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Recent insights into USP7: Construct, pathophysiology, and inhibitors

Yuanming He[1], Yueya Zhong[1], Yiqian Wang[2], and Xinliang Mao[1]*

[1]Guangzhou and Guangdong Key Laboratory of Protein Modification and Degradation, School of Basic Medical Sciences and State Key Laboratory of Respiratory Diseases, Guangzhou Medical University, Panyu District, Guangzhou, 511436, China

[2]School of Biological Sciences, Guangzhou Medical University, Panyu District, Guangzhou, 511436, China

Abstract

The ubiquitin-proteasome pathway (UPP) is essential for proteostasis and cellular homeostasis. Most of the human proteins are degraded through the UPP in which proteins should be tagged with a specific polyubiquitin chain in a sequential cascade of E1 ubiquitin (Ub)-activating enzymes, namely, E2 Ub-conjugating enzymes and E3 Ub ligases. Meanwhile, the ubiquitination process can be reversed by deubiquitinating enzymes (DUBs), which protect the target proteins from ubiquitination, and so far, around 100 DUBs have been reported to present in human cells. Ubiquitin-specific protease 7 (USP7) is a member of the DUBs family, which has been reported to play crucial role in the development of human tumors and diseases; however, the molecular mechanisms of disease and malignant tumor progression mediated by USP7 has not been fully elucidated. In addition, the therapeutic potential of USP7 in cancer treatment remains to be further explored. Therefore, this review begins with a review of the structure and function of USP7, and then focuses on the development of USP7 inhibitors and their potential applications in various human diseases.

Keywords: Degradation; Ubiquitin-proteasome pathway; Deubiquitinating enzymes; Ubiquitin specific protease 7; Molecule inhibitors

***Corresponding author:**
Xinliang Mao
(xinliangmao@gzhmu.edu.cn)

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1. Introduction

Ubiquitination is an essential and important post-translational modification process for most of the proteins, through which the proteins are covalently tagged with ubiquitin (Ub) molecules. Ub molecule, which is composed of 76 amino acids, is widely expressed, and the structure of the molecules is highly conserved across different species[1]. At the consumption of ATP, Ub molecules are covalently conjugated to a certain lysine residue of the target protein, which is further catalyzed by the E1 Ub-activating enzymes (for activation), E2 Ub-conjugating enzymes (for conjugation), and E3 Ub ligases (for ligation)[2]. It has been reported that there are around 2 Ub-activating enzymes (E1s), at least 38 Ub-conjugating enzymes (E2s), and more than 600 Ub ligases (E3s) in human, and the specific combinations of these enzymes determine the specificity of the protein ubiquitination process. Interestingly, Ub molecules contain seven lysine residues, namely K6, K11, K27, K29, K33, K48, and K63, which could be conjugated to other Ub molecules, providing diversity, and specificity for the ubiquitination

process of the substrate proteins[3]. On the other hand, ubiquitination is a reversible and dynamic process, where Ub molecule chains can be cleaved away from the target proteins by certain deubiquitinating enzymes (DUBs), protecting the target protein from degradation[4]. In brief, DUBs are a type of ubiquitin-specific proteases (USPs), which can induce the hydrolysis of Ub chains from the specific substrate proteins, leading to recycling of the Ub molecules, processing of the Ub precursors, and reversing of the Ub conjugation[5,6]. In terms of biological functions, DUBs can regulate several cellular processes in humans, such as protein stabilization[7], gene transcription[7], signal transduction[8,9], cell cycle progression, protein localization[10], DNA damage response, kinase activation[11,12], and many other functions.

Further, there are around 100 DUBs in human cells, which are able to reverse the ubiquitination reaction by removing the covalently attached Ub molecules from the substrates. Based on their structure and functional characteristics, DUBs can be divided into five subfamilies: (1) USPs, the largest subfamily; (2) Ub C-terminal hydrolase; (3) ovarian tumor; (4) Machado-Josephin disease protein; and (5) Jab1/Mov34/Mpr1-Pad1N-terminal+(JAMM)[13]. USP7 is a cysteine protease, which belongs to the USP subfamily. It has been widely reported that USP7 interacts with the substrates to prevent ubiquitination and degradation of the target proteins[14]. In this review, the recent research advances about USP7 in terms of its structure, pathological processes, and development as specific inhibitors are discussed.

2. The structure of the USP7

USP7, also known as herpes virus-associated ubiquitin-specific protease (HAUSP), has been demonstrated to participate in various pathological processes and diseases, including neurological disorders, metabolic disorders, immune dysfunction, and particularly carcinogenesis. In addition, USP7 is highly expressed in different types of cancers, including breast cancer[15], medulloblastoma cancer[16], T-cell leukemia[17], ovarian cancer[18], lung cancer[19], and multiple myeloma (MM)[20]. Furthermore, USP7 is closely related to malignant progression through its deubiquitinating activity in stabilizing the oncogene proteins, such as c-Maf and MafB transcription factors[20], E3 Ub ligase human homolog of double minute 2 (HDM2) protein[21], oncoprotein c-Myc, and enhancer of zeste homolog 2 (EZH2) protein[22,23]. Interestingly, USP7 also has been shown to stabilize several tumor suppressor proteins, including p53 and phosphatase and tensin homolog (PTEN)[10,24]. Due to the diversity of its substrates, it is difficult to determine whether USP7 functions as an oncogene or as a tumor suppressor; therefore, it is essential to identify the specific substrate proteins, to understand better the roles of USP7 in specific clinical setting. Thus, the structural domains of USP7 and their effects on the USP7 activity, and the correlation between USP7 and intracellular signaling pathways, as well as the molecular mechanisms underlying the effects of USP7 on cancer and other diseases are further discussed in this article. Finally, the application of USP7-specific inhibitors and their potential applications in human diseases are included in this article as well.

2.1. The tumor necrosis factor-receptor associated factor (TRAF) domain

USP7 belongs to the UBP subfamily featured with an N-terminal TRAF-like domain[25]. The TRAF domain consists of 160–165 amino acid residues, which can mediate substrate recognition and interaction[26]. It is well-known that TRAF domain binds to both p53 and HDM2, thereby mediating their deubiquitination[26,27]. However, the deletion of the N-terminal TRAF-like domain does not prevent the deubiquitination of p53 and HDM2 by USP7, suggesting the presence of a secondary binding site in USP7 with the substrate proteins. Later, this secondary binding motif in USP7 is believed to be the ubiquitin-like (UBL) domain[27], indicating that there are different binding modes between USP7 and the substrates.

2.2. The UBL domain

In addition to the TRAF domain, UBL domain is another common structural domain to UBPs. Most of the proteins within the UBP subfamily have one or more UBL domains, including USP4, USP6, USP7, USP9X/Y, USP11, USP14, USP15, USP19, USP24, USP31, USP32, USP34, USP43, USP47, USP48, and USP52[28]. Of note, the UBL domain exhibits different regulatory functions. For example, the UBL domain in USP4 has dual functions; it modulates USP4 localization to the proteasome to enhance its catalytic activity, and at the same time, the UBL domain can mimic Ub molecule and competes for Ub binding, subsequently causing a reduction in the ubiquitination of the substrate[29]. Interestingly, USP7 has five UBL domains (UBL1/2/3/4/5) at the C-terminus spanning from 560 to 1050 amino acids, and they are organized in a UBL1/2-UBL3-UBL4/5 sequence. The last two of the UBL domains are found to modulate the catalytic activity of USP7, specifically, by promoting a conformational change of USP7 through interacting with the catalytic domain (CD), leading to binding and reshaping of the catalytic center[25,29,30]. In contrast, in the absence of these UBL domains, USP7 loses its catalytic activity about 100-fold[31], meanwhile the UBL4/5 domains can activate

USP7 through binding and rearranging the switching loop in the CD, leading to about 100-fold increase in USP7 enzymatic activity[30]. In addition, this process can be increased with the help of allosteric activator guanosine 5'-monophosphate synthase (GMPS)[32], where GMPS can binds to UBL1/2/3, subsequently increases the interaction between CDs and UBL4/5, thereby promoting the USP7 activity[32]. This process suggests that the UBL domains are indispensable for USP7 to perform its deubiquitinating functions.

2.3. The CD

The CD, which is essential for the cleaving process of the polyubiquitin chains, in USP7 is composed of 208–560 amino acids. It should be noted that the proteolytic activity of USP7 is highly diverse and varies depending on the specific substrate proteins[25]. The catalytic triad contains three types of amino acids, including cystine (Cys), histidine (His), and asparagine (Asn)/aspartic acid (Asp) residues[33], of which the Asn/Asp residue is important for polarization of His residue, which in return stabilizes the catalytic activity of DUBs[28]. Moreover, the triad is rearranged in the presence of a covalently bound Ub aldehyde to generate a catalytically competent state of the CD[34]. It is important to note that, in the absence of the UBL domains, the CD will lose almost all of its activity.

3. USP7 regulates diverse types of ubiquitination

DUBs can hydrolyze the polyubiquitin chain of target proteins, thereby protecting them from degradation or modulating their function or cellular localization, depending on the types of ubiquitination process[35]. As discussed above, ubiquitination is a process that covalently attaches a Ub molecule to the specific lysine (K) residue on a substrate protein. In a Ub molecule, there is a highly conserved region, which is composed of the seven lysine residues, namely, K6, K11, K27, K29, K23, K48, and K63, which may lead to the diverse forms of Ub modification. Based on the Ub chain, Ub modifications could be classified into monoubiquitination (substrate protein tagged with a single Ub molecule) and polyubiquitination (substrate protein tagged with a multiple Ub molecule), and according to the Ub binding sites, ubiquitination are accordingly named K6-, K11-, K27-, K29-, K23-, K48-, and K63-linked ubiquitination[36]. Importantly, USP7 can hydrolyze almost all types of Ub through monoubiquitination as well as K48- and K63-linked polyubiquitination[10,37]. Furthermore, USP7 has been shown to markedly reduce the polyubiquitination levels of the substrate proteins, thereby exerting diverse functions[20,38,39].

3.1. Targeting monoubiquitination by USP7

In monoubiquitination, a single Ub molecule attaches to substrate proteins. PTEN protein, one of the best-known tumor suppressors which is involved in a plethora of cancer development, is a typical protein that is subject to monoubiquitination. PTEN can be ubiquitinated in various ways, including monoubiquitination, K27-, K48-, and K63- linked polyubiquitination, to modulate its subcellular localization, aggregation, stability, and functionality[40-42]. It is known that nuclear localization of PTEN is associated with monoubiquitination of PTEN at K289, which is indispensable for its nuclear import and tumor suppression[43]. In addition, USP7 hydrolyzes monoubiquitination of PTEN, which leads to PTEN nuclear exclusion and loss of phosphatase activity, eventually promoting prostate cancer tumorigenesis. Another example is mothers against decapentaplegic homolog 3 (SMAD3) protein. The biological activity of SMAD3 depends on the monoubiquitination modification. USP7 interacts with SMAD3 and subsequently deubiquitinates its monoubiquitination level, thereby repressing cancer progression in p53-deficient lung cancer. Furthermore, USP7 also deubiquitinates monoubiquitination of other proteins including forkhead box protein O4, proliferating cell nuclear antigen, histone H2B, and others[44-46].

3.2. Hydrolyzing K48-linked polyubiquitination by USP7

Compared with monoubiquitination, polyubiquitination is more common in protein modification, and there are seven types of polyubiquitination on thousands of proteins. At present, USP7 is believed to have the largest number of substrate proteins in terms of deubiquitination as shown in Table 1. It is known that intratumoral hypoxia can induce hypoxia-inducible factor 1-alpha (HIF-1α) and subsequently promote tumorigenesis, metastasis, and treatment resistance. A previous study has revealed that USP7 can remove the K48-linked polyubiquitination by physically interacts with HIF-1α, thereby increasing the protein stability and resulting in tumor cell epithelial-mesenchymal transition, metastasis, and tumor progression[47].

In addition, ADP-ribosylation factor 4 (ARF4) is a small guanine nucleotide-binding protein, which belongs to Ras superfamily of small G proteins. Previous studies have demonstrated that ARF4 is an anti-apoptotic protein, which acts as a BAX inhibitor, and its function is indispensable in glioblastoma tumorgenesis[52,115]. Interestingly, USP7 has been shown to be significantly upregulated in glioblastoma patient samples. Further study revealed that USP7 directly binds to ARF4, catalyzes the removal of the K48-linked

Table 1. List of identified USP7 substrates

Substrates	Ref	Substrates	Ref	Substrates	Ref	Substrates	Ref
AR	[48]	GATA1	[49]	NF-κB	[50]	SIRT1	[51]
ARF4	[52]	GMPS	[32]	NHE3	[53]	SOCS1	[54]
ARMC5	[55]	HDM2	[56]	NLRP3	[57]	So×9	[58]
BCR-ABL	[38]	HIF-α	[47]	N-Myc	[59]	SPRTN	[60]
Bmi1	[61]	Histone H2B	[32]	NOTCH1	[62]	SUMO	[63]
Bub3	[64]	Histone H3	[65]	Nrf1	[66]	Tip60	[67]
Cdc25A	[68]	HLTF	[69]	p53	[24]	TPP1	[70]
CDK1	[71]	ICP0	[72]	PHF8	[15]	TRAF6	[73]
Chk1	[74]	IKKγ	[75]	PLK1	[76]	TRIM27	[77]
Clapsin	[76]	IRSs	[78]	Polymerase η	[45]	UbE2E1	[79]
c-MYC	[80]	JMJD3	[81]	POT1	[82]	UHRF1	[83]
CSB	[84]	KDM6B	[85]	PPARγ	[86]	UL35	[87]
DAF16	[88]	LANA	[89]	PRC1	[90]	UVSSA	[91]
DLC1	[92]	LSD1	[93]	PTEN	[10]	vIRF1	[94]
DNMT1	[95]	MAF	[20]	Rb	[96]	vIRF4	[97]
E1B	[98]	MCL1	[99]	RECQL4	[100]	WDR5	[101]
EBNA1	[102]	MDMX	[103]	RING1B	[104]	XPC	[105]
ERα	[106]	MLL2	[101]	RIP1	[98]	YAP	[107]
EZH2	[108]	Mule/ARF-BP1	[109]	RNF168	[110]	ZNF638	[111]
FOXO4	[44]	NEK2	[112]	RUNX2	[113]	β-catenin	[114]

polyubiquitinated chain from ARF4, and promotes malignant progression of glioblastoma. In addition, *in vivo* experiments revealed that treatment of USP7 specific inhibitor, P5091, can significantly suppress the growth of tumor models through ARF4 degradation[52].

3.3. Hydrolyzing other polyubiquitination by USP7

The Maf proteins are critical factors in myelomagenesis, and it is an independent biomarker indicating poor prognosis in MM, a malignant cancer that is derived from plasma cells. In our previous work, wefound that Maf proteins, including c-Maf and MafB, are substrates of USP7, indicated by affinity-purification couple tandem mass spectrometry analysis of c-Maf and MafB interactomes[20]. In addition, USP7 can interact with Maf proteins through both TRAF and UBL domains, thereby preventing c-Maf and MafB from polyubiquitination and increasing their stability by prolonging their half-lives. Further, knockdown of USP7 or treatment with a specific small molecule inhibitor against USP7 leads to Maf protein degradation, followed by MM cell apoptosis[20].

In addition, we also identified the fusion protein BCR-ABL, the fundamental non-receptor tyrosine kinase in chronic myelogenous leukemia (CML), which acts as a substrate of USP7[38]. Cell-based experiments demonstrated that USP7 specifically binds to BCR-ABL protein, subsequently protects them from proteasome degradation, resulting in CML cell proliferation. Further, overexpression of USP7 increases the protein stabilization of BCR-ABL and induces CML cell survival; in contrast, knockdown of UPS7 decreases the protein level of BCR-ABL and its downstream target protein, phosphorylated STAT5, resulting in the inhibition of CML cell growth[38].

4. The broad substrate spectrum of USP7

The synthesis and degradation of proteins are a dynamic equilibrium process, which maintains the homeostasis of the cells. In addition, protein degradation is an essential process, which is regulated through the UPP pathway, and this process can be reversed by the DUB. USP7 is a DUB with a long list of substrate proteins (oncoproteins or tumor suppressor proteins); therefore, USP7 is known to be widely involved in the development and progression of various cancers. Abnormal activation of an oncogene or dysfunction of a tumor suppressor gene in cells may result in malignancy and induction of a series of abnormal gene expression.

TP53, also known as p53, is a protein encoded by the *TP53* gene in human and plays an important role in tumor

suppression. The tumor suppressive role of p53 protein has been widely reported, and as a transcriptional factor, p53 regulates numerous physiology processes, such as cell cycle, DNA damage repair, cell apoptosis, antitumor activity, and cell stress response[116]. In contrast, mutations and dysregulation of p53 have been reported to occur in more than 50% of all malignancies, leading to the loss of its antitumor activity[117]. The stability of p53 is regulated through the UPP and its polyubiquitination, and mediated by HDM2, an E3 Ub ligase[118]. Interestingly, HDM2 is also degraded through the UPP in an autoubiquitination pattern, at the same time p53 and HDM2 interacts with each other by forming a feedback loop[119]. Interestingly, USP7 can regulate both p53 and mouse double minute 2 homolog (MDM2). USP7 interacts with p53 through its TRAF-like domain and stabilizes the p53 protein level by decreasing its ubiquitination level, even in the presence of HDM2[24]. Meanwhile, USP7 also binds with HDM2 and inhibits its polyubiquitination[21]. Thus, these three proteins form a complex, as evidenced by their crystal structure analyses, where both HDM2 and p53 interacts with the TRAF-like domain of USP7, further, the interaction of HDM2/USP7 is closer than p53/USP7[120,121]. The previous studies have shown that partial knockdown of USP7 induces the degradation of p53, while the complete inhibition of USP7 expression leads to the stabilization of p53, and this phenomenon is related to HDM2[21,122]. Another study reported that USP7 stabilizes both p53 and HDM2 protein *in vivo*. However, it is believed that USP7 maintains HDM2 to a certain protein level, to regulate the polyubiquitination degradation of p53.

In addition, UPS7 has been shown to have other substrate proteins, including PTEN, c-Maf, MafB, trans-activator of transcription, NAD-dependent deacetylase sirtuin-1, BCR-ABL, GATA-binding factor 1 (also known as GATA1), and ring finger protein 168[10,20,21,24,38,49,51,110,123]. Many of these proteins are associated with cell cycle, DNA damage, regulation of transcription, and tumorigenesis. In addition, some of the substrate proteins have been shown to function as a mediator in certain signaling pathways, indicating the complexity of the substrate proteins function in human cells, thus, more studies are required to explore and understand its functions.

5. USP7 modulates signaling transduction

It has been reported that USP7 is involved in multiple cellular signaling pathways, such as PI3K/PTEN/AKT signaling[10,124], Wnt/β-catenin signaling[39], Hippo pathway[107], NF-κB signaling[125], type I IFN signaling[126], and DNA damage signaling[110] (Table 2). These pathways have different effects on cells, although their activities are regulated by USP7. For example, in multiple cellular systems, USP7 directly interacts with and stabilizes Axin protein by decreasing its polyubiquitination and inhibiting the Wnt/β-catenin pathway thereby suppressing Wnt-induced osteoblast differentiation[39]. In addition, Hippo pathway is essential to the organ development, and its deregulation has been identified in a wide variety of tumors. Further, a transcription coactivator Yorkie has been demonstrated to be stabilized by USP7 in hepatocellular carcinoma (HCC) cells; interestingly, this protein is the upstream of the Hippo signaling[107]. Taken together, USP7, which regulates Hippo pathway, could bea potential therapeutic target for HCC. In addition, the nuclear factor kappa light chain enhancer of activated B cells (NF-κB) signal transduction pathway has been described previously to participate in the development and dysfunction of the immune system. Most of the proteins in this pathway are known to regulate biological processes, such as innate and adaptive immunity, inflammation, and stress responses. USP7 stabilizes NF-κB signaling and increases its transcription, leading to the expression of downstream genes in response to the immune system activation[127].

Table 2. Signaling pathway regulated by USP7

Signaling pathway	Ref	Signaling pathway	Ref
p300-p53/p21 pathway	[128]	BCR-ABL signaling	[38]
EZH2-CCF-cGAS signaling	[129]	MDM2/MDMX-p53 pathway	[130]
FBP1-DNMT1 pathway	[131]	NEDD4L-SMAD pathway	[132]
Cell cycle and EMT pathway	[133]	JMJD3/CLU signaling	[81]
p53/TfR1 pathway	[134]	Wnt/β-catenin signaling	[39]
PI3K/Akt pathway	[124]	Hippo pathway	[107]
Akt/ERK signaling	[135]	NF-κB signaling	[136]
AMPK pathway	[124]	Shh pathway	[16]
NOX4/NLRP3 pathway	[137]	Glucose Metabolism signaling	[138]
So×9-PTHrP-PTH1R axis	[58]	Insulin/IGF-1-like signaling	[88]
HIF-1α signaling pathway	[139]	Hedgehog signaling	[140]
Shoc2-ERK1/2 pathway	[141]	p53-MDM2 pathway	[21]

6. USP7 and diseases

6.1. The roles of USP7 in viral infection and inflammation

Interferon (IFN) is a low molecular glycoprotein induced by virus, bacteria, and IFN inducers acting on cells. IFN is not toxic to the cell itself, but it inhibits the replication of a variety of viruses and possesses antitumor activity[142].

In general, IFN can be divided into three types: (1) type I IFN, including IFN-α (20 subtypes) and IFN-β (1 subtype), which are produced mainly by white blood cells, fibroblasts, and virus-infected tissue cells; (2) type II IFN, including IFN-γ, and it has only one subtype, which is produced by activated T cells and NK cells; and (3) type III IFN, including IFN-γ1, IFN-γ2, and IFN-γ3. The main functions of type I IFN are inhibiting viral replication, providing resistance to parasitic infection, inhibiting cell proliferation, stimulating immune cells, eliciting antitumor activity, and regulating immunomodulatory system. Meanwhile, type II IFN possesses antiviral and anti-proliferation activities, and its main function is in immune regulation[143,144]. For example, in response to virus invasion, the body produces IFN, and the process is mediated by several factors. USP7 has been reported previously as an important negative modulator of virus-induced signaling, where USP7 interacts with the E3 Ub ligase tripartite motif 27 (TRIM27), and their interaction is further enhanced after virus invasion. In addition, it has been reported that TNF receptor-associated factor family member-associated NF-κB binding kinase (TBK)-1, which phosphorylates IFN regulatory factor (IRF)-3 and IRF-7, promotes the nuclear translocation and induces the expression of antiviral products[145,146]. Interestingly, TBK-1 is degraded through the UPP, which is mediated by TRIM27. More remarkably, USP7 decreases TBK-1 expression and inhibits IFN antiviral efficacy by stabilizing TRIM27 protein[126]. In another example, the suppressor of cytokine signaling 1 is a negative regulator of IFN-induced gene expression, which inhibits IFN antiviral efficacy by interacting with USP7 through its deubiquitinase activity[54,147,148]. In addition, the p53 protein has been identified as a positive regulator in response to virus infection[149]. Kaposoi's sarcoma-associated herpesvirus (KSHV)-encoded viral interferon regulatory factor 4 (vIRF4), is one of the KSHV protein which interacts with USP7 and suppresses its enzyme activity, resulting in p53 degradation. Further studies have identified that vIRF4 stabilizes HDM2 by inhibiting its autoubiquitination process, and destabilizes p53[97,150]. The above findings suggest the crucial role of USP7 in antiviral response; therefore, USP7 can be treated as a potential target for antiviral therapy. However, USP7 also plays an important role in homeostasis of normal cells; therefore, these factors should be considered when using USP7 inhibitors.

6.2. USP7 in diabetic foot

Diabetes mellitus (DM) is a common disease that happens worldwide. Blood vessel disorders are frequently seen in patients with DM, and it is commonly associated with diabetic foot, one of the most common complications of a diabetic patients. However, at present, there is no effective treatment for diabetic foot. USP7 expression is found to be upregulated in human umbilical vein endothelial cells (HUVECs), when advanced glycation end products are used to establish the diabetic cell model[151]. Inhibition of USP7 was shown to attenuate HUVECs cell cycle arrest and cell senescence. It has been further noted that the mechanism is regulated by USP7, which promotes cycle arrest and senescence of HUVECs cells by regulating the level of p53 polyubiquitination. The downregulation of p53 can reverse USP7-mediated HUVECs cell cycle arrest and cell senescence. Treatment of diabetic rat models with USP7 inhibitors can relieve the symptoms of diabetic foot. In conclusion, inhibition of USP7 induces p53 protein degradation and alleviates the symptoms of diabetic foot. These results showed that USP7 is a potential target for the treatment of diabetic foot ulcers.

6.3. USP7 in pulmonary hypertension

Pulmonary hypertension is a hemodynamic and pathophysiological condition in which the pulmonary artery pressure increases beyond a certain threshold. Pulmonary hypertension can be a group of independent diseases, complications, or syndromes. Pulmonary hypertension can be caused by the changes in the pulmonary artery itself, while others factors which can contribute to the development of this disease include genetic factors, drugs, toxins, and other diseases, such as congenital heart disease[152,153].

Recent work has uncovered the role of USP7 in the development of pulmonary hypertension[154]. Abnormal hyperplasia of pulmonary smooth muscle cells (PASMCs) is an important pathological feature of pulmonary hypertension, and platelet-derived growth factor (PDGF)-induced PASMCs proliferation is a critical factor in the development of pulmonary hypertension. Studies have revealed that PDGF increases the protein expression of USP7 and its downstream MDM2 and cyclinD1, resulting in the induction of PASMCs proliferation. In addition, downregulation of USP7 can attenuate PDGF-induced MDM2, cyclinD1 stabilization, and cell proliferation. On the other hand, MG132 treatment can also abolish PDGF-induced cyclinD1 elevation and cell proliferation. In short, inhibition of USP7 activity might be a potential therapeutic strategy for the treatment of pulmonary hypertension. Notably, USP7 inhibits tumor progression in p53-deficient lung cancer cells, and USP7 maintains homeostasis in normal cells. Therefore, other factors should be considered when USP7 inhibitors are used for pulmonary hypertension.

6.4. USP7 in cancers

Among the diseases, cancers are the most intensively investigated research area in terms of USP7. USP7 is highly overexpressed in most tumors, such as breast cancer, medulloblastoma, T-cell leukemia, ovarian cancer, HCC, MM, prostate cancer, and CML[15-17,20,23,38,107], suggesting the role of USP7 in tumor promotion. Relative protein expression in Figure 1 shows USP7 expression in several cancers[155].

USP7 is overexpressed in human breast cancer, and its expression is positively correlated with its substrate protein, PHF8. USP7 decreases the polyubiquitination of PHF8 and increases the expression of cyclin A2 protein, which is an essential and important protein for the development of breast cancer[15]. Estrogen receptor α (ERα) is reported to be overexpressed in about 70% breast tumors. Studies have identified the positive correlation between ERα and USP7, depending on the deubiquitinase activity of USP7 and their interactions, where USP7 silencing led to cell growth inhibition and delayed tumor growth[106]. In addition, USP7 has also been proven to be associated with poor prognosis of breast cancer, suggesting USP7 as a potential target for clinical treatment. Further, USP7 acts as a DUB of p53; therefore, the negative effects of p53 protein degradation should be considered when using USP7 inhibitors for breast cancer treatment.

Prostate cancer is a form of cancer that develops in the prostate, and is considered a slow-growing tumor. The incidence of prostate cancer is increasing by 2–3% every year, with more than 10% of death in male[156]. As a histone methylase, EZH2 plays an important role in the development of diverse tumor, including prostate cancer. Studies identified that the deubiquitinase USP7 is highly expressed in prostate cancer, and more importantly, USP7 interacts with EZH2 and increases its protein stabilization through its deubiquitinating activity. In contrast, a reduction in USP7 expression fails to rescue the degradation of EZH2 through the UPP, resulting in the inhibition of cell growth and the suppression of tumor progression[23]. Consistent with previous reports, USP7-specific inhibitors in combination with PARP inhibitor can produce a more lethal effect on prostate cancer cells, suggesting USP7 as a promising therapeutic target for prostate cancer.

HCC is one of the most common malignancies in China, and its incidence is ranked the third highest across the country[157]. Studies have identified that USP7 is frequently overexpressed in HCC tissues, and positively correlated with poor prognosis, indicating UPP's role in the development of HCC[158]. In addition, recent studies have demonstrated that USP7 promotes the proliferation, invasion, and migration of HCC cells through activating the bcl-2-like protein 4 (Bax), which subsequently

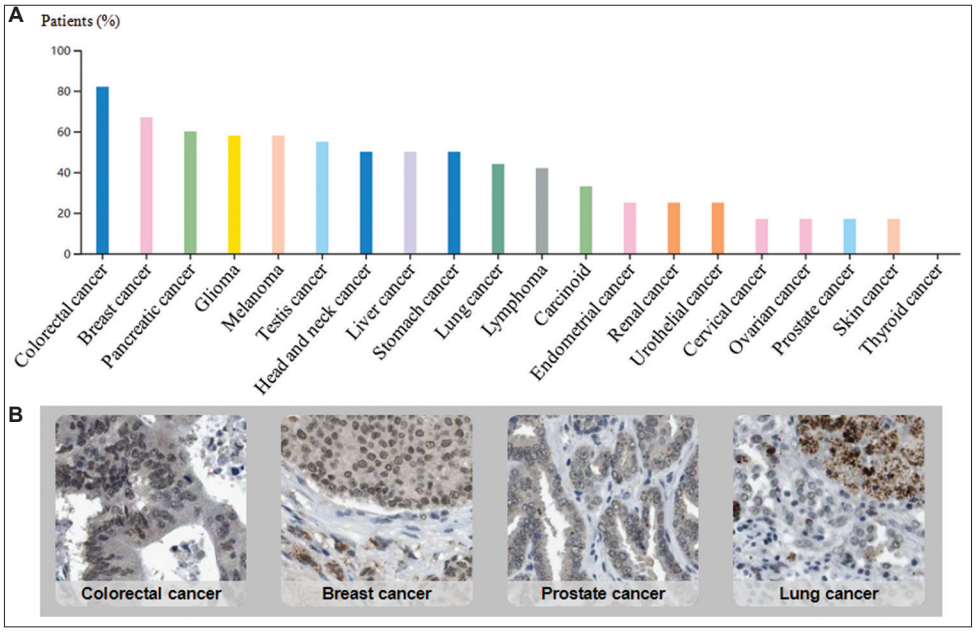


Figure 1. USP7 is highly expressed in cancer. (A) USP7 expression analysis of TCGA samples from The Human Protein Atlas database. Image reproduced from USP7 Protein Expression Summary; Malignant cells showed weak to moderate nuclear and cytoplasmic immunoreactivity (antibody CAB008108); available from https://www.proteinatlas.org/ENSG00000187555-USP7/pathology (image credit: The Human Protein Atlas). (B) Immunohistochemical staining of USP7 in representative tumors via the Human Protein Atlas (HPA) database. USP7 is highly expressed in a variety of tumors, including colorectal cancer, breast cancer, prostate cancer, and lung cancer. Image reproduced from USP7 Protein Expression; available from https://www.proteinatlas.org/ENSG00000187555-USP7/pathology (image credit: The Human Protein Atlas).

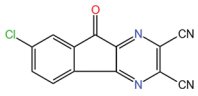
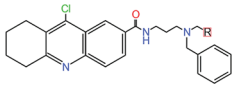
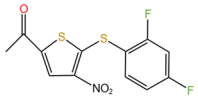
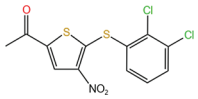
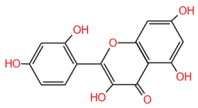
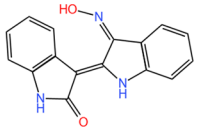
induces tumorigenesis and chemoresistance[159]. On the other hand, USP7 stabilizes thyroid hormone receptor-interacting protein 12, which subsequently induces the polyubiquitination of p14(ARF), inactivate p14(ARF), and lastly promotes HCC progression[160]. The above studies corroborate USP7 as the novel potential therapeutic target for HCC treatment.

Hematological malignancies are usually caused by uncontrolled cell proliferation. MM is a cancer of blood plasma cells with high incidence and mortality rates, and currently there is no effective treatment strategy. MafB/c-Maf are highly expressed in several myeloma cell lines, such as RPMI-8226 and LP1, and they are critical transcription factors in myelomagenesis, promoting the cell growth, proliferation, metastasis, and cell cycle progression[161]. USP7 has been shown to participate in MM progression by increasing the stabilization of MafB/c-Maf proteins. In addition, CML is a clonal malignancy of hematopoietic stem cells, featured with fusion protein kinase BCR-ABL. It has been demonstrated that deubiquitinase USP7 binds to BCR-ABL and reduces its polyubiquitination, thereby protecting it from degradation and inducing CML cell proliferation[38]. Therefore, inhibition of USP7 kinase activity could serve as a potential clinical treatment strategy for hematological disease.

7. Development of USP7-specific inhibitors

Given the diverse roles of USP7 in various diseases, USP7 has been widely believed to be an ideal therapeutic target, and many inhibitors against USP7 have been developed. The structural characteristic of USP7 has been described earlier in this article. The TRAF-like domain of USP7 is important for substrate binding. According to the role of TRAF domain in USP7, researchers have found the first inhibitor of USP7 through high-throughput screening (Table 3). Studies have revealed that HBX41108 disrupts the interaction between USP7 and HDM2, which inhibits USP7 deubiquitinating activity and fails to stabilize HDM2 protein, thereby inducing p53 accumulation and resulting in cell cycle arrest and apoptosis in tumor cells[162]. Since USP7 belongs to the Cys protease family, which are highly conserved in terms of the structural composition, such as USP5, USP8, USP10 and CYLD, it has been demonstrated that both of their activity can be inhibited by HBX41108[163,164], suggesting that the inhibition effect of HBX41108 on USP7 activity is not specific enough and further research is needed.

Table 3. The chemical structure of USP7 inhibitors, their validated targets, their effect on cell level and tumor model growth

Name	Structural formula	Validated targets	Functional consequence	*In vitro* cell suppression	Ref
HBX 41108		↓MDM2↑p53; p21	Cell cycle arrest Apotosis	Colon cancer cells	[162]
HBX 19818		↓MDM2↑p53; p21	Cell cycle arrest Apoptosis Growth inhibition	Colon cancer cells	[164]
P22077		↓MDM2; claspin; Pchk1; DDB1; TIP60↑p53; p21; Cle-Caspase-3	Growth inhibition Apotosis	Colon cancer cells; Neuroblastoma cells; Hepatocellular cells; Lung cancer cells	[67,159,165-167]
P5091		↓MDM2; MDMX; MafB; c-Maf; BCR-ABL; EZH2↑p53; p21	Cell cycle arrest Apotosis Autophagy growth inhibition	Colon cancer cells; Neuroblastoma cells; Hepatocellular cells; Glioblastoma cells; Prostate cancer cells; Ovarian cancer cells Multiple myeloma cells	[18,20,52,161,168]
Morin		↓ Prickle1, mTORC2	Cell migration inhibition	Rheumatoid arthritis cells	[169]
I3MO		↓ NEK2, PA28γ, PA200 NF-κB signaling	Apotosis DNA damage Cell cycle arrest	Multiple myeloma cells	[170]

In addition, CD plays a key role in cleaving polyubiquitin chains, especially the Cys223 residue, which is essential for the deubiquitinase activity of USP7. Using biochemical assays and activity-based protein profiling in living systems, HBX19818 and HBX28258 were found to be catalytic activity inhibitors of USP7, which can selectively inhibit the USP7 deubiquitinase activity by binding to its catalytic active site[165] (Table 3). In addition, these two compounds have a higher selectivity to USP7, and have been shown to decrease its downstream proteins, leading to cell cycle arrest and growth inhibition in several tumor cells[164].

Two new compounds, P22077 and P5091, which were discovered through a high-throughput screen, have been shown to selectively inhibit USP7 activity[161,165]. P22077 can activate p53 and its downstream protein p21 in human colon carcinoma cells. Further studies found that P22077 stabilizes p53 by inducing the degradation of HDM2[57].

P5091, the most recognized inhibitor against USP7 activity, has been identified to induce MM cell apoptosis and inhibit xenograft tumor growth. Mechanistically, P5091 leads to the decrease of HDM2, and subsequently stabilizes p53 and p21 in tumor cells by inhibiting USP7 activity. Interestingly, when MM cell line KMS11 was treated with P5091, there was no obvious increase of p53, suggesting that p53 is dispensable for the cytotoxicity of P5091[57]. It's worth pointing out that P5091 shows high specificity without affecting other protease activity, except for USP7[161]. These findings suggest that the USP7 inhibitors have potential value in clinical therapy.

Recent studies have found that Morin (3, 5, 7, 2', 4'-pentahydroxyflavone), an anti-arthritis compound that is present in foods of plant origin, suppresses the pathological migration of fibroblast-like synoviocytes, and prevents focal adhesion turnover[169]. A molecular operating environment software has been used to show that Morin could bind closely to His461, Met292, and Phe409 amino acid residues in the CD of USP7 through hydrogen bonds, thus hindering the rotation of the Phe409 side chain and subsequently inhibiting the binding of USP7 and substrate Ub. Further, USP7 protects Prickle1 from degradation, and this process can be reversed by Morin to block FLS migration.

Furthermore, indirubin-3'-monoxime (I3MO), is one of the derivatives of indirubin. The previous study has reported that the anti-MM activity of I3MO in both drug-sensitive and drug-resistant MM cells by sensitizing MM cells to bortezomib-induced apoptosis[170]. In return, I3MO suppresses the growth of MM cells via down-regulating the USP7 expression, inducing NEK2 degradation, and suppressing NF-κB signaling in MM.

In summary, exploring the potential inhibitors against USP7 can provide a novel therapeutic strategy in tumor treatment.

8. Conclusions

Ubiquitination and deubiquitination are two opposite biological processes, which work together to regulate the post-translational modification of proteins. Various biological functions of USP7 have been discovered, including its role as a vital regulator of transcription[20], nuclear export[10], inflammatory responses[57], DNA damage repair[11], antiviral responses[54], and induction of cell apoptosis[20,171]. Furthermore, USP7 is considered a cancer-promoting protein in a variety of tumors, including lung cancer, prostate cancer, HCC, as well MM. The progression of all the above diseases can be related to the substrate proteins of USP7. USP7 binds to its substrates and stabilizes their proteins or maintains their activity, thereby inducing abnormal cell proliferation and tumor development. Moreover, studies have uncovered that USP7 interacts with HDM2, which is a critical negative regulator of p53, to stabilize its protein level[24]. Contrary to the oncogenic role of USP7, several studies have found that it has dual function in cancer development. For example, in colon carcinoma, USP7 inhibits cell proliferation *in vitro* and tumor growth *in vivo* in the presence of stress due to the constitutive expression level of p53 protein[172]. Therefore, further studies are required to better understand the role of USP7 in tumors. More remarkably, in recent years, accumulating research has focused on designing small molecule inhibitors of USP7, mainly based on its physical structure or enzyme activity, to provide potential strategies for cancer treatment. However, the premise is we need to fully understand the role or mechanism of USP7 in tumor development, since USP7 stabilizes p53 and its function is unclear in the presence of stress or radiation damage[172]. The diversity of USP7 substrates determines the complexity of its function in different diseases and tumors, and the complications of diseases bring new challenges for USP7 as a target in cancer therapy. Therefore, further investigation is required to evaluate the benefits and adverse effects of inhibiting the enzymatic activity of USP7. In addition, with the emergence of new molecular tools and in-depth exploration of USP7 substrates and different strategies to modulate USP7 activity, the therapeutic potential of USP7 in diseases will be further evaluated.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Xinliang Mao
Supervision: Xinliang Mao
Writing – original draft: Yuanming He, Yueya Zhong
Writing – review & editing: Yuanming He, Yiqian Wang, Xinliang Mao

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