two tumors in A1 (upper panel) and PCR analysis of genomic DNA from the tumors in A1 (lower panel). Clearly, TR1 is present in the smaller tumor generated in the TR1 knockdown LLC1 cells (upper panel). PCR analysis was carried out to identify the presence or absence of the control or knockdown vector in the tumor and the data show that the TR1 knockdown vector is lost from the tumor formed in mice injected with the knockdown vector (lower panel). Overall, these data demonstrate that TR1 expression is required for tumor formation in this experimental model. In A3, Western blot analysis of TR1 in LLC1 cells that were transfected with either the control vector or the TR1 knockdown vector prior to the injections of these cells into mice. The data illustrate the expression of TR1 in injected cells encoding the control or knockdown vector. In B1, metastasis was assessed after four weeks in the lungs of mice injected in their tails with LLC1 cells encoding either the control vector or the TR1 knockdown vector. The data show that TR1 expression is required for tumor formation in lungs following metastasis. In B2, tissue slices from the lungs in B1 are shown wherein pathological changes were observed in the tissue from of the control mice (see arrows), but not in the mice carrying the TR1 knockdown vector. The figure was taken with slight modification from Ref. [39] with permission from the *Journal of Biological Chemistry*.

induced by injection with pristane. Virtually none of the mice injected with pristane and maintained on a selenium-deficient diet developed PCT, whereas about 40% of the control mice maintained on two different selenium-adequate diets developed PCT. The investigators suggested that selenium in the form of selenoproteins was implicated in PCT development and that selenoprotein inhibition might be a means of preventing cancers associated with chronic inflammation such as PCT [49].

Selenoprotein deficiency, as well as high levels of selenium compounds, were also reported to inhibit liver tumor formation in transforming growth factor (TGFα)/c-Myc oncogene transgenic mice [50]. The development of hepatocarcinomas is well-established in the TGFα/c-Myc transgenic mouse line wherein co-expression of two transgenes results in high penetrance of liver cancer in about 6–8 months [51]. Mice carrying both transgenes were maintained on a selenium-deficient, yeast-based diet or the same diet supplemented with either 0.1 ppm, 0.4 ppm or 2.25 ppm selenium as sodium selenite [50]. Relatively few tumors were found in the 0 ppm and 2.25 ppm selenium-supplemented diets, whereas many more were found in the 0.1 and 0.4 ppm selenium groups. The highest incidence was found in the 0.4 ppm selenium group and the fewest in the 0 ppm group. It appears that 0 ppm and 2.25 ppm diets were associated with induction of detoxification genes due to selenoprotein deficiency and selenite toxicity, respectively. Both of these dietary treatments also promoted apoptosis and inhibited cell proliferation. These factors (alteration in selenoprotein levels,

enhanced detoxification, apoptotic enhancement and cell propagation) likely contributed to the protection against tumor formation [50]. Thus, alterations in selenoprotein expression may both suppress or enhance malignancy depending on cell type and genotype.

6. Concluding remarks

Although our knowledge is increasing at a dramatic pace in the selenium field (e.g., see this volume on "Selenoprotein expression and function" and [1]), we are only beginning to learn about the consequences of selenium imbalance and the role of selenium in promoting cancer through the action of selenoproteins, as well as the role of selenium deficiency in inhibiting specific malignancies. TR1 and Sep15, and perhaps other selenoproteins, appear to act in cancer prevention in normal cells, but in malignancy their roles are switched to cancer promotion. An analysis of TR1 is beginning to shed light on the consequences of the over-expression of this selenoenzyme on growth, metastasis and resistance against cellular stress in cancer cells [e.g., see [22]]. However, there is still much to be done in this area. Similarly, there are, to our knowledge, only two examples of selenium deficiency causing cancer inhibition [49,50], but clearly, selenium may be the culprit as its abundance is what may be promoting such disorders at least in some situations. Most likely, there are other malignancies that might be reduced by selenium deficiency, and therefore, selenoprotein, inadequacy.

It is tempting to speculate on a possible mechanism of how selenium deficiency may inhibit tumorigenesis. One possibility would seem that the expression of those selenoproteins which are more susceptible to selenium status (e.g., stress-related selenoproteins [10,52,53]) may play a role in this process. Whether the reduced levels of selenoproteins result in compensatory or adaptive changes in other protective systems during the initiation stage of carcinogenesis, or they inhibit the growth of already established tumors, should be addressed in further research.

An important point to emphasize from an examination of the role of selenium in promoting cancer is that our understanding of selenium biology is by in large inadequate. Numerous human clinical trials involving thousands of subjects have administered selenium-supplemented diets and more are likely to be undertaken. It would seem, in light of our lack of knowledge in many areas of selenium function, to be more prudent to wait for additional genetic, mechanistic and animal studies before undertaking large, very expensive human trials.

Acknowledgements

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