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Review

USP39 promote post-translational modifiers to stimulate the progress of cancer

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Abstract
Deubiquitinating enzymes (DUBs) are a class of crucial peptidyl hydrolases within the ubiquitin system, playing a significant role in reversing and strictly regulating ubiquitination, which is essential for various biological processes such as protein stability and cellular signal transduction. Ubiquitin-specific protease 39 (USP39) is an important member of the DUBs family. Recent studies have revealed that USP39 is involved in the regulation of multiple cellular activities including cell proliferation, migration, invasion, apoptosis, and DNA damage repair. USP39 also plays a significant role in the development and progression of various cancers. It is believed that USP39 is a unique enzyme that controls the ubiquitin process and is closely associated with the occurrence and progression of many cancers, including hepatocellular, lung, gastric, breast, and ovarian cancer. This review summarizes the structural and functional aspects of USP39 and its research advancements in tumors, investigates the key molecular mechanisms related to USP39, and provides references for tumor diagnosis and treatment.

Keywords USP39 · Ubiquitin · Deubiquitination · Cancers

1 Introduction

Proteins within cells maintain cellular homeostasis through dynamic equilibrium, which relies on various post-translational modifications(PTMs), such as ubiquitination, phosphorylation, lactylation, and glycosylation. Ubiquitination is a key PTM that involves modification of target proteins by ubiquitin molecules under the action of a series of specific enzymes, including ubiquitin-activating enzymes, conjugating enzymes, ligases, and degrading enzymes. These enzymes play crucial roles in the localization, metabolism, function, regulation, and degradation of proteins [1]. The ubiquitination process is reversible and is catalyzed by deubiquitinating enzymes (DUBs), which play a central role in maintaining cellular homeostasis [2]. DUBs regulate cellular functions through various mechanisms including proteasome-dependent and lysosome-dependent protein hydrolysis, gene expression, and cell cycle progression. Alterations in DUB function are associated with many diseases including cancer [3]. In human tumors, DUBs can act as oncogenes or tumor suppressors [4] and have become a hot target for the development of new antitumor drugs.

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The human genome encodes approximately 100 DUBs, which can be divided into six subfamilies based on their sequences and structural differences, including ubiquitin-specific proteases (USPs) [5]. USPs are the largest subfamily of DUBs, comprising 58 members, characterized by the presence of one catalytic core associated with ubiquitin binding and three conserved catalytic domains [6]. Dysfunction of the USP family can lead to many diseases including cancer [3], metabolic diseases [7], and neurodegenerative diseases [8]. Among these, research on the relationship between USPs and malignant tumors has become an emerging area of research, and many studies have shown that targeted intervention of this pathway is expected to become an ideal anti-tumor therapy strategy. The functions of various USPs in carcinogenesis are summarized in Table 1. For example, ubiquitin-specific protease 2 (USP2) deubiquitinates and stabilizes PD-1 to promote tumor immune evasion [9]. High expression of ubiquitin-specific peptidase 10 (USP10) promotes tumor progression by blocking KLF4 [10]. Knocking out USP22 in lenvatinib-resistant hepatocellular carcinoma (HCC) cells reduces cell invasion and migration. USP22 knockout inhibits the survival rate of drug-resistant HCC cells and promotes apoptosis [11]. USP28 can mediate the deubiquitination of PKM2, thereby activating the downstream HIF1-α signaling pathway, promoting glycolysis and energy supply, and ultimately promoting tumor progression [12]. Modulation of USP activity is an emerging therapeutic approach that can limit cancer growth or improve responses to chemotherapy and immunotherapy. Targeting USPs for intervention holds promise as an ideal anti-tumor treatment strategy.

Ubiquitin-specific protease 39 (USP39), a member of the USP family, is widely distributed in human tissues and its functional abnormalities are associated with various human diseases, particularly the occurrence and development of tumors [13–15]. USP39, first identified as a deubiquitinating enzyme in 2008, has since attracted increasing attention due to its distinct roles in cellular processes (Fig. 1). Subsequent studies have progressively unveiled its significance, particularly in cancer biology. In recent years, the importance of USP39, particularly in cancer, has been increasingly revealed. USP39 plays a significant role in the regulation of cell cycle, cell proliferation, DNA damage repair, and drug resistance in tumors. This article aims to review the structural and functional aspects of USP39 and its progress in tumor research to provide new perspectives for future research and treatment.

2 USP39 structure and function, deubiquitination mechanism

2.1 Molecular structural features of USP39

USP39, also known as sad1, was initially identified in yeasts. Sad1 is an essential splicing factor initially identified in a genetic screen in Saccharomyces cerevisiae for snRNP assembly defects. Based on sequence homology, Sad1, or USP39 in humans, is predicted to comprise two domains: a zinc finger ubiquitin binding domain (ZnF-UBP) and an inactive ubiquitin-specific protease (iUSP) domain, both of which are well conserved [85]. The human USP39 gene is located in the 2p11.2 region of chromosome 2, spanning approximately 46 kb and consists of 16 exons. The encoded protein has a relative molecular mass of approximately 65 kDa. USP39 contains two main functional domains: an N-terminal RS-like zinc finger ubiquitin-binding domain(ZnF-UBD) and C-terminal ubiquitin-specific protease domain(USP) [86]. Although the catalytic activity of USP family enzymes typically relies on three core amino acid residues (cysteine, histidine, and aspartic acid/asparagine) that form the catalytic triad necessary for enzymatic activity [87], the three corresponding residues in USP39 (aspartic acid, serine, and glutamic acid) are different from traditional USP family members, leading to the initial belief that it might not possess ubiquitin protease activity. However, with ongoing research, new insights into the functions of USP39 have emerged.

2.2 Biological functions of USP39

As research progresses, it has been discovered that USP39 indeed possesses deubiquitination capabilities, able to stabilize CHK2, enhance its stability, and thereby promote cell cycle arrest, apoptosis, and DNA repair. Docking between USP39 and CHK2 proteins (Fig. 2A) [88]. Additionally, USP39 maintains the stable expression of STAT1 through deubiquitination, thereby regulating the antiviral effects induced by interferons [89]. In hepatocellular carcinoma(HCC), USP39 stabilizes β-catenin by deubiquitination and inhibits the maturation of E3 ligase TRIM26 pre-mRNA, thus promoting the proliferation, invasion, and metastasis of liver cancer cells [90]. USP39 also has an additional RS domain (AA1-100) at its N-terminus, similar to the RS domain of SR (Ser-Arg rich protein, SR protein) related proteins. Functional studies have shown that USP39 can recruit U4/U6-U5 tri-snRNPs to the spliceosome precursor, affecting the formation of the mature spliceosome and participating in pre-mRNA splicing [91]. Research by Y. Ríos et al. has shown that USP39 gene mutations

Table 1 The role of ubiquitin specific proteases (USPs) in cancer progression

USP	Functions	Cancer of type	Substrates	References
USP1	Promote tumor progression through deubiquitination of PARP1	Cholangiocarcinoma	PARP1	[16]
	Modulate HCC progression through the Hippo/TAZ axis	Hepatocellular carcinoma	Hippo/TAZ	[17]
	Disrupt the stability of KPNA2 and inhibit metastasis	Breast cancer	KPNA2	[18]
USP2	Maintain ErbB2 abundance	Breast cancer	ErbB2	[19]
USP3	Promote cell migration and invasion through deubiquitination of SUZ12	Gastric cancer	SUZ12	[20]
	Promote invasion and transition via stabilizing Snai	Glioblastoma	Snail	[21]
	Stabilize Aurora A to promote proliferation	Esophageal squamous cell carcinoma	Aurora A	[22]
USP4	Promote the proliferation, migration, and invasion	Esophageal squamous cell carcinoma	TAK1	[23]
	By binding with cortactin, cell migration can be enhanced	Colon cancer	cortactin	[24]
USP5	Promote transition by stabilizing SLUG	Hepatocellular carcinoma	SLUG	[25]
	Facilitate tumor progression through stabilization of PD-L1	Non-small cell lung cancer	PD-L1	[26]
	Promote proliferation and metastasis by stabilizing HIF2α	Breast cancer	HIF2α	[27]
	Activate PARP1-mediated mTOR signaling pathway	Lung cancer	PARP1 mTOR	[28]
USP6	Deubiquitination of GOLPH3 induces platinum resistance	Colon cancer	GOLPH3	[29]
USP7	Downregulate PD-L1 and sensitize cells to T cells killing	Gastric cancer	PD-L1	[30]
USP8	Promote gemcitabine resistance via stabilizing Nrf2	Pancreatic cancer	Nrf2	[31]
USP9X	Promote tumor cell survival and confer chemoresistance through YAP1 stabilization	Breast cancer	YAP1	[32]
USP10	Regulate KLF4 stability and suppress tumorigenesis	Lung cancer	KLF4	[10]
	Promote proliferation by stabilizing YAP/TAZ	Hepatocellular carcinoma	YAP/TAZ	[33]
USP11	Promote chemoresistance by stabilizing BIP	Ovarian cancer	BIP	[34]
USP12	Facilitate cancer progression via stabilizing YAP	Gastric cancer	YAP	[35]
	Promote cancer progression by stabilizing RRM2	Non-small cell lung cancer	RRM2	[36]
USP13	Promote deubiquitination of ZHX2 and tumorigenesis	Kidney cancer	ZHX2	[37]
	Stabilize cyclin D1 to promote proliferation	Gastric cancer	Cyclin D1	[38]
USP14	Promote progression by targeting JNK for stabilization	Colorectal cancer	JNK	[39]
USP15	Stabilize ERα and promote progression	Breast cancer	ERα	[40]
USP16	Promote proliferation by stabilizing c-Myc	Prostate cancer	c-Myc	[41]
USP17	Promote inflammation and stemness	Lung cancer	TRAF2/TRAF3	[42]
USP18	Promote proliferation via activating AKT signaling pathway	Cervical cancer	AKT	[43]
USP19	Facilitate HCC progression through stabilizing YAP	Hepatocellular carcinoma	YAP	[44]
USP20	Promote metastasis by stabilizing SNAI2	Breast cancer	SNAI2	[45]
USP21	Promote cancer cell stemness via Wnt pathway activation	Pancreatic cancer	Wnt pathway	[46]
USP22	Exert tumor-suppressive functions by decreasing mTOR activity	Colorectal cancer	mTOR	[47]
USP24	Accelerate aerobic glycolysis and tumor progression through stabilizing PLK1	Gastric carcinoma	PLK1	[48]
USP25	Promote pathological HIF-1-driven metabolic reprogramming	Pancreatic cancer	HIF-1	[49]

Table 1 (continued)

USP	Functions	Cancer of type	Substrates	References
USP26	Promote tumor progression by stabilizing TAZ	Anaplastic thyroid cancer	TAZ	[50]
USP27	By stabilizing SETD33 enhances cell proliferation	Hepatocellular carcinoma	SETD3	[51]
USP28	Promote progress by stabilizing FOXM1	Pancreatic cancer	FOXM1	[52]
USP29	Promote AURKB stability and oncogenic functions	Gastric cancer	AURKB	[53]
USP30	Stabilize DRP1 to promote Hepatocarcinogenesis	Hepatocellular carcinoma	DRP1	[54]
USP31	Enhance NFκB activity to promote sarcomagenesis	Sarcoma	NFκB	[55]
USP32	Promote tumorigenesis and chemoresistance via upregulation of SMAD2	Gastric carcinoma	SMAD2	[56]
	Deubiquitinate BAG3 facilitates cancer progression	Non-small cell lung cancer	BAG3	[57]
USP33	Mediate Slit-Robo signaling in inhibiting migration	Colorectal cancer	Slit-Robo	[58]
	Stabilization of CBX2	Ovarian cancer	CBX2	[59]
USP34	Stabilization of Pin1 promotes protein sumoylation	Glioma stem cells	Pin1	[60]
USP35	Promote metastasis by increasing the stability of Snail1	Gastric Cancer	Snail1	[61]
	Promote proliferation through stabilizing FUCA1	Colorectal cancer	FUCA1	[62]
	Mediate cisplatin-induced apoptosis by stabilizing BIRC3	Non-small cell lung cancer	BIRC3	[63]
USP36	Promote tumorigenesis and drug sensitivity by stabilizing ALKBH5	Glioblastoma	ALKBH5	[64]
USP37	Deubiquitinate and stabilize c-Myc	Lung cancer	c-Myc	[65]
	Promote deubiquitination of HIF2α	Kidney cancer	HIF2α	[66]
USP38	Regulate the stemness and chemoresistance via regulation of HDAC3	Colorectal cancer	HDAC3	[67]
USP39	Promote proliferation and migration	Hepatocellular carcinoma	ZEB1 TRIM26	[68]
USP40	Promote proliferation, migration and stemness	Hepatocellular carcinoma	Claudin1	[69]
USP41	Enhance Epithelial-Mesenchymal transition	Breast Cancer	Snail	[70]
USP43	Promote glycolysis and transport by stabilizing c-Myc	Bladder cancer	C-Myc	[71]
USP44	Suppress tumor progression by inhibiting Hedgehog signaling and PDL1 expression	Hepatocellular carcinoma	PDL1 Hedgehog signaling	[72]
	Accelerate tumor progression by inducing p21 degradation	Thyroid cancer	p21	[73]
USP45	By deubiquitinating Snail and promoting cancer carcinogenesis, progression	Serous ovarian cancer	MYH10 MYH9 Snail	[74]
USP46	As a tumor suppressor by controlling PHLPP-dependent attenuation of AKT signaling	Colon cancer	PHLPP	[75]
USP47	Deubiquitination of SATB1 regulates tumor proliferation and progression	Colon cancer	SATB1	[76]
USP48	Blockade of USP48 degrades HMGA2 and inhibit tumor invasion and metastasis	Colorectal cancer	HMGA2	[77]
USP49	Mediate tumor progression and poor prognosis through a YAP1-dependent feedback loop	Gastric cancer	YAP1	[78]
USP50	Regulate NLRP3 inflammasome activation	Gastric tumor	NLRP3	[79]
USP51	Facilitate stemness and chemoresistance	Colorectal cancer	HIF1 A	[80]
USP52	Modulate ferroptosis by stabilizing SLC7 A11/xCT	Bladder cancer	SLC7 A11/xCT	[81]
USP53	Play an antitumor role through deubiquitination of cytochrome c	Hepatocellular carcinoma	Cytochrome c	[82]

Table 1 (continued)

USP	Functions	Cancer of type	Substrates	References
USP54	Regulate GLUT1-mediated aerobic glycolysis to inhibit tumor progression by modifying p53 degradation	Lung adenocarcinoma	GLUT1 p53	[83]
CYLD	Enhance metabolic reprogramming and tumor progression via PFKFB3	Nasopharyngeal carcinoma	PFKFB3	[84]

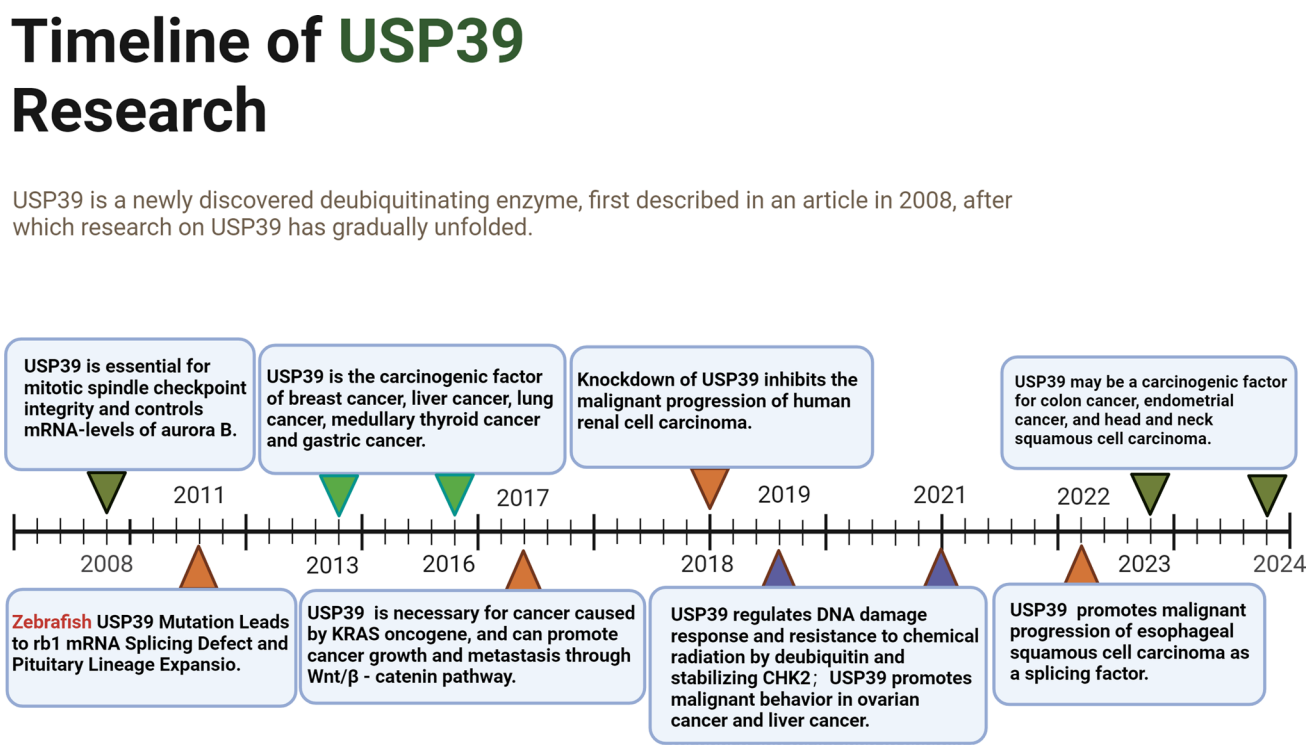

Fig. 1 Timeline of USP39 Research. This figure depicts the research progress of USP39 in recent years and emphasizes several new aspects of USP39 in cancer

lead to defects in rb1 mRNA splicing in zebrafish, inhibiting rb1 protein expression and promoting the development of pituitary tumors [92]. Other studies have reported that USP39 plays a significant oncogenic role in the development of prostate cancer by regulating EGFR pre-mRNA splicing, thereby affecting transcription elongation and maturation [93]. USP39 is also involved in the splicing of Aurora B and other mRNAs, which is crucial for maintaining spindle checkpoint [94]. Researchers have also revealed a close relationship between USP39 and drug tolerance in tumor cells. USP39 is associated with the sensitivity of colon cancer cells to cisplatin. USP39 depletion enhanced cisplatin-induced apoptosis in colon cancer cells, whereas USP39 overexpression diminished cisplatin-induced apoptosis [95]. USP39 has also been found to be associated with tumor glycolysis. USP39 can be recruited together with the key rate-limiting enzyme of glycolysis, PFKL, to the scaffold protein DNAAF5, which is highly expressed in HCC [96]. DNAAF5 enhances the stability of PFKL protein by recruiting USP39, thereby promoting the malignant progression of HCC. The interaction between USP39 and PFKL in liver cancer cells has been confirmed, and the downregulation of USP39 inhibits the increase in PFKL expression caused by DNAAF5 overexpression. Recent studies have found that USP39 regulates VEGF-A165b alternative splicing as a driving factor for angiogenesis [97]. In summary, the structure and function of USP39 are highly complex and involved in the regulation of various cellular activities, including cell proliferation, cell invasion and metastasis, cell apoptosis, DNA damage repair, and tumor metabolic reprogramming (Fig. 2B).

2.3 The deubiquitination mechanism of USP39

Deubiquitination is an essential protein modification process within cells that corresponds to the ubiquitination process. Ubiquitination is a post-translational modification process, in which ubiquitin molecules are attached to substrate proteins through a series of enzymatic reactions. This process involves three enzymes: ubiquitin-activating enzymes(E1), ubiquitin-conjugating enzymes(E2), and ubiquitin-protein ligases(E3). E1 first activates ubiquitin and forms a covalent bond with it before transferring it to E2, and then E3 catalyzes the transfer of ubiquitin from E2 to the lysine residues of the substrate protein, forming a ubiquitin-protein chain. These chains can be distinguished by different ubiquitin linkage types (such as lysine residues of ubiquitin molecules or K6, K48, or M1), thereby determining the fate of the protein, such as proteasomal degradation or non-degradative functional regulation [98, 99].

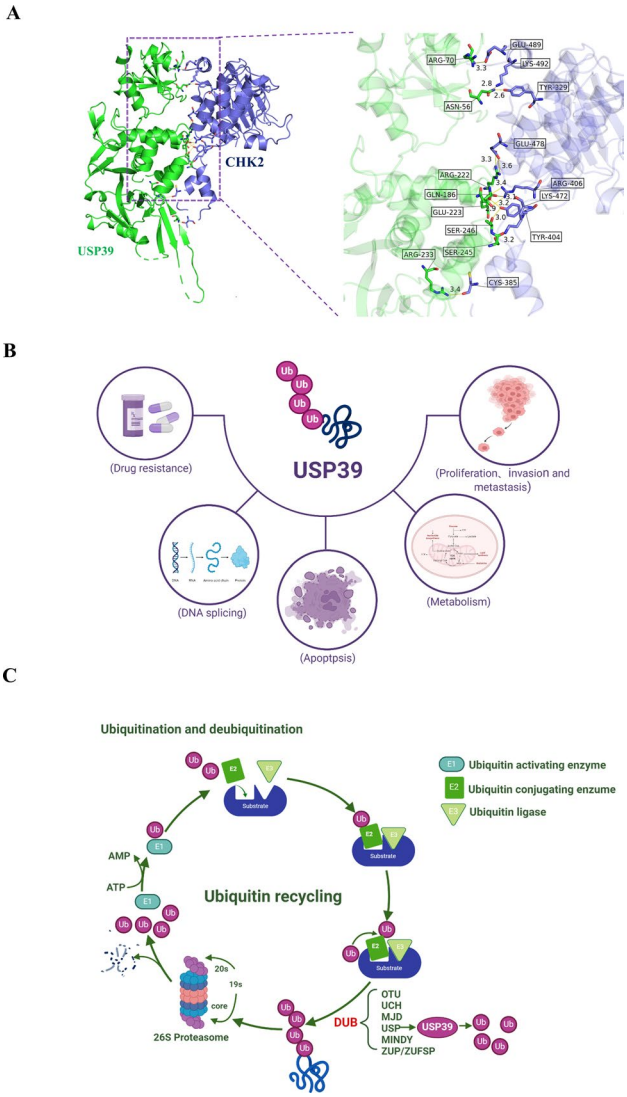

Fig. 2 Structure and function of USP39, mechanism of deubiquitination. **A** Docking structure diagram of USP39 protein and CHK2 protein; **B** Biological functional diagram of USP39, USP39 is closely associated with cell proliferation, cell invasion and metastasis, cell apoptosis, DNA damage repair, and tumor metabolic reprogramming; **C** The deubiquitination process involving USP39

USP39 is a deubiquitinating enzyme (DUB) belongs to the ubiquitin-specific protease family. USP39 recognizes and binds ubiquitinated proteins by specific domains, often relying on ubiquitin chains or ubiquitination sites on substrates. It removes ubiquitin molecules by cutting the bonds between substrate proteins and ubiquitin or within ubiquitin chains. This process not only protects the substrate from degradation but also releases free ubiquitin that can be reused, further participating in the ubiquitination process (as shown in Fig. 2C). The catalytic domain of USP39 (usually the cysteine protease domain) attacks the isopeptide bond between ubiquitin and the substrate through a cysteine residue in the active site, hydrolyzes the bond, and removes the ubiquitin molecule. USP39 cleaves various ubiquitin linkages including K6, K11, K29, and K48, thereby affecting the stability and function of substrate proteins [90, 100, 101]. The deubiquitination activity of USP39 is crucial for its biological function. If the substrate is deubiquitinated and stabilized by USP39, it may exhibit antitumor activity. Conversely, if the substrate is an oncogene, the activity of USP39 may promote tumor development.

3 USP39 and cancer

3.1 The role and expression of USP39 in different cancers

Current cancer research has revealed the critical role of ubiquitination signaling in maintaining cellular homeostasis, especially in the development of tumors, where its dysregulation often leads to malignant progression [102]. USP39 is an important RNA-splicing regulatory factor that participates in mRNA splicing during cell proliferation. The expression pattern of USP39 across different human tissues showed that it is highly expressed in the brain, endocrine tissues, respiratory system, liver, kidney, and pancreas (Fig. 3). USP39 plays a pro cancer role in various cancers by regulating the cell cycle, p53 pathway, and epithelial mesenchymal transition (EMT). USP39 promotes G2/M phase transition by regulating spliceosomes and cell cycle related proteins such as Cyclin B1 and CDK1, leading to genomic instability and driving tumor proliferation [103]. USP39 indirectly regulates MDM2 or directly binds to p53, affecting its stability and transcriptional activity, and inhibiting tumor suppressive function [104]. In addition, USP39 promotes EMT and enhances tumor invasion and metastasis through splicing regulation or transcription factors such as Snail and ZEB1. USP39 regulates splicing of TGF-β pathway related genes (such as SMADs) and enhances EMT signaling. USP39 leads to upregulation of mesenchymal markers (N-cadherin, vimentin) and downregulation of epithelial markers (E-cadherin) [105].

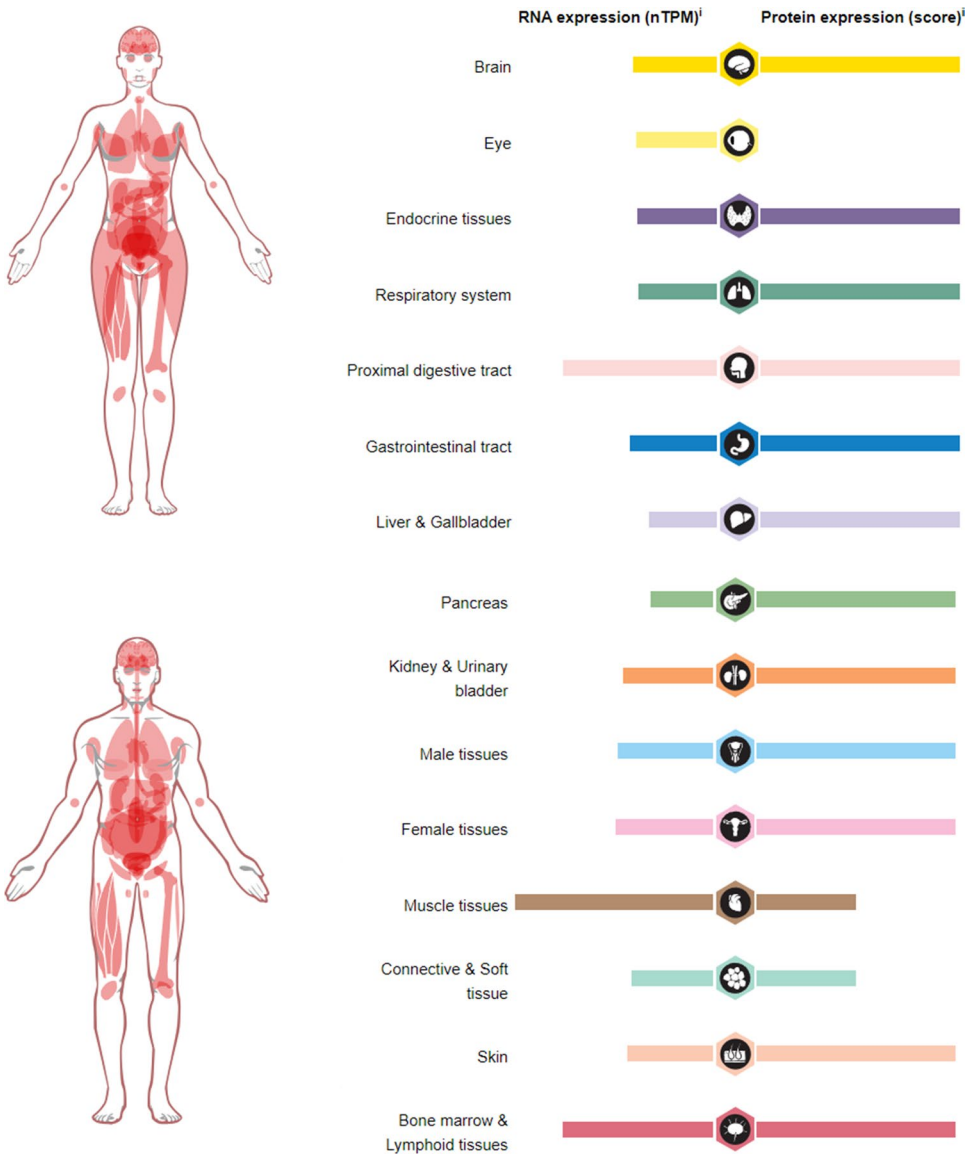

Fig. 3 Expression of USP39 RNA and protein in various human tissues. Available online: https://www.proteinatlas.org/ENSG00000168883-USP39/tissue (Accessed on August 15, 2024)

Furthermore, Kaplan–Meier survival analysis and log-rank testing revealed that the expression level of USP39 was correlated with the overall survival (OS) rate of cancer patients (Fig. 4). Several studies have further confirmed the significant role of USP39 in the progression of various types of human tumors and its widespread influence as a splicing factor. USP39 plays a crucial role in the development and progression of cancers, and its expression has been associated with adverse clinicopathological features and poor prognosis in various cancer types, including HCC [93, 95, 96]. High USP39 expression has been linked to the promotion of cell cycle progression and DNA replication pathways in tumors, as indicated by gene set enrichment analysis (GSEA) [8]. These findings underscore the significance of USP39 overexpression in the pathogenesis of tumors and its impact on cell cycle signaling.

3.2 The role of USP39 in hepatocellular carcinoma(HCC)

HCC is a malignant tumor with a high incidence and mortality rate worldwide [106]. The role of USP39 in HCC has attracted considerable research attention. Numerous studies have found that USP39 may serve as a biomarker and therapeutic target for many patients with HCC [68, 90, 107]. USP39 promotes hepatocellular carcinogenesis through regulating alternative splicing in cooperation with SRSF6/HNRNPC in both humans and mice [103]**.** USP39 is not only expressed at significantly higher levels in liver cancer tissue than in adjacent normal tissue, but its high expression is also closely associated with poor prognosis in patients with liver cancer [68, 107, 108]. Studies have shown that overexpression of USP39 can promote the proliferation, invasion, and metastasis of liver cancer cells. Li et al. found that depleting USP39 could promote the degradation of ZEB1, thereby inhibiting HCC cell proliferation and metastasis in the human HCC cell lines (SK-hep-1 and HepG2) [68]. Additionally, USP39 directly interacts with the E3 ligase TRIM26, which is underexpressed in human HCC tissues, and can inhibit the proliferation and migration of HCC cells. TRIM26 promotes ubiquitination

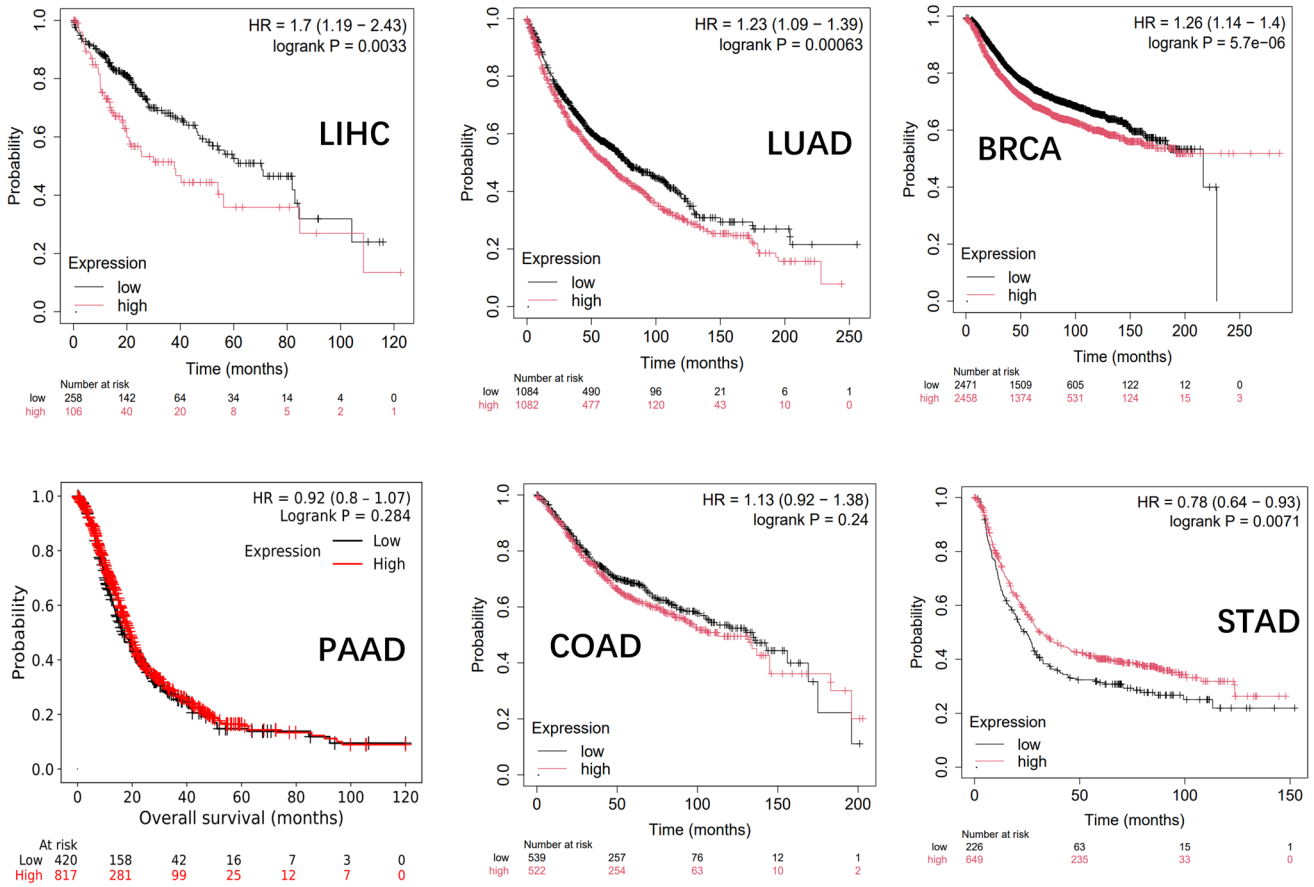

Fig. 4 Correlation Analysis between USP39 Expression Levels and Overall Survival. The Kaplan–Meier and log-rank tests were used for the analysis. Liver hepatocellular carcinoma(LIHC), lung adenocarcinoma(LUAD), breast invasive carcinoma(BRCA), pancreatic adenocarcinoma(PAAD), colon adenocarcinoma (COAD), and stomach adenocarcinoma(STAD). Available online: Kaplan–Meier plotter (https://kmplot.com/analysis/, accessed on August 15, 2024)

and degradation of ZEB1. USP39 and TRIM26 regulate the stability of ZEB1 in an antagonistic rather than a competitive manner, playing a key role in the progression of HCC. This finding provides new insights into targeted therapy, that is, restoring TRIM26 or inhibiting the expression of USP39 in HCC cases with high levels of ZEB1 protein to suppress the development of HCC. Further research has revealed the dual function of USP39 in HCC, it promotes the progression of HCC by deubiquitinating β-catenin, reducing its degradation, and promoting the proliferation and invasion of HCC cells by inhibiting the splicing of TRIM26, affecting the ubiquitination of β-catenin induced by TRIM26 [90]. Moreover, studies have revealed that USP39 also stabilizes specific protein 1 (SP1) through the deubiquitination pathway, and high expression of SP1 can reverse cell apoptosis and cell cycle arrest caused by USP39 interference [107].

These studies indicated that the role of USP39 in HCC, as it directly or indirectly regulates β-catenin through deubiquitination and RNA splicing, thereby promoting the progression of HCC. These findings not only provide new perspectives for understanding the molecular mechanisms of HCC but may also offer potential targets for the development of new therapeutic strategies.

3.3 The role of USP39 in lung cancer

Lung cancer is one of the most commonly diagnosed and deadliest malignant tumors worldwide and poses a severe threat to human health [109]. Studies have shown that USP39 is universally expressed at higher levels in human lung cancer tissues than in normal tissues and is closely associated with poor prognosis in patients with lung cancer [110, 111]. Interfered the expression of USP39 could significantly reduce the proliferation and colony-forming ability of lung cancer cells(A549 and HCC827 cells), inhibited their migration and invasion of lung cancer cells, induced G2/M phase arrest, and enhanced apoptosis. Specifically, the knockdown of USP39 leads to cell cycle arrest at the G2/M phase, followed by apoptosis through the activation of the p53 pathway, including the upregulation of p21, cleaved-Caspase3, cleaved-Caspase9, and the downregulation of CDC2 and CyclinB1 [111]. These results not only confirm the role of USP39 as an oncogene in lung cancer but also reveal that USP39 plays an important role in regulating cell proliferation and metastasis by activating the p53 pathway [111]. These studies suggest that targeting USP39 may provide a promising therapeutic avenue for the treatment of lung cancer. Further investigation of the potential mechanisms of USP39 in lung cancer could provide valuable insights into the development of innovative treatment methods.

3.4 USP39 promotes the development of breast cancer

Breast cancer is one of the most common malignant tumors in women and is a leading cause of cancer-related deaths [110]. Owing to the complex molecular mechanisms that regulate tumor occurrence and development, the selection of treatment plans and disease prognosis for breast cancer is challenging. USP39 is considered a potential therapeutic target in breast cancer research, and has therefore received widespread attention from researchers. Studies have shown that USP39 is selectively highly expressed in different types of human breast cancer cells [112]. Compared with normal breast tissue, the expression level of USP39 protein in human breast cancer tissue is higher, and there is a significant correlation between high USP39 levels and low survival rates [113]. USP39 deubiquitinates and stabilizes the transcription factor Foxm1, promoting proliferation, colony formation, and in vivo tumor growth in breast cancer cells(MCF10 A, MDA-MB-231). High expression of USP39 reduces the ubiquitination level of Foxm1, thereby increasing the transcriptional activity of Foxm1 and regulating the expression of the downstream genes CDC25B and PLK1, which are involved in cell cycle control [112]. Additionally, USP39 is closely related to triple-negative breast cancer, regulating tumor suppressors associated with cancer, and the downregulation of USP39 significantly reduces the proliferation and colony-forming ability of triple-negative breast cancer cells [114]. These findings suggest that USP39 plays an important role in breast cancer and may be a relevant target for therapeutic intervention. Therapeutic strategies targeting USP39 may provide a new approach to breast cancer treatment.

3.5 USP39 stimulates the malignant behaviors of gastric cancer

Gastric cancer(GC) has the second highest mortality rate after lung cancer and is often diagnosed at an advanced stage with a high propensity for metastasis and recurrence [109]. Despite recent improvements in cancer treatment, the prognosis of patients with gastric cancer remains poor. Understanding the molecular aberrations underlying the occurrence and progression of gastric cancer is crucial for identifying new molecular markers for early diagnosis, targeted therapy, and prognostic assessment. Researchers have found a close association between USP39 and the

malignant behavior of gastric cancer. USP39 is universally expressed at higher levels in human GC tissues than in normal tissues, and GC cells (MGC80-3, SGC-7901 and AGS) with disrupted USP39 expression show significantly reduced proliferation and colony-forming abilities [115]. Inhibition of USP39 expression induces G2/M phase arrest. Dong et al. in their 2018 study found that USP39 expression was higher in tumor tissues than in adjacent normal tissues [116]. They also confirmed that USP39 is a direct target of miR-133a, with a negative correlation between the two. Low miR-133a expression or USP39 overexpression predicts poor prognosis. These findings suggest that the miR-133a/USP39 axis may be a new therapeutic target for inhibiting the proliferation of GC cells; however, its role in the progression of GC requires further investigation. There is currently no further mechanism to explain how miR-133a affects GC proliferation through USP39, which should be considered a limitation of this study. The role of USP39 in the molecular mechanisms of gastric cancer migration and invasion requires further research. In addition, studies have found that USP39 may regulate the proliferation, invasion, and metastasis of gastric cancer cells by affecting signaling pathways such as Wnt/β-catenin and PI3 K/AKT [117]. In summary, USP39 is crucial for the proliferation of GC cells and therapeutic strategies targeting USP39 may provide new avenues for GC treatment. Further research is needed to explore the potential mechanisms of USP39 in gastric cancer to develop innovative treatment methods.

3.6 The role of USP39 in other tumors

Colorectal cancer(CRC) is the third most common cancer worldwide, with early symptoms often non-specific, and most patients are diagnosed at an advanced stage [109, 118, 119]. Cisplatin is an effective chemotherapeutic drug for the treatment of colorectal cancer; however, its efficacy is limited by its intrinsic or acquired resistance and detrimental side effects. Yuan et al. found that USP39 was related to the sensitivity of colon cancer cells to cisplatin [95]. USP39 depletion enhanced cisplatin-induced apoptosis in colon cancer cells HCT116, while USP39 overexpression attenuated apoptosis in RKO colon cancer cells. USP39 depletion promotes cisplatin-induced apoptosis, which is associated with the induction of oxidative stress and the DNA damage response. Further studies have shown that USP39 regulates p53-dependent cisplatin-induced apoptosis in colon cancer, with a potential mechanism involving upregulation of p53 following USP39 knockdown associated with an extended half-life of p53. These findings suggest that USP39 may be a negative factor in p53-mediated cisplatin sensitivity in colorectal cancer and indicate that USP39 is a potential molecular target for cisplatin chemotherapy in colorectal cancer.

Ovarian cancer (OC) is the third most common gynecological malignancy worldwide and one of the deadliest gynecological cancers. Owing to the late detection of ovarian cancer and its propensity to develop resistance to various drugs, understanding its pathogenesis is crucial [109]. Researchers have observed that USP39 is overexpressed in human ovarian cancer and is highly correlated with TNM stages. Inhibition of USP39 expression significantly suppresses the growth and migration of ovarian cancer cells. USP39 knockdown induces G2/M phase arrest in ovarian cancer cells, and the downregulation of USP39 is associated with the expression of CDK1 and cyclin B1 [120]. These results strongly support a role for USP39 in the malignant growth of ovarian cancer. Additionally, in xenograft models, interference with USP39 inhibits the growth of ovarian tumors. USP39 interference-induced cell cycle arrest may involve the p53/p21 signaling pathway. Following USP39 gene knockout, there is a reduction in the expression of β-catenin, N-cadherin (CDH2), and Slug and an increase in E-cadherin expression [120]. These results suggest that the silencing of USP39 inhibits the migration of ovarian cancer cells by blocking the EMT. Wang et al. found that USP39 promotes ovarian cancer malignancy by facilitating HMGA2 splicing [121].

Pancreatic cancer(PC) is a highly invasive tumor [122]. Typically, early pancreatic cancer has no obvious symptoms and most cases spread to other parts of the body at the time of diagnosis. Cai et al. found that USP39 expression in PC tissues was higher than that in adjacent non-tumor tissues, and USP39 overexpression was closely related to tumor progression and poor survival rates in PC patients [123]. Furthermore, high and ectopic expression of USP39 in PC cell lines significantly enhances cell proliferation in vitro and promotes tumor growth in vivo, whereas inhibition of USP39 hinders the growth of PC cells. Additionally, USP39 may affect the proliferation, invasion, and metastasis of pancreatic cancer cells by regulating signaling pathways such as Wnt/β-catenin, PI3 K/AKT, and MAPK [124]. These studies highlight the important role of USP39 in various cancers and suggest that it may be a potential target for cancer therapy.

USP39 inhibitors may be effective in some cancers, but not for all cancers. The challenges of targeted therapy include selectivity, drug resistance, and patient heterogeneity that need to be addressed by further studies. It may be used in the future as a personalized treatment option for a specific cancer.

4 Impact of USP39 on cancer cell biological behaviors

4.1 USP39 and cancer cell proliferation

USP39 plays a crucial role in promoting the malignant behaviors of various tumors, including their proliferation. USP39 is highly expressed in human liver cancer tissues and is associated with a poor prognosis. USP39 depletion inhibits the proliferation and metastasis of liver cancer cells by promoting ZEB1 [68]. USP39 may act on other proteins that regulate ZEB1, such as E3 ubiquitin ligases, to reduce the ubiquitination of ZEB1 and thus increase its stability [68]. Other researchers have reported the overexpression of USP39 in human lung cancer tissues and non-small cell lung cancer(NSCLC) cell lines. Silencing USP39 suppresses the proliferation and colony formation of human lung cancer cells and reduces tumorigenic potential in nude mice [110, 111]. USP39 expression in osteosarcoma cells significantly reduces cell proliferation and impairs colony-forming ability [125]. Additionally, high USP39 expression and ectopic expression of USP39 in pancreatic cancer cell lines significantly enhance cell proliferation in vitro and promote tumor growth in vivo, whereas inhibition of USP39 expression suppresses the growth of pancreatic cancer cells [123]. The effects of USP39 on cancer cell biological behaviors showed in Fig. 5.

4.2 USP39 and tumor invasion and metastasis

Glioma cells exhibit high migration and invasion capabilities; USP39 knockdown in glioma cells significantly inhibits cell migration and invasion [126]. After interfering with USP39 expression, human disintegrin-like metalloproteinase 9 (ADAM9), which is related to tumor cell migration and invasion, was significantly downregulated; overexpression of ADAM9 inhibits the migration and invasion of glioma cells caused by USP39 depletion in vitro. USP39 also promotes the invasion of glioma cells in vivo, thereby reducing the overall survival of mice. Another study found that USP39 knockout significantly inhibited the migration and invasion of lung cancer cells by activating the p53 pathway and downregulating matrix metalloproteinase 2(MMP2) and Matrix metalloproteinase 9(MMP9). This revealed the important role of USP39 in regulating cell proliferation and metastasis through activation of the p53 pathway [111]. USP39 promotes the proliferation and migration of liver cancer

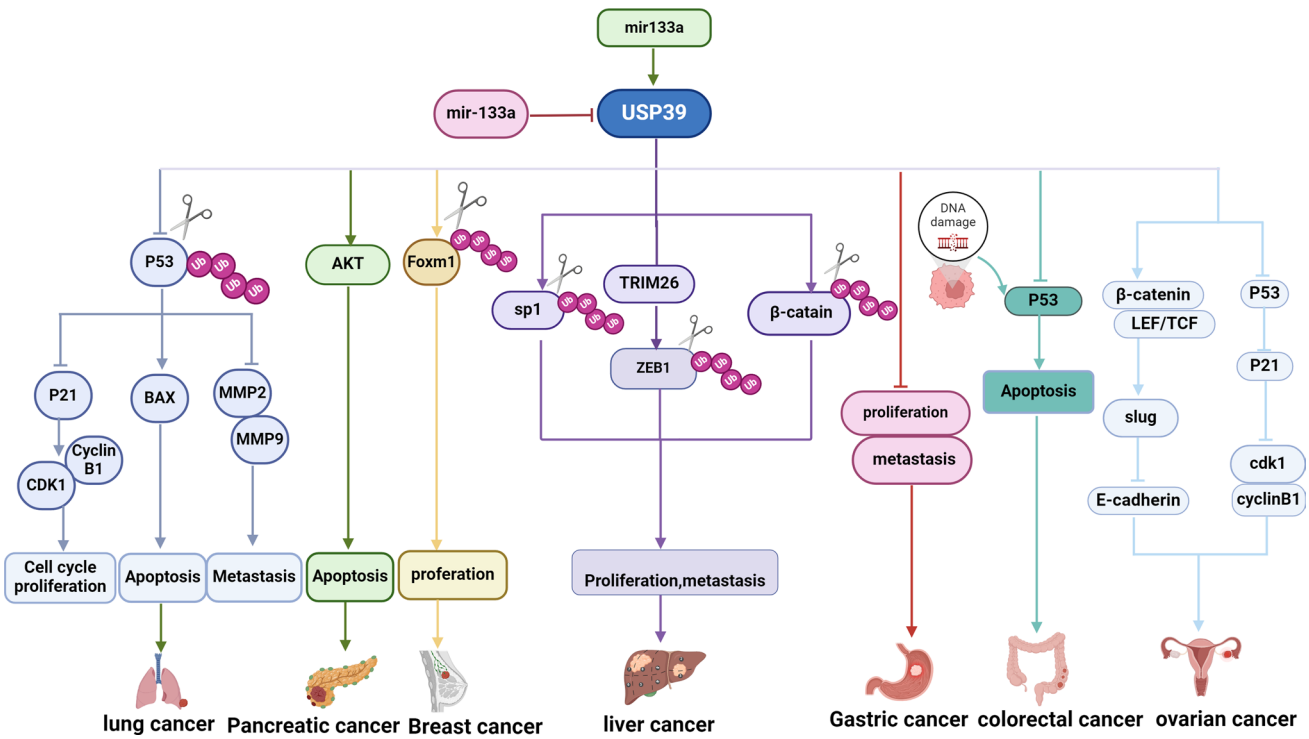

Fig. 5 USP39 plays a key role in the regulation of various cancer-related signaling pathways. Solid arrows and flat arrows represent activation and inhibition, respectively

cells by directly deubiquitinating and reducing the maturation and splicing of the E3 ligase TRIM26, thus providing a new target for the clinical treatment of liver cancer [90]. Moreover, depletion of USP39 inhibits the proliferation and metastasis of liver cancer cells by promoting the degradation of ZEB1 [68], and when USP39 is overexpressed in ovarian cancer cells, cell migration and invasion behaviors are also enhanced [127]. In gastric cancer cells, USP39 promotes the growth and metastasis of gastric cancer cells by regulating the degradation of RNA-binding proteins [128]. In colorectal cancer, high USP39 expression mainly plays a role in promoting carcinogenesis in cell growth and metastasis through the Wnt/β-catenin pathway [117].

4.3 USP39 inhibits tumor cell apoptosis

Silencing USP39 significantly increased the apoptosis rate of liver cancer cells [68]. In liver cancer cells, USP39 knockout can induce apoptosis by altering the expression of the apoptotic genes Bax, Caspase9, Caspase3, and PARP. USP39 significantly upregulates the expression of Bax, which belongs to the Bcl-2 family of pro-apoptotic proteins [129]. This further confirms that USP39 knockout could inhibits the growth of liver cancer cells by inducing apoptosis [68]. USP39 knockdown was able to induce colon cancer cell apoptosis [95]. Inhibits the expression of USP39 could promote apoptosis in osteosarcoma cells [125]. Additionally, USP39 suppresses apoptosis in lung cancer cells, and the depletion of USP39 hinders the activation of the AKT, MTR, P53, and PAP signaling pathways [110]. USP39 inhibits apoptosis by activating the AKT signaling pathway. In human pancreatic cancer cells, silencing USP39 significantly increased the growth rate [123]. Knockout *USP39* gene could induce apoptosis in pancreatic cancer cells by inhibiting the AKT signaling pathway. Furthermore, USP39 downregulation significantly increased the number of cancer cells undergoing apoptosis induced by 5-Fu.

4.4 USP39 and tumor drug resistance

In addition to being closely related to tumor progression, USP39 also plays an important role in promoting drug resistance. USP39 can deubiquitinate and stabilize CHK2, and USP39 knockdown can lead to disruption of CHK2, which also results in impaired DNA damage-induced G2/M checkpoint, reduced apoptosis, and resistance to chemotherapy drugs and radiotherapy in cancer cells [88]. Cisplatin is an effective chemotherapeutic drug for the treatment of colorectal cancer; however, its therapeutic effect is limited by its intrinsic or acquired resistance and harmful side effects. Researchers have revealed that USP39 is related to the sensitivity of colon cancer cells to cisplatin. USP39 depletion enhances cisplatin-induced apoptosis in colon cancer cells. Conversely, USP39 overexpression attenuated apoptosis in colon cancer cells. Further studies have shown that USP39 regulates cisplatin-induced apoptosis in a p53-dependent manner. The potential mechanism has been demonstrated by knocking out USP39, which leads to the upregulation of p53 and is associated with an extended half-life of p53. Overall, these results suggest that USP39 may be a negative factor in p53-mediated cisplatin sensitivity in colorectal cancer and indicate that USP39 is a potential molecular target for cisplatin chemotherapy in colorectal cancer [95]. Another study found that USP39 is highly expressed in carboplatin-resistant ovarian cancer samples. USP39 deficiency enhances carboplatin-induced apoptosis in ovarian cancer cells by activating poly(ADP-ribose) polymerase and Caspase3. These results suggest that USP39 may play an important role in regulating the malignant phenotype and carboplatin resistance of ovarian cancer. Therefore, USP39 may be a promising therapeutic target in patients with ovarian cancer [127]. Targeting USP39 provides new possibilities for overcoming drug resistance in chemotherapy and improving tumor treatment efficacy. The current research on USP39 is still in the preclinical stage and lacks effective inhibitors. Future research directions may include the development of inhibitors or degradation agents for USP39. For example, small molecule inhibitors, RNA interference, antisense oligonucleotides, etc. These methods each have their own advantages and disadvantages. In addition, evaluating the safety and toxicity of inhibiting USP39 is also important to avoid serious side effects in clinical trials. Finally, combination chemotherapy or targeted therapy may improve efficacy and reduce drug resistance. This may involve mechanism research to examine the synergistic effects of USP39 inhibitors with other drugs.

Based on existing research, USP39 plays a significant role in tumor proliferation, invasion, metastasis, and drug resistance. However, further in-depth exploration of the specific mechanisms involved in this process is required.

5 USP39-mediated cancer signaling pathways

USP39 plays a pivotal role in the regulation of various cancer-associated signaling pathways, including nuclear factor kappa-B (NF-κB), Hippo, Wnt/β-catenin, and phosphatidylinositol-3-kinase (PI3 K)/threonine kinase (AKT) signaling. USP39 participates in these pathways by interacting with specific proteins and subsequent deubiquitination effects (Fig. 6),

thereby influencing the activation, stability, and expression of downstream genes of key proteins. Dysregulation of these signaling pathways is closely related to the occurrence and development of cancer.

5.1 NF-κB signaling pathway

The NF-κB signaling pathway plays a crucial role in a variety of biological processes, including inflammatory responses, cell adhesion, cytokine production, and growth factor secretion. This pathway is associated with numerous diseases, including infections and cancer [130, 131]. NF-κB consists of five subunits: NF-κB1(p50), NF-κB2 (p52), RelA (p65), RelB, and Rel(c-Rel) [132]. Activation of the NF-κB signaling pathway involves interactions and phosphorylation of multiple proteins, ultimately leading to the translocation of NF-κB complexes from the cytoplasm to the nucleus and activation of target gene transcription such as CyclinD1, c-Myc, MMP-9, and VEGF. Therefore, the continuous activation of this pathway can lead to uncontrolled cell growth.

The NF-κB pathway is a key mediator of inflammatory responses and its activation is tightly regulated from multiple angles to prevent inflammatory damage. An increasing number of studies have reported that deubiquitinating enzymes regulate inflammation, such as USP19, which deubiquitinates TAK1 and negatively regulates TNF-α- and IL-1β-mediated NF-κB activation [133]. CYLD deubiquitinates NLRP6 to attenuate IL-18 release and suppresses excessive inflammation in colonic mucosal inflammatory diseases [134]. USP15 has been shown to bind and deubiquitinate E3 ligase Hard1 to stabilize basal levels of IκBα [135]. IκBα is a key protein that inhibits NF-κB nuclear translocation, thus inhibiting the NF-κB pathway, and its abundance affects the activation state of NF-κB. Studies have found that USP39 increases the stability of IκBα by reducing its K48-linked ubiquitination, thereby inhibiting NF-κB nuclear translocation and the expression of downstream inflammatory genes [100]. In lipopolysaccharide(LPS)-induced inflammation models, the expression of USP39 in macrophages is reduced. USP39 knockout in macrophages could significantly increase the expression and

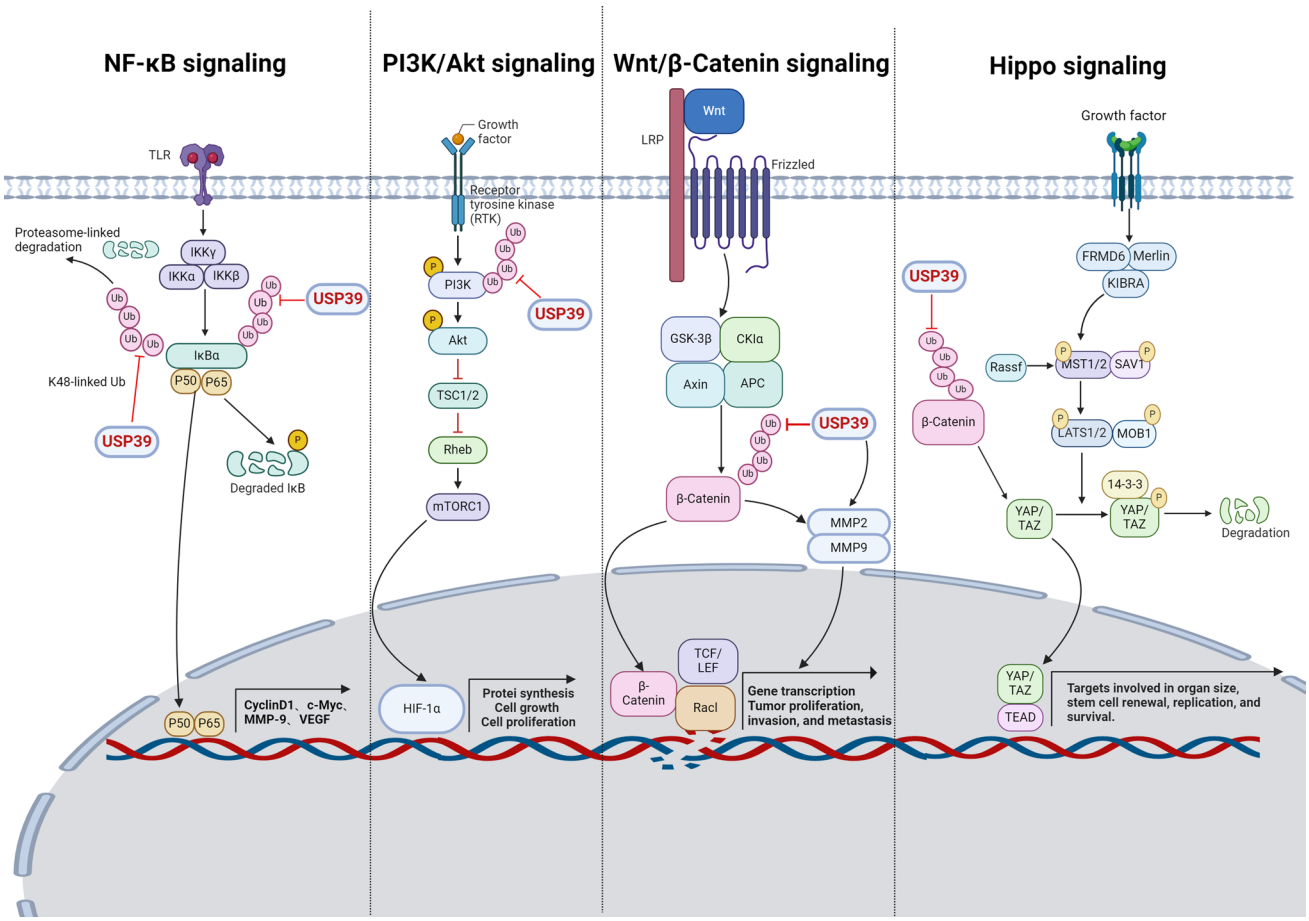

Fig. 6 Regulatory mechanisms of USP39 in different types of cancer (hepatocellular carcinoma, lung cancer, pancreatic cancer, breast cancer, gastric cancer, colorectal cancer, and ovarian cancer). Solid arrows and flat arrows represent activation and inhibition, respectively

secretion of pro-inflammatory cytokines after LPS or E. coli exposure, thereby promoting NF-κB-mediated inflammatory responses. Conversely, re-expression of exogenous USP39 in USP39-deficient macrophages reversed this phenomenon. USP39-deficient mice are more sensitive to LPS-or E. coli-induced systemic sepsis. Mechanistically, USP39 interacts with and stabilizes IκBβ by reducing the K48-linked ubiquitination of IκBα, thereby inhibiting the activation of the NF-κB pathway. USP39-deficient macrophages synthesize less IκBα protein and produce lower levels of p-IκBα, leading to stronger and faster phosphorylation of p65, resulting in excessive inflammatory responses. These findings reveal the regulatory role of USP39 in the NF-κB signaling pathway, suggesting that USP39 may be a key factor in controlling inflammatory responses and cancer development.

5.2 Wnt/β-catenin signaling pathway

The Wnt/β-catenin signaling pathway, which comprises multiple ligands, receptors, co-receptors, intracellular mediators, and transcriptional effectors, is a complex protein network that plays a significant role in regulating cell proliferation, differentiation, and morphogenesis [136]. Activation of this pathway is typically initiated by the binding of Wnt ligands to Frizzled family receptors, leading to the stabilization and accumulation of β-catenin in the cytoplasm. Subsequently, free β-catenin is transported to the nucleus, where it acts as a co-activator of transcription factor Rac1 and T cell factor/lymphoid enhancer-binding factor(TCF/LEF), regulating gene expression or leading to tumors [137].

The Wnt signaling pathway and its regulators play a significant oncogenic role in colorectal cancer(CRC) [138, 139]. β-catenin is a key molecule in this pathway, acting as a multifunctional protein that plays a central role in the regulation of cell proliferation and migration [140, 141]. Yuan et al. found that USP39 knockdown significantly affected β-catenin levels, which was consistent with a reduction in cell growth and migration [117]. USP39 knockout led to the downregulation of the expression of four key proteins in the Wnt/β-catenin signaling pathway: β-catenin, transcription factor (TCF4), matrix metalloproteinase-2(MMP2), and matrix metalloproteinase-9(MMP9). MMP2 and MMP9 are expressed in many tumor cells and can serve as potential indicators of colorectal tumor invasion or metastasis [142–144]. These Matrix metalloproteinases(MMPs) are regulated by the Wnt/β-catenin signaling pathway [145, 146]. It has been reported that β-catenin-mediated expression of matrix metalloproteinases(MMPs) promotes epithelial-mesenchymal transition[147]. A key feature of tumor invasion and metastasis is the degradation of the extracellular matrix, in which MMPs participate and are closely related to the occurrence and development of tumors [148]. Therefore, downregulation of MMP2 and MMP9 expression by USP39 is consistent with its role of USP39 in promoting the growth and metastasis of colorectal cancer cells. Mechanistically, the effects of USP39 are mediated through the Wnt/β-catenin pathway as its inhibition significantly reduces the expression of many proteins in this pathway. These results suggest that USP39 promotes the growth and metastasis of CRC cells through the Wnt/β-catenin signaling pathway.

Another study found that USP39 promotes the proliferation and migration of HCC cells by directly deubiquitinating β-catenin, a key molecule in the Wnt/β-catenin signaling pathway. Abnormal expression or activation of β-catenin after colocalization with USP39 can lead to various tumors. In this process, the expression of the E3 ligase TRIM26 tends to decrease, and the splicing and maturation of TRIM26 precursor mRNA is inhibited by USP39, accompanied by a reduction in ubiquitinated β-catenin, indirectly promoting the progression of HCC. These data reveal that USP39 increased β-catenin levels by directly deubiquitinating and reducing the maturation and splicing of TRIM26 pre-mRNA, thereby promoting the proliferation and migration of HCC, which may provide new insights and targets for the clinical treatment of HCC [90].

5.3 PI3 K/AKT signaling pathway

Phosphatidylinositol 3-kinase(PI3 K) is a family of lipid kinases characterized by its ability to specifically catalyze the phosphorylation of the 3-position hydroxyl group of phosphatidylinositol, generating the second messenger phosphatidylinositol-3,4,5- trisphosphate(PI-3,4,5-P3) [149]. PI3 K converts phosphatidylinositol-4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-trisphosphate(PIP3), which in turn recruits oncogenic signaling proteins, including the serine and threonine kinase AKT [150]. AKT activation involves phosphorylation of multiple substrates and participates in the regulation of cell survival, cell cycle progression, and cell growth. The PI3 K/AKT signaling pathway plays a significant role in various types of cancer [151], controlling many hallmarks of cancer, including cell survival, metastasis, and metabolism. Additionally, this pathway plays an important role in the tumor microenvironment, including angiogenesis and the recruitment of inflammatory factors. The PI3 K/AKT pathway can be aberrantly activated through various mechanisms, including genomic alterations such as mutations in PIK3 CA, phosphatase and tensin homolog(PTEN), AKT, tuberous

sclerosis complex 1(TSC1), and mechanistic target of rapamycin (mTOR), which are frequently mutated and activated in cancer [152, 153].

Recent studies have revealed a close link between USP39 and the PI3 K/AKT pathway [13]. KEGG pathway enrichment analysis showed that the PI3 K/AKT pathway was one of the pathways most significantly enriched by USP39. Further research has found that in endometrial cancer(EC) cells, phosphatidylglyceride kinase 1(PGK1) interacts endogenously with USP39, and USP39 stabilizes the expression of PGK1 through deubiquitination. USP39 regulates the PI3 K/AKT/HIF-1α signaling pathway through its interaction with PGK1. Treatment with the glycolysis inhibitor, 2-DG, significantly inhibited the levels of PI3 K, phospho-PI3 K(p-PI3 K), AKT, phospho-AKT(p-AKT), and HIF-1α in EC cells. USP39 effectively induced phosphorylation of PI3 K and AKT and increased the expression of HIF-1α in EC cells. Furthermore, USP39 reversed the decrease in p-PI3 K, p-AKT, and HIF-1α levels induced by 2-DG. The treatment of EC cells(Ishikawa and KLE cells) transfected with a USP39 overexpression vector with the PI3 K inhibitor LY294002 effectively reduced the levels of PI3 K, p-PI3 K, AKT, p-AKT, and HIF-1α. These studies showed that USP39 promoted PI3 K/AKT- and HIF-1α-mediated glycolysis in EC.

5.4 Hippo signaling pathway

The Hippo signaling pathway, composed of a group of conserved kinases, is a key pathway that regulates cell growth [154]. TAZ (WWTR1) and Yes-related protein (YAP) are the core effector proteins in the Hippo signaling pathway and are mainly associated with cell proliferation, apoptosis, tumor metastasis, and maintenance of cancer stem cell characteristicsx [155–158]. The upstream kinases MST1 and MST2 activate LATS1 and LATS2 by binding to the adapter protein SAV1/WW45, which in turn phosphorylates TAZ and YAP [155]. Phosphorylated TAZ is primarily localized in the cytoplasm, whereas non-phosphorylated TAZ enters the nucleus and promotes tumor growth by inducing gene transcription [159, 160]. Its expression and activity are elevated in various human cancers, including melanoma, HCC, breast cancer, and colorectal cancer [161–164]. USP39 is a novel regulatory factor that modulates TAZ and promotes malignant behavior in gliomas [124]. Luciferase reporter gene analysis indicated that in gliomas, downstream events of the Hippo signaling pathway are significantly affected by the levels of USP39. In glioma cells where USP39 expression was disrupted, the activity of the Hippo pathway was reduced by 92%, whereas the luciferase activity of the other six cancer pathways remained unchanged. Additionally, TAZ protein expression in glioma cells with USP39 interference was significantly reduced. The IHC scores of USP39 in primary human glioma samples were positively correlated with TAZ scores. Therefore, USP39 and TAZ proteins were positively correlated.

TAZ is a transcriptional co-activator that cannot directly bind to DNA but interacts with various oncogenic transcription factors such as TEADs to activate transcription [165]. Studies have shown that TAZ mutants with defects in interaction with TEADs did not accumulate in the nucleus. Therefore, USP39 may affect the interaction between TAZ and transcription factors, thereby inhibiting the Hippo signal transduction. Experimental evidence suggests that USP39 regulates TAZ protein levels by controlling mRNA maturation. In USP39 knockdown cells, the splicing efficiency of TAZ pre-mRNA decreased, indicating that USP39 plays a role in the maturation process of TAZ mRNA. TAZ is a component of the β-catenin destruction complex, which can effectively sequester TAZ in the cytoplasm. USP39 knockout also reduced β-catenin expression. Therefore, USP39 silencing may enhance the β-catenin destruction complex, leading to the cytoplasmic retention of TAZ and reduced nuclear localization. However, further research is required to elucidate the specific mechanism of action of USP39. USP39 plays a central role in several cancer-associated signaling pathways, promoting cell proliferation, inhibiting apoptosis, enhancing invasion and metastasis ability, regulating metabolic adaptation, and repairing DNA damage by regulating the stability of key proteins. These functions make USP39 a key regulatory node, conferring multiple survival and proliferative advantages to cancer cells. Thus, USP39 is not only an important molecule for understanding cancer biology, but also a potential target for the development of novel anticancer therapies.

5.5 The interaction of signaling pathway

USP39 plays an important role in the NF-κB, Wnt/β-catenin, PI3 K/AKT, and Hippo signaling pathways, which have complex interactions and jointly regulate processes such as cell proliferation, apoptosis, differentiation, and immune response. The following are the interactions and possible mechanisms of USP39 between these pathways: The interaction between NF-κB and Wnt/β-catenin pathways, USP39 may stabilize key proteins in NF-κB or Wnt/β-catenin pathways (such as β-catenin or IκBα) through deubiquitination, thereby regulating their activity. NF-κB can indirectly activate Wnt/β-catenin signaling by inhibiting GSK-3β (a negative regulator of Wnt/β-catenin), and USP39 may play a role in this process. The synergistic effect of the two in inflammation and cancer may be regulated by USP39 [90].

The interaction between NF-κB and PI3 K/AKT pathway by USP39 may affect the activity of NF-κB by stabilizing key proteins in the PI3 K/AKT pathway (such as AKT or PTEN) through deubiquitination. The PI3 K/AKT pathway promotes nuclear translocation of NF-κB by activating IKK complexes, while USP39 may indirectly affect NF-κB signaling by regulating AKT stability. The synergistic effect of the two in cell survival and inflammatory response may be regulated by USP39 [88]. The interaction between Wnt/β-catenin and PI3 K/AKT pathways by USP39 may promote their synergistic effect by stabilizing β-catenin or AKT through deubiquitination. The PI3 K/AKT pathway stabilizes β-catenin by inhibiting GSK-3β, while USP39 may enhance this process by regulating the stability of AKT or β-catenin. The synergistic effect of the two in cancer development and stem cell maintenance may be regulated by USP39 [166]. The interaction between Hippo and Wnt/β-catenin pathway by USP39 may promote their synergistic effect by stabilizing YAP/TAZ or β-catenin through deubiquitination. YAP/TAZ can form a complex with β-catenin to synergistically regulate target gene expression, while USP39 may enhance this process by regulating the stability of both. The synergistic effect of the two in tissue regeneration and cancer may be regulated by USP39 [167]. The interaction between Hippo and PI3 K/AKT pathways in USP39 may promote their synergistic effect by stabilizing YAP/TAZ or AKT through deubiquitination. The PI3 K/AKT pathway can affect the activity of YAP/TAZ by regulating LATS1/2 (the core kinase of the Hippo pathway), while USP39 may enhance this process by regulating the stability of AKT or YAP/TAZ. The synergistic effect of the two in cell growth and metabolism may be regulated by USP39 [168]. The interaction between USP39 and the Hippo and NF-κB pathway. USP39 may stabilize key proteins in the YAP/TAZ or NF-κB pathways (such as IκBα) through deubiquitination, thereby regulating their activity. YAP/TAZ can regulate the expression of target genes of NF-κB, while USP39 may enhance this process by regulating the stability of YAP/TAZ. The synergistic effect of the two in inflammation and cancer may be regulated by USP39 [169].

6 USP39 and tumor metabolic reprogramming

Tumor metabolic reprogramming is an important metabolic pathway that occurs in tumor cells to adapt to rapid proliferation and survival. This process involves the readjustment of multiple metabolic pathways to meet the energy, biosynthesis, and redox balance requirements of tumor cells. Recent studies have shown that USP39 plays an important role in the metabolic reprogramming of tumors.

6.1 Glutamine metabolism

Mitochondrial glutamine metabolism is the most common energy source in cancer cells [170]. Glutamine enters the cell through amino acid transporters(such as ASCT2/SLC1 A5) and is then catalyzed to convert glutamine to α-ketoglutarate (α-KG), which can enter the tricarboxylic acid(TCA) cycle, providing energy and biosynthetic precursors for the cell [171, 172]. Glutamine is a non-essential amino acid (NEAA), but in tumor cells, it becomes a"conditionally essential amino acid,"as the survival and proliferation of proliferating cancer cells mainly depend on glutamine metabolism [173]. In addition, the metabolic product of glutamine, glutamate, is involved in the synthesis of glutathione(GSH), which is crucial for scavenging reactive oxygen species(ROS) and maintaining intracellular redox balance [174, 175]. The link between USP39 and glutamine metabolism has been studied in non-small cell lung cancer (NSCLC) cells. It has been found that the loss of mitochondrial ribosomal protein L35(MRPL35) inhibits glutamine metabolism in NSCLC cells, and USP39 stabilizes the expression of MRPL35 through deubiquitination [176]. Furthermore, the absence of USP39 can inhibit the proliferation, invasion, and glutamine metabolism of NSCLC cells and induce apoptosis, whereas the overexpression of MRPL35 can reverse these effects [176]. USP39 maintains the stability and function of MRPL35 by deubiquitinating it, preventing its degradation by the ubiquitin proteasome system. Although the specific E3 ligases that interact with USP39 are not yet fully understood, research suggests that USP39 may inhibit the activity of certain E3 ligases (such as MDM2, TRIM family members, etc.) to prevent ubiquitination and degradation of MRPL35. This suggests that the effect of MRPL35 on NSCLC cells may be related to stabilization induced by USP39-mediated deubiquitination. These findings reveal the role of USP39 in regulating glutamine metabolism in tumor cells, providing new potential targets for cancer therapy. Targeting USP39 or its regulated proteins such as MRPL35 may provide new therapeutic strategies for inhibiting glutamine metabolism and tumor growth in tumor cells.

6.2 Glucose metabolism

The abnormal activation of glucose metabolism in tumor cells is a key area of cancer research. The Warburg effect, which is the preference of tumor cells for the relatively low-energy-yielding glycolytic pathway for self-energization even in the presence of oxygen, is a well-known metabolic characteristic. This phenomenon, first discovered by Warburg in 1956, revealed that tumor cells produce a large amount of ATP through aerobic glycolysis to meet their rapid growth needs and maintain cellular redox homeostasis [177]. USP39, as a deubiquitinating enzyme, has been found to be associated with tumor sugar metabolism. Studies have shown that USP39 can be recruited together with the key rate-limiting enzyme of glycolysis, phosphofructokinase(PFKL), to the highly expressed scaffold protein DNAAF5 in HCC [96]. DNAAF5 enhances the stability of PFKL protein by recruiting USP39, thereby promoting the malignant progression of HCC. In liver cancer cells Hep3B, the interaction between USP39 and PFKL was confirmed, and downregulation of USP39 inhibited the increase in PFKL expression caused by DNAAF5 overexpression. Docking structure diagram of USP39 and PFKL (Fig. 7A).

In addition, the expression level of USP39 in EC cells is affected by treatment with the glycolysis inhibitor 2-DG, with significant reductions in its mRNA and protein expression levels [13]. USP39 overexpression accelerates tumor growth and reverses the tumor-suppressive effects of 2-DG. The ATP content was reduced after 2-DG treatment but was relatively increased after reversing the levels of USP39. Overexpression of USP39 also enhanced the reversal of the reduced expression of the glycolysis-related proteins GLUT-1, HK2, LDHA, MCT-1, and MCT-4 caused by 2-DG treatment. These results indicated that USP39 promotes glycolysis in EC cells and is closely related to sugar metabolism. Phosphoglycerate kinase 1(PGK1) is the first ATP-generating enzyme in the glycolytic pathway and has been reported to activate the sugar metabolic pathway of the PI3 K/AKT pathway [178]. Researchers have identified the interaction between USP39 and PGK1 using Co-IP and mass spectrometry(MS), and the downregulation of USP39 leads to a decrease in PGK1 protein levels in EC cells. USP39 stabilizes PGK1 protein in EC cells through proteasome-dependent deubiquitination Most importantly, USP39 regulates the PI3 K/AKT/HIF-1α signaling pathway through its interaction with PGK1. Docking structure diagram of USP39 and PGK1 proteins (as shown in Fig. 7B).

USP39 plays an important role in glucose metabolism by regulating the stability and activity of key glycolytic enzymes (Fig. 7C). These findings emphasize the importance of post-translational modifications in the activity and stability of enzymes involved in glucose metabolism and their impact on the overall energy balance of cancer cells. Therefore, the development of targeted inhibitors of USP39 combined with traditional chemotherapy may improve therapeutic effects by addressing multiple aspects of tumor metabolism and growth.

6.3 Autophagy

The relationship between USP39 and autophagy in tumor cells is gradually receiving attention. Research has shown that USP39 affects the survival, proliferation, and drug resistance of tumor cells by regulating the expression or function of autophagy related genes [179]. Autophagy is a process in which cells maintain homeostasis by degrading damaged organelles and proteins, and plays a dual role in tumor development and progression. USP39 may regulate autophagy related proteins (such as ATG protein, Beclin-1, etc.) through deubiquitination modification, affecting autophagy activity. In tumor cells, USP39 may promote cell survival by inhibiting autophagy, especially in nutrient deficiency or chemotherapy stress, helping tumor cells resist apoptosis. USP39 may affect the sensitivity of tumor cells to chemotherapy drugs by regulating autophagy. Inhibition of autophagy may enhance tumor cells'resistance to drugs, while USP39 may promote drug resistance by regulating this process [179].

7 Conclusion

Disubiquitinases (DUBs) are an important class of peptidyl hydrolases in the ubiquitin system, playing a crucial role in reversing and strictly regulating the ubiquitination process, which is essential for protein stability and various biological processes such as cell signal transduction. USP39 is an important member of the DUBs family and is involved in regulating various cellular activities, including cell proliferation, migration, invasion, apoptosis, and DNA damage repair. We believe that USP39 is a unique enzyme that controls the ubiquitin process and is closely related to the occurrence and progression of many cancers, including hepatocellular carcinoma, lung cancer, gastric cancer, breast cancer and ovarian cancer.

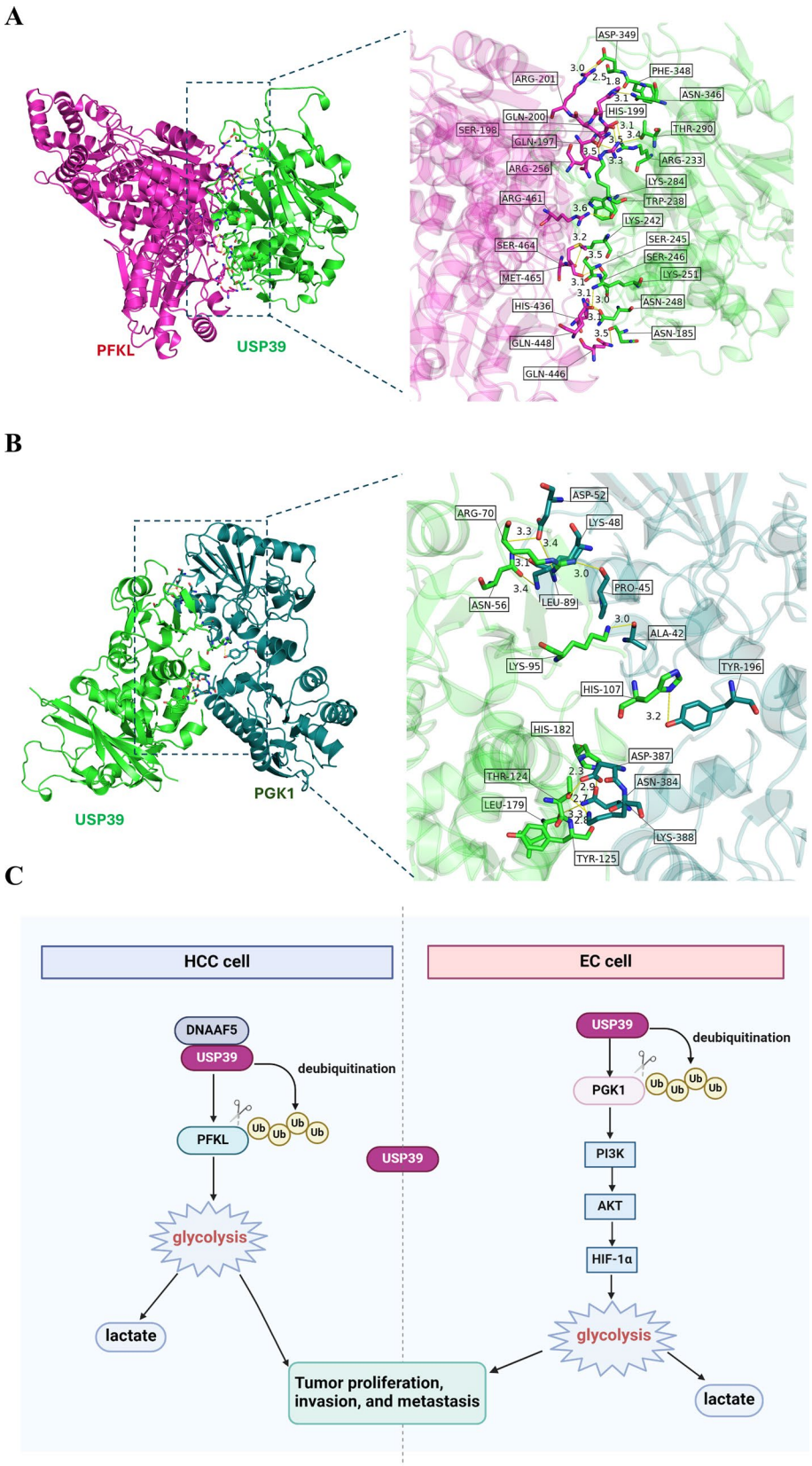

Fig. 7 The relationship between USP39 and glucose metabolism. **A** Docking structure diagram of USP39 protein and PFKL protein; **B** Docking structure diagram of USP39 protein and PGK1 protein; **C** Mechanism diagram of USP39 and glucose metabolism, USP39 is closely related to sugar metabolism related proteins PGK1 and PFKL

USP39 is an important regulatory molecule for post-translational modifications, which can deubiquitinate oncogenes and promote malignant behavior of cancer cells. Targeted inhibition of USP39 will become an important strategy for cancer treatment, exploring key molecular mechanisms related to USP39 and providing reference for tumor diagnosis and treatment.

8 Prospects and outlook

This review comprehensively summarizes the recent research on the deubiquitinating enzyme USP39 and its cancer-related functions, emphasizing its multifaceted involvement. USP39 plays a key role in tumorigenesis, making it one of the most important post-translational modifiers in this field. USP39 overexpression in several types of cancers is often associated with poor prognosis and lower patient survival rates. Its ability to regulate major cancer characteristics such as tumorigenesis, invasion, and metastasis makes it an exciting target for cancer therapy. However, further research is required considering the diversity of substrates and their regulation in highly dependent contexts. The potency and specificity of compounds that target USP39 are currently being explored to achieve adequate and effective pharmacokinetics. Future research should focus on several key areas.

8.1 In-depth exploration of molecular mechanisms

Although existing studies have revealed multiple roles for USP39 in tumor development, its exact molecular mechanisms, particularly its substrate selectivity and regulatory networks, still need further clarification. In-depth research on the substrate recognition mechanisms of USP39 and its role in tumor metabolic reprogramming will provide a theoretical basis for the development of specific inhibitors.

8.2 Development of specific inhibitors

Despite progress in research, studies on USP39 inhibitors are relatively limited, and the exact molecular mechanisms of USP39 in tumor regulation are not fully understood. The development of USP39 inhibitors with high specificity and minimal side effects is a priority for future research. The understanding of USP39's direct substrates, the mechanisms of substrate recognition, and its upstream regulation is still limited and requires more in-depth analysis. The development of USP39 inhibitors requires further research to determine their efficacy, safety, and potential side effects. As research progresses, these inhibitors are expected to become new strategies in cancer treatment. Analyzing the specific biological functions of USP39 and the spectrum of indications for USP39 inhibitors in various cancers will aid in the precise treatment of USP39-driven cancers. USP39 inhibitors may be effective in some cancers, but not for all cancers. The challenges of targeted therapy include selectivity, drug resistance, and patient heterogeneity that need to be addressed by further studies. It may be used in the future as a personalized treatment option for a specific cancer.

8.3 Exploration of clinical applications

The value of USP39 as a potential biomarker for tumor diagnosis and prognosis assessment needs to be validated in large-scale clinical samples. Additionally, the clinical application potential of USP39 inhibitors must be assessed in clinical trials.

8.4 Combination with other treatment strategies

Considering the potential resistance issues with single-target therapy, future research could explore the combined application of USP39 inhibitors with other treatment methods (such as chemotherapy, radiotherapy, and immunotherapy) to improve the therapeutic effects and reduce the occurrence of resistance.

8.5 Impact on the tumor microenvironment

The role of USP39 in the tumor microenvironment and its impact on tumor immune evasion are important topics for future research. Understanding the mechanisms of USP39 in the tumor immune microenvironment may provide clues for developing new tumor immunotherapy strategies. Furthermore, the overexpression of USP39 in many tumors contributes

to drug resistance, and the discovery of new effective USP39 inhibitors may be a feasible strategy to overcome difficulties in cancer treatment. Analyzing the specific biological functions of USP39 and the spectrum of indications for USP39 inhibitors in various cancers will promote precise treatment of USP39-driven cancers. In summary, the multifaceted roles of USP39 in tumors make it a potential therapeutic target. With further research, we look forward to using USP39 inhibitors as new treatment options for patients with cancer. However, research in this field is still in its early stages and more basic and clinical studies are needed to verify the efficacy and safety of USP39 inhibitors.

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Availability of data and materials The database used for the analysis of biological information in this manuscript can be accessed through the website provided, the Kaplan–Meier survival analysis database website link: Kaplan–Meier Plotter (http://kmplot.com/analysis/index.php?p = background).

Declarations

Consent for publication All authors have read and agreed to publish this manuscript.

Human and animal rights and informed This article does not contain any studies with human or animal subjects performed by any of the authors.

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