The role of SELENBP1 and its epigenetic regulation in carcinogenic progression

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SPECIALTY SECTION
This article was submitted to Cancer Genetics and Oncogenomics, a section of the journal Frontiers in Genetics

RECEIVED 25 August 2022
ACCEPTED 10 October 2022
PUBLISHED 01 November 2022

CITATION
Zhang Y and He Q (2022), The role of SELENBP1 and its epigenetic regulation in carcinogenic progression. Front. Genet. 13:1027726. doi: 10.3389/fgene.2022.1027726

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KEYWORDS
SELENBP1, carcinogenesis, epigenetic modification, post-translational modification, therapeutical target

Introduction

Cancer incidence and mortality rate are increasing at an alarming rate worldwide, with an estimated 19.3 million new cases and almost 10.0 million deaths having occurred in 2020 (Sung et al., 2021). Both genetic and epigenetic modifications contribute to carcinogenic progression. Epigenetics refers to heritable changes in the chromatin structure and gene expression during post-transcriptional and translational stages without DNA sequence alterations, including DNA methylation, histone modification, and RNA-based mechanisms. DNA methylation that occurs in cytosine–guanine (CpG) islands of the gene promoter regions is associated with gene silencing (Jones and Baylin, 2002; Feinberg, 2018). Histone post-translational modifications (PTMs) include methylation, phosphorylation, acetylation, ubiquitination, glycosylation, and chromatin remodeling, and also could be regulated by non-coding RNAs such as microRNAs (miRNAs), siRNAs, and long-non-coding RNAs (lncRNAs). (Hussain et al., 2022; Zhang et al., 2021; Millan-
Epigenetic changes are closely associated with regulation of tumor suppressors and/or oncogenes via DNA hypermethylaiton, histone modification, and non-coding RNAs (Jones and Baylin, 2002; Hussain et al., 2022).

The study of epigenetics in cancer epidemiology is emerging in the recent 2 decades, and its role in oncogene/tumor suppressor regulation and cancer progression is being emphasized increasingly. Epigenetic changes have opened the way to innovative diagnostic and treatment strategies for a variety of cancers in clinics (Laird, 2003). Epigenetic drugs targeting to inhibit epigenetic modifiers, such as DNA methyltransferase and histone deacetylase (DNMTI and HDACI), have been approved for treat different malignant cancers and showed promising outcomes (Hussain et al., 2022).

### Structural and biochemical characteristics of SELENBP1

Mammalian selenium-containing proteins can be divided into three groups: specific selenium-binding proteins, specific incorporation proteins (also called selenoproteins), and non-specific incorporation proteins (Behne and Kyriakopoulos, 2001; Kryukov et al., 2003). The human SELENBP1 (also known as Sbp1, human 56 kDa selenium-binding protein/hSP56, EHMTO, HEL–S–134P, LPSB, MTO, and SBP56 or hSBP) belonging to the specific selenium-binding protein is located at chromosome 1q21–22. The neighbor-joining phylogenetic tree of SELENBP1 has been reported in a previous study (Pol et al., 2018). Its mouse homolog is the SP56 gene (also known as SLP-56, Lp56, Lpsb, MTO, or SBP56) (Bansal et al., 1990; Lanfear et al., 1993; Chang et al., 1997; Porat et al., 2000). The gene sequences of mouse and human SELENBP1 are shown in Figure 1 (A, B) using GSDS2.0 (Hu et al., 2015). The degree of homology between mouse and human SELENBP1 is 86% (Flemetakis et al., 2002), which means many mechanisms apply to both. Selenbp2, as a highly homologous isoform of Selenbp1 differing by only 14 residues, exists in mice but not in humans (Lanfear et al., 1993). Both Selenbp1 and Selenbp2 mRNA levels are downregulated in liver cell lines but remain high in diethylnitrosamine (DEN)-induced mouse liver tumors in vivo (Lanfear et al., 1993). This may be due to the redundant role of each other. However, the expressions or functions of Selenbp2 in cancers are scarcely published yet. Both mouse and human SELENBP1 are ubiquitously expressed in the colon, lung, and 17 other tissues (Fagerberg et al., 2014; Yue et al., 2014). Selenium (Se), as the sixth main characteristic of SELENBP1, is downregulated in primary RCC and 59 specimens of control kidney tissues, the mRNA level of SELENBP1 is significantly downregulated in the RCC tissues than in normal adjacent kidney tissues (p < 0.001) and is correlated with pathologic (T-stage and Fuhrman grade), prognostic variables (progression and cancer-specific death) as well as cancer-specific death (log-rank test, p = 0.014) (Ha et al., 2014). SELENBP1 is downregulated by hepatocyte nuclear factor 4 alpha (HNF4alp), a tissue-specific transcription factor in RCC microarray studies (Lucas et al., 2005). However, the exact mechanism of SELENBP1 still needs to be elucidated.

Kidney cancer: SELENBP1 could be a useful prognostic factor in renal cell carcinoma (RCC). Using 139 specimens of primary RCC and 59 specimens of control kidney tissues, the mRNA level of SELENBP1 is significantly downregulated in the RCC tissues than in normal adjacent kidney tissues (p < 0.001) and is correlated with pathologic (T-stage and Fuhrman grade), prognostic variables (progression and cancer-specific death) as well as cancer-specific death (log-rank test, p = 0.014) (Ha et al., 2014). SELENBP1 is downregulated by hepatocyte nuclear factor 4 alpha (HNF4alp), a tissue-specific transcription factor in RCC microarray studies (Lucas et al., 2005). However, the exact mechanism of SELENBP1 still needs to be elucidated.

Lung cancer: SELENBP1 is downregulated in basaloid carcinoma, large cell carcinoma, lung squamous cell...
carcinoma (LSCC), and adenocarcinoma (Li et al., 2004). Using quantitative two-dimensional polyacrylamide gel electrophoresis (2-D PAGE), two isoforms of SELENBP1 are significantly decreased in lung adenocarcinomas at both mRNA and protein levels. Its expression correlates with poor survival, and downregulation of SELENBP1 may increase cell proliferation and decreased differentiation (Chen et al., 2004). The protein level of SELENBP1 is significantly lower in LSCC tissues than in the corresponding normal bronchial epithelium (NBE) tissues ($p = 0.000$) and is associated with higher lymph node metastasis and lower overall survival rate ($p < 0.05$) (Tan et al., 2016). Knockdown of SELENBP1 can increase benzo(a)pyrene (B[a]P)-induced human NBE cell transformation to participate in NBE carcinogenesis (Zeng et al., 2013).

Thyroid cancer: Proteomic analysis of papillary thyroid carcinoma (PTC) compared with normal thyroid tissue using difference gel electrophoresis (DIGE), and mass spectrometry confirmed lower expression of SELENBP1 ($p = 0.00097$) (Brown et al., 2006). More studies are needed to examine its function in thyroid tissue and thyroid cancer progression.

Stomach cancer: SELENBP1 was significantly decreased in a proteomic analysis of gastric cancer specimens. Its expression is correlated with differentiation, TNM stage, and lymph node metastasis ($p < 0.05$). It can serve as a potential novel prognostic biomarker (He et al., 2004; Zhang et al., 2011a; Xia et al., 2011), and its level is associated with a poor survival rate in gastric carcinoma (Zhang et al., 2011b). SELENBP1 promotes proliferation, colony formation, and senescence in vitro and in vivo. In addition, it suppresses tumor growth and metastasis and increases the chemoresistance of gastric cancer cells via apoptotic signaling pathways (Zhang et al., 2013). The exact mechanism is not known yet.

Esophagus cancer: SELENBP1 is decreased significantly in esophageal adenocarcinoma (EAC) tissues. Downregulation of SELENBP1 in Barrett’s esophagus to adenocarcinoma progression could enhance apoptosis, cellular senescence, and cisplatin cytotoxicity in EAC cells (Silvers et al., 2010).

Liver cancer: The protein level of SELENBP1 is decreased in HCC (Raucci et al., 2011). Decreased expression of SELENBP1 could promote tumor invasiveness by increasing GPX1 activity and diminishing hypoxia-inducible protein-
H2S and consequential activation of AMP-activated protein kinase (AMPK), a major regulator of energy homeostasis, especially in patients with advanced HCC (Huang et al., 2012). However, in another study, SELENBP1 mRNA is downregulated in liver cell lines in vitro but upregulated in DEN-induced mouse liver tumors compared with the normal tissues in vivo, though the function is not known for certain at present. They hypothesized that binding of selenium or acetylaminophen metabolites in hepatocytotoxicity might play a role in the processes (Lanfear et al., 1993). Downregulation of SELENBP1 could increase C-X-C motif chemokine receptor 4 (CXCR4) expression and results in epithelial–mesenchymal transition (EMT) of HCC cells (Gao et al., 2018). The 3D model of human protein SELENBP1 was reported to have one cysteine residue, which binds the selenium in HCC and can be used as a therapeutic target (Raucci et al., 2011).

Breast cancer: SELENBP1 remains low in mammary carcinoma (Lanfear et al., 1993). Lower SELENBP1 expression in breast cancer tissues compared to normal control is significantly associated with poor survival (p < 0.01). SELENBP1 expression is regulated by estrogen in vitro. Supplemental dietary selenium could inhibit cell proliferation in cells expressing high level of SELENBP1 (Zhang S. et al., 2013). SELENBP1 is likely to play roles in modulating selenium-mediated cytotoxicity and the extracellular microenvironment by regulating the levels of extracellular glutathione (GSH) (Wang et al., 2015). The interaction between SELENBP1 and GPX1 is found in MCF-7 breast carcinoma cells (Fang et al., 2010). SELENBP1 can also interact with the retinoid-receptor RARs in the nuclear material, whose interaction is reduced by all-trans-retinoic acid (ATRA, a cancer drug) in the breast cancer cell line (Gianni et al., 2019). SELENBP1 interacts with the nuclear receptor estrogen receptor 2 (ESR2, ERβ) to modulate cell proliferation and tumor growth in breast cancer (Giurato et al., 2018).

Prostate cancer: SELENBP1 is observed to be at lower levels in prostate cancer (Yang and Syrkowski, 1998; Ansong et al., 2015). As to energy metabolism, SELENBP1 produces H2O2 and H2S and consequential activation of AMP-activated protein kinase (AMPK), a major regulator of energy homeostasis as well as inhibited oxidative phosphorylation (OXPHOS) in prostate cancer cells. In addition, HNF4 alpha, a novel transcriptional inhibitor of SELENBP1, plays a role in prostate cancer by binding to the SELENBP1 promoter region (Elbodaky et al., 2020). SELENBP1 may influence the plasma selenium levels and may be associated with the risk of advanced prostate cancer (Xie et al., 2016). GPx enzyme activity is inversely correlated with SELENBP1 levels in prostate cancer tissue (Jerome-Morais et al., 2012). SELENBP1 is found to coprecipitate with the androgen receptor (AR) in prostate tumor cells (Veldscholte et al., 1992). In prostate cancer, expressed prostatic secretions (EPS), proximal fluids of the prostate, can be utilized for diagnostic and prognostic assays. SELENBP1 is found in the EPS according to a shotgun proteomics (Principe et al., 2013).

Colon cancer: SELENBP1 is downregulated in the proteomic analysis of colorectal cancer (CRC) (Wang et al., 2012). Both mRNA and protein levels of SELENBP1 are downregulated in CRC, which are correlated with the degree of differentiation, and its levels are higher in benign polyps than in CRC tissues (Kim et al., 2006; Li et al., 2008; Wang et al., 2014). SELENBP1 induces H2O2-mediated apoptosis in colon cancer cells and inhibits cancer cell migration in vitro and tumor growth in vivo (Pohl et al., 2009). SELENBP1 can also inhibit CRC through lipid/glucose metabolic signaling pathways (Ying et al., 2015a) and participate in mitochondrial function in the HCT116 human colorectal carcinoma cell line through cysteine 57 in SELENBP1 (Ying et al., 2015b). The interaction between SELENBP1 and GPX1 is found in colon-derived HCT116 cells (Fang et al., 2010).

Pancreatic cancer: SELENBP1 is downregulated in pancreatic ductal adenocarcinoma (PDAC) patients with skin rash (SR) treated with erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (Caba et al., 2016). SELENBP1 interacted with anterior gradient 2 (AGR2), with the latter promoting phosphorylation of RICTOR (T1135), leading to pancreatic tumor metastasis (Tiemann et al., 2019).

Head and neck cancer: SELENBP1 is downregulated in head and neck squamous cell carcinoma (HNSCC) including nasopharyngeal (NPC), laryngeal (LC), oral cancer (OC), tonsil (TC), and hypopharyngeal (HPC), which have no association with tumor T-stage, N-stage, and tumor grade. NPC patients with low expression of SELENBP1 have a poor survival rate. Therefore, SELENBP1 could be a novel biomarker for predicting NPC prognosis (Chen et al., 2016). SELENBP1 downregulation in both mRNA and protein levels is also positively correlated with poor prognosis for oral squamous cell carcinoma (OSCC) patients.

Skin cancer: SELENBP1 concentration remains low in skin carcinoma (Lanfear et al., 1993). SELENBP1 is identified to be downregulated in cutaneous melanoma influenced by glutathione peroxidase 1 (GPX1) to regulate proliferation and tumor microenvironment (Schott et al., 2018). An in vivo mouse study shows that HIF-1α can transactivate SELENBP1 during murine skin chemical carcinogenesis (Scortegagna et al., 2009).

Bladder cancer: SELENBP1 is significantly downregulated in bladder cancer (Wang et al., 2020).

Uterine cancer: Decreased protein expression of SELENBP1 is found in uterine leiomyoma than in normal myometrium (Zhang C. et al., 2010).

Nerve cancer: SELENBP1 is found at the growing tips of the neurites in SH-SYSY neuroblastoma cells/T98G glioma cells involved in the initial sequential events in rapid cell outgrowth; however, the exact expression change is still unknown (Miyaguchi, 2004).
Malignant pleural mesothelioma (MPM): Gene expression analyses from MPM patients show that SELENBP1 might be associated with the risk of having MPM (Pass et al., 2004).

Uveal melanoma tumor: SELENBP1 expression is induced in uveal melanomas that subsequently develop distant metastases compared with those that do not (Linge et al., 2012).

Ovary cancer: In a membrane proteome profiling analysis, SELENBP1 is decreased in ovary cancer through the selenium/androgen pathway (Huang et al., 2006). In addition, high anti-SELENBP1 levels are also observed in patients with serous ovary cancer, which suggests SELENBP1 participates in an autoimmune process during ovary cancer development (Yu-Rice et al., 2017). Downregulation of SELENBP1 also increases epithelial proliferation and papillary complexity in tumorigenesis of ovarian serous borderline tumor, micropapillary serous borderline tumor, and low-grade serous carcinoma (Zhang P. et al., 2010). SELENBP1 is identified as one of the candidate stromal epithelial cross-talk genes by analyzing common single-nucleotide polymorphisms (SNPs) for their association between the risk of serous ovarian cancer and telomerase reverse transcriptase (TERT), a cancer susceptibility “hot-spot” (Johnatty et al., 2010).

SELENBP1 also displays high expression in other tissues, such as the fetal and adult heart, spleen, thymus, and other tissues (Pol et al., 2018); however, no studies have been reported whether SELENBP1 also participates in their carcinogenesis.

Epigenetic mechanisms of SELENBP1

The expression of SELENBP1 is downregulated in almost all cancers, indicating some suppressing functions of SELENBP1 in cancers. Epigenetic changes are likely to account for reduction of SELENBP1 expression.

Epigenetic modification of SELENBP1 through promoter methylation in cancer has been demonstrated in many studies: DNA methylation at CpG islands in promoter regions is regulated by the DNA methyltransferase (DNMT) enzyme. This phenomenon often occurs at an early stage and is a common mechanism of gene silencing during carcinogenesis (Jones and Baylin, 2002; Laird, 2003; Nazemalhosseini et al., 2013; Huss+6aini et al., 2022). Several CpG sites were found in the 5′-untranslated region of SELENBP1 (Pohl et al., 2009; Silvers et al., 2010). Gene hypermethylation in the “epidermal differentiation complex” is located within 700 kb of the SELENBP1 locus (Marenholz et al., 2001; Elder and Zhao, 2002). So, it is possible that the SELENBP1 promoter may be methylated in tumors and results in low expression levels of SELENBP1. Deubiquitinating enzymes (Dubs) function to remove covalently attached ubiquitin from proteins to control substrate activity and/or abundance. SELENBP1 is the bait of USP15 (ubiquitin-specific proteases 15, a Dub) in a global proteomic analysis of Dubs and their associated protein complexes in 293T cells, indicating SELENBP1 levels might also be regulated by USP15 (Sowa et al., 2009). PLEKHA4 sequester E ubiquitin ligase adapter controls disheveled polyubiquitination at the plasma membrane to tune sensitivities of cells. SELENBP1 interacts with PLEKHA4 in HEK293 cells, which further directs the crucial function of epigenetic modification in modulating SELENBP1 expression (Shami et al., 2019).

Lung cancer: Nkx2-1 is a transcription factor that suppresses malignant progression of lung adenocarcinoma. SELENBP1 is regulated by Nkx2-1 in lung adenocarcinoma in both the human lung adenocarcinoma and mouse lung cancer model. Nkx2-1 binds to the promoter regions of SELENBP1, which are associated with H3K4me3 and H3K27ac; Nkx2-1 binds to the enhancer regions at H3K4me1 and H3K27ac, which collectively indicate that Nkx2-1 likely regulates the expression of SELENBP1 through epigenetics regulation. In addition, they function in a positive feedback loop during the suppression of malignant progression of lung adenocarcinoma (Caswell et al., 2018).

Esophageal adenocarcinoma: Several CpG sites are found near the predicted promoter region of SELENBP1, where hypermethylation occurred at −95 to +90 and in the 5′-untranslated region of SELENBP1 (Silvers et al., 2010). A histone deacetylase inhibitor trichostatin A (TSA)/valproic acid (VPA) alone and/or the demethylating agent 5-Aza could increase SELENBP1 mRNA expression but not the protein level in EAC cell line Fl-1 cells. In addition, demethylating and acetylase-enhancing agents increased sensitivity of Fl-1 cells to apoptosis with cisplatin, which all indicate that inducible SELENBP1 expression may be regulated at the epigenetic level and play an important role during drug resistance in EAC (Silvers et al., 2010). However, the histone acetylation sites remain unknown.

Liver cancer: Human hepatitis B virus (HBV) is a leading cause of HCC (Beasley et al., 1981). SELENBP1 is decreased in HCC cells expressing the HBV X protein (HBx), and the SELENBP1 promoter is repressed by HBx. In addition, the stepwise deletion of 5′ flanking promoter sequences resulted in a gradual decrease in basal promoter activity and inhibition of SELENBP1 expression by HBx (Lee et al., 2020), which indicates the potential epigenetic regulation of SELENBP1 by HBx; however, whether the promoter hypermethylation exists has not been confirmed yet.

Prostate cancer: SELENBP1 could induce phosphorylation of the p53 tumor suppressor at serine 15 to suppress carcinogenesis (Ansong et al., 2015). In human prostate cancer cells, SELENBP1 interacts with von Hippel–Lindau protein (pVHL)-interacting deubiquitinating enzyme 1 (VDU1), and VDU1 incorporates selenium into SELENBP1. These findings imply the role of SELENBP1 in ubiquitination/de-ubiquitination-mediated protein degradation pathways dependent of selenium. However, the specific mechanism has
not been elucidated (Jeong et al., 2009). SELENBP1 also interacted with VDU2, a closely related isoform of VDU1 (Jeong et al., 2014). VDU2 can interact with HIF-1α, a tumor suppressor, to deubiquitinate and stabilize HIF-1α (Li et al., 2005). SELENBP1 inhibits HIF-1α protein levels and downregulates its stabilization in prostate cells without affecting the mRNA levels of HIF-1α, which indicates SELENBP1 may affect epigenetic regulation of other genes. Whether HIF-1α is regulated by the interaction between SELENBP1 with VDU1 and/or 2 is unknown (Jeong et al., 2014). SELENBP1 can downregulate HIF-1α protein levels without altering mRNA levels in the human lung carcinoma cell line as well (Jeong et al., 2014). The downregulation of HIF-1α by SELENBP1 also exists in liver cancer (Huang et al., 2012); however, the mechanism is not quite clear yet. SELENBP1 serves as the target gene of HIF-1α in skin squamous carcinogenesis (Scortegagna et al., 2009). SELENBP1 interacts with embryonic ectoderm development (EED), a core component of polycomb repressive complexes 2 (PRC2) and is critical for PRC2 to methylate histone H3 at lysine 27 (H3K27me3). Then, EED recruits polycomb repressive complex 1 (PRC1) directly to the tri-methylated H3K27 loci and enhances PRC1-mediated H2A ubiquitin E3 ligase activity, indicating a potential role for SELENBP1 as an epigenetic exchange factor in prostate cancer (Cao et al., 2014).

Colon cancer: In colon cancer, the promoter of SELENBP1 was methylated in both human colon tissues and cell lines (HCT116, SW480, Caco-2, and HT-29 cells), while it was mostly unmethylated in LSI174T cells (Pohl et al., 2009). Treating HCT116 with 5-Aza-dC (5′-Aza-2′-deoxycytidine), a DNA methylation inhibitor (DNMTi), could decrease methylation of the SELENBP1 promoter, increase SELENBP1 promoter activity, and rescue SELENBP1 mRNA and protein expression levels (Pohl et al., 2009). However, very little methylation in the SELENBP1 promoter was detected in the colon cancer cell line SW480 in another study (Silvers et al., 2010). Treating SW480, SW620, and HT-29 cells with 5-Aza-dC alone did not significantly alter SELENBP1 protein and mRNA levels (Wang et al., 2014). However, TSA alone or in combination with 5-Aza-dC could upregulate SELENBP1 expression in the SW480 and SW620 cells, indicating its regulation by histone modification, while no significant change was observed in HT-29 cells (Wang et al., 2014). There are no consistent results about the DNA methylation in colon cancer. NACHT, LRR, and PYD domain-containing protein 7 (NLRP7) are potential biomarkers of CRC. NLRP7 is deubiquitinated by ubiquitin-specific protease 10 (USP10), leading to increased NLRP7 protein stability (Li et al., 2021). SELENBP1 physically interacts with NLRP7, indicating the potential impact of SELENBP1 in epigenetic regulation; however, the specific mechanism remains unknown (Li et al., 2021).

Head and neck cancer: miRNA belongs to the non-coding RNAs (Hussain et al., 2022). SELENBP1 can be epigenetically modified through miRNA in cancer. SELENBP1 downregulation in OSCC is induced by miR-4786-3p binding to the 3′ untranslated region (UTR) of SELENBP1. Nuclear factor erythroid 2-related factor 2 (NRF2, an oncogenic transcription factor) is a downstream responder upon SELENBP1 downregulation. SELENBP1 reduces NRF2 protein levels by promoting its polyubiquitination and degradation. Kelch-like ECH-associated protein 1 (KEAP1) binds to NRF2 to promote ubiquitin–proteasomal degradation of NRF2 (Itoh et al., 1999; Adam et al., 2011). SELENBP1 also acts as a transcriptional factor to induce KEAP1 transcription by binding the KEAP1 promoter (Zeng et al., 2021). Targeting at the miR-4786-3p–SELENBP1–KEAP1–NRF2 signaling axis may enhance the efficacy of chemotheraphy for OSCC (Zeng et al., 2021).

Bladder cancer: By using the MEXPRESS tool (http://mexpress.be/), SELENBP1 expression in bladder cancer was found to relate to DNA hypermethylation in its promoter region located close to the transcription start site (TSS) and the first exon. Gene body methylation is negatively associated with SELENBP1 expression; however, DNA methylation in its 3′UTR was positively associated with SELENBP1 expression, which highlights that multiple DNA methylation sites may be differentially involved in regulating SELENBP1 expression. DNA hypermethylation, especially in the gene body, accounts for the reduction of SELENBP1 expression in bladder cancer. While p53-responsive elements are located in −1,394 bp and −2,285 bp regions of cyclin-dependent kinase inhibitor 1A (CDKN1A; also known as p21) promoter, SELENBP1-responsive elements are located within approximately −1,300 bp to −200 bp region of the p21 upstream promoter, and SELENBP1 upregulates p21 expression through a p53-independent mechanism transcriptionally and through phosphorylation attenuation of c-Jun and STAT1, leading to the G0/G1 phase cell cycle arrest, thereby inducing attenuation of cancer cell growth (Wang et al., 2020).

The epigenetic regulation of SELENBP1 during carcinogenesis is listed in Table 1 and described in Figure 3. In esophageal adenocarcinoma and colon cancer, histone deacetylase inhibitors or demethylating agents could target SELENBP1 expression (Pohl et al., 2009; Silvers et al., 2010). This leads to the usage of DNA methyltransferase and histone deacetylase to treat cancers targeting SELENBP1.

Selenium and treatment strategies

Se has been widely known to play a role in tumor prevention (Bansal et al., 1990). Studies regarding effects of Se on DNA methylation, DNMT expression or activity, and histone acetylation have been reported in various tissues and cells (Speckmann and Grune, 2015; Jablonska and Reszka, 2017).
FIGURE 3
Different SELENBP1 epigenetic functions during carcinogenesis. (A) Lung cancer: Nkx2-1 binds to the promoter and enhancer regions of SELENBP1 through methylation and acetylation. They also function in a positive feedback loop. SELENBP1 can downregulate HIF-1α protein levels. (B) Esophageal adenocarcinoma, methylation occurred at −95 to +90 as well as in the 5′-untranslated region of SELENBP1. The histone acetylation also exists with unknown sites. (C) Liver cancer: SELENBP1 is decreased in HCC and the SELENBP1 5′ flanking promoter is repressed by HBx. (D) Prostate cancer: SELENBP1 inducits phosphorylation of p53. SELENBP1 interacted with VDU1 and VDU2. VDU2 can deubiquitinate HIF-1α. Sub., potential substrates of VDU1. SELENBP1 inhibits HIF-1α protein levels. SELENBP1 interacts with EED. EED is critical for downstream methylation and ubiquitinylation. (E) Colon cancer: whether SELENBP1 promoter hypermethylation or histone acetylation exists in human colon cancer cells remain controversial. NLRP7 is deubiquitinated by USP10 in colon cancer. SELENBP1 interacted with NLRP7. The specific mechanism between SELENBP1 and NLRP7 remains unclear. (F) Head and neck cancer: downregulation of SELENBP1 is induced by miR-4786-3p targeting at the 3′-UTR of SELENBP1. SELENBP1 reduces NRF2 protein levels by promoting its polyubiquitination and degradation. SELENBP1 induces KEAP1 transcription by binding to KEAP1 promoter. (G) Bladder cancer: SELENBP1 expression was inversely associated with DNA methylation in the promoter and gene body, but positively correlates with DNA methylation in the 3′-UTR region. SELENBP1-responsive elements located in the upper region of the p21 upstream promoter than p53’s to increase p21 expression. SELENBP1-mediated transcriptional induction of p21 protein through combined phosphorylation suppression of e-Jun and STAT1. Ub, ubiquitin; P, phosphorylation; Ac, acetylation.

TABLE 1 List of SELENBP1 regulated by epigenetic modifications during carcinogenesis.

| Cancer type                    | Epigenetic modification                                      | Reference                        |
|-------------------------------|-------------------------------------------------------------|----------------------------------|
| Lung cancer                   | Histone modification (H3K4me3, H3K4me1, and H3K27ac)        | Caswell et al. (2018)            |
| Esophageal adenocarcinoma (EAC)| Promoter hypermethylation                                  | Silvers et al. (2010)           |
|                               | Histone modification (acetylation)                          |                                  |
| Liver cancer                  | Potential promoter modification                             | Lee et al. (2020)                |
| Prostate cancer               | Inducting phosphorylation of the p53 (serine 15)            | Ansong et al. (2015)             |
|                               | Histone modification (ubiquitination)                       | Jeong et al. (2009)              |
|                               | Potential promoter modification                             | Jeong et al. (2014)              |
|                               | Potential promoter modification                             | Elhodaky et al. (2020)           |
|                               | Potential histone modification (H3K27me3 and ubiquitination)| Cao et al. (2014)                |
| Colon cancer                  | Promoter hypermethylation                                  | Pohl et al. (2009)               |
|                               | Histone modification (acetylation) and promoter hypermethylation | Wang et al. (2014)              |
|                               | Potential histone modification (ubiquitination)             | Li et al. (2021)                 |
| Head and neck cancer          | miR-4786-3p and histone modification (ubiquitination)       | Zeng et al. (2021)               |
| Bladder cancer                | DNA hypermethylation and histone modification (phosphorylation) | Wang et al. (2020)               |
| Cancer type                      | Variation trend | Level                  | Functional classification                                                                 | Roles in cancer                                                                                      | Reference                                                                                     |
|---------------------------------|-----------------|------------------------|-------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Kidney cancer                   | Downregulation | mRNA and mRNA         | Potential prognostic factor                                                                | Specific mechanism remains unknown                                                                  | Ha et al. (2014)                                                                                             |
|                                 |                 |                        |                                            | Regulated by HNF4alpha                                                                               | Lucas et al. (2005)                                                                                       |
| Lung cancer                     | Downregulation | Protein and mRNA      | Decreased inactivation of carcinogens                                                       | Positive feedback loop with Nkx2-1                                                                 | Caswell et al. (2018)                                                                                  |
|                                 |                 |                        | Potential prognostic factor of LSCC                                                         | Specific mechanism remains unknown                                                                  | Tan et al. (2016)                                                                                          |
|                                 |                 |                        | Poor survival                                                                               | Proliferation and differentiation                                                                  | Chen et al. (2004)                                                                                          |
|                                 |                 |                        | mRNA and protein                                                                           | Cell transformation                                                                                    | Zeng et al. (2013)                                                                                          |
|                                 |                 |                        | Potential biomarker for early detection of LSCC                                             |                                                                                                      |                                                                                                           |
| Thyroid cancer                  | Downregulation | Protein               | Unknown                                                                                    | Unknown                                                                                                | Brown et al. (2006)                                                                                         |
| Stomach cancer                  | Downregulation | Protein               | Potential suppression target, impact on drug efficacy, and toxicity                          | Inhibit proliferation and migration                                                                  | Zhang et al. (2013a)                                                                                         |
|                                 |                 |                        | Diagnostic marker                                                                           | Unknown                                                                                                | (Zhang et al., 2011a; Xia et al., 2011)                                                                 |
|                                 |                 |                        |                                               |                                                                                                      |                                                                                                           |
| Esophageal adenocarcinoma (EAC) | Downregulation | Protein               | Predictor of response to chemoprevention or chemosensitization                            | Epigenetic and posttranscriptional mechanisms                                                      | Silvers et al. (2010)                                                                                       |
| Liver cancer                    | Downregulation | Protein               | Prognosis biomarker                                                                         | Increasing GPX1 activity and diminishing HIF-1α expression                                           | Huang et al. (2012)                                                                                         |
|                                 |                 |                        |                                            | EMT                                                                                                   | Gao et al. (2018)                                                                                          |
|                                 |                 |                        |                                            | Epigenetic regulation                                                                                | Lee et al. (2020)                                                                                          |
|                                 | Upregulation in vivo |                        | Potential biomarkers and therapeutic targets                                                | Selenium or acetaminophen metabolites                                                               | Lanfear et al. (1993)                                                                                       |
|                                 | Downregulation in vitro |                        | Unknown                                                                                    |                                                                                                      |                                                                                                           |
| Breast cancer                   | Downregulation | Protein               | Potential biomarker predicting survival and effectiveness of selenium supplementation         | Regulated via estrogen                                                                                | (Lanfear et al., 1993; Zhang et al., 2013b)                                                                  |
|                                 |                 |                        |                                            | Environment                                                                                           | Wang et al. (2015)                                                                                            |
|                                 |                 |                        |                                            | GPX1                                                                                                   | Fang et al. (2010)                                                                                            |
|                                 |                 |                        |                                            | RARα                                                                                                    | Gianni et al. (2019)                                                                                       |
|                                 |                 |                        |                                            | ESR2                                                                                                    | Guirato et al. (2018)                                                                                       |
| Prostate cancer                 | Downregulation | Protein               | Distinguishing indolent from aggressive disease                                             | Inducting phosphorylation of the p53                                                               | Anoong et al. (2015)                                                                                         |
|                                 |                 |                        | Candidate anti-oncogene product                                                            | Epigenetic regulation                                                                                 | Jeong et al. (2009)                                                                                         |
|                                 |                 |                        |                                            | Inhibited HIF-1α protein levels                                                                     | Jeong et al. (2014)                                                                                         |
|                                 |                 |                        |                                            | Energy metabolism                                                                                     | Elhodaky et al. (2020)                                                                                     |
|                                 |                 |                        |                                            |姘眶-grade metabolic signaling pathways                                                            | Xie et al. (2016)                                                                                           |
|                                 |                 |                        |                                            | Selenium levels in plasma                                                                             | Jerome-Morais et al. (2012)                                                                               |
|                                 |                 |                        |                                            | GPx enzyme activity                                                                                   |                                                                                                           |
|                                 |                 |                        |                                            |                                                                                                      |                                                                                                           |
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|                                 |                 |                        |                                            |                                                                                                      |                                                                                                           |
|                                 |                 |                        |                                            |                                                                                                      |                                                                                                           |
| Colon cancer                    | Downregulation | Protein               | Potential pharmacological target                                                           | Epigenetic regulation                                                                                 | (Pohl et al., 2009; Wang et al., 2014)                                                                         |
|                                 |                 |                        |                                            | Epithelial differentiation                                                                         | Li et al. (2008)                                                                                            |
|                                 |                 |                        |                                            | Lipid/glucose metabolic signaling pathways                                                          | Ying et al. (2013a)                                                                                         |
|                                 |                 |                        |                                            |                                                                                                      |                                                                                                           |
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|                                 |                 |                        |                                            |                                                                                                      |                                                                                                           |
|                                 |                 |                        |                                            |                                                                                                      |                                                                                                           |
| Pancreatic cancer               | Downregulation | Unknown               | Positive prognostic factor                                                                | Mitochondrial function                                                                               | Fang et al. (2010)                                                                                            |
|                                 |                 |                        |                                            | GPX1                                                                                                    | Li et al. (2021)                                                                                            |
|                                 |                 |                        |                                            | Potential epigenetic regulation                                                                       |                                                                                                           |
|                                 |                 |                        |                                            |                                                                                                      |                                                                                                           |
|                                 |                 |                        |                                            |                                                                                                      |                                                                                                           |
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| (Continued on following page)  |                 |                        |                                            |                                                                                                      |                                                                                                           |
| **TABLE 2** List of differentially expressed SELENBP1 during carcinogenesis and their functions. | | | | | |
High Se exposure leads to inhibition of DNMT expression/activity in prostate cancer (Xiang et al., 2008; Lee et al., 2009), breast carcinoma (de Miranda et al., 2014), and human colon cancer (Uthus et al., 2011). In addition, Se causes demethylation in LNCaP prostate cancer cells (Xiang et al., 2008) and human colon cancer Caco-2 cells (Uthus et al., 2011) and HDAC inhibition in prostate (Xiang et al., 2008; Lee et al., 2009), lymphoma (Kassam et al., 2011), and skin melanoma (Gowda et al., 2012). The epigenome changes influenced by Se may provide potential disease therapies and prevention strategies in cancers (Jablonska and Reszka, 2017).

Since SELENBP1 belongs to specific selenium-binding protein and its potential regulation in epigenetics during carcinogenesis, combined treatment targeting SELENBP1 and selenium might be a potential treatment strategy. In prostate cancer, SELENBP1 may play a role in controlling plasma selenium levels (Xie et al., 2016). For diseases such as prostate cancer, both SELENBP1 and selenium levels should be further examined for better treatment outcomes. The 3D model of human protein SELENBP1 with four cysteine residues was reported to have an alpha–beta structure characterized by four short alpha-helices, one 310 helix (residues 207–210), and 30 antiparallel beta-strands. Only one cysteine (Cys57) is able to bind the selenium in hepatocellular carcinoma, which may serve as a treatment target too (Raucci et al., 2011). The selenium-containing HDAC inhibitor or organic selenium compound

### TABLE 2 (Continued) List of differentially expressed SELENBP1 during carcinogenesis and their functions.

| Cancer type                  | Variation trend | Level                     | Functional classification                                      | Roles in cancer                                                                 | Reference |
|------------------------------|-----------------|---------------------------|----------------------------------------------------------------|--------------------------------------------------------------------------------|-----------|
| Head and neck cancer         | Downregulation  | Novel prognostic biomarker| Unknown                                                         | Epigenetic regulation, transcriptional factors, and miRNA in oral cancer        | Chen et al. (2016) Zeng et al. (2023) |
| Skin cancer                  | Downregulation  | Unknown                   | Unknown                                                         | Demethylation and tumor microenvironment HIF-1α                                | (Lanfear et al., 1993; Schott et al., 2018) Scortegagna et al. (2009) |
| Bladder cancer               | Downregulation  | Potential prognostic biomarker and therapeutic target | Epigenetic regulation                                           | Wang et al., (2020)                                                            |
| Uterine cancer               | Downregulation  | Protein                   | Unknown                                                         | Unknown                                                                         | Zhang et al. (2010a) |
| Nerve cancer                 | Unknown / Risk  | Unknown                   | Cell outgrowth                                                  | Pass et al. (2004)                                                             |
| Malignant pleural mesothelioma| Unknown / Risk  | Risk                      | Proliferation and transformation                                 |                                                                                   |
| Uveal melanoma tumor         | Upregulation    | Metastatic prediction     | Unknown                                                         | Linge et al. (2012)                                                            |
| Ovary cancer                 | Downregulation  | Protein                   | Potential prognostic indicator                                  | Selenium/androgen pathways Epithelial proliferation and papillary complexity     | Huang et al. (2006) Zhang et al. (2010b) |
|                              |                 |                           | Risk                                                           | Stromal epithelial cross-talk                                                  | Johnatty et al. (2010) |

### TABLE 3 List of Se regulated by epigenetic modifications during carcinogenesis.

| Cancer Type                  | Cell type                        | Epigenetic modifications          | Reference                          |
|------------------------------|----------------------------------|-----------------------------------|------------------------------------|
| Prostate cancer              | LNCaP cells                      | Demethylation; DNMT1 inhibition;  | Xiang et al. (2008)                |
| Breast cancer                | LNCaP cells                      | HDAC inhibition                   | Lee et al. (2009)                  |
| Colon cancer                 | MCF-7                            | DNMT1 inhibition                  | de Miranda et al. (2014)           |
| Diffuse large B-cell lymphoma| Human colonic epithelial Caco-2 cell | Demethylation                 | Uthus et al. (2011)                |
| Cervical carcinoma           | Lymphoma cell lines              | HDAC inhibition                   | Kassam et al. (2011)               |
| Skin melanoma                | Hela cells and melanoma cell line| HDAC inhibition                   | Desai et al. (2010)                |

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becomes the novel inhibitor for cancer treatment (Lee et al., 2009; Desai et al., 2010; Kassam et al., 2011), which merits favorable outcomes in vitro and in vivo. There is no evidence of a dose–response relation between selenium status and cancer risk (Vinceti et al., 2018). Whether supplemental dietary selenium should be considered as an adjuvant therapy for cancers still lacks certainty of evidence. Epigenetic drugs such as DNMTi and HDACi targeting SELENBP1 need further investigation before approval to treat different cancers clinically. In addition, microRNA has been reported for years as a potential target in cancers, such as lung, breast, prostate, colon, and liver carcinomas (Szczepanek et al., 2022). In OSCC, SELENBP1 is downregulated by miR-4786-3p through binding to the 3’UTR of SELENBP1 (Zeng et al., 2021). The antagomir of miR-4786-3p implies a potential treatment target of SELENBP1 in OSCC. Since the number of studies about microRNAs’ role in regulating SELENBP1 in other cancers is still limited, more studies should be performed to discover the role of microRNAs on SELENBP1 and develop potential treatment strategies.

Conclusion and future prospects

The expression of SELENBP1 is significantly downregulated in various cancers, which means SELENBP1 plays an important role in cancer progression. Although the molecular aspect of epigenetic changes of SELENBP1 in cancer remains largely unexplored and has not been used clinically in the diagnosis and treatments of patients with cancer yet, the prospects of novel discoveries and potential application of SELENBP1 are promising. Ongoing studies and tremendous progresses in the field of epigenetics have been made through transcriptome analysis and in vitro/in vivo experiments to unravel the potential epigenetic markers for future cancer therapeutics and prognosis. So, with the limited published articles, we summarize recent findings on the function and regulatory mechanisms of SELENBP1 during carcinogenic progression, with emphasis on epigenetic mechanisms.

There are still some crucial questions that should be addressed but can be easily neglected. 1) Whether the epigenetics change of SELENBP1 is one of the most important mechanisms for its expression and function during carcinogenesis. Many other mechanisms, such as metabolic signaling pathways (Ying et al., 2015a; Elhodaky et al., 2020), estrogen (Lanfear et al., 1993; Zhang C. et al., 2013), also effect the role of SELENBP1 in carcinogenesis. 2) If targeting only one specific epigenetic change at individual loci of SELENBP1 is enough to rescue its levels and activity during carcinogenesis, such as DNA methylation and protein ubiquitination. 3) Could the regulatory role of SELENBP1 epigenetic modification lead to therapy or prognosis? Further investigation is needed to identify novel epigenetic modifications of SELENBP1 through new technologies and dissect out the fundamental roles of these modifications on SELENBP1 expression and activities. Pharmacologic inhibition of epigenetic modifications could be key to reducing carcinogenic progression. Using specific inhibitors to target SELENBP1 might serve as therapeutic targets and lead to the desired clinical outcome (Table 2, Table 3) (Waddington, 1942; Porat et al., 2000; Haig, 2004; Feinberg, 2018; Millan-Zambrano et al., 2022).

Author contributions

YZ: investigation, validation, analysis, writing—original draft preparation, writing—review and editing, and visualization. QH: conceptualization, funding acquisition, writing—review and editing, and visualization. All authors approved the manuscript and agree to be accountable for the work.

Funding

This work was supported by the National Natural Science Foundation of China (82072483), the Natural Science Foundation of Hubei Province (ZRMS2020000955), and the Key Research and Development Program of Hubei Province (2022BCA052).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**Glossary**

RCC Renal cell carcinoma  
LSCC Lung squamous cell carcinoma  
NBE Bronchial epithelium  
PTC Papillary thyroid carcinoma  
DIGE Difference gel electrophoresis  
HCC Hepatocellular carcinoma  
VDU1 Hippel–Lindau protein (pVHL)-interacting deubiquitinating enzyme 1  
HIF-1α Hypoxia-inducible protein-1alpha  
Oxidosomes Oxidative phosphorylation  
AMPK AMP-activated protein kinase  
CRC Colorectal cancer  
TSA Trichostatin A  
VPA Valproic acid  
5-Aza-dC 5′-Aza-2′-deoxycytidine  
2-D PAGE Two-dimensional polyacrylamide gel electrophoresis  
Se Selenium  
hSP56 Human 56 kDa selenium-binding protein  
DEN Diethylnitrosamine  
OSCC Oral squamous cell carcinoma  
UTR Untranslated region  
NRF2 Nuclear factor erythroid 2-related factor 2  
KEAPI Kelch-like ECH-associated protein 1  
GPX1 Glutathione peroxidase 1  
HNSCC Head and neck squamous cell carcinoma  
NPC Nasopharyngeal carcinoma  
LC Laryngeal cancer  
OC Oral cancer  
TC Tonsil cancer  
HPC Hypopharyngeal cancer  
EAC Esophageal adenocarcinoma  
USP33 Ubiquitin-Specific Peptidase 33  
STRING Search Tool for the Retrieval of Interacting Genes/Proteins  
PPI Protein–protein interaction  
CXCR4 C-X-C motif chemokine receptor 4  
EMT Epithelial–mesenchymal transition  
B[a]P Benzo(a)pyrene  
GSH Glutathione  
PDAC Pancreatic ductal adenocarcinoma  
SR Skin rash  
HNF4α Hepatocyte nuclear factor 4 alpha  
HBx Hepatitis B virus-X  
CpG Cytosine–guanine  
MPM Malignant pleural mesothelioma  
AR Androgen receptor  
ATRA All trans-retinoic acid  
NLRP7 NACHT, LRR, and PYD domain-containing protein 7  
TERT Telomerase reverse transcriptase  
BRCT BRCA1 carboxyl-terminal  
DDR Damage response  
AGR2 Anterior gradient 2  
Dubs Deubiquitinating enzymes  
USP15 Ubiquitin-specific proteases 15  
EPS Expressed prostatic secretions  
ESR2 Estrogen receptor 2  
EED Embryonic ectoderm development  
PRC2 Polycomb repressive complexes 2  
H3K27me3 Histone H3 at lysine 27  
PRC1 Polycomb repressive complexes 1  
VCaP Vertebral Cancer of the prostate  
DNMTi DNA methylation inhibitor  
DNMTs DNA methyltransferase  
HDACi Histone deacetylase inhibitor  
MDS Myelodysplastic syndromes  
AML Acute myeloid leukemia  
PTMs Post-translational modifications  
miRNAs MicroRNAs  
IncRNAs Long-non-coding RNAs  
MS Multiple sclerosis  
Scz Schizophrenia  
COVID-19 Corona virus disease 2019  
CNS Central nervous system  
TSS Transcription start site  
CDKN1A Cyclin-dependent kinase inhibitor 1A  
USP10 Ubiquitin-specific protease 10