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Molecular cross-talk between members of distinct families of selenium containing proteins

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Abstract

Dietary intake of selenium has been associated with reduced risk of several cancer types, and this is likely due to its role as a specific constituent of selenium containing proteins. One of these, selenium binding protein 1 (SBP1), is a protein of unknown function which has been shown to be reduced in tumors of diverse tissue types as compared to the corresponding normal tissue. More importantly, SBP1 has also been reported to be a predictor of clinical outcome. Levels of SBP1 are inversely associated with the levels of another protein representative of a different class of selenoproteins, glutathione peroxidase1 (GPx-1). GPx-1 is an anti-oxidant, selenocysteine-containing enzyme implicated in several diseases, including cancer, due to the association of specific alleles with disease risk. The relationship between SBP1 and GPx-1 represents a unique example of a molecular interaction between selenium-containing proteins with a likely significant impact on human health and disease.

Keywords

Selenium binding protein 1; glutathione peroxidase; clinical outcome; cancer

1 Introduction

The essential trace element selenium has received considerable attention for decades as its dietary intake has been associated with the reduced risk of a wide range of human diseases, including cardiovascular disease, diabetes, viral infections and cancer. These effects have been speculated to be due to the impact of selenium status on signaling pathways, immunity, cellular metabolism and reactive oxygen homeostasis. How selenium can affect these processes and ultimately human health continues to be an active research focus, and many of its properties have been attributed to selenium's role as a critical constituent of proteins in which selenium is specifically incorporated either during selenoprotein synthesis or post-translationally.

The most common and best studied class of selenium containing proteins includes those that contain the amino acid selenocysteine (Sec), which is incorporated co-translationally by its insertion in response to UGA codons that otherwise would serve as translational termination signals [1]. The recognition of UGA as Sec requires a regulatory sequence, called a Selenium Insertion Sequence (SECIS) element, in the 3'-untranslated region of the selenoprotein mRNA [2]. All in-frame UGA codons contained in a SECIS-including mRNA

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are recognized as encoding Sec, which is incorporated into the elongating peptide through unique translational machinery that includes a highly unusual tRNA, an elongation factor, as well as other proteins required for selenoprotein synthesis [3, 4]. Based on *in silico* analyses, there are 25 Sec-containing selenoprotein genes in humans and 24 in mice [5]. Comprehensive reviews of the functions of the human selenocysteine-containing proteins and their possible role in disease risk and etiology have recently been published [6, 7].

The other class of selenium-containing proteins includes those in which selenium is tightly associated with the peptide although not as a component of selenocysteine. This is a much smaller family and the best studied of them is Selenium Binding Protein 1 (SBP1). The SBP1 gene is located on chromosome 1 at q21–22, and is the homologue of the mouse SP56 gene that was originally reported as a 56 kDa mouse protein that stably bound ⁷⁵selenium [8]. The human cDNA contains a 472 amino acid encoding open reading frame [9] and the protein was first reported to reside both in the nucleus and cytoplasm [10], although subsequent reports would indicate that its cellular location may be influenced by cell type, degree of differentiation and environmental signals [11, 12]. It is expressed in a variety of tissue types, including the heart, lung, kidney and intestine. The form of selenium in SBP1 is unknown as is the nature of its association: the selenium remains bound to the protein when electrophoresed in SDS acrylamide gels but dissociates at extremes of pH [8]. Additionally, data has recently been presented indicating that the selenium is bound to a cysteine residue (Cys57) [11]. The function of SBP1 is unknown although it may be involved in intra-golgi transport [13] and its reported association with the von Hippel-Lindau protein interacting deubiquitinating enzyme 1 (VDU1) indicates SBP1 may have functions in protein degradation [14]. The role of SBP1 in human health and its interaction with the selenocysteine-containing protein, glutathione peroxidase 1 (GPx-1) is the focus of this review.

2 SBP1 levels are reduced in human cancers

The earliest indication that reduced levels of SBP1 were associated with carcinogenesis was published in 1998 by Yang and Sytkowski [15]. SBP1 was detected as a gene that was differentially expressed in the LNCaP human prostate cancer cell line as compared to the slower growing DU145 and PC-3 lines, with the authors noting that only 4 of 11 tumor derived cell lines expressed detectable SBP1 mRNA levels [15].

Subsequent work examining the levels of proteins obtained from gastric adenocarcinomas and adjacent non-tumor tissues by 2-dimensional electrophoresis indicated that SBP-1 levels were reduced 2-fold in the tumor tissue [16] and using this same approach, similar results were reported for a different bank of paired gastric tumors and normal mucosa [17]. While also reporting a reduction in SBP1 levels in gastric tumors compared to normal tissue from the same individuals using tissue microarrays, Zhang et al. noted higher levels of SBP1 in normal and preneoplastic tissues as compared to that observed in tumors, providing evidence that the reduction in SBP1 seen in gastric carcinoma is likely to occur in the latter stages of tumor development [18]. This observation is consistent with data reported indicating a progressive loss of SBP1 levels from non-dysplastic Barrett's esophagus to Barrett's esophagus with high grade dysplasia and ultimately esophageal adenocarcinoma [19]. In the case of uterine leiomyomas, SBP1 levels were shown to be lower in tumors as compared to normal myometrium, with a trend towards a progressive loss with increasing tumor size [20].

By comparing the expression of SBP1 in tumor vs. normal tissues using 2D electrophoresis, expression arrays or tissue microarray analysis, the list of cancer types demonstrating reduced SBP1 levels now also includes adenocarcinoma of the lung [10], colorectal cancers

[21, 22], esophageal adenocarcinoma [19], hepatocellular carcinoma [12, 23], liposarcoma [24] and ovarian cancer [25, 26]. In the case of ovarian cancer, reduced levels of SBP1 were also reported in ovarian tumors that developed in the only spontaneous model of human ovarian cancer, the laying hen [27]. A list of the types of human cancers in which carcinogenesis was accompanied by a reduction in SBP1 levels is presented in Table I.

The mechanism by which SBP1 is down-regulated in human cancers remains to be determined. One possible explanation would be the loss of one or two copies of the SBP1 gene during tumor progression. However, examination of DNA obtained from cells and tissues for either loss of heterozygosity or reduced gene copy number have not revealed any examples of *SBP1* loss [10, 15, 19, 21]. Less clear is whether epigenetic mechanisms of transcriptional control are involved with the changes in SBP1 levels observed in tumor cells, with gene methylation status having been investigated in several instances. The examination of whether SBP1 is regulated by gene methylation using either bisulfite sequencing, MS-PCR or expression induction following treatment with the demethylating agent 5-azacytidine have yielded conflicting results, perhaps due to the different cell types being investigated [10, 19, 21, 28]. Data in support of the regulation of *SBP1* by promoter methylation was, however, obtained using human tissues by examining colon tumor cells and matched normal colonic epithelial cells from the same patients, revealing elevated *SBP1* promoter methylation in tumor DNA [28].

3 SBP1 as a marker of differentiation and as a prognostic indicator of clinical outcome

Decreased expression of SBP1 with increasing tumor stage may be a result of SBP1 levels also being associated with cellular differentiation, as dedifferentiation is a hallmark of advanced tumor stage. SBP1 levels were examined in longitudinal sections of normal human colonic tissue by immunohistochemistry to assess SBP1 expression during different stages of colon cell differentiation [22]. As colon cells migrated along the crypt-luminal axis and became more differentiated, SBP1 expression also increased with maximal expression at the top of the intestinal villi. Evidence that SBP1 may play a functional role in this process was presented by showing that down regulation of SBP1 using siRNA in the Caco-2 absorptive colon cell line resulted in expression of the epithelial differentiation marker carcinoembryonic antigen (CEA) also being reduced [22]. These results were consistent with those previously reporting that SBP1 was less differentiated in lung cancers [10].

SBP1 was detected by gene expression profiling as one of 27 genes shown to comprise an expression profile that predicted both survival and progression among patients diagnosed with pleural mesothelioma [29]. Using a different approach- 2-dimensional electrophoretic separation of proteins from tumor vs. normal tissue- reduced levels of SBP1 protein was shown to be associated with poor survival among patients with colorectal cancer [21] and lung adenocarcinoma [10]. Specifically assessing the relationship between SBP1 levels and clinical outcome, reduced levels of SBP1 were shown to be an indicator of poor prognosis among patients with gastric cancer [30], hepatocellular carcinoma [12], breast cancer [31] and colorectal cancer [22], with an example of a Kaplan-Meier plot from the latter manuscript showing the association between low SBP1 levels and both reduced disease free survival and overall survival presented in Figure 1. The situation may be less clear for ovarian cancer. Although SBP1 levels were reduced in 87% of the invasive ovarian carcinomas examined, high SBP1 levels were associated with poor overall survival, in contrast to what has been reported for other tumor types [25]. A summary of those studies indicating an association between SBP1 levels in tumors and clinical outcome is also included in Table I.

4 The interaction between SBP1 and another selenium-containing protein, GPx-1

Given the association of SBP1 with selenium and the volume of data indicating a likely involvement of SBP1 in cancer development and outcome, studies were initiated to assess whether there was a relationship between SBP1 and the first characterized and best studied Sec-containing protein, the ubiquitously expressed glutathione peroxidase-1 (GPx-1). This enzyme uses reducing equivalents from glutathione to detoxify lipid and hydrogen peroxides, and its levels are sensitive to selenium availability [32]. Changes in the levels of GPx-1 have been associated with a variety of human diseases, and increasing or decreasing its expression in cell culture models typically results in changes that can be attributed to consequential effects on cellular oxidative stress [33, 34].

GPx-1 has been implicated in several diseases by genetic analysis GPx-1 variants; either a single nucleotide polymorphism resulting in either a proline (pro) vs. leucine (leu) variation at codon 198, or a variable number of alanine (ala) codon repeats that result in 5, 6, or 7 ala in the amino terminus of the protein (reviewed in [35]). These variations are functional and interactive, determining the levels of GPx-1 enzyme activity for a given concentration of available selenium [36, 37]. The *leu* allele has been associated with increased risk of cancers of several types while no clear pattern of association has emerged between the number of ala repeats and cancer risk [35]. In addition to cancer, allelic variants of GPx-1 have also been associated with the risk of cardiomyopathy [38], coronary heart disease [39, 40], hypertension [41], autism [42], intracerebral hemorrhage [43], asthma [44] and the metabolic syndrome [45].

An interaction between SBP1 and GPx-1 was first reported using human cell lines that express undetectable levels of either SBP1 or GPx-1 [46]. Ectopic expression of SBP1 in the HCT116 human colon cancer-derived cells that do not express SBP1 resulted in a substantial decline in GPx-1 enzyme activity without any apparent effects on either GPx-1 mRNA or protein levels. Consistent with this observation, knock-down of SBP1 in the SMMC7721 non-transformed human liver cell line resulted in a 4–5 fold increase in GPx-1 activity, also without detectable changes in GPx-1 protein levels [12]. In contrast, ectopic expression of GPx-1 in human MCF-7 cells that negligibly express GPx-1 resulted in a reduction of SBP1 protein levels as well as reduced levels of the SBP1 mRNA [46].

The inverse association between GPx-1 and SBP1 was also demonstrated in mouse intestinal cells where GPx-1 levels were altered by feeding C57Bl/6 mice a selenium-deficient, -adequate, or -enriched diet and examining the levels of SBP1 by western blotting of extracts prepared from colonic and duodenal epithelial cells [46]. As GPx-1 levels increased in the tissues of mice fed the diets with elevated selenium content, there was a corresponding decline in SBP1 levels [46]. In humans, an inverse association between SBP1 and GPx-1 levels has been reported for both prostatic [47] and liver tissues [48] obtained from patients with cancer.

5 How do SBP1 and GPx-1 regulate the levels of the other?

The mechanism by which SBP1 and GPx-1 regulate each other's levels remains to be determined. One possible mechanism of inverse regulation might involve competition for available stores of selenium in the cell. This possibility is unlikely however as it was shown that increasing the amount of selenium in MCF-7 cells expressing both GPx-1 and SBP1 resulted in an increase in the levels of the GPx-1 protein and a decline in SBP1 levels, but the same selenium supplementation of the media of MCF-7 cells that did not express GPx-1 has no effect on SBP1 [46]. This result indicating the dependence on GPx-1 for the selenium

effect, as well as the observed inverse change in GPx-1 enzyme activity seen when SBP1 levels are increased or decreased was achieved without apparent changes in the GPx-1 mRNA or protein amounts [46, 48], suggest that there might be a physical interaction between the two proteins. This notion is supported by work showing that the analysis of immunoprecipitated Green Fluorescent Protein (GFP) tagged GPx-1 by western blotting detected co-precipitated HA-tagged SBP1 [46]. These results indicate that the two proteins likely participate in a single complex, and since the GPx-1 used in this experiment contained a cysteine replacing the selenium-containing selenocysteine, that the selenium moiety of GPx-1 is not required for that complex to form. Further evidence for the interaction of these proteins was obtained by demonstrating that SBP1 localized in both the cytoplasm and nucleus of liver cells, while GPx-1 was exclusively in the cytoplasm, but that both proteins co-localized in the nucleus of these cells following challenge with H₂O₂ [48].

How GPx-1 regulates the levels of SBP1, in addition to complex formation, may involve control at the transcriptional level. As an anti-oxidant enzyme, GPx-1 can alter the levels of reactive oxygen species (ROS), which can have a profound impact on signal transduction pathways and ROS-responsive transcriptional elements. SBP1 has been identified as a target of the oxygen-responsive HIF-1 α transcription factor [49], considered a “master regulator of oxygen sensitive gene transcription”[50], although it remains to be determined whether the effects of GPx-1 on SBP1 transcription is mediated through this pathway.

6 The biological and clinical consequences of the SBP1 and GPx-1 interaction

Based on the available information, it is likely that SBP1 and GPx-1 interact in such a way to modify the activity of one or both proteins. In the case of GPx-1, its ability to reduce hydroperoxides can have an impact on oxidative damage to biomolecules, DNA repair and a host of signaling pathways that are responsive to ROS, and this has been extensively reviewed [32]. To date, no particular enzyme activity has been associated with SBP1. However, increasing or decreasing its levels in cultured mammalian cells resulted in changes in several phenotypes associated with cancer, including proliferative capacity, apoptosis, cell migration, senescence, resistance to H₂O₂ and cisplatin, and growth of tumors in immunocompromised animals [19, 28, 48, 51]. What is noteworthy is that these observations have been made in cells obtained from different tissues and there has been consistency with regard to obtaining opposite results when SBP1 is over-expressed and knocked down. It is intriguing to consider whether any and which of the phenotypes attributed to SBP1 are due to its own intrinsic activity, its interaction with GPx-1, or its interaction with other proteins, such as VDU1 [14].

Both GPx-1 and SBP1 are selenium-containing proteins associated with several human diseases and belong to classes of proteins distinguished by the nature of the selenium moiety they are associated with. SBP1 levels are often reduced in tumors compared to corresponding normal tissue and lower levels are typically associated with a poorer clinical prognosis. GPx-1 is an anti-oxidant enzyme implicated in disease etiology due to the association of specific alleles with risk of certain diseases. The inverse association in the levels of these proteins in cells, animals and human tissues, as well as data indicating a direct interaction, reveal a need for the continued investigation of their biochemistry as well as determining whether they are participants or bystanders in the disease process.

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Abbreviations

GPx-1	glutathione peroxidase 1
SBP1	selenium binding protein 1
Sec	selenocysteine
SECIS	selenium insertion sequence

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Figure 1.

Reduced levels of SBP1 in colorectal cancer are associated with poor clinical outcome. The expression of SBP1 was determined by immunohistochemistry of tissue microarrays and classified at “tumor-high SBP1” or “tumor-low SBP-1” based on the number of positively stained epithelial cells compared to all of the epithelial cells observed in the core, using a mean level of 22.5% as the discriminator. The graphs are Kaplan-Meier estimates of the association between SBP1 levels and either disease free survival (panel A) or overall survival (panel B). These data were obtained from [22].

Table I

Reduced levels of SBP1 in human cancers and as a predictor of poor clinical outcome

Organ	SBP1 status	Patient groups	Ref
Lung	SBP1 acidic isoform & mRNA down regulated in adenocarcinoma and poorly differentiated tumors. Low levels of SBP1 correlated with poor survival.	Stage I cancer (n=64) Stage III cancer (n=29) Lung adenocarcinoma (n=80) Squamous cell carcinoma (n=45)	[10]
Ovary	SBP1 was reduced in 87% of invasive ovarian cancers & borderline tumors vs. normal & benign tissue.	Normal tissue & benign tumor (n=12) Borderline & invasive ovarian cancer (n=153)	[25]
	SBP1 expression decrease associated with increased epithelial proliferation and invasiveness.	Borderline carcinoma (n=73) Low grade carcinoma (n=7)	[26]
Colorectal	SBP1 markedly decreased in 12/14 carcinoma samples compared to matched non-tumor mucosa.	Colorectal cancer & paired normal tissue (n=14)	[21]
	3.5 fold less SBP1 in Stage III vs. normal. Low levels correlated with poor survival compared with patients with high SBP1 tumors.	Stage III colorectal cancer & paired normal tissue (n=80)	[22]
Uterus	SBP1 decreased in leiomyoma tissue vs. normal myometrium.	Non-tumor tissue (n=20) Uterine leiomyoma (n=20)	[20]
Esophagus	SBP1 decreased during progression from Barrett's esophagus to adenocarcinoma.	Barrett's esophagus (n=31) Esophageal adenocarcinoma (n=37)	[19]
Stomach	Decreased SBP1 in gastric adenocarcinoma vs. normal tissues.	Gastric adenocarcinoma & paired normal (n=10)	[16]
	Decreased SBP1 in gastric adenocarcinoma vs. normal tissue.	Stage III gastric cancer & paired normal tissues (n=3)	[17]
	Lower SBP1 in carcinoma tissue, with 8/25 patients showing negative tissue SBP1 staining.	Precursor lesions (n=89) Gastric cancer & paired normal tissue (n=25)	[18]
	Negative tissue SBP1 staining correlated with advanced stage and poor prognosis	Stage II/III gastric cancer & paired nonneoplastic tissue (n=65)	[30]
Liver	SBP1 expression decreased as tumor grade increased.	Grade I (n=6) Grade II (n=12) Grade III (n=8), all with paired cirrhotic controls.	[11]
	Decreased SBP1 associated with vascular invasion. Low SBP1 expression is an independent risk factor for shorter overall survival and increased recurrence rates.	Hepatocellular carcinoma (n=342)	[12]
Prostate	SBP1 inversely correlated with GPx activity. GPx activity directly correlated with Gleason score.	Prostate cancer (n=24)	[47]
Breast	Low SBP1 in ER+ cancer patients associated with poor survival. SBP1 expression decreased with advanced clinical stage.	Breast cancer with paired normal tissue (n=95)	[31]
Fat	Nuclear & cytoplasmic staining decreased in well differentiated components. Lower SBP1 associated with decreased metastasis-free survival.	Atypical lipomatous tumor (ALT) (n=30) Dedifferentiated liposarcoma (DDL) (n=28)	[24]