Siah1 in cancer and nervous system diseases (Review)

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Abstract. The dysregulation of the ubiquitin-proteasome system will result in the abnormal accumulation and dysfunction of proteins, thus leading to severe diseases. Seven in absentia homolog 1 (Siah1), an E3 ubiquitin ligase, has attracted wide attention due to its varied functions in physiological and pathological conditions, and the numerous newly discovered Siah1 substrates. In cancer and nervous system diseases, the functions of Siah1 as a promoter or a suppressor of diseases are related to the change in cellular microenvironment and subcellular localization. At the same time, complex upstream regulations make Siah1 different from other E3 ubiquitin ligases. Understanding the molecular mechanism of Siah1 will help the study of various signaling pathways and benefit the therapeutic strategy of human diseases (e.g., cancer and nervous system diseases). In the present review, the functions and regulations of Siah1 are described. Moreover, novel substrates of Siah1 discovered in recent studies will be highlighted in cancer and nervous system diseases, providing ideas for future research and clinical targeted therapies using Siah1.

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1. Introduction

Ubiquitination is a key process of the post-translational modification of proteins, playing an important role in the stability of the intracellular environment, the proliferation and differentiation of cells, and a number of cellular functions (1), whereas the imbalance of ubiquitination-mediated protein degradation is a molecular basis for human diseases. Ubiquitin is activated in an ATP-dependent reaction catalyzed by the ubiquitin-activating enzyme (E1). Under the action of the ubiquitin-conjugating enzyme (E2), the activated ubiquitin is transferred into a specific substrate along with E3 ubiquitin ligase, which is responsible for the substrate specificity for ubiquitin ligation (2,3).

Increasing attention has been focused on E3 ubiquitin ligases due to their unique functions compared with E1 and E2. E3 ubiquitin ligases regulate a range of cellular physiological processes, such as cell proliferation and differentiation, participate in DNA damage and repair, and control the cell cycle (1,4-6). In pathological processes (i.e., cancer and nervous system diseases), E3 ubiquitin ligases promote or suppress various diseases (7). For example, the speckle-type POZ protein (SPOP), a typical E3 ubiquitin ligase, is known as a tumor suppressor protein in prostate cancer (PC) and an oncoprotein in kidney cancer (8). In addition, E3 ubiquitin ligases with high-frequency mutations (mutations in *SPOP* occur in up to 11.13% of PC cases; The Cancer Genome Atlas, https://portal.gdc.cancer.gov/) in diseases prove their important role in the development of disease (4,7).

Currently, E3 ubiquitin ligases can be classified in three main types [i.e., RING E3s (~600 in humans), homologous to the E6AP carboxyl terminus (HECT) E3s (~30 in humans) and RING-between-RING (RBR) E3s (~12 in humans)] depending on the characteristic domains and the mechanism of ubiquitin transfer to the substrates (9). Notably, some E3s, including some RING E3s, all HECT E3s and all RBR E3s, interact with E2 alone to transfer the ubiquitin to the substrates, whereas other RING E3s transfer ubiquitin by forming the ubiquitin-ligase complex (9). The mechanism of ubiquitin transfer to the substrates gets little research attention.

The seven in absentia homolog (Siah) family of proteins, which belong to the RING E3s, are the mammalian homologs of the *Drosophila* sina proteins, which are responsible for the ubiquitination of substrate proteins to promote functional changes or degradation of substrate proteins through the

proteasomal pathway (10,11). In the human proteome, two proteins belonging to the Siah family of proteins have been identified and are known as Siah1 and Siah2. Mice have three Siah family proteins, termed Siah1a, Siah1b (collectively Siah1 due to their 98% similarity) and Siah2 (11).

Siah1 and Siah2 share high sequence similarity (86%) and presumably high structural homology. The difference between Siah1 and Siah2 is the additional amino acid sequence in the N terminal of Siah2 (11-14). However, the functions of Siah1 and Siah2 are almost completely different due to their unique substrates and different affinity and types of ubiquitination for the shared substrates (11). Previous studies focused on the oncoprotein functions of Siah2 (11,15). However, in recent years, a number of novel substrates of Siah1 have been discovered, and the functions of Siah1 as an important E3 ubiquitin ligase have been gradually recognized (10,11,16,17). A systematic review summarizing the functions of Siah1 in human diseases, such as cancer and nervous system diseases, is not available. Siah1 knockout mice exhibit severe growth retardation, poor bone formation, early lethality and a block in meiotic cell division during the meiosis I of spermatogenesis (18,19). However, the Siah2 mutant or knockout mice are fertile and largely phenotypically normal. Notably, the loss of a single copy of Siah2 enhances the phenotype of early lethality caused by Siah1 homozygous mutation. This phenotype is further enhanced by the removal of both copies of Siah2, with $Siah1^{-/-}Siah2^{-/-}$ mice subsequently dying within hours of birth, showing that Siah1 and Siah2 appear to perform partially overlapping functions *in vivo* (18,19). The functional compensation by Siah1 may maintain the normal regulation of Siah2 substrate proteins in $Siah2^{-/-}$ mice, suggesting the critical biological functions of Siah1 (18,19). In addition, in contrast to that of other E3 ubiquitin ligases (the regulations of SPOP have rarely been discovered), the regulations of Siah1 vary greatly (Table I; Fig. 1A), indicating that Siah1 plays a role as a bridge factor in various signaling pathways and is a promising therapeutic target (11,18). The present review will summarize the structure of Siah1 and the characteristics of its substrates, the regulations of Siah1 in physiological and pathological conditions, and its function and clinical significance in cancer and nervous system diseases to provide help for future researchers to understand Siah1.

2. Structure of Siah1 and characteristics of Siah1-interacting proteins (SIPs)

Siah family proteins usually consist of an N-terminal catalytic RING domain, two zinc finger domains and a C-terminal substrate-binding domain (SBD) that includes the first two zinc finger domains (Fig. 1B) (13). The RING domain is essential for ubiquitin ligase activity, and the SBD mediates homodimerization and the interaction with substrates (14). In contrast with other E3 ubiquitin ligases, Siah1 can interact with E2 alone and become an essential part of the ubiquitin-ligase complex, which includes calcyclin-binding protein (CacyBP)/SIP, and adapters SKP1, F-box-like/WD repeat-containing protein TBL1 or EBI and Siah1 (Fig. 1C) (20). CacyBP/SIP is suggested to position the substrates and improve the affinity between Siah1 and the substrate. Thus, Siah1 is most powerful when complexed (21,22).

The characteristics of the SIPs have also been studied (13). A consensus Pro-X-Ala-X-Val-X-Pro (VxP, core sequence; where X is not conserved) motif is common to a family of SIPs (Table I) (11,14,21,23-26). Some SIPs are also substrates of Siah1 and are targeted by Siah1 for degradation or functional modification. Dysregulation between Siah1 and substrates will lead to serious human diseases (e.g., cancer and nervous system diseases) (Table II) (11,15,16,18,27).

3. Siah1 in cancer

Siah1 in hepatocellular carcinoma (HCC). HCC is one of the most common malignancies worldwide (in 2020, there were 910,000 new cases of HCC worldwide, ranking sixth among all cancer types; The Cancer Genome Atlas, https://portal.gdc.cancer.gov/), with extremely high recurrence and metastasis rates (28). *Siah1* was identified as one of the tumor-suppressing genes of HCC in 2003 (29). Siah1 is significantly downregulated in advanced HCC, including poorly differentiated tumors, large tumors and tumors in advanced stages (29,30).

Wnt/β-catenin signaling pathways are one of the key cascades regulating cell growth, cell development and differentiation of normal stem cells, and have also been tightly associated with cancers made up of several key proteins, including Wnt, β-catenin, AXIN1, adenomatous polyposis coli protein (APC) and glycogen synthase kinase-3β (GSK-3β) (31-33). β-catenin, AXIN1, APC and GSK-3β form a degradation complex without Wnt signaling, inducing the phosphorylation of β-catenin and leading to the degradation of β-catenin through the ubiquitin proteasome pathway (31-36). The degradation complex is destroyed in response to Wnt signaling, releasing β-catenin and activating the transcription of downstream genes to promote the proliferation and survival of cells (Fig. 1D) (31-36). β-catenin is widely considered to be a major oncoprotein in HCC based on the frequency of mutations [15-33% of patients with HCC carry activating mutations in *ctnnb1* (coding for β-catenin)] associated with aberrant Wnt/β-catenin signaling pathways in patients with HCC (37). Siah1 functions in the ubiquitination-dependent degradation of β-catenin, thus inhibiting the abnormal activation of Wnt/β-catenin signaling pathways [whether wild-type or mutant Wnt/β-catenin signaling pathways; HepG2 (β-catenin with activating mutations), SNU475 (AXIN1 with dysfunctional mutation) and Huh7 (wild-type β-catenin and AXIN1)] and promoting cell apoptosis and growth arrest of HCC cells (30).

However, some studies have reported that Siah1 also promotes Wnt/β-catenin signaling pathways by inducing the ubiquitination and proteasomal degradation of AXIN1, suggesting the positive regulation of Siah1 in Wnt/β-catenin signaling pathways (38). The positive and negative regulations of Siah1 in Wnt/β-catenin signaling pathways indicate that Siah1 plays a key role in the dynamic balance of these pathways, suggesting that targeted therapy of Siah1 for HCC is a promising but prudent choice (Fig. 1D).

Acquired chemoresistance during long-term chemotherapy is one of the most important factors to limit the application of some chemotherapy drugs, such as doxorubicin (Dox), for the clinical treatment of patients with HCC (39,40). In addition, chemotherapy-resistant HCC shows a malignant phenotype,

Table I. Regulations of Siah1 ubiquitin ligase.

Level of regulation	Regulator	Mode of regulation
Transcriptional regulation	p53	p53 acts directly on *Siah1*, to promote the transcription of *Siah1*.
	Jab1	Jab1 inhibit the expression of p53 to suppress the transcription of *Siah1*.
	HIF-1α	HIF-1α trans-activates the transcription of *Siah1* by coordinating key histone modifications on the *Siah1* promoter.
	p21	The transcription of *Siah1* is directly activated by p21.
	E2F1	E2F1 can activate transcription from the *Siah1* promoter.
Translational regulation	miR-135a, miR-424, miR-944, miR-299-5p, miR-15b-5p, miR-107	MicroRNAs inhibit the translation of *Siah1* mRNA by targeting the 3'UTR.
	lncRNA RP11, hnRNPA2B1	RP11 directly binds to the CDS of *Siah1* and significantly downregulates the mRNA stability of *Siah1* by forming the RP11-hnRNPA2B1-mRNA. complex
Post-translational regulation	ASK1	Phosphorylation of Siah1 by ASK1 triggers GAPDH-Siah1 stress signaling.
	CacyBP/SIP	Overexpression of CacyBP/SIP promotes the interaction between Siah1 and cytoplasmic p27, which in turn increases the ubiquitination and degradation of cytoplasmic p27.
	HCF1/2	HCF1 and HCF2 antagonize the E3 ligase activity of Siah1 by binding and blocking the substrate-binding domain.
	AFF4	The AFF4-ELL2 interaction sequesters ELL2 away from Siah1 thereby inhibiting Siah1 ubiquitination of ELL2.
	UBCH8	Ubiquitin conjugase UbcH8 interacts with Siah1 to form a complex to ensure the function of Siah1.

p53, tumor suppressor p53; Jab1, c-Jun activation domain-binding protein 1; HIF-1α, hypoxia-inducible factor 1α; p21, cyclin-dependent kinase inhibitor p21; E2F1, E2F transcription factor 1; CDS, coding sequence; ASK1, apoptosis signal-regulating kinase 1; CacyBP/SIP, calcyclin-binding protein/Siah-1-interacting protein; HCF1/2, host cell factor 1/2; AFF4, AF4/FMR2 family member 4; UBCH8, ubiquitin conjugating enzyme human 8; miR, microRNA; lncRNA, long non-coding RNA.

suggesting that the changes in cancer-related factors occur in the HCC cells (41). Recent studies have shown that zinc finger E-box-binding homeobox 1 (ZEB1), a powerful epithelial mesenchymal transition-related transcription factor, is upregulated in Dox-resistant HCC cells and accompanied by a decrease in the protein expression of Siah1 (41-43). ZEB1 is degraded by the proteasomal pathway as a substrate for Siah1, but the low protein level of Siah1 induces the accumulation of ZEB1 (44,45). The same phenomenon also occurs in colorectal cancer (CRC) cells and Dox-resistant osteosarcoma cells (44,46). Some studies have suggested that long non-coding RNA (lncRNA) RP11 accelerates the mRNA degradation of Siah1 in CRC, thus leading to the accumulation of ZEB1 (46). Whether the cause of ZEB1 accumulation in HCC is related to RP11 remains unclear, but the lncRNA-Siah1-ZEB1 axis may be an important target against Dox resistance and ZEB1-related cancer.

Notably, Siah1 in HCC functions as a tumor suppressor protein and as an oncoprotein (11,15). Some studies have reported that the nuclear expression of Siah1 induces proliferation and migration and prevents the apoptosis of HCC cells (47). In addition, in HCC tissues, the decrease in cytoplasmic Siah1 and the nuclear accumulation of Siah1 are positively correlated with HCC progression, suggesting that the functions of Siah1 may be closely related to subcellular localization (47). The nuclear Siah1 accumulation is significantly correlated with the expression of the transcription factor far-upstream element-binding protein 3 (FBP-3). FBP-3 predominantly supports proliferation but cannot explain the reason for HCC cell migration being affected by Siah1 (47). Thus, the mechanisms for the high expression of Siah1 in the nucleus of HCC cells and the promotion of HCC by nuclear Siah1 accumulation are still unclear and should be studied in the future.

Siah1 in breast cancer (BC). BC is the most common cancer in women and is considered the second leading cause of cancer-related death in women (in 2020, there were 2,260,000 new cases of BC worldwide, ranking first among all cancer types of women; The Cancer Genome Atlas, https://portal.gdc.cancer.gov/) (48-51). BC is a type of cancer with complex phenotypes and heterogeneity. Thus, traditional pathology has been unable to meet the needs of BC diagnosis (52,53). The accurate diagnosis of BC requires entirely new tumor markers, such as Siah1.

Siah1 was originally identified as a tumor suppressor gene in BC (54-56). The expression of Siah1 is downregulated in BC tissues and is correlated with well to moderately differentiated and early stage BC (23). In addition, the inhibition of Siah1 expression promotes human BC cell

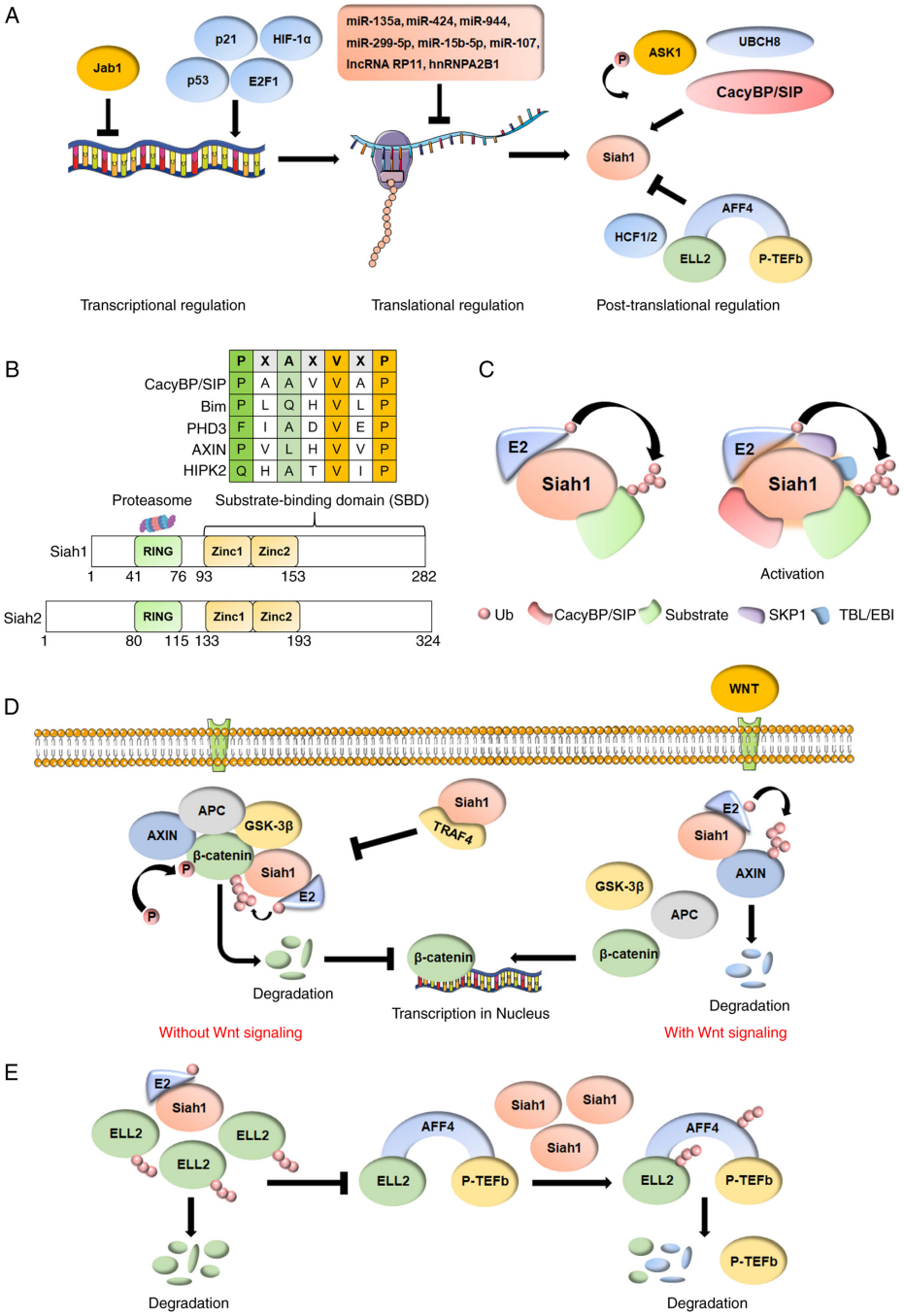

Figure 1. (A) The regulations of Siah1 vary greatly. At the transcriptional regulation level, p53, p21, E2F1 and HIF-1α trans-activate the transcription of Siah1. At the translational regulation level, microRNAs and lncRNAs inhibit the translation of Siah1 mRNA. At the post-translational regulation level, ASK1 induces the phosphorylation of Siah1. Overexpression of CacyBP/SIP promotes the interaction between Siah1 and cytoplasmic p27, which in turn increases the ubiquitination and degradation of cytoplasmic p27. Ubiquitin conjugase UbcH8 interacts with Siah1 to form a complex to ensure the functions of Siah1. HCF1 and HCF2 antagonize the E3 ligase activity of Siah1 through binding and blocking the substrate-binding domain. The AFF4-ELL2 interaction sequesters ELL2 away from Siah1, thereby inhibiting Siah1 ubiquitination of ELL2. (B) Siah1 consists of a N-terminal catalytic RING domain, two zinc finger domains and a C-terminal substrate binding domain that includes the first two zinc finger domains. A consensus Pro-X-Ala-X-Val-X-Pro (VxP, core sequence; where X is not conserved) motif is common to a family of SIPs (for example, CacyBP/SIP, Bim, PHD3, AXIN, HIPK2). Compared with Siah1, Siah2 has an additional amino acid sequence (~40 amino acids) at the N terminal. (C) Siah1 can interact with E2 ubiquitin-conjugating enzyme alone or become an essential part of the ubiquitin-ligase complex, which includes CacyBP/SIP, SKP1, TBL or EBI and Siah1. (D) β-catenin, AXIN1, APC and GSK-3β form a degradation complex without Wnt signaling, inducing the phosphorylation of β-catenin and finally leading to the degradation of β-catenin through the ubiquitin-proteasome pathway. The degradation complex is destroyed in response to Wnt signaling, releasing β-catenin, and thus activating transcription of downstream genes to promote the proliferation and survival of cells. Siah1 also induces the ubiquitination and proteasomal degradation of AXIN1 to promote the Wnt/β-catenin signaling pathways with Wnt signaling. TRAF4 protects β-catenin from Siah1-mediated degradation by competing with β-catenin for binding to Siah1 and replacing it for degradation. (E) The low protein level of Siah1 induces the degradation of dissociative ELL2 to prevent the formation of new SECs. The high protein level of Siah1 degrades all SECs. Siah1, seven in absentia homolog family proteins 1; Jab1, c-Jun activation domain-binding protein 1; ASK1, apoptosis signal-regulating kinase 1; UBCH8, ubiquitin conjugating enzyme human 8; Ub, ubiquitin; HCF1/2, host cell factor 1/2; P-TEFb, positive transcription elongation factor b; TRAF4, TNF receptor-associated factor 4; APC, adenomatous polyposis coli protein; GSK-3β, glycogen synthase kinase-3β; ELL2, elongation factor for RNA polymerase II 2; AFF4, AF4/FMR2 family member 4; miR, microRNA; lncRNA, long non-coding RNA; CacyBP, calcyclin-binding protein; Bim, Bcl-2-interacting mediator of cell death; PHD3, prolyl-hydroxylase protein 3; HIPK2, homeodomain-interacting protein kinase 2; SIP, Siah1-interacting protein; TBL/EBI, F-box-like/WD repeat-containing protein TBL1 or EBI.

Table II. SIPs of Siah1 ubiquitin ligase in human diseases.

Disease type	Substrate	Function of the SIPs	Degradation of the substrate	Physiological evidence (cell or animal model)
Cancer				
Breast cancer	JNK	Promotion of cell apoptosis and inhibition of MAPK signaling pathways.	No	The inhibition of Siah1 expression promotes human breast cancer cell proliferation, colony formation, migration and invasion, and inhibits apoptosis (15,23,57).
	Bim	DNA-binding transcription factor activity.	No	
	TRAF4	Protection of β-catenin from Siah1-mediated degradation and leading chemotherapy resistance.	Yes	
Glioma	HIPK2	Response to DNA damage and promotion of cells apoptosis.	Yes	The knockdown of Siah1 by shRNA severely suppresses the migration and invasion of human glioma U251 cells under hypoxia, while overexpression of Siah1 promotes it. However, when Siah1 interacts with CacyBP/SIP, the overexpression of Siah1 suppresses the migration and invasion of human glioma U251 and U87 cells (22,26).
	PHD3	Degradation of the HIF-1α.	Yes	
	CacyBP/SIP	The part of Siah1 ubiquitin-ligase complexes.	No	
	p27/kip1	Negative regulation of the cell cycle.	Yes	
Hepatocellular carcinoma	Axin, β-catenin	Cell migration and cell differentiation.	Yes	The overexpression of Siah1 induces growth arrest and apoptosis in HepG2, SNU475 and Huh7 cells (30).
	ZEB1	Epithelial-mesenchymal transition.	Yes	
Leukemogenesis	PML-RARa	The fusion protein of leukemia.	Yes	In the murine myeloblastic cell line M1 (generated from a spontaneous leukemia), expression of a stably introduced temperature-sensitive mutant of the tumor suppressor p53 activates the *Siah1* gene (27,74).
	ELL2	An elongation factor that modulates gene expression.	Yes	
	AML1-ETO AF4-MLL	The fusion protein of leukemia.	Yes	
Colorectal cancer	AKT, YAP	Inhibition of cells apoptosis	Yes	The knockdown of Siah1 by shRNA promotes HCT116/SW480 colorectal cancer cell proliferation and migration, and results in faster tumor growth and a markedly larger tumor volume in nude mice (108).
	ZEB1	Epithelial-mesenchymal transition.	Yes	
Osteosarcoma	ZEB1	Epithelial-mesenchymal transition.	Yes	None.
Nervous system diseases				
Development delay	Axin	Neuronal development and cell differentiation.	Yes	The development of skin and hair follicle development in the angora rabbit is affected by the level of Siah1 protein (132).
	Akt3	Neuronal development.	Yes	
Neuronal damage	GAPDH	Glycolysis and promotion of cell apoptosis.	No	Siah1 is upregulated after spinal cord injury in adult rats (138,139,143).
Parkinson's disease`	α-synuclein	The development of Parkinson's disease and the formation of LBs.	No	Inhibition of Siah1 by siRNA increases cell proliferation and inhibits apoptosis in SH-SY5Y neuroblastoma cells (113,115).
	Synphilin-1	The development of Parkinson's disease and the formation of LBs.	Yes	

Table II. Continued.

Disease type	Substrate	Function of the SIPs	Degradation of the substrate	Physiological evidence (cell or animal model)
Alzheimer's disease	CacyBP/SIP	Part of the Siah1 ubiquitin-ligase complexes and de-phosphorylation of tau protein.	No	In tau transgenic mice, localization of CacyBP/SIP and Siah1 is similar to that observed for patients with Alzheimer's disease (150).

JNK, c-Jun N-terminal kinase; Bim, Bcl-2-interacting mediator of cell death; TRAF4, TNF receptor-associated factor 4; HIPK2, homeodomain-interacting protein kinase 2; PHD3, prolyl-hydroxylase proteins 3; CacyBP/SIP, calcyclin-binding protein/Siah1 interacting protein; p27/kip1, p27 kinase inhibitory protein 1; ZEB1, zinc finger E-box-binding homeobox 1; ELL2, elongation factor for RNA polymerase II 2; PML-RARα, t(15;17)(q24;q21), generating the promyelocytic leukemia-retinoic acid receptor α fusion protein; AML1-ETO, t(8;21)(q22;q22), RUNX family transcription factor 1 fusion protein; AF4-MLL, t(4;11)(q21;q23), ectopic activator of transcript initiation fusion protein; AKT, targeting protein kinase; YAP, transcriptional coactivator YAP1; AKT3, targeting protein kinase-b3; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; LBs, Lewy bodies; siRNA, small interfering RNA; shRNA, small hairpin RNA.

proliferation, colony formation, migration and invasion, and inhibits apoptosis (15,23,57), suggesting the key role of Siah1 in the occurrence and development of BC. Some studies have further reported that Siah1 induces apoptosis, that inhibited invasion in BC cells may by upregulation of the level of Bcl-2-interacting mediator of cell death through the activation of the c-Jun NH2-terminal kinase signaling pathway, and that the suppression of Siah1 expression increases migration via the activation of the extracellular-regulated protein kinases signaling pathway (23,57).

The classification of BC is complex. Under the general trend of the development of precision medicine, oncologists prefer to classify breast cancer by molecular classification (51-53). Therefore, based on the expression of the three key factors for BC [estrogen receptor (ER), progesterone receptor (PR) and the human epidermal growth factor receptor 2 (HER2) subtype], oncologists classify BC into six subtypes: Luminal A (low-grade and ER-positive), luminal B (high-grade and ER-positive), HER2-overexpressing, triple-negative BC (TNBC; lacking ER, PR and HER2), normal breast-like tumors and claudin-low (TNBC with a low expression level of cell adhesion molecules) (15,49,51,52). TNBC is the most lethal subtype of BC due to its high heterogeneity, aggressive nature and lack of treatment options (58). Notably, the expression of Siah1 is significantly decreased in TNBC cells (MDA-MB-231), and the inhibition of Siah1 expression has recently been shown to be mediated by microRNA (miRNA/miR)-107 (an over-expression miRNA in BC, especially in TNBC) (59). miR-107 is considered to be a good predictive parameter of TNBC recurrence and promotes cell proliferation, colony formation, migration, invasion and cell cycle progression in human BC cells (i.e., MCF-7 and MDA-MB-231) through the down-regulation of Siah1 expression (59-61). In a previous study, the inhibition of Siah1 was relieved by the silencing of miR-107, which inhibited tumor growth in a nude mouse model of TNBC. This phenomenon suggests that the miR-107-Siah1 axis will be a promising therapeutic target in TNBC (59). In addition, miR-944 exhibits a similar function to miR-107, strongly supporting the importance of the regulation of Siah1 expression by miRNA (62).

Chemotherapy is the basic treatment of BC, and has made marked progress over the last few decades, with the emergence of new beneficial treatment methods, such as neoadjuvant chemotherapy (63-65). However, chemoresistance in BC is still common, leading to a poor prognosis and high mortality rate (66). One study has shown that Siah1 is associated with the chemoresistance of BC, which may be due to the interaction of Siah1 with tumor necrosis factor receptor associated-factor 4 (TRAF4) (63). Siah1 mediates the ubiquitination and degradation of β-catenin, thus inhibiting the activation of the Wnt/β-catenin signaling pathways, promoting cell apoptosis and preventing tumor progression (38). However, TRAF4 protects β-catenin from Siah1-mediated degradation by competing with β-catenin for binding to Siah1 and replacing it for degradation (Fig. 1D) (63). TRAF4 is highly expressed in chemotherapy-resistant breast cancer cells, and patients with BC and low TRAF4 expression levels benefit from chemotherapy (67-69). Notably, the chemoresistance mediated by TRAF4 appears to be strongest to etoposide (a chemotherapeutic agent that induces Siah1-mediated

degradation of β-catenin), suggesting that the key role of the Siah1-TRAF4/β-catenin axis in the chemoresistance of BC and further study of this axis may lead to new treatments (63).

Siah1 in leukemia. The dysregulation of the ubiquitin-proteasome system (UPS) is observed in solid tumors and leukemia (27). Increased substrates of Siah in leukemia have been found, suggesting the critical roles of Siah in leukemogenesis (27,70).

Acute promyelocytic leukemia (APL) is one of the most characterized forms of acute myeloid leukemia (AML) (71). t(15;17)(q24;q21), generating the promyelocytic leukemia-retinoic acid receptor α (*PML-RARα*) fusion gene, is the hallmark of APL (72,73). Notably, Pietschmann *et al* reported that the Siah1/2 cooperates with the E2 ubiquitin conjugase, i.e., ubiquitin-conjugating enzyme human 8 (UBCH8), leading to the proteasomal degradation of PML-RARα (74). In addition, this degradation of PML-RARα by the UBCH8-Siah1 complex can be significantly enhanced by all-trans-retinoic acid and sodium valproate (drug combination against APL), promoting the differentiation and maturation of APL cells (74,75). Moreover, other leukemia fusion proteins, including t(8;21)(q22;q22), RUNX family transcription factor 1 (AML1-ETO) fusion protein, have been identified as substrates of Siah1, but not Siah2, suggesting the powerful tumor suppressor effects of Siah1 in leukemia (27,76,77).

Super elongation complexes (SECs) promote the transcription of normal and leukemia-associated gene expression (78). SECs contain two different transcription elongation factors, namely positive transcription elongation factor b and elongation factor for RNA polymerase II 1/2 (ELL1/2), linked by the scaffolding protein AF4/FMR2 family member 1/4 (AFF1/4) (79). ELL2, a stoichiometrically limiting protein of SECs and an oncoprotein in leukemia, is specifically targeted for ubiquitin-mediated degradation by Siah1, but not by Siah2 (70,80,81). Notably, when AFF4 interacts with ELL2 to form SECs, the half-life of ELL2 against the Siah1-mediated ubiquitination is significantly prolonged (70). Through the proteasomal degradation induced by Siah1, AFF4 appears to have a lower affinity for Siah1 than ELL2. Thus, AFF4 is not adequately degraded by the low protein level of Siah1 (70). Notably, at relatively low protein levels of Siah1 in cells under physiological conditions, ELL2, especially the parts of ELL2 outside SECs, is highly sensitive to Siah1-induced ubiquitin-mediated degradation, suggesting that the primary effect of Siah1 is to prevent the formation of new SECs (Fig. 1E) (27,70). However, when the protein level of Siah1 becomes high, all remaining SECs are destroyed through Siah1-induced ubiquitin-mediated degradation (27,70). The abundance of Siah1 changes rapidly in response to various stresses, which may be to regulate SECs for the maintenance of a suitable transcription level of cells to adapt to stresses (11,71,73,74,77,82). Therefore, regulating the abundance of Siah1 in leukemia with disordered SECs may be a feasible method (Fig. 1E).

Siah1 in glioblastoma (GBM). GBM is the most common brain cancer (48%), with high tumor heterogeneity and poor survival time (median overall survival time, 12-14 months) in adults (83-85). Siah1 is widely regarded as a tumor suppressor in the majority of cancer types, with the exception of GBM (26,86). The knockdown of Siah1 by short-hairpin RNA (shRNA) severely suppresses the migration and invasion of human GBM cells (U251), whereas the overexpression of Siah1 has the opposite effect (26). Furthermore, recent studies have suggested that the tumor promotion of Siah1 in GBM is associated with hypoxic stress (11,16,26,87,88). Hypoxia-inducible factor 1α (HIF-1α) is the key transcription factor that regulates hypoxia-induced genes and enables cells to adapt to hypoxia (89,90). HIF-1α is extremely unstable under normal oxygen conditions (21% O_2), as the prolyl-hydroxylation of HIF-1α promotes the binding of von Hippel-Lindau disease tumor suppressor to HIF-1α, resulting in the degradation of HIF-1α through the ubiquitin-proteasome pathway (89,91,92). The prolyl-hydroxylation of HIF-1α is mediated by the prolyl-hydroxylase protein (PHD) family, and the activity of PHD is inhibited in hypoxia (16,89,92). Notably, PHD3 has been identified as a substrate of Siah1, and Siah1 mediates the ubiquitination of PHD3 and induces the degradation of PHD3 through the UPS (11,26,93). The degradation of PHD3 increases the abundance of HIF-1α, thus promoting cells to adapt to hypoxia (16,26,87,88,93). Moreover, HIF-1α trans-activates the transcription of *Siah1* by coordinating key histone modifications on the *Siah1* promoter to increase its expression continuously and form a positive feedback loop, thus leading to the progression of GBM via the tolerance of tumor cells to hypoxia (16,26,87,88,93). Siah1 may be a potential molecular target for the treatment of GBM through the interference of the Siah1-PHD3-HIF-1α axis (Fig. 2A).

Additionally, some studies have suggested that the Siah1-homeodomain-interacting protein kinase 2 (HIPK2)-p53Ser46 axis plays a key role in the promotion of glioma progression (86,94). HIPK2 functions as the key factor that is activated in DNA damage or cell response to stress and that triggers the phosphorylation of p53 at Ser46 (95,96). The best-known tumor suppressor gene, *TP53*, is mutated in >50% of malignancies and encodes a protein known as p53, a transcription factor that controls the initiation of the cell cycle (97-100). However, when p53 is phosphorylated at Ser46, its functional activity as a transcription factor is inactivated, whereas the function of apoptosis promotion is activated, thus leading cells to apoptosis under stress response (101,102). However, Siah1 has been considered as the negative regulatory E3 ubiquitin ligase of HIPK2 that targets HIPK2 for poly-ubiquitination and proteasomal degradation, thereby inhibiting cell apoptosis by HIPK2 and resulting in the survival and proliferation of GBM cells (86,94,103,104). Notably, p53 acts directly on *Siah1* to promote its transcription (11). As a tumor suppressor, p53 is supposed to promote the apoptosis of tumor cells, but the regulation of p53 on Siah1 in GBM seems to be a contradiction. p53 continuously activates the transcription of *Siah1*, whereas the increased abundance of Siah1 targets the degradation of HIPK2 and blocks the phosphorylation of p53 at Ser46, which keeps the activity of p53 as a transcription factor, continues to activate the transcription of *Siah1* and promotes the progression of GBM. This phenomenon may also be explained by the hypoxic microenvironment of GBM, as HIF-1α can promote *p53* transcription and stabilize the function of p53 in hypoxic stress (105,106). Siah1, p53, HIPK2, PHD3 and HIF-1α constitute an extremely complex network in

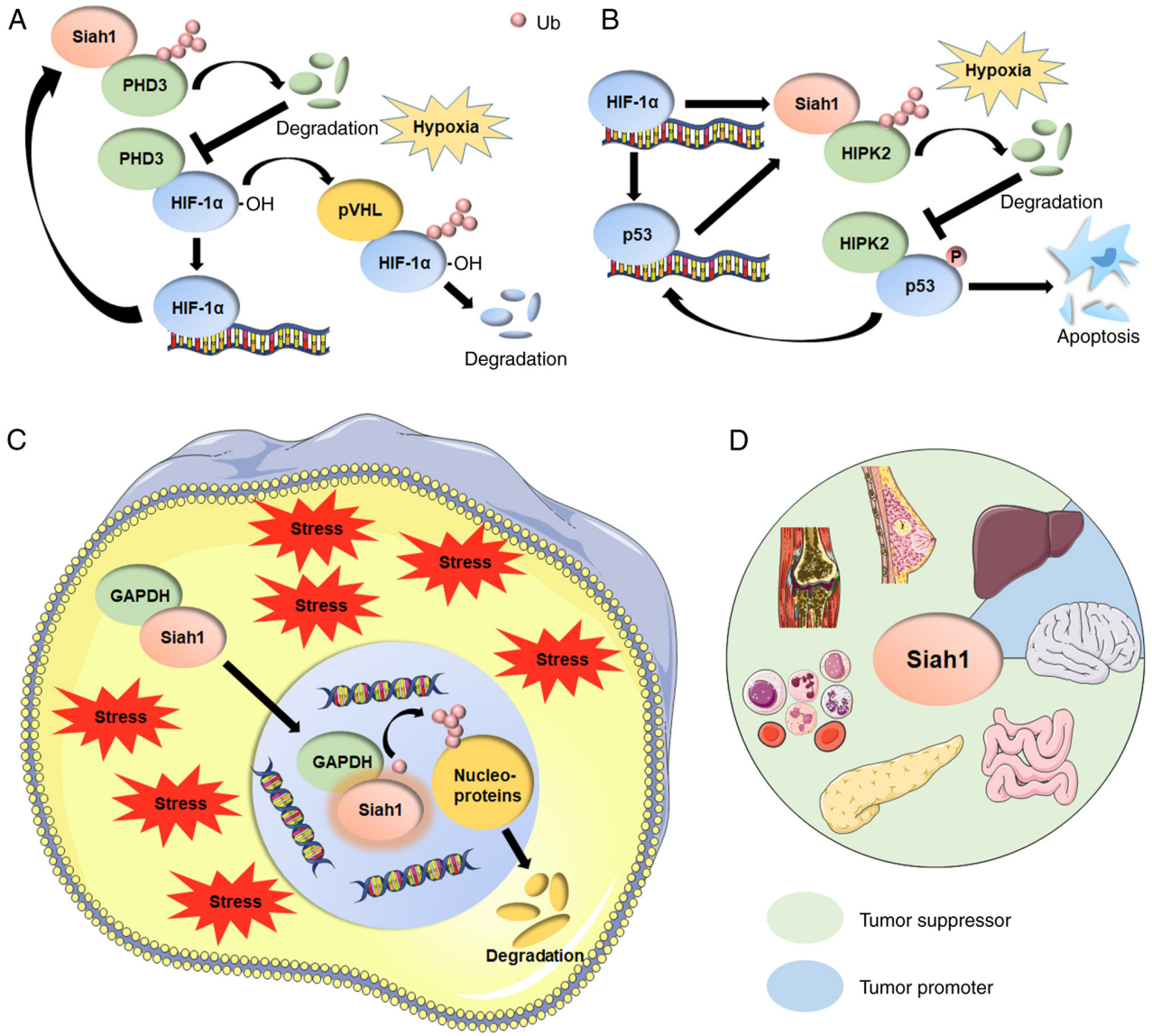

Figure 2. (A) Siah1 mediates the ubiquitination of PHD3 and induces the degradation of PHD3, increasing the abundance of HIF-1α and promoting cells to adapt to hypoxia. HIF-1α trans-activates the transcription of Siah1 by coordinating key histone modifications on the Siah1 promoter to continuously increase HIF-1α expression and form a positive feedback loop. (B) Siah1 targets HIPK2 for poly-ubiquitination and proteasomal degradation, thereby inhibiting the phosphorylation of p53 at Ser46 and preventing cell apoptosis. p53 continues to activate the transcription of Siah1 and forms a positive feedback loop. The initiation of this positive feedback mechanism may be mediated by HIF-1α under hypoxic stress. (C) Under cell stress, GAPDH translocates to the nucleus in a Siah1-dependent manner upon glutamate stimulation and stabilizes Siah1 to facilitate degradation of nuclear proteins by Siah1, resulting in cell apoptosis and neuronal damage. (D) Siah1 functions as a tumor suppressor in the vast majority of tumors (breast cancer, hepatocellular cancer, leukemia, colorectal cancer and osteosarcoma). In some cancer types, such as glioblastoma and a part of hepatocellular carcinoma (where Siah1 is localized to the nucleus), Siah1 functions as an oncoprotein. Siah1, seven in absentia homolog family proteins 1; PHD3, prolyl-hydroxylase proteins 3; HIF-1α, hypoxia-inducible factor 1α; pVHL, von Hippel-Lindau disease tumor suppressor protein; HIPK2, homeodomain-interacting protein kinase 2; p53, tumor suppressor p53; P, phosphate group; GAPDH, glyceraldehyde 3-phosphate dehydrogenase.

the process of promoting the development of GBM (Fig. 2B), in which Siah1, as a key bridge factor, has the potential to be a future therapeutic target.

Siah1 may also partially act as a tumor suppressor in GBM when it interacts with CacyBP/SIP. CacyBP/SIP inhibits the migration and invasion behaviors of GBM cells by activating Siah1-mediated ubiquitination and degradation of cytoplasmic p27/kip1 (a key transcription factor and an oncoprotein highly expressed in GBM tissues) (22).

Siah1 as an oncoprotein. Studies have shown that Siah1 promotes cancer progression only in GBM and HCC, and only when Siah1 is localized in the nucleus (11,47,86,94). The varying biological functions in these studies are most probably associated with differences in cell types and the differential subcellular localization of Siah1.

The functions of Siah1 to induce the proliferation of cancer cells may be due to increased protein levels of FBP-3 (47). In addition, the Siah1-PHD3-HIF-1 and HIPK2-p53Ser46 axes explain how Siah1 inhibits apoptosis (26,86,87,94,107). However, the functions of Siah1 as an oncoprotein have not been systematically studied and summarized. Thus, future studies are needed to provide evidence for the targeted therapy of Siah1 as an oncoprotein.

Siah1 in other cancer types. Siah1 also acts as a tumor suppressor in CRC and pancreatic carcinogenesis. The knock down of Siah1 by shRNA promotes HCT116/SW480 CRC cell proliferation and migration, and results in fast tumor growth and a markedly large tumor volume in nude mice. Mechanically, Siah1 represses the occurrence and development of CRC by promoting the ubiquitylation of AKT and inhibiting the activity of the MAPK, PI3K-AKT and Hippo pathways (108). Additionally, the mutations of p53 in pancreatic cancer act in the opposite manner to the wild-type p53, inhibiting the transcription of Siah1 and leading to the accumulation of the oncoprotein. This phenomenon suggests the novel regulation of Siah1 in cancer (109).

4. Siah1 in nervous system diseases

Siah1 in Parkinson's Disease (PD). PD, one of the most common neurodegenerative diseases, is manifested by a series of movement disorders, such as static tremor, bradykinesia, myotonia, and postural and gait disorders (110,111). Dopamine neurons and formation of Lewy bodies (LBs) in the substantia nigra striatum of the midbrain are regarded as typical pathological features of PD (112). LBs contain misfolded and abnormally stacked α-synuclein (α-syn), synphilin-1, ubiquitin and UPS-related enzymes, e.g., Siah1 (113-115), F-box only protein 7 (116), and Parkin (117), suggesting that the disorder of UPS plays a key role in the pathogenesis of PD (118-120). Notably, Siah1 is reported to monoubiquitinate or diubiquitinate α-syn, but without degradation, and is capable of ubiquitination and proteasomal degradation of synphilin-1, thus limiting the availability of α-syn for binding to synphilin-1 and the formation of LBs (114,115), suggesting the key pathological role of Siah1 in the development of PD. In addition, one study reported the cases of 7 patients with PD and *Siah1* mutations (113), but the function of these mutations in PD is not fully known yet. Increasing evidence shows that the PTEN-induced putative kinase 1, synphilin-1 and Siah1 complex constitutes a novel mitophagy pathway (mitochondrial dysfunction is also considered to be one of the main pathological features of PD] (7,12,13), and that the complex has the function of clearing damaged mitochondria in PD (121), suggesting that drugs that activate Siah1 provide a novel strategy to promote the clearance of damaged mitochondria in PD (116,122-127).

Siah1 in developmental delay. Developmental delay is defined as the skills of a child in one or a number aspects, including physical, motor, socioemotional, speech and language, and cognitive development, being significantly slower than those of other children of the same age (128-131). Developmental delay occurs in up to 5% of children <5 years of age, and patients can benefit from the early detection of developmental delay and appropriate therapeutic measures (129,130). Genetic factors are the main causes of development delay, and a recent case report showed *de novo* monoallelic variants (Cys41Gly, Pro50Leu, Cys128Phe, Thr168Ala and Gly174Arg) in Siah1 in 5 unrelated patients within a phenotypic spectrum of developmental delay, infantile hypotonia, dysmorphism, strabismus and laryngomalacia (128). All patients with Siah1 mutations, except Pro50Leu, presented with moderate or severe developmental delay (128).

The overinhibition of the Wnt/β-catenin signaling pathways is one of the important pathogenesis factors of developmental delay (34,35). Previous studies have reported that wild-type Siah1 enhances the Wnt/β-catenin signaling pathways by mediating the Wnt-induced degradation of Axin (38,132). However, in 293T cells, exogenous Siah1 mutations (i.e., Cys41Gly, Pro50Leu, Cys128Phe, Thr168Ala and Gly174Arg) lose the ability to degrade Axin compared with the wild-type Siah1, resulting in the overinhibition of the Wnt/β-catenin signaling pathways (128). The best treatment for developmental delay is early detection. Thus, the prenatal examination for *Siah1* is a highly effective option.

In addition, Siah1 has recently been identified as an upstream regulator of Akt3 (Akt signaling is an important regulator of neural development) (133-135), and it is responsible for the ubiquitination and degradation of Akt3, suggesting that Siah1 may play a key role in neural development (135).

Siah1 in neuronal damage. Neuronal damage includes a series of diseases, including spinal cord injury and cerebral ischemia reperfusion, and the common feature of these diseases is the excessive apoptosis of nerve cells (136,137). Previous studies have reported that glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is conventionally considered a critical factor in the process of nerve cell apoptosis (138-143). GAPDH is important in glutamate-induced neuronal excitotoxicity, and evidence also demonstrates that GAPDH nuclear translocation plays a critical role in cell death (143,144). Notably, recent studies have shown that GAPDH is translocated to the nucleus in a Siah1-dependent manner upon glutamate stimulation and that it stabilizes Siah1 to facilitate the degradation of nuclear proteins by Siah1, resulting in cell apoptosis and neuronal damage (Fig. 2C) (138,144,145). Notably, the GAPDH/Siah1 cascade can be inhibited by the administration of the interfering peptide, the cannabinoid agonist WIN55212-2 and Sivelestat sodium, thus preventing neuronal damage (138,143,144) and suggesting that the GAPDH/Siah1 cascade can serve as a potential therapeutic target for neuronal damage treatment.

Siah1 was previously considered to be only a neuroprotective factor (113,128,128), but in neuronal damage, it appears to play a role in promoting the progression of neuronal damage (143,144). This abnormal phenomenon may be related to the subcellular localization of Siah1, and the function of nuclear Siah1 seems to be opposite to Siah1 under normal physiological conditions (114). Notably, Siah1, a tumor suppressor, functions as an oncoprotein in some types of liver cancer, and Siah1 in liver cancer is localized in the nucleus (11,146). Thus, the subcellular localization of Siah1 is an important focus and may become a novel treatment strategy for some diseases.

Siah1 in Alzheimer's Disease (AD). AD, the most common chronic and irreversible neurodegenerative disease in the world, is characterized by impaired cognitive function and loss of self-care ability (147). The hyperphosphorylation of Tau is considered to be one of the main pathological features of AD (148,149). A recent study showed the CacyBP/SIP could mediate the dephosphorylation of phosphorylated-Tau (150), suggesting the neuroprotective effects of CacyBP/SIP. CacyBP/SIP has long been identified as a SIP (21,22). However,

the function of Siah1 in AD has been rarely studied and should be clarified in future studies.

5. Clinical significance of Siah1 in human diseases

Siah1 functions as a tumor suppressor in the vast majority of tumors [e.g., BC (23), HCC (30), leukemia (27), CRC (108) and osteosarcoma (44)]. However, in some cancer types, such as GBM (86) and a part of HCC (where Siah1 is localized to the nucleus) (47), Siah1 functions as an oncoprotein (Table II). The activator lncRNA SNHG1(151) and inhibitors miR-135a (152), miR-424 (153), miR-944 (62), miR-299-5p (146), miR-15b-5p (151) and miR-107 (59), are all good choices to regulate the functions of Siah1 depending on the different cancer contexts (Table I). Notably, the oncoprotein functions of Siah1 may be due to the nuclear localization of Siah1, thus suggesting that the inhibition of the Siah1 nuclear localization signal is a way to inhibit the oncoprotein functions of Siah1 but one that does not destroy the normal physiological function of Siah1 in the cytoplasm (47). This idea is also suitable for the treatment of nervous system diseases, as the nuclear localization of Siah1 often promotes nerve apoptosis and leads to the occurrence of nervous system diseases (138-140,142,143).

6. Discussion

The functions of a protein depend on a number of elements, including post-translational modification, cell types, cellular microenvironment and binding to other proteins. Siah1 was originally identified as a tumor-suppressing protein for BC (54-56). However, new functions of Siah1 are continuously being discovered, suggesting that Siah1 is not only a tumor-suppressing protein.

As an E3 ubiquitin ligase, the most important function of Siah1 is the ubiquitination of substrates to promote their degradation or change their function (11,13). However, the types of ubiquitin modifications of Siah1 in cancer and nervous system diseases seem to differ markedly. In cancer, Siah1 is responsible for the ubiquitination-mediated degradation of substrates, whether the substrates are oncoproteins or tumor-suppressing proteins (16,74,76,94,154,155). In nervous system diseases, Siah1 does more to change the function of substrates than to degrade them via non-degradative ubiquitination (140,142,156). This difference may be related to the formation of the Siah1 ubiquitin-ligase complex. Siah1 can interact with E2 alone or become an essential part of the ubiquitin-ligase complex (13,20). Notably, CacyBP/SIP, one of the parts of the complex, has the highest protein levels in the brain and maintains lower protein levels in other organs, suggesting that the complex may affect the Siah1-mediated ubiquitination of substrates (21). Siah1 has been reported to monoubiquitinate or diubiquitinate α-syn. Upon interaction with CacyBP/SIP, Siah1 can inhibit the development of GBM by inducing the degradation of p27/kip1, suggesting that the status of Siah1 (interacting with E2 alone or forming the ubiquitin-ligase complex) significantly affects the functions of Siah1 (22,114,115). Numerous studies are limited to substrate degradation by Siah1, but they ignore the special status of Siah1 in this process, thus requiring future supplemental studies (23,26,57,86). The studies on the Siah1 ubiquitin-ligase complex may be the key to study the function of Siah1 thoroughly and for targeting of Siah1 in the future.

The subcellular localization of Siah1 also determines the function of Siah1. The nuclear localization of Siah1 promotes the occurrence of cancer and nerve apoptosis, suggesting that the nuclear localization of Siah1 is a pathological phenomenon (47,138). Although the mechanism that causes Siah1 to transfer to the nucleus is not clear, we believe that the inhibition of the Siah1 nuclear localization signal can be identified as a favorable choice in the treatment of diseases.

The oncoprotein functions of Siah1 in GBM seem to be closely related to the tumor hypoxic microenvironment (26,93). However, the function of Siah1 as an oncoprotein in the hypoxic microenvironment has not been reported in other tumors, especially in HCC, which is most closely associated with the hypoxic microenvironment (89). GBM belongs to the diseases of the nervous system. Thus, studying the functional differences of Siah1 in cancer and neurological diseases is a notable and promising topic.

The dysregulation of UPS is usually caused by the mutations of E3 ubiquitin ligase, such as SPOP (8,157) and leucine zipper-like transcription regulator 1 (LZTR1) (158). The mutations of SPOP and LZTR1 occur mostly in domains bound to the substrate, severely affecting their ability to bind to substrates, inhibiting the ubiquitination and degradation of substrates, and leading to the accumulation of substrates (4,6,159). Notably, although one study showed the lack of somatic mutation in the coding sequence of Siah1 (55), the mutations of Siah1 are rarely reported. The regulations of SPOP and LZTR1 are rarely recorded, whereas the regulations of Siah1 are various (Table I), suggesting that Siah1 plays a core role as a bridge factor in various signaling pathways (11). Slight changes in Siah1 protein levels and protein localization lead to significant changes in its functions, which may be as the mutations affect the function of Siah1 significantly and cause death in the earliest embryos (knockout of both Siah1 genes is embryonically lethal in mice). This phenomenon results in little spread of Siah1 mutation heritage lines (11,27).

Although numerous studies have focused on the upstream regulations of Siah1 (Table I), studies on agonists and inhibitors specifically targeting Siah1 remain lacking. The only drug targeting Siah that has been described so far is vitamin K3 (menadione), which has been identified as an inhibitor of Siah2 ubiquitin ligase activity in a screen of U.S. Food and Drug Administration-approved therapeutic drugs (158). Therefore, the future drug research of Siah1 is still needed.

The present review summarized the novel substrates and complex upstream regulations of Siah1, describes the functions of Siah1 as a tumor suppressor protein and an oncoprotein, and discusses the potential mechanisms of the different roles of Siah1 in the nervous system and cancer. In addition, the review focused on the effects of Siah1 nuclear localization and the special status of Siah1 (interacting with E2 alone or forming the ubiquitin-ligase complex). Moreover, it highlighted the clinical significance of Siah1 in human diseases. This review may provide inspiration for future Siah1 research.

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Availability of data and materials

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Authors' contributions

XJ conceived the present study. HZ drafted the manuscript. YG, JW and MY made substantial contributions to the interpretation and drafting of the study, and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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