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Review

Exploring the cancerous nexus: the pivotal and diverse roles of USP39 in cancer development

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Abstract
The ubiquitin–proteasome system enables post-transcriptional protein modification and is a major pathway for the degradation of most of them in eukaryotic cells. Among these, the ubiquitin-specific protease (USP) family is the most extensively studied. As an important member of the USP family, ubiquitin-specific protease 39 (USP39) plays an essential role in RNA splicing and protein regulation. This review comprehensively summarizes the structural characteristics and molecular functions of USP39, emphasizing its pivotal role in the regulation of cellular processes. Dysregulation of USP39 is closely associated with the progression of various cancers through mechanisms such as immune evasion, modulation of oncogenic signaling pathways, and altered RNA splicing. These processes impact key aspects of cancer biology, including proliferation, metastasis, and therapy resistance, underscoring the broad implications of USP39 in tumor progression. Recent studies position USP39 as a promising target for cancer treatment. Future research should explore its upstream regulatory networks, develop small-molecule inhibitors, and evaluate its potential for precision oncology. This review integrates the latest insight into USP39, providing a foundation for its clinical application in cancer therapy.

Keywords Ubiquitin-specific protease 39 (USP39) · Cancer · Deubiquitination · RNA splicing · Ubiquitin–proteasome system inhibitors

1 Introduction

Cancer remains one of the most challenging diseases to understand and treat owing to its complex biology and the diverse mechanisms that drive its progression. Among the myriad of molecular pathways implicated in cancer, the ubiquitin–proteasome system is crucial in maintaining cellular homeostasis by regulating protein degradation and post-translational modifications [1]. The ubiquitin–proteasome system is intricately associated with a multitude of cellular processes, including protein modification, DNA damage repair, cell cycle regulation, signaling pathways, and immune responses. It is also involved in protein activation and localization, the modulation of protein–protein interactions, and

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protein degradation [2–4]. Furthermore, it plays a pivotal role in the onset and progression of various human diseases, particularly cancer [5–9].

More than 100 deubiquitinating enzymes (DUBs) have been identified in the human genome, which can be classified under six groups: ubiquitin-specific proteases (USPs), ubiquitin C-terminal hydrolases (UCHs), ovarian tumor-associated protein (OTAP), protease families (ovarian tumor-related proteases, OTUs), JAMM domain-associated metallopeptidases (JAMMs), Machado-Joseph disease proteases (MJDs), and the latest addition, the monocyte chemotactic protein-induced protein family (MCPIP) [10–12]. USPs account for approximately 60% of all DUBs, making them the largest and most diverse among DUB family members [13]. The USP structure comprises three subdomains: palm, thumb, and fingers. These subdomains are arranged with the critical catalytic center located at the junction of the palm and thumb subdomains. The finger subdomains grasp the ubiquitin molecule and position it at the catalytic center. This unique structural feature allows USPs to efficiently recognize and remove ubiquitin from target proteins, thereby regulating protein stability, localization, and function within the cell [14–16]. USPs play critical roles in cellular processes by regulating ubiquitination and deubiquitination, ensuring homeostasis and precise control of functions such as signal transduction, cell cycle progression, and DNA damage repair. USP dysregulation disrupts this balance, contributing to tumorigenesis through mechanisms that include stabilization of oncogenic factors, repression of tumor suppressors, and modulation of the immune microenvironment [17].

2 The fundamental characteristic of USP39

Ubiquitin-specific protease 39 (USP39), a member of the USP family, was originally discovered during a study on the spliceosome U4/U6-U5 triple-small nuclear ribonucleoprotein complex in yeast [18]. The gene encoding the USP39 protein is located in the 2p11.2 region of human chromosome 2 and is highly conserved across humans, mice, zebrafish, and yeast [18]. As an important protein involved in a wide range of physiological processes, USP39 contains two key functional regions: the N-terminal RS-like zinc finger ubiquitin-binding structural domain (ZnF-DBP, amino acids 29–121) and the C-terminal ubiquitin-specific protease structural domain (iUSP, amino acids 148–448) [19]. The ZnF-DBP is essential for the localization of USP39 in the RNA splicing complex and in the regulation of spliceosome activity. The iUSP enhances the interaction with specific proteins necessary for maintaining the integrity and function of the splicing complex [20]. In USP39, glutamic acid, serine, and aspartic acid replace the trimeric core residues comprising cysteine, histidine, and aspartate/asparagine, which are prevalent in the family of USPs and play a unique role in the regulation of the DNA damage response [21, 22].

In humans, nearly all genes undergo post-transcriptional precursor mRNA modifications before they perform a function, including the addition of 5′ and 3′ ends, modification of RNA nucleotides, and selective splicing [23]. Human precursor mRNAs consist primarily of exons in the coding region separated by introns in the non-coding region, which are converted to mature mRNAs by the selective splicing of introns [24, 25]. The spliceosome consists of small nuclear ribonucleoproteins (snRNPs) and various splice factors that function through the selective excision of exons and the ligation of introns for assembly [26]. As a core splicing factor, USP39 recognizes and removes non-coding introns on pre-mRNAs and participates in the formation and stabilization of small nuclear ribosomal complexes (especially U4/U6-U5 tri-snRNP), and interacts with other proteins in the spliceosome to co-regulate the spliceosome assembly and activation processes [18, 20, 26]. USP39 is also involved in the DNA damage response and repair through splicing regulation of key DNA repair proteins, such as homologous recombination (HR) and non-homologous end-joining (NHEJ), in addition to interactions with poly ADP-ribose chains [27]. Furthermore, USP39 is pivotal in the RNA splicing machinery and maintaining the expression of CTLA-4 through RNA-splicing mechanisms to regulate regulatory T cell (Treg) functionality. This regulation is mechanistically enhanced by lactate, which promotes the activity USP39 during RNA splicing, thereby facilitating CTLA-4 expression in a manner dependent on Foxp3 [28]. Such precise control of gene expression via splicing factors is critical; deviations can disrupt normal gene expression, leading to physiological dysfunction and the development of disease [29].

Research has highlighted the marked overexpression of USP39 in various cancer cells. This overexpression shifts the splicing patterns of integral proteins toward proliferation, cell cycle regulation, and apoptotic processes, thereby driving the progression of malignancies. This evidence underscores the importance of USP39 in both the maintenance of immune homeostasis and the pathological advancement of cancers, illustrating the complex interplay between splicing regulation and disease development.

USP39 is involved in maintaining the integrity of the mitotic spindle checkpoint, especially at microtubule attachments lacking tension. The microtubule-based bipolar spindle is essential for mitosis and ensures that chromosomes with genetic material are equally segregated into two daughter cells [30]. USP39 regulates the proper assembly and function of the spindle through the regulation of key proteins such as Aurora B. In the absence of USP39, a marked disruption in mitotic fidelity was observed, which was characterized by abnormal chromosome alignment, segregation errors, and cytoplasmic division failure in both normal and neoplastic cells. This phenomenon underscores the essential function of USP39 in maintaining genomic stability during cell division [31].

3 Expression of USP39 and immune evasion in various cancers

According to the Gene Expression Profiling Interaction Analysis (GEPIA) database analysis, except for acute myeloid leukemia, the expression levels of USP39 are elevated in tumor samples from several cancer types when compared to those present in normal tissue. Although certain differences did not reach the statistical significance threshold ($p < 0.05$), numerous comparisons demonstrated significant increases (Fig. 1a–c). Similarly, survival analysis demonstrated that higher USP39 expression levels were associated with lower survival rates in patients with multiple cancers (Fig. 1d), with varying degrees of statistical significance across cancer types. These findings indicate that USP39 may play a key role in the malignant progression of tumors. To date, functional studies on USP39 have mainly focused on its downstream effector proteins in the intracellular regulatory network of cancer cells; less is known about its potential upstream regulators (Table 1). USP39 is involved in many pathways, such as the FOXM1, Wnt/β-catenin, AKT/mTOR, PARP, Hippo, ERK, and p53/p21 signaling pathways (Table 2). An in-depth study of the molecular mechanisms by which USP39 regulates tumor development and progression is of great significance for the development of novel tumor therapeutic strategies.

USPs can influence the efficacy of immunotherapy by modulating immune cell function and immune responses in the tumor microenvironment [57–59]. Using the TISIDB database (an integrated repository portal for tumor–immune system interactions), we analyzed the relationship between the abundance of tumor-infiltrating lymphocytes (TIL), USP39 expression, and their methylation status. The relative abundance of TIL was inferred for each cancer type using a gene set variation analysis (GSVA) approach based on gene expression profiling. Analysis of the immune profiles of the 28 TIL types revealed that USP39 was negatively correlated with various immune cells, suggesting that it may be involved in tumor immune escape mechanisms. Tumor cells may avoid recognition and attack by the immune system by altering the function of immune cells within the microenvironment. USP39 may also affect immune cell functions, including differentiation, proliferation, and apoptosis.

4 Roles of USP39 in cancer

4.1 USP39 and liver cancer

In human hepatocellular carcinoma (HCC) cells, the expression level of USP39 is significantly upregulated, which interacts with multiple proteins, affecting multiple physiological processes, such as the proliferation, differentiation, and apoptosis of HCC. According to the GEPIA database analysis, Kaplan–Meier survival curves indicate that higher USP39 expression levels in HCC are significantly associated with poorer survival outcomes ($p = 0.00048$; Fig. 1d). This highlights the prognostic relevance of USP39 in HCC and underscores its potential role in tumor progression. USP39 promotes the malignant progression of HCC [60, 61] (Fig. 2). Knockdown of USP39 expression in HCC can significantly inhibit cell proliferation, resulting in cell cycle arrest at the G2/M phase [62]. USP39 affects HCC cell proliferation through multiple pathways, including the recruitment of the dynamin axonemal assembly factor 5 (DNAAF5) and its downstream pathway protein PFKl (a rate-limiting enzyme in glucose metabolism) for cellular energy, in addition to its involvement in key protein splicing in the Wnt/β-catenin signaling pathway, and its regulation of alternative nucleic acids through its effects on the splicing factor, SRSF6 and the hnRNPC [33, 36, 37]. USP39 may also affect HCC cell cycle arrest by regulating the phosphorylation status of CDC2 (a key cell cycle kinase), CDC25 C, and MYT1. USP39 knockdown upregulates phosphorylated (p)-CDC2 and downregulates p-CDC25 C and p-MYT1 expression, whereas no significant changes were observed in total CDC2, CDC25 C, or MYT1 expression. This inhibits the splicing of the precursor mRNA of the transcription factor FOXM1, further decreasing the expression levels of FOXM1 and its downstream target genes, PLK1 and Cyclin b1, suggesting that USP39 may affect the behavior of hepatic tumor cells in the G2/M phase and mitosis

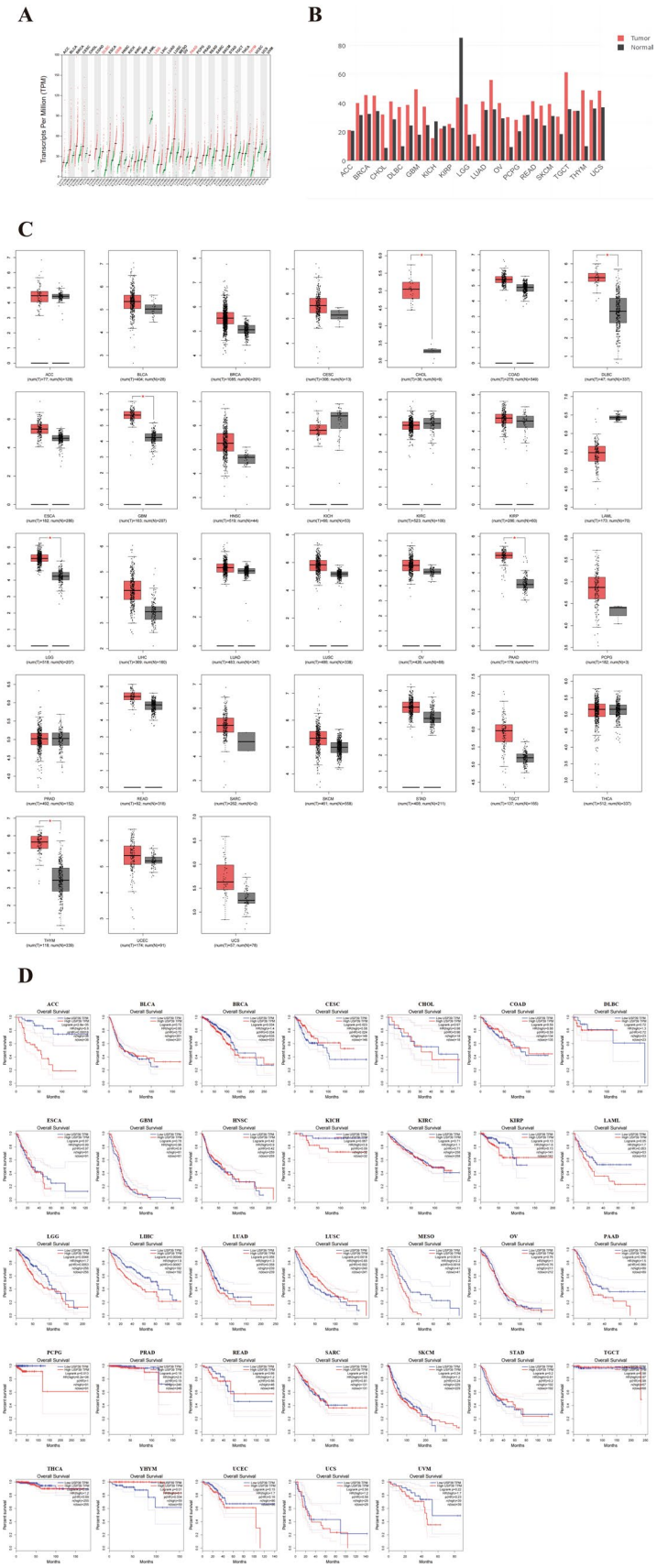

Fig. 1 Differential expression of USP39 in various cancers using gene expression profiling interactive analysis (GEPIA). **a** Expression levels of ubiquitin-specific protease 39 (USP39) in various tumor samples and adjacent normal tissues (transcripts per million, TPM). **b** Gene expression profile across all tumor samples and paired normal tissues. **c** Differential expression of USP39 in various cancers, with significance levels noted (*$p < 0.05$). **d** Kaplan–Meier plots showing differences in survival between patient groups stratified according to their USP39 expression levels, with significant differences in survival highlighted (*$p < 0.05$). Statistical analysis was performed to substantiate the claims

Table 1 USP39-associated substrate proteins and their protein localizations in various cancers

Cancer	Involved protein	Functions	Protein type	Substrate protein position	References
Liver cancer	MYST1	Acetylation	Histone acetyltransferase	Upstream	[32]
	SIRT7	Deacetylation	NAD^+-dependent deacetylase	Upstream	[32]
	DNAAF5	Glycolysis	Axonemal motor protein complex assembly factor	Upstream	[33]
	FoxM1	Cell cycle	Transcription factor	Downstream	[34]
	SP1	Cell proliferation	Transcription factor	Downstream	[35]
	β-Catenin	Proliferative	Signaling pathway proteins	Downstream	[36]
	SRSF6	RNA Processing and splicing	Shearing factor	Downstream	[37]
	HNRNPC	RNA processing and splicing	Shearing factor	Downstream	[37]
	ZEB1	Invasion, metastasis	Transcription factor	Downstream	[38]
Lymphoma	FoxM1	Cell cycle	Transcription factor	Downstream	[39]
Gastric cancer	PARP 1	DNA damage repair	ADP-ribose polymerase	Downstream	[40]
Colorectal cancer	p53	Cell cycle	Cell cycle regulatory proteins	Downstream	[41]
	Caspase	Apoptosis	Cysteine protease	Downstream	[41]
	P21	Cell cycle	Cell cycle inhibitory protein	Downstream	[42]
Osteosarcoma	P21	Cell cycle	Cell cycle inhibitory protein	Downstream	[43]
Glioma	Cyclin B1	Cell cycle	Cell cycle regulatory proteins	Downstream	[44]
	TAZ	Transcriptional regulation	Transcriptional coactivator	Downstream	[45]
	ADAM9	Protein shearing and signaling	Transmembrane metalloproteinase	Downstream	[46]
	Integrin β1	Cell adhesion and signaling	Transmembrane receptor	Downstream	[46]
Prostate cancer	EGFR	Cell proliferation	Tyrosine kinase-type receptor	Downstream	[47]

Table 2 Signaling pathways involving USP39 in various cancers

Cancer	Pathway	References
Liver cancer	FOXM1	[34, 48]
	Wnt/β-catenin	[36]
Lymphoma	FOXM1	[39]
Ovaries	p53/p21, Wnt/β-catenin	[49]
Esophageal cancer	AKT/mTOR	[50]
Colorectal cancer	Wnt/β-catenin	[51]
	P53/p21	[41, 42]
Pancreatic	AKT/mTOR	[52]
Lung cancer	AKT/mTOR, p53/p21, PARP	[53]
	P53/p21	[53, 54]
Glioma	Hippo	[45]
Kidney cancer	ERK, AKT/mTOR	[55]
Melanoma	ERK pathway	[56]
Osteosarcoma	p53/p21	[43]

by regulating the phosphorylation levels of key cell cycle proteins and positively regulating the FOXM signaling pathway [34, 48]. The zinc finger E-box binding homology cassette (ZEB1) is a key inducer of epithelial–mesenchymal transition (EMT), promoting cancer cell metastasis; USP39 inhibits the degradation of ZEB1 and promotes the development of EMT through deubiquitylation, further accelerating the invasion and metastasis of HCC cells [38]. USP39 affects the stability of the downstream signaling target protein SP1 through the ubiquitination pathway, and its stability is enhanced by SIRT7 deacetylation [32, 35].

Researchers have thoroughly analyzed the expression patterns and clinical relevance of eight USP members in HCC using the TCGA database; these findings highlight the significant role of USP39 in this context [63]. Bioinformatics analysis

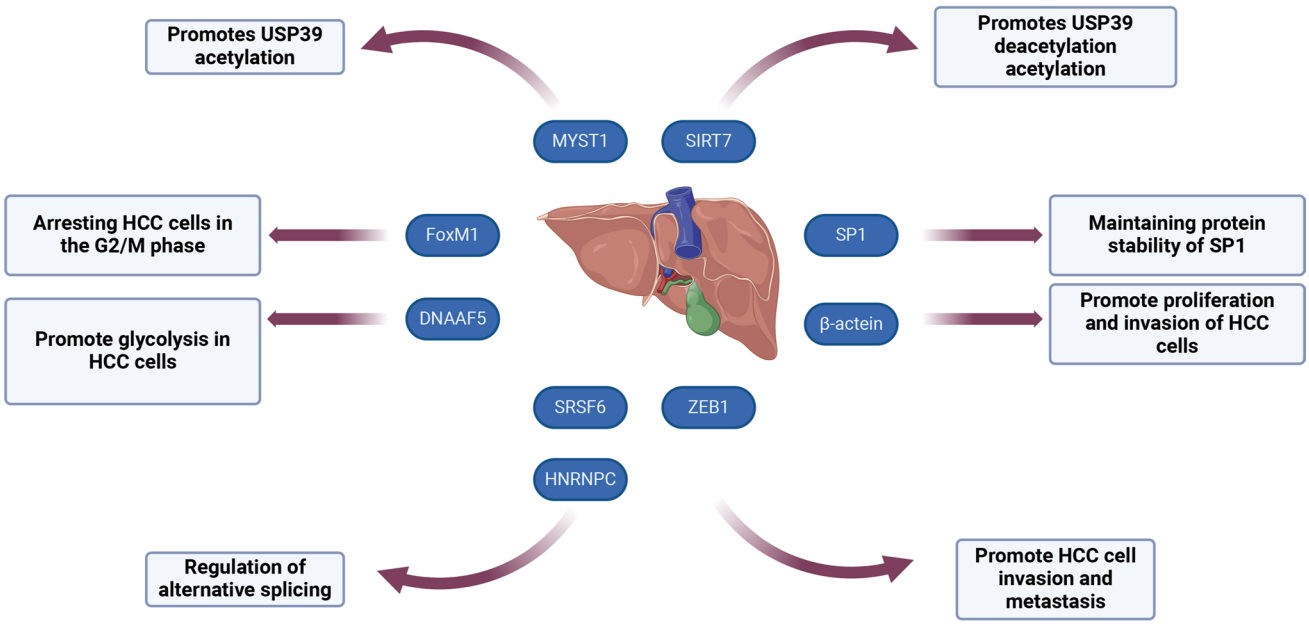

Fig. 2 Expression of ubiquitin-specific protease 39 in hepatocellular carcinoma and its role

has shown that USP39 was significantly differentially expressed in normal and HCC tissues and is closely associated with adverse clinical features, such as T stage, pathological stage, tumor status, age, and histological grading, revealing its potential value as a biomarker for the diagnosis and prognostic assessment of HCC [64].

In summary, USP39 significantly promotes the proliferation of HCC cells and enhances their capacity for invasion and metastasis through mechanisms that include the regulation of the Wnt/β-catenin signaling pathway, metabolic reprogramming, and EMT. Additionally, its role in the stabilization of ZEB1 and modulation of the FOXM1 axis highlights its critical function in HCC progression. Clinically, USP39 holds potential as a biomarker for diagnosis and prognostic assessment, offering new possibilities for targeted therapeutic strategies in HCC.

4.2 USP39 and breast cancer

Aberrant USP39 expression in breast cancer cells is considered a key factor in promoting tumor development. USP39 is an important prognostic indicator of therapeutic efficacy and is a potential molecular target for gene therapy in breast cancer [65]. A rare splice variant, USP39 c.*208G>C, may increase breast cancer susceptibility, as demonstrated in a study of Russian patients with breast cancer [66]. Downregulation of USP39 significantly reduces the proliferation and colony-forming ability of triple-negative breast cancer cells [65, 67]. USP39 promotes breast cancer proliferation by regulating FOXM1 levels via deubiquitination [39]. The UPS pathway may be critical for the treatment of patients with breast cancer receiving anthracyclines [68]. The development of USP39 inhibitors offers new possibilities for the treatment of breast cancer [69]. USP39 plays a multifaceted role in breast cancer, influencing tumor progression and resistance to therapy. Its potential as both a prognostic marker and therapeutic target warrants further investigation to refine the treatment strategies for breast cancer.

4.3 USP39 and ovarian cancer (OC)

Due to the lack of obvious clinical symptoms in patients with early OC, most patients are diagnosed in the middle or late stages and have to undergo palliative treatments, such as chemotherapy and radiotherapy [70]; however, resistance to chemotherapy and radiotherapy has emerged as an urgent problem [71]. USP39 knockdown effectively reduces resistance to chemotherapeutic drugs, such as carboplatin, and enhances the sensitivity of OC cells to radiation therapy [72]. Therefore, the knockdown of USP39 effectively overcomes resistance to chemotherapy and radiotherapy in ovarian cancer, highlighting its potential as a therapeutic target. This suggests that USP39 inhibition could enhance the efficacy of existing treatments and address critical challenges in the management of late-stage ovarian cancer.

4.4 USP39 and esophageal squamous cell carcinoma (ESCC)

The expression level of USP39 in ESCC cells is significantly higher than that in normal human esophageal epithelial cells, which promotes cell proliferation and closely correlates with the degree of cancer malignancy. Zhao et al. further indicated that USP39 promoted the proliferation of ESCC cells by enhancing the splicing and maturation of Rictor mRNA, a component of the mTOR complex, and regulating the mTORC2 signaling pathway [50]. USP39 interacts with several spliceosome components, including EFTUD2, PRPF3, SART1, DDX23, and hnRNPU, further driving malignant cancer progression [73]. This highlights USP39 as a potential therapeutic target, especially for interventions aimed at disrupting spliceosome-associated oncogenic processes.

4.5 USP39 and gastric cancer (GC)

To date, studies have focused on the effect of USP39 on the proliferation mechanism of GC cells, especially its role in the splicing of the oncogenic factor miR-133a and how it accelerates cell proliferation and cancer progression by promoting the degradation of the PARP1 protein, which is involved in DNA repair [40, 74, 75]. The expression level of USP39 correlates with the immune infiltration of GC tissues. Positive expression is associated with the upregulation of $CD3^+$ and $CD4^+$ cells and the downregulation of $CD8^+$ and $CD68^+$ cells, which are closely related to the differentiation of cancer tissues and lymph node metastasis. The prognosis of patients with positive expression is poor, suggesting that USP39 is a significant tumor marker for evaluating the prognosis of GC. Furthermore, USP39 has a unique role in predicting the efficacy of platinum-based neoadjuvant chemotherapy for the treatment of GC. These findings indicate that USP39 not only influences tumor proliferation but also modulates the tumor microenvironment by altering the infiltration patterns of immune cells. This dual role highlights its potential as both a therapeutic target and a biomarker for personalized treatment strategies. Further studies investigating its interactions with DNA repair pathways and immune modulation could uncover novel mechanisms driving GC progression and resistance to chemotherapy.

4.6 USP39 and colorectal cancer (CRC)

CRC is the third most common cancer in men and the second most common in women, with high morbidity and mortality rates. The global burden of colorectal cancer continues to rise, highlighting the need for molecular insights to improve existing therapeutic strategies [76]. Compared to normal tissues, USP39 is highly expressed in CRC tissues and is closely associated with tumor stage and differentiation, clinicopathological features, survival, and prognosis, making it a potential molecular target for CRC therapy.

Mutations in the KRAS gene have been implicated in many types of cancer, making it a promising target for gene-targeted therapies. Using synthetic lethal gene RNAi screening technology, Fraile et al. [77] identified USP39 as an important splicing factor of KRAS that correlates with poor clinical outcomes, providing new therapeutic approaches against targeted KRAS.

The effect of USP39 on CRC involves multiple signaling pathways, such as the Wnt/β-catenin pathway and the p53/p21 pathway. Knocking down USP39 results in the downregulation of key proteins of pathways, such as β-catenin, TCF4, MMP2, MMP9, and p21, along with increasing the expression levels of apoptosis-associated proteins, such as p53, p-p53, PARP, and caspase-3 [41, 42, 51]. Therefore, exploring the crosstalk between USP39-mediated splicing regulation and apoptosis pathways may reveal novel strategies to enhance the efficacy of the treatment for CRC, particularly in advanced or drug-resistant cases.

4.7 USP39 and pancreatic cancer (PC)

The global burden of PC is rising rapidly; thus, there is an urgent need to address this issue. With its high mortality and limited treatment options, pancreatic cancer poses a growing challenge, particularly for aging populations [78]. According to the GEPIA database, USP39 expression is significantly upregulated in pancreatic cancer tissues compared to adjacent normal tissues ($p < 0.05$; Fig. 1c). This suggests a potential role for USP39 in PC progression. Cai et al. [52] reported that USP39 promotes PC cell apoptosis by regulating the AKT signaling pathway. Wang et al. reported high expression of USP39 in pancreatic ductal adenocarcinoma (PDAC) and noted its positive correlation with clinicopathological features and survival rates. Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway

analyses suggest the key role of USP39 in cell cycle progression in PDAC [79]. These findings, combined with the GEPIA data, underscore the dual role of USP39 in PC, influencing both apoptosis through the AKT pathway and cell cycle progression, and suggesting its potential as a critical regulator of tumor growth and therapeutic response in PDAC.

4.8 USP39 and lung cancer

The expression levels of USP39 in non-small cell lung cancer (NSCLC) tissues and cells are significantly higher than those in paracancerous tissues or normal bronchial epithelial cells, promoting the proliferation of cancer cells, closely correlated with the tumor stage. Kaplan–Meier survival analysis from the GEPIA database further supports the prognostic value of USP39, showing that higher USP39 expression in lung squamous cell carcinoma (LUSC) is significantly associated with poorer survival outcomes ($p = 0.0018$; Fig. 1d).

The existing literature indicates that USP39 can affect the activity of the AKT, mTOR, p53, and PARP signaling pathways and participate in regulating lung cancer cell proliferation and migration [53, 54, 80]. The PI3 K/AKT/mTOR [81], RAS/RAF/MEK/ERK [82], Wnt/β-catenin [83], and NF-κB pathways [84] are closely associated with the development and progression of NSCLC. Inhibition of key proteins within these pathways may represent an effective treatment strategy for NSCLC [85]. Epigenetic alterations are widespread in cancer. Karlow et al. identified specific methylation alterations associated with smoking status by analyzing differentially expressed genes in NSCLC tissue samples from smokers and non-smokers, with non-smokers experiencing more hypomethylated repeats in the promoter region of USP39 [86].

4.9 USP39 and other cancer types

In addition to the cancer types mentioned above, USP39 has carcinogenic implications for glioma, osteosarcoma, melanoma, renal, bladder, prostaglandin, and thyroid cancers, affecting multiple physiological processes, including cell proliferation, cell cycle, apoptosis, migration, and invasion. As a member of the DUB family, USP39 is considered a potential biomarker and therapeutic target for tumors of the central nervous system [87].

In glioma, USP39 acts as a splicing factor by altering the 3′ splice site to increase the expression of high mobility group protein A2 (HMGA2) and promotes the maturation of migratory invasion-associated proteins and TAZ mRNA, a key protein in the ADAM9 and Hippo signaling pathways. Analysis from the GEPIA database indicates that USP39 is significantly overexpressed in lower grade glioma (LGG) in brain tissues compared to normal brain tissues ($p < 0.05$; Fig. 1c). Furthermore, Kaplan–Meier survival analysis demonstrates that higher USP39 expression is significantly associated with poorer survival outcomes in patients with LGG ($p < 0.05$; Fig. 1d). These findings highlight the potential prognostic value of USP39 in glioma and its role in tumor progression.

USP39 stabilizes Cyclin B1 protein expression by deubiquitinating the K29-linked polyubiquitin chain at Lys242 [44–46, 88]. Knocking down USP39 can activate the caspase cascade, upregulate the expression of p53 to inhibit the proliferation of bladder cancer, and inhibit the proliferation of thyroid cancer through the activity of CDK1/CyclinB1 [89].

In renal cancer cells (RCCs), USP39 promotes malignant progression by regulating the anti-angiogenic variant of vascular endothelial growth factor A (VEGF-A), VEGF-A_{165}b, in addition to the RNA splicing-related proteins SRSF1 and SRPK1 [90]. Xu et al. reported that the knockdown of USP39 increased the levels of apoptosis-related proteins, such as caspase-3, caspase-8, caspase-9, and PARP, in RCCs, and inhibited the activation of ERK and AKT signaling pathways, resulting in an increase in the apoptosis rate of cancer cells [55]. Similarly, USP39 promotes malignant melanoma progression by regulating ERK signaling [56].

In prostate cancer, USP39 promotes cell proliferation by modulating mutations at the K6, K16, K29, K51, and K73 loci of SUMO and regulating EGFR mRNA transcription [47, 91]. Furthermore, silencing of USP39, a target of miR-1281 in human osteosarcoma cells, inhibits survival under endoplasmic reticulum stress and slows the metastasis of malignant bone tumors to other tissues and organs by increasing the expression of Cyclin A2 and p21, leading to cell cycle arrest in the G2/M phase and promoting apoptosis [43, 92, 93]. Additionally, histone lactylation promotes the interaction with PGK1 by enhancing USP39 expression. This interaction stabilizes PGK1 and results in the targeted activation of the PI3 K/AKT/HIF-1α signaling pathway in endometrial cancer, which in turn stimulates the glycolytic process, thereby accelerating its malignant progression [94]. Its differential methylation patterns in smokers and non-smokers highlight its potential role as a bridge between environmental factors and molecular mechanisms in cancer. These findings suggest that USP39 serves as a central regulator in NSCLC, influencing tumor progression through its involvement in multiple key pathways and epigenetic modifications. Further investigations into its pathway-specific functions and its unique role in smoking-related NSCLC could provide valuable insights for the development of targeted therapeutic approaches.

In summary, USP39 exhibits cancer-specific mechanisms across diverse tumor types, highlighting its ability to adapt its oncogenic role to the unique context of each cancer. These interconnected roles suggest that USP39 not only drives tumor progression but also tailors its mechanism of action according to the specific cancer type. Exploring how USP39 coordinates signaling pathways, splicing events, and metabolic regulation within specific tumor microenvironments could lead to the development of novel, cancer-specific therapeutic strategies.

5 Conclusion and future perspectives

Numerous studies have demonstrated that USP39 plays a key role in cancer development, affects the stability of the cell cycle and signaling pathway-related proteins, participates in DNA damage response mechanisms, regulates key oncogene expression through various pathways, such as mRNA shearing, maintains the stability of spindle checkpoints, and regulates deubiquitination. It influences multiple physiological processes, such as tumor cell proliferation, apoptosis, invasion, and the promotion of malignant tumor progression [95]. Furthermore, drug resistance significantly reduces the effectiveness of drug therapy [96]. The aberrant expression of USP39 is closely related to the clinical characteristics and pathological stages of liver, breast, and other cancers. USP39 knockdown enhances the sensitivity to radiotherapy and overcomes resistance to chemotherapy in OC and GC, offering a new approach for radiotherapy and chemotherapy combination therapy using USP39 as an adjuvant. This suggests that USP39 is not only an important target for cancer treatment but could also be used as a biomarker to help diagnose and evaluate tumor status [97].

However, the regulatory mechanisms of USP39 in many cancers are not fully understood. Most identified interacting proteins are downstream of USP39, with fewer known upstream-related proteins, and the complex cancer microenvironment and related signaling pathways have not yet been fully clarified (Table 1). Deletion of the USP39 gene could cause the failure of primitive streak formation and embryonic lethality in mice by biological analysis. Most existing studies on USP39 are primarily based on in vitro experiments; there is a lack of extensive in vivo studies and clinical trials. Although USP39 is a potential target for cancer therapy, precise therapeutic approaches targeting USP39 remain to be explored.

It is important to develop effective and specific USP inhibitors that only deubiquitinate substrates without altering overall protein levels [6, 98]. Since the Food and Drug Association approval of the proteasome inhibitor bortezomib for the treatment of multiple myeloma and condyloma, researchers have increasingly explored drugs targeting the USPs as a cancer treatment strategy [99]. Advanced techniques for screening and identifying USP inhibitors, such as activity-based probes (ABPs), ubiquitin (Ub)–7-amido-4-methylcoumarin (AMC) assays, Ub-phospholipase A2 (PLA2) methods, time-resolved fluorescence resonance energy transfer (TR-FRET) assays, sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) Coomassie blue staining, and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry are dedicated to precisely identifying and altering the configuration of USP catalytic sites and structural domains to inhibit its deubiquitinating enzyme activity [100, 101]. Future research should explore the function and mechanism of USP39 from multiple perspectives and aim to develop novel therapeutic approaches, such as small-molecule inhibitors, monoclonal antibodies, and RNA interference, to inhibit USP39 expression and cancer development. Although inhibitors targeting USP39 have not been extensively studied, their development is feasible and may significantly affect cancer therapy in the future.

USP39-based comprehensive therapeutic strategies are expected to be developed in the future to achieve more precise and effective cancer treatments, facilitating the clinical application of USP39 inhibitors.

6 Generative AI and AI-assisted technologies in the writing process

Not applicable.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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