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Review Article

Pathological role of deubiquitinating enzymes in lung cancer: recent insights and advances

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Abstract: Lung cancer remains the leading cause of cancer-related death worldwide. Following extensive investigations into the mechanisms of lung cancer and targeted therapy, clinical treatment options are now more abundant than ever. However, the overall rates of treatment success and long-term survival remain low among patients with lung cancer, and the prognosis is even poorer for patients with metastatic disease. In this context, a more comprehensive review of the targeted regulatory mechanisms involved in the occurrence and progression of lung cancer could expand the population of patients benefiting from existing clinical treatments and ultimately improve the prognosis of this malignancy. Deubiquitinating enzymes (DUBs) are a specialized class of cellular proteases. These enzymes cleave ubiquitin moieties from substrate proteins or ubiquitin chains, thereby modulating ubiquitination dynamics. Through this catalytic process, DUBs maintain the dynamic balance of ubiquitination within cells. In recent years, accumulating evidence has demonstrated that DUBs serve diverse regulatory functions in multiple molecular events associated with tumorigenesis and malignant progression. Rather than acting through a single mechanism, DUBs participate in tumor progression through multifaceted pathways. In this comprehensive review, we systematically summarize the recent advances in our understanding of the biological functions of DUBs during the pathogenesis and progression of lung cancer. We highlight the mechanistic roles of various DUBs in tumor initiation, development, and metastasis. The topics covered include the regulation of cancer-associated signaling pathways by DUBs, their role in metabolic reprogramming, the DUB-induced modulation of tumor immune responses, the control of cell cycle progression and proliferation by DUBs, as well as other fundamental cellular processes modulated by these enzymes. In addition, we clarify the pathological mechanisms linking DUBs with lung cancer, including upstream regulators and the corresponding downstream molecular signals. Furthermore, we assess the therapeutic potential of these DUBs as candidate therapeutic targets and mediators of drug resistance. This synthesis of the literature provides a strategic framework for identifying clinically relevant DUB targets in lung cancer.

Keywords: Lung cancer, deubiquitinating enzymes (DUBs), molecular mechanisms, targeted therapy, immunotherapy

Introduction

Lung cancer is the most lethal human malignancy worldwide and has one of the highest incidence rates of all cancers. It is estimated that there are 2 million new cases of lung cancer each year and 1.76 million related deaths [1-4]. According to tumor histology, lung cancer can be broadly classified into two types: small cell lung cancer (SCLC) and non-small cell lung

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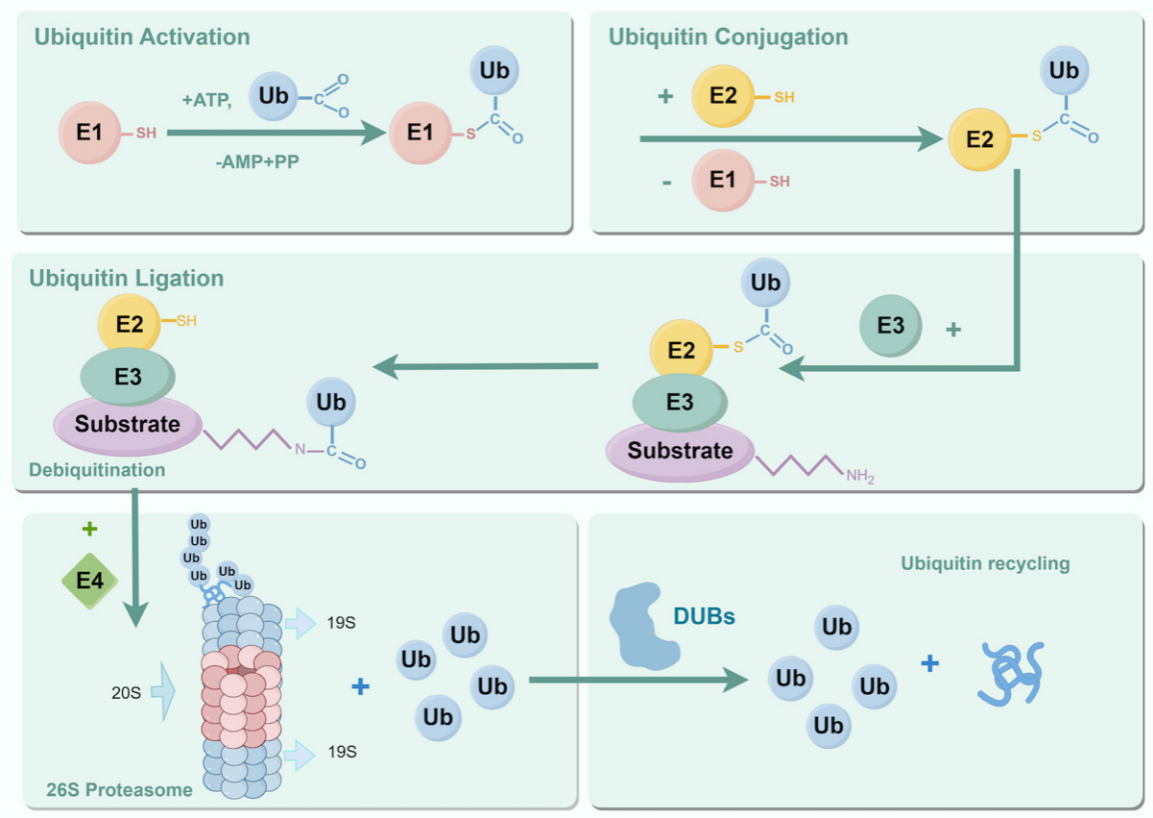


Figure 1. The ubiquitination-deubiquitination cycle. Key components include: the ubiquitin-activating enzyme (E1), the ubiquitin-conjugating enzyme (E2), the ubiquitin-protein ligase (E3), and ubiquitin (Ub). The cycle begins with the activation of ubiquitin, wherein the E1 enzyme utilizes energy derived from ATP to activate the C-terminal carboxyl group of ubiquitin, forming a covalent thioester bond at its active-site cysteine residue. Subsequently, ubiquitin is transferred from E1 to E2 through trans-thioesterification, establishing a new thioester linkage. Ultimately, E3 either facilitates or directly catalyzes the transfer of ubiquitin from E2 to substrate proteins.

cancer (NSCLC). Of these, NSCLC is the most common subtype, accounting for 85% to 90% of all lung cancer cases. There are multiple histological subtypes of NSCLC, including lung adenocarcinoma (LUAD), lung squamous cell carcinoma, and large cell lung cancer [5, 6]. Although the clinical outcomes of early-stage lung cancer can improve significantly following surgical resection or radical radiotherapy, a large proportion of patients eventually experience local or distant recurrence and fail to achieve long-term disease control [3, 7]. Therefore, breakthrough advances are urgently needed in the field of lung cancer treatment. In particular, there is a need to develop innovative treatment strategies, develop new targeted drugs, and obtain a systematic understanding of the molecular mechanisms underlying rapid drug resistance in tumors.

Ubiquitination is a key post-translational modification that involves the covalent attachment of ubiquitin (Ub) to target proteins through an enzymatic cascade, while deubiquitination involves the enzymatic removal of these Ub moieties. Both ubiquitination and deubiquitination are critical cellular processes in eukaryotes and dynamically regulate the stability and functional activity of proteins. The ubiquitination process is executed by the coordinated activity of three classes of enzymes working in concert: E1 ubiquitin-activating enzymes, E2 ubiquitin-conjugating enzymes, and E3 ubiquitin ligases [6, 8, 9]. Meanwhile, the cleavage of Ub moieties from ubiquitinated substrates is catalyzed by DUBs [10]. Notably, the ubiquitination and deubiquitination together influence substrate degradation in eukaryotic cells, with the ubiquitin-proteasome system mediating more than 80% of intracellular protein turnover (**Figure 1**) [11-13]. This Ub-mediated control of protein expression is essential for maintaining a wide range of cellular processes, including cell cycle progression, transcriptional

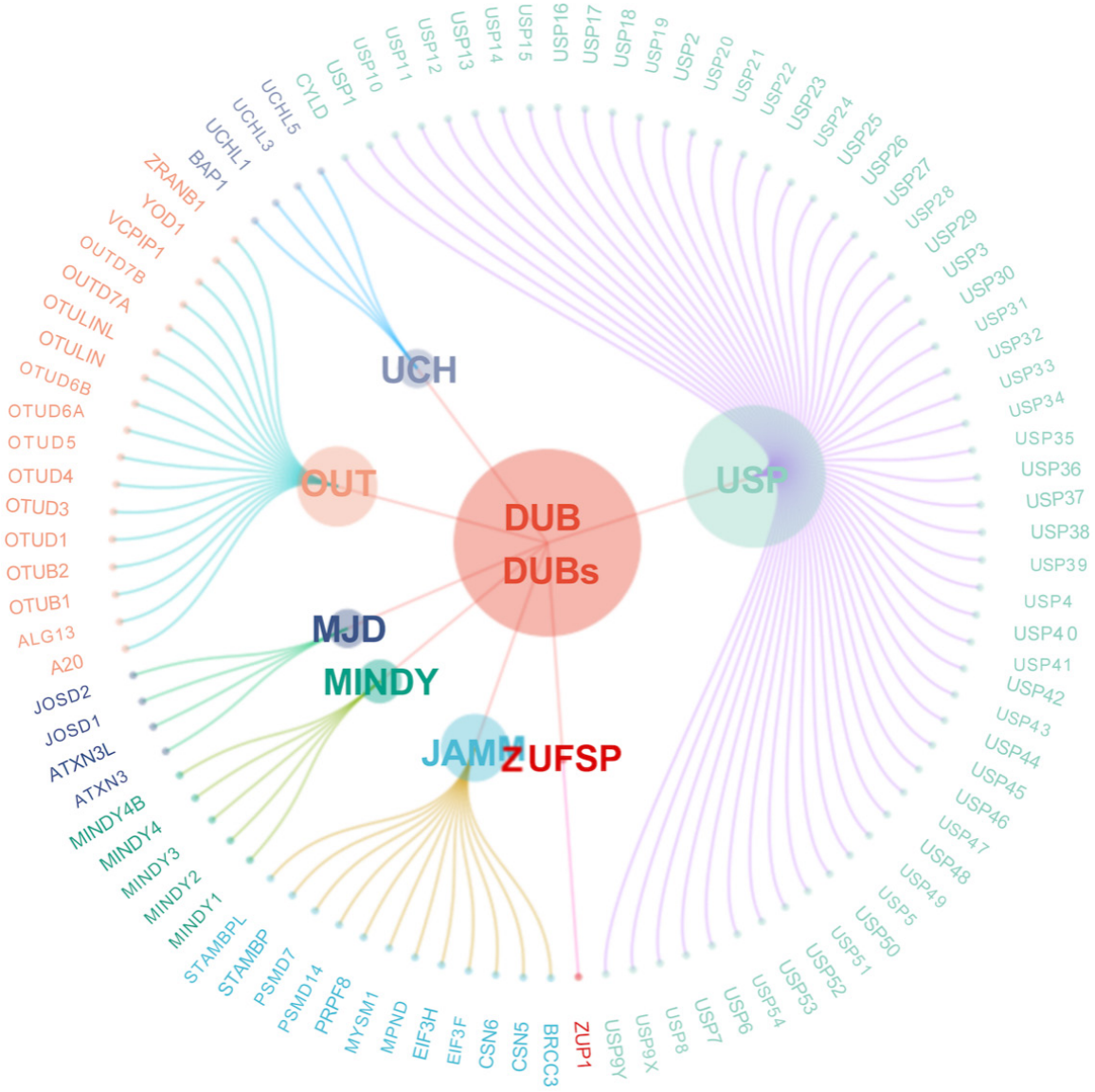


Figure 2. Members of the DUB family. The DUB family comprises diverse members categorized into seven specialized subfamilies.

regulation, signal transduction, and programmed cell death. By precisely orchestrating the degradation of specific protein substrates, the ubiquitin system enables cells to respond rapidly to both intrinsic and extrinsic stimuli [13, 14]. Therefore, the ubiquitin system has been implicated in the pathogenesis of various diseases, including cancer. Interestingly, emerging evidence from recent cancer studies has unequivocally established the pivotal role of deubiquitinating enzymes (DUBs) in human cancer development [15, 16].

Through extensive research, nearly 100 DUBs have been identified so far (**Figure 2**) [17]. These DUBs can be classified into seven subfamilies: ubiquitin-specific proteases (USPs), ovarian tumor domain-containing proteases (OTUs), ubiquitin C-terminal hydrolases (UCHs), Machado-Joseph disease domain proteases (MJDs), JAB1/MPN/MOV34 metalloproteases (JAMMs), motif interacting with ubiquitin-containing novel DUB family (MINDYs), and zinc finger with UFM1-specific peptidase domain proteins (ZUFSPs) [18-20].

USPs and lung cancer

The USP family represents the largest group of identified DUBs. It is characterized by a catalytic domain with a length of 300 to 800 amino acids [21-23]. Although the catalytic domains

Table 1. The list of USPs involved in lung cancers

DUBs	Upstream Regulatory Events	Substrate(s)	Detailed mechanisms	Biological Effects On LC	Ref.
USP5	Not mentioned	HDAC1	USP5-dependent HDAC1 facilitates cisplatin resistance and aggressive progression in non-small cell lung cancer through modulation of RILP acetylation.	+	[13]
	Not mentioned	mTOR	USP5 drives lung cancer progression via the mTOR pathway and functional interplay with PARP1.	+	[27]
	EOAI	P53	By inducing DNA damage, USP5 transcriptionally activates p53, leading to elevated apoptosis, autophagy, and cell cycle arrest.	-	[26]
	ROS	Becline 1	USP5 or Beclin 1 inhibition triggers senescence and autophagy suppression, markedly impairing KRAS-driven lung tumorigenesis.	+	[19]
	Not mentioned	PD-L1	USP5 facilitates lung tumor progression through modulation of PD-L1 protein stability.	+	[29]
USP7	p38 MAPK	TAM PD-L1+PD1	USP7 mediates tumor suppression through downregulation of immunoregulatory factors PD-L1, Tim-3 and TGF-β.	-	[33]
	Not mentioned	c-Abl k48	USP7 induces NSCLC proliferation and survival by increasing cytoplasmic c-Abl accumulation and promoting glycolysis in NSCLC cells.	+	[35]
	Not mentioned	SMAD3	USP7-mediated SMAD3 autoregulation inhibits tumor progression	-	[37]
	Not mentioned	ERβ	USP7 stabilizes ERβ to reduce oxidative stress and drive osimertinib resistance.	+	[36]
	Not mentioned	KRAS	USP7 drives NSCLC progression through KRAS deubiquitination at K147, eliminating K48-linked polyubiquitin chains.	+	[34]
USP8	Not mentioned	PTK7	USP8-mediated stabilization of PTK7 promotes cellular proliferation, invasion, and macrophage M2 polarization in NSCLC.	+	[41]
	Not mentioned	MET	Targeted silencing of the deubiquitinase USP8 overcomes HGF-induced gefitinib resistance in EGFR-mutant lung adenocarcinoma.	+	[44]
	Not mentioned	MT1	USP8 promotes the proliferation of lung adenocarcinoma cells by deubiquitinating and stabilizing the MT1 receptor.	+	[40]
	LncRNA SNHG12+HuR	PD-L1	The long non-codi ng RNA SNHG12 promotes immune evasion in NSCLC by upregulating PD-L1 and USP8 expression.	+	[42]
USP32	Not mentioned	MET	USP32 silencing overcomes gefitinib resistance in EGFR mutation-positive lung adenocarcinoma by promoting MET degradation.	+	[44]
USP9X	Not mentioned	RIT1	Genetic knockout of USP9X prevents RIT1 deubiquitination, thereby promoting RIT1 proteasomal degradation and abolishing oncogenic phenotypes.	+	[46]
	Not mentioned	REV1	USP9X induces remodeling of the amino acid metabolic microenvironment by stabilizing REV1 expression, thereby promoting radiation resistance in lung cancer cells.	+	[11]

	Not mentioned	KDM4C	USP9X-mediated deubiquitination of KDM4C activates the TGF-β2/Smad signaling pathway, thereby promoting radiation resistance.	+	[48]
	Not mentioned	PYCR3	USP9X serves as a novel regulator of the proline biosynthesis pathway, influencing the growth and progression of lung cancer.	+	[47]
USP10	Not mentioned	KLE4	Elevated USP10 expression inhibits KLF4 degradation, resulting in reduced lung cancer cell growth and migration.	-	[53]
	Not mentioned	HDAC7	HDAC7, stabilized and activated by USP10, promotes NSCLC progression through the β-catenin-FGF18 signaling pathway.	+	[51]
	Not mentioned	EIF4G1	USP10 promotes NSCLC proliferation, migration, and invasion by upregulating EIF4G1 protein levels.	+	[52]
	TRIM25	PTEN	USP10 interacts with PTEN and inhibits NSCLC cell proliferation and migration by preventing K63-linked polyubiquitination of PTEN.	-	[54]
USP11	HK2, CD133	CD133	The interaction between HK2 and CD133 facilitates USP11 binding to CD133, which enhances the expression of murine cell renewal regulators, promotes SCLC stemness, and accelerates tumor growth.	+	[57]
	Not mentioned	NRF2	USP11 stabilizes NRF2 to regulate cell proliferation and ferroptosis.	+	[15]
	RanBPM	p21	RanBPM recruits the deubiquitinase USP11 to stabilize p21 through deubiquitination, thereby modulating DDR in NSCLC.	-	[61]
USP12	Not mentioned	RRM2	USP12 interacts with RRM2 and stabilizes it by directly cleaving its polyubiquitin chains, thereby positively regulating tumor growth.	+	[27]
	Circ-ADRM1	MMP14	Circ-ADRM1 recruits USP12 to inhibit MMP14 ubiquitination, thereby enhancing MMP14 protein stability and promoting LUAD cell proliferation, invasion, and migration.	+	[66]
	AKT-mTOR	PPM1B	USP12 inhibits lung tumor growth and NF-κB-dependent chemokine expression by deubiquitinating and stabilizing PPM1B.	-	[67]
USP13	KRAS	NFE2L2	USP13 promotes the transition from ferroptosis to autophagy by activating the NFE2L2-SQSTM1-KEAP1 axis and suppresses KRAS-mutant LUAD.	-	[73]
	Not mentioned	MYC	USP13 overexpression increase MYC protein levels in the early stages of club cell-derived tumor development, which contribute to LUSC progression.	+	[74]
	RREB1 2-Methoxyestradiol	β-catenin	USP13 removes K63-linked polyubiquitination of β-catenin and promotes β-catenin/TCF4 interaction, thereby suppressing metastasis and progression in RAS-mutant tumors.	-	[76]
	Not mentioned	FASN	USP13 promotes SCLC stemness and lipogenesis by inhibiting proteasome-dependent degradation of FASN.	+	[75]
USP14	Not mentioned	CERS1	CERS1 exerts inhibitory effects in NSCLC BM by interacting with USP14 and downregulating the PI3K/AKT/mTOR signaling pathway.	-	[81]

	Not mentioned	Acf7	USP14 plays a critical role in NSCLC migration by regulating Acf7 stability.	+	[84]
	Not mentioned	Not mentioned	Not mentioned.	+	[145]
	IR	NHEJ, HR	USP14 negatively regulates NHEJ and promotes HR, thereby reducing the ability of NSCLC cells to repair IR-induced DSBs and consequently enhancing radiosensitivity.	+	[82]
	Not mentioned	EGFR	USP14 silencing suppresses DDP resistance via the EGFR/PI3K/AKT signaling pathway.	+	[8]
	Not mentioned	ERStress, UPR, JNK	USP14 inhibition triggers autophagy in A549 cells via ER stress-mediated activation of the UPR.	+	[83]
USP15	Not mentioned	TRAF6-BECN1	USP15 negatively regulates lung cancer progression by inducing autophagy through the TRAF6-BECN1 signaling axis.	-	[87]
	Not mentioned	SRSF1	USP15 and USP4 promote lung cancer cell proliferation by modulating the alternative splicing of SRSF1.	+	[88]
	Not mentioned	MMP3, MMP9	USP15 knockdown suppresses the expression of MMP3 and MMP9 in NSCLC cells, thereby inhibiting NSCLC progression.	+	[89]
	ABHD11-AS1-SART3	CD44 RNA	The ABHD11-AS1-SART3 interaction enhances nuclear localization of USP15, regulates CD44 alternative splicing, and promotes lung tumorigenesis.	+	[90]
USP18	Not mentioned	ATG1, UCP1Protein	USP18 modulates lipid metabolism by regulating ATGL and UCP1 expression, thereby influencing carcinogenesis.	+	[92]
	Not mentioned	14-3-3ζ Protein	USP18 deficiency destabilizes 14-3-3ζ protein and suppresses lung cancer metastasis.	+	[94]
	Not mentioned	Shank1	USP18 stabilizes Shank1 expression through deubiquitination, consequently leading to paclitaxel resistance.	+	[95]
	Not mentioned	POU4F1	USP18 mediates migration, apoptosis, and ferroptosis in lung adenocarcinoma cells through the POU4F1/PRKAA2 axis.	+	[97]
USP22	LINC01426	SHH	LINC01426 promotes SHH protein deubiquitination by recruiting USP22, thereby activating the Hedgehog signaling pathway and accelerating LUAD progression.	+	[103]
	Not mentioned	MDM2	USP22 promotes gefitinib resistance and suppresses ferroptosis in NSCLC by deubiquitinating MDM2.	+	[100]
	Not mentioned	MYO1B, KDELR1	USP22 promotes invasive pseudopod formation in LUAD cells by stabilizing MYO1B and KDELR1 to activate the SRC signaling pathway.	+	[102]
	miR-30e-5p	Not mentioned	circFAT1(e2) knockdown reduces USP22 expression levels by sponging miR-30e-5p.	+	[106]
	AP2, c-Myc, SP1, ATF3	Not mentioned	USP22 expression is promoted by AP2 and c-Myc, while being transcriptionally repressed by SP1 and ATF3.	+	[99]
	Not mentioned	PD-L1, CSN5	USP22 interacts with CSN5 to deubiquitinate PD-L1 and inhibit its proteasomal degradation, thereby mediating immune evasion.	+	[162]
	Not mentioned	COL17A1	USP22 stabilizes and upregulates COL17A1 by enhancing its deubiquitination, thereby promoting cell growth, invasion, and migration while inhibiting apoptosis and ferroptosis.	+	[104]

	SP1	Not mentioned	USP7 inhibitors may reduce SP1 levels by enhancing β-catenin degradation, thereby relieving transcriptional repression of USP22 and upregulating its expression.	+	[105]
USP28	Not mentioned	SREBP2	USP28 regulates MVP-driven LSCC tumor growth by enhancing SREBP2 stability.	+	[107]
	Not mentioned	FOXK1	USP28-mediated deubiquitination of FOXK1 activates the Hippo signaling pathway, thereby regulating lung cancer cell proliferation and radiosensitivity.	+	[113]
	Not mentioned	c-MYC	USP28 deletion and small-molecule inhibition destabilize c-MYC and induce SCC regression.	+	[117]
	miR-143-3p	Not mentioned	LINC01426 upregulates USP28 expression by functioning as a ceRNA for miR-143-3p.	+	[112]
	Not mentioned	ΔNp63	Targeting USP28 may disrupt ΔNp63 stability, consequently affecting SCC cell proliferation.	+	[114]
	AZ1	c-MYC	Targeting USP28 promotes c-MYC degradation, leading to cell cycle arrest and impaired DNA repair.	+	[116]
USP35	FUS	VEGFA	FUS-stabilized USP35 promotes NSCLC growth, invasion, and angiogenesis by deubiquitinating VEGFA.	+	[121]
	Not mentioned	BIRC3	USP35 mediates cisplatin-induced apoptosis in NSCLC by stabilizing BIRC3.	-	[122]
	Not mentioned	RRBP1	USP35 alleviates ER stress-induced apoptosis by stabilizing RRBP1.	-	[123]
	Not mentioned	erastin/RSL FPN	USP35 knockdown promotes ferroptosis in lung cancer cells while inhibiting cell growth, colony formation, and tumor progression.	+	[118]
USP51	Not mentioned	PD-L1	USP51 promotes chemotherapy resistance through deubiquitination of PD-L1.	+	[126]
	CDK4/6	ZEB1	USP51 is phosphorylated and activated by CDK4/6, thereby stabilizing ZEB1 protein and promoting lung adenocarcinoma metastasis.	+	[127]
	Not mentioned	TWIST1	USP51 maintains stemness and promotes growth in NSCLC cells by deubiquitinating TWIST1.	+	[125]
	Not mentioned	γ - H2AX	USP51 promotes DNA repair by regulating γ-H2AX.	+	[128]
	Not mentioned	ZEB1	USP51 inhibition attenuates DDP resistance through ubiquitin-mediated degradation of ZEB1.	+	[129]
CYLD	Not mentioned	m 6 A	The downregulation of m6A reader YTHDC2 promotes malignant lung cell proliferation and migration through the CYLD/NF-κB pathway.	-	[135]
	Not mentioned	Not mentioned	In both PC-9 and PC-9/GR cell lines, altered CYLD expression modulates gefitinib-induced cellular proliferation, apoptosis, and TAE-associated inflammatory responses.	-	[131]
	miR - 587	Not mentioned	miR-587 functions as an oncogene in NSCLC by downregulating CYLD expression.	-	[134]
	Not mentioned	NF-κB	CYLD is expressed in dendritic cells and participates in immune regulation of lung adenocarcinoma through the NF-κB pathway.	-	[136]
	miR-135b	NF-κB	miR-135b directly targets the 3'-UTR of the deubiquitinase CYLD, thereby modulating ubiquitination and NF-κB signaling activation.	+	[133]

OTHERs					
USP4	Not mentioned	SRSF1	USP15 and USP4 promote lung cancer cell proliferation by modulating the alternative splicing of SRSF1.	+	[88]
	Not mentioned	Twist1	USP4 stabilizes Twist1 protein to promote stemness in lung cancer cells.	+	[139]
	Not mentioned	VEGF, MMP2, p53 Protein, EMT	USP4 promotes proliferation and metastasis in human lung adenocarcinoma.	+	[140]
USP1	Not mentioned	NK Cell	USP1 contributes to poor prognosis in SCLC by suppressing NK cell-mediated anti-tumor immune responses.	+	[137]
USP2	Not mentioned	p53 Protein	USP2 suppresses cisplatin resistance in NSCLC cells by stabilizing p53 protein through inhibition of its ubiquitination, thereby promoting ferroptosis.	-	[138]
USP19	Gastrodin	Not mentioned	Gastrodin induces apoptosis in NSCLC cells by disrupting the interaction between USP19 and Survivin Thr34.	-	[141]
USP25	Not mentioned	RNF31, KRAS G12mut	The oncogenic KRAS4B mutant promotes NSCLC progression through the interaction between deubiquitinase USP25 and RNF31.	+	[142]
USP41	Not mentioned	Not mentioned	USP41 knockdown promotes apoptosis in lung cancer cells.	+	[143]

+: promote; -: inhibit.

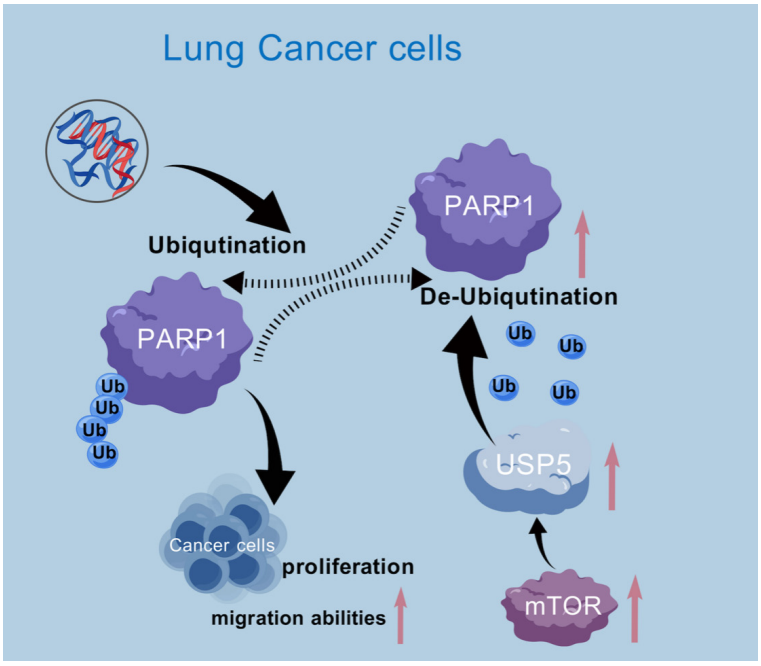
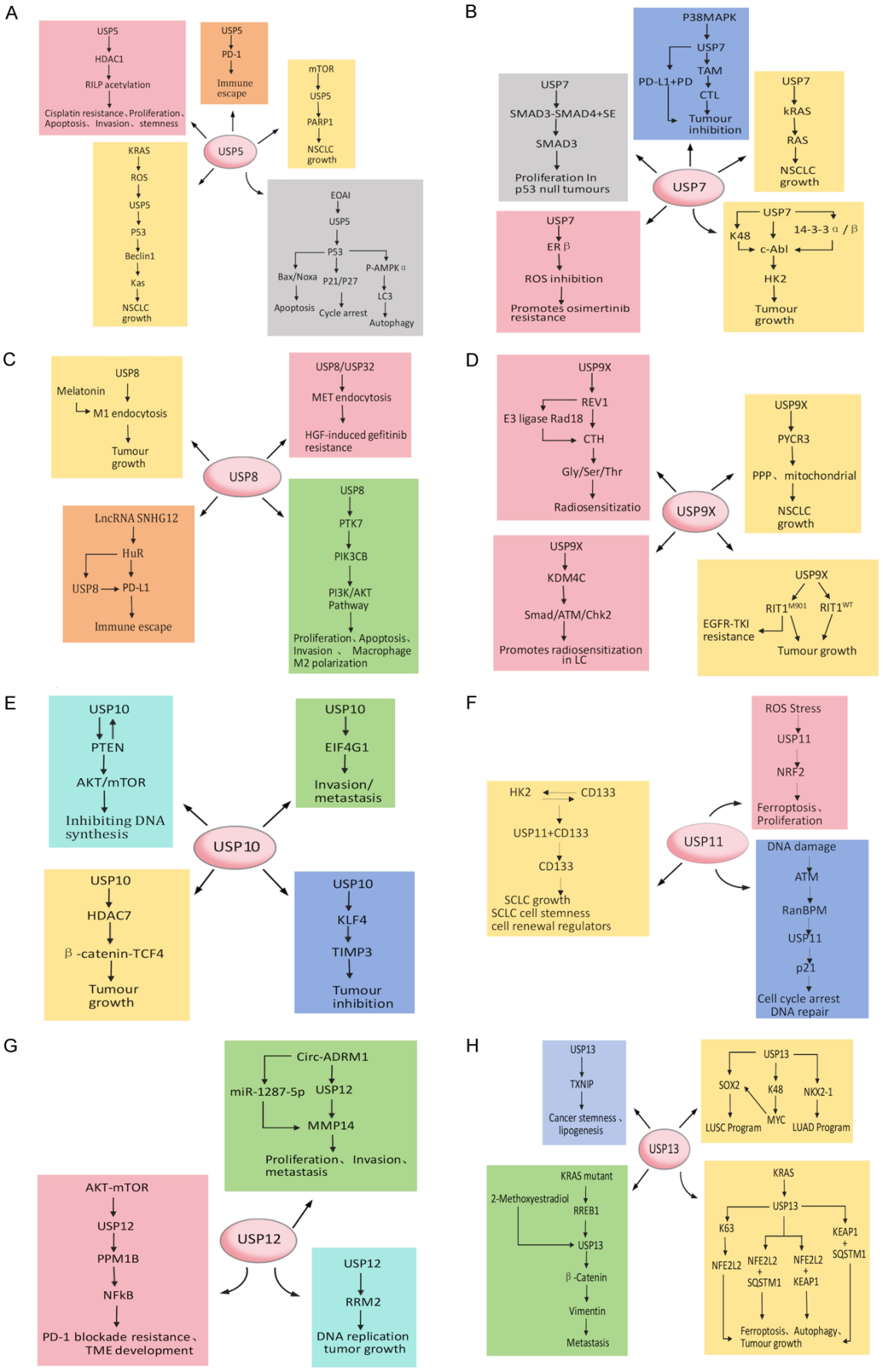


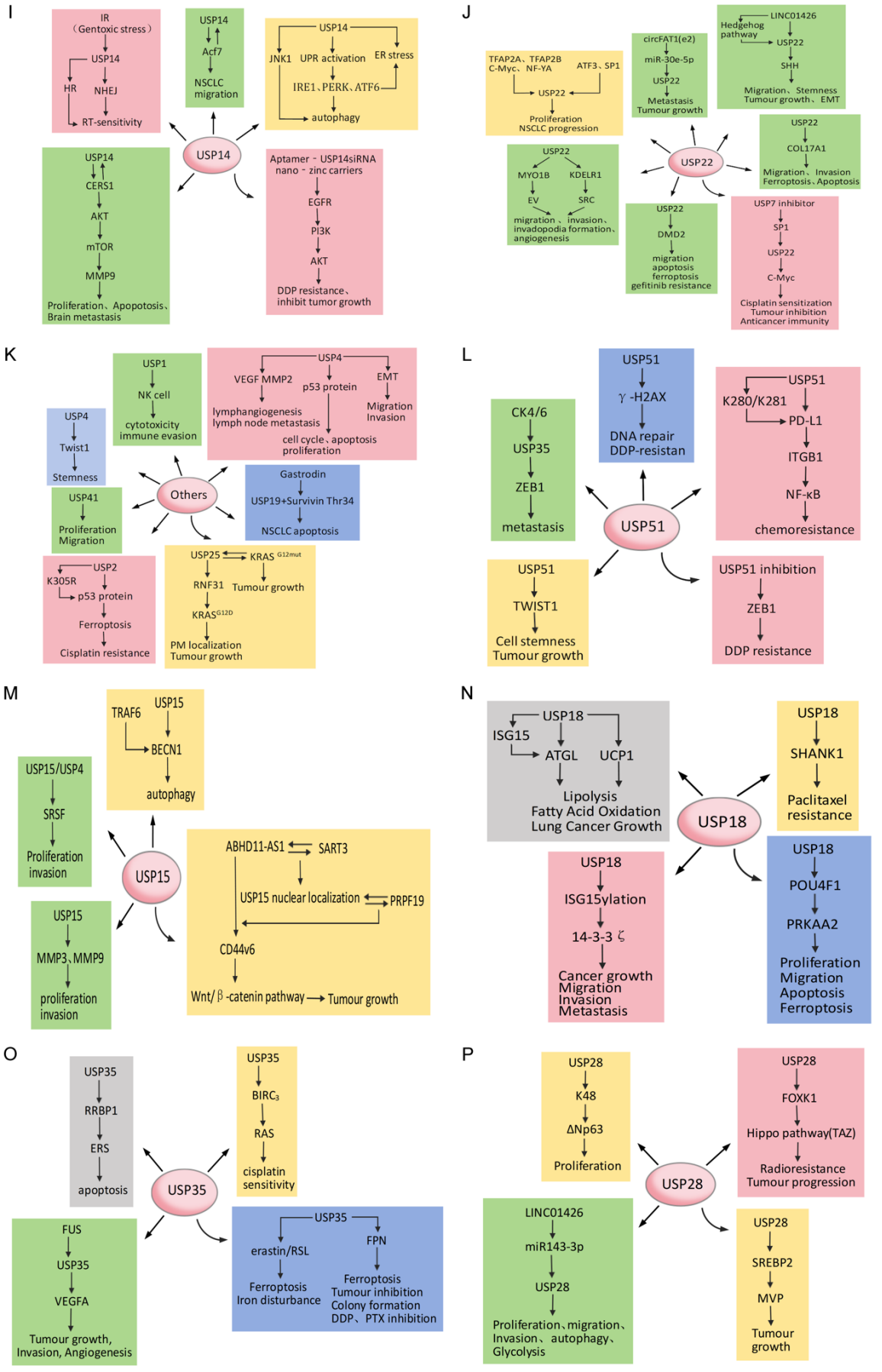
Figure 3. USP5 drives lung cancer progression via mTOR signaling and functional interaction with ARP1 (Created with BioGDP.com).

of different USPs differ in size and sequence, their distinctive palm-thumb-finger structural architecture remains highly conserved [18]. As members of the most extensively studied family of DUBs, more than 20 USPs (**Table 1**; **Figure 4**) play significant mechanistic roles in the pathogenesis of lung cancer. Thus, they show potential as targets for the clinical treatment of this disease.

Ubiquitin-specific protease 5

Ubiquitin-specific protease 5 (USP5), a cysteine-dependent deubiquitinase belonging to the USP family, is encoded by a gene located on chromosome 12p13. This 93.3-kDa protein contains five distinct structural domains and participates in various pathophysiological processes across different cancer types [11, 24]. USP5 exhibits unique specificity in recognizing and cleaving proximal Ub moieties from unanchored Ub chains [13]. Notably, numerous studies (**Figure 3**) [25] conducted in recent years have brought attention to USP5 as a focus in the field of DUB research, especially in the context of its role in lung can-


A
USP5
HDAC1
RILP acetylation
Cisplatin resistance、Proliferation、Apoptosis、Invasion、stemness
USP5
PD-1
Immune escape
mTOR
USP5
PARP1
NSCLC growth
KRAS
ROS
USP5
P53
Beclin1
Kas
NSCLC growth
USP5
EOAI
USP5
P53
Bax/Noxa
P21/P27
P-AMPK α
Apoptosis
Cycle arrest
LC3
Autophagy
B
P38MAPK
USP7
TAM
PD-L1+PD
CTL
Tumour inhibition
USP7
SMAD3-SMAD4+SE
SMAD3
Proliferation In p53 null tumours
USP7
kRAS
RAS
NSCLC growth
USP7
USP7
ER β
ROS inhibition
Promotes osimertinib resistance
USP7
K48
14-3-3 α / β
c-Abl
HK2
Tumour growth
C
USP8
Melatonin
M1 endocytosis
Tumour growth
USP8/USP32
MET endocytosis
HGF-induced gefitinib resistance
USP8
LncRNA SNHG12
HuR
USP8
PD-L1
Immune escape
USP8
PTK7
PIK3CB
PI3K/AKT Pathway
Proliferation、Apoptosis、Invasion 、 Macrophage M2 polarization
D
USP9X
REV1
E3 ligase Rad18
CTH
Gly/Ser/Thr
Radiosensitizatio
USP9X
USP9X
PYCR3
PPP、mitochondrial
NSCLC growth
USP9X
KDM4C
Smad/ATM/Chk2
Promotes radiosensitization in LC
USP9X
RIT1M901
RIT1WT
EGFR-TKI resistance
Tumour growth
E
USP10
PTEN
AKT/mTOR
Inhibiting DNA synthesis
USP10
EIF4G1
Invasion/ metastasis
USP10
HDAC7
β -catenin-TCF4
Tumour growth
USP10
KLF4
TIMP3
Tumour inhibition
F
ROS Stress
USP11
NRF2
Ferroptosis、Proliferation
HK2
CD133
USP11+CD133
CD133
SCLC growth
SCLC cell stemness
cell renewal regulators
USP11
DNA damage
ATM
RanBPM
USP11
p21
Cell cycle arrest
DNA repair
G
Circ-ADRM1
miR-1287-5p
USP12
MMP14
Proliferation、Invasion、metastasis
AKT-mTOR
USP12
PPM1B
NFkB
PD-1 blockade resistance、TME development
USP12
USP12
RRM2
DNA replication tumor growth
H
USP13
TXNIP
Cancer stemness、lipogenesis
USP13
SOX2
K48
NKX2-1
LUSC Program
MYC
LUAD Program
KRAS mutant
2-Methoxyestradiol
RREB1
USP13
β -Catenin
Vimentin
Metastasis
KRAS
USP13
K63
KEAP1 + SQSTM1
NFE2L2
NFE2L2 + SQSTM1
NFE2L2 + KEAP1
Ferroptosis、Autophagy、Tumour growth


I
IR (Gentoxic stress)
USP14
HR
NHEJ
RT-sensitivity
USP14
Acf7
NSCLC migration
USP14
JNK1
UPR activation
ER stress
IRE1、PERK、ATF6
autophagy
USP14
CERS1
AKT
mTOR
MMP9
Proliferation、Apopotosis、Brain metastasis
Aptamer - USP14siRNA nano - zinc carriers
EGFR
PI3K
AKT
DDP resistance、inhibit tumor growth
J
TFAP2A、TFAP2B C-Myc、NF-YA
ATF3、SP1
USP22
Proliferation NSCLC progression
circFAT1(e2)
miR-30e-5p
USP22
Metastasis Tumour growth
LINC01426
Hedgehog pathway
USP22
SHH
Migration、Stemness Tumour growth、EMT
USP22
USP22
COL17A1
Migration、Invasion Ferroptosis、Apoptosis
USP22
MYO1B
KDELR1
EV
SRC
migration、invasion、invadopodia formation、angiogenesis
USP22
DMD2
migration apoptosis ferroptosis gefitinib resistance
USP7 inhibitor
SP1
USP22
C-Myc
Cisplatin sensitization Tumour inhibition Anticancer immunity
K
USP1
NK cell
cytotoxicity immune evasion
USP4
VEGF MMP2
p53 protein
EMT
lymphangiogenesis lymph node metastasis
Migration Invasion
cell cycle、apoptosis proliferation
USP4
Twist1
Stemness
Others
Gastrodin
USP19+Survivin Thr34
NSCLC apoptosis
USP41
Proliferation Migration
USP2
K305R
p53 protein
Ferroptosis
Cisplatin resistance
USP25
KRAS G12mut
RNF31
Tumour growth
KRASG12D
PM localization Tumour growth
L
USP51
γ -H2AX
DNA repair DDP-resistan
CK4/6
USP35
ZEB1
metastasis
USP51
K280/K281
PD-L1
ITGB1
NF-κB
chemoresistance
USP51
USP51
TWIST1
Cell stemness Tumour growth
USP51 inhibition
ZEB1
DDP resistance
M
TRAF6
USP15
BECN1
autophagy
USP15/USP4
SRSF
Proliferation invasion
USP15
ABHD11-AS1
SART3
USP15 nuclear localization
PRPF19
CD44v6
Wnt/β-catenin pathway
Tumour growth
USP15
MMP3、MMP9
proliferation invasion
N
USP18
ISG15
ATGL
UCP1
Lipolysis Fatty Acid Oxidation Lung Cancer Growth
USP18
SHANK1
Paclitaxel resistance
USP18
USP18
ISG15ylation
14-3-3 ζ
Cancer growth Migration Invasion Metastasis
USP18
POU4F1
PRKAA2
Proliferation Migration Apoptosis Ferroptosis
O
USP35
RRBP1
ERS
apoptosis
USP35
BIRC3
RAS
cisplatin sensitivity
USP35
FUS
USP35
VEGFA
Tumour growth, Invasion, Angiogenesis
USP35
erastin/RSL
FPN
Ferroptosis Iron disturbance
Ferroptosis Tumour inhibition Colony formation DDP、PTX inhibition
P
USP28
K48
ΔNp63
Proliferation
USP28
FOXK1
Hippo pathway(TAZ)
Radioresistance Tumour progression
LINC01426
miR143-3p
USP28
Proliferation、migration、Invasion、autophagy、Glycolysis
USP28
SREBP2
MVP
Tumour growth

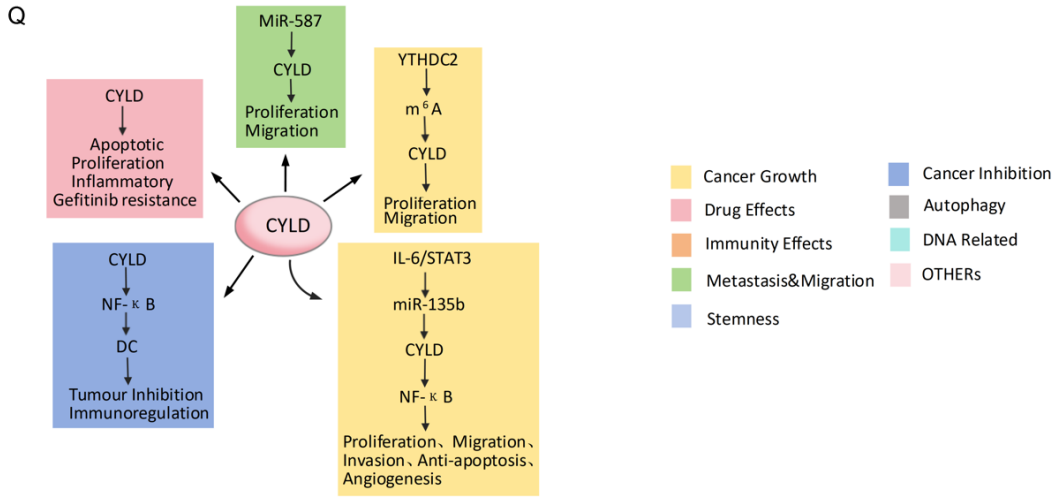


Figure 4. Summarizes the mechanistic pathways of DUBs implicated in lung cancer. The highlighted members of the USP family - including USP5 (A), USP7 (B), USP8 (C), USP9X (D), USP10 (E), USP11 (F), USP12 (G), USP13 (H), USP14 (I), USP22 (J), Others (K), USP51 (L), USP15 (M), USP18 (N), USP35 (O), USP28 (P), and CYLD (Q) - exhibit potential as novel therapeutic targets for lung cancer treatment.

cer. Specifically, USP5 has been implicated in cisplatin resistance, immune escape, apoptosis regulation, and autophagy regulation in this malignancy.

Recent studies indicate that both EOAI (a novel small-molecule inhibitor) and histone deacetylase 1 (HDAC1) functionally interact with cisplatin (DDP) to collectively regulate lung cancer progression through distinct molecular pathways [13, 26]. *In vivo* studies have shown that EOAI inhibits tumor growth and synergistically boosts the anti-cancer activity of DDP. Conversely, HDAC1 promotes NSCLC progression and confers NSCLC cells with chemoresistance to DDP. Mechanistically, EOAI inactivates USP5 by inducing DNA damage and activating the transcription factor p53, thereby triggering G2/M cell cycle arrest, apoptosis, and autophagy in lung cancer cells [26]. Lu et al. demonstrated that USP5 deubiquitinates HDAC1, thereby increasing its protein levels and inhibiting RILP acetylation. These molecular events confer DDP resistance to NSCLC cells; promote cell proliferation, invasion, and cancer stemness; and inhibit cellular apoptosis [13]. Furthermore, USP5 regulates the proliferative and migratory capacities of lung cancer cells by modulating the mammalian target of rapamycin (mTOR) signaling pathway and functionally interacting with poly (ADP-ribose) polymerase 1 (PARP1) [27, 28].

Through its deubiquitinating activity, USP5 stabilizes substrate proteins, thereby modulating downstream signaling pathways. Specifically, activated USP5 stabilizes Beclin 1, which promotes autophagic flux, while concurrently destabilizing the p53 protein - a mechanism that facilitates KRAS-driven lung tumorigenesis [19]. Notably, while USP7 exhibits broad-spectrum activity against diverse KRAS mutations and can effectively overcome resistance to small-molecule KRAS inhibitors, USP5 does not directly interact with KRAS. PD-L1, as a pivotal immune checkpoint molecule, is subject to stringent regulation by the ubiquitin-proteasome system. Moreover, USP5 enhances the stability of the PD-L1 protein via deubiquitination, thereby influencing the immunosuppressive tumor microenvironment (TME) through the regulation of the PD-1/PD-L1 axis [29].

Ubiquitin-specific protease 7

Ubiquitin-specific protease 7 (USP7), a cysteine-dependent peptidase, is among the most extensively characterized members of the USP deubiquitinase family, which constitutes the largest subclass of DUBs identified so far [23, 30]. USP7 has been found to play a role in cancer pathogenesis through its interactions with various substrates. Notably, research has shown that the overexpression of USP7 is clinically associated with poor survival outcomes across various malignancies [31]. On a mecha-

nistic level, USP7 facilitates oncogenic progression through ten key mechanisms: (i) the stabilization of oncogenic growth receptors and non-receptor kinases, which promotes tumor cell proliferation; (ii) the reduction of sensitivity to growth signals; (iii) the modulation of autophagy, which enables cancer cells to evade apoptosis; (iv) the maintenance of limitless replicative potential; (v) the promotion of sustained angiogenic signaling; (vi) the facilitation of invasive and metastatic processes; (vii) the modulation of genomic instability in cancer cells; (viii) the activation of pro-tumorigenic inflammation; (ix) the regulation of immune evasion within the TME; and (x) contribution toward the dysregulation of cellular energetics [10, 31, 32]. In a key previous study, Dai et al. demonstrated that targeting USP7 can reverse the immunosuppressive function of tumor-associated macrophages (TAMs). In this study, by specifically silencing USP7 through the use of siRNA and pharmacological inhibitors, the researchers effectively reprogrammed TAMs, transitioning them from a pro-tumor M2 phenotype to a tumor-suppressive M1 phenotype [33]. Within the TME, this phenotypic switch activates cytotoxic T lymphocyte (CTL)-mediated antitumor immunity, resulting in increased infiltration of M1 macrophages and IFN-γ-positive $CD8^+$ T cells into tumors and ultimately suppressing tumor growth [33]. Furthermore, targeted USP7 inhibition was found to trigger macrophage reprogramming by activating the p38 MAPK signaling pathway and upregulating tumoral PD-L1 expression. Interestingly, combined treatment with targeted USP7 inhibitors and an anti-PD-1 monoclonal antibody resulted in a stronger synergistic anti-tumor effect [33]. In line with these findings, USP5 and USP51 have also been shown to prevent PD-L1 degradation through similar mechanisms. However, these enzymes differ subtly with regard to their substrate specificity and responsiveness to upstream signals. For example, USP5 and USP51 exhibit different affinities for different types of Ub chain linkages (such as K48- or K63-linked chains) and may be activated under different cellular stress conditions. Despite these differences, both enzymes ultimately increase PD-L1 expression.

In NSCLC, a variety of USP7 substrates have been extensively studied. These include Raf-1, CCDC6, Ki67, and WDR79 [10]. More recently, studies by Huang et al., He et al., and Meng et al. have further revealed the mechanisms by which USP7 contributes to the pathogenesis of NSCLC. In particular, the study by Huang et al. demonstrated that USP7 plays a key role in oncogenic RAS mutations, which act as core driving factors of tumor development. Specifically, this research group found that USP7 interacts with KRAS through its TRAF domain. Thereafter, it removes the K48-linked polyubiquitin chain from the 147th lysine (K147) residue of KRAS [34]. In addition to this targeted deubiquitination, USP7 also exhibits some substrate promiscuity by non-selectively stabilizing both active and inactive KRAS mutant proteins, thereby facilitating NSCLC progression [34]. It is worth noting that USP7 inhibitors can effectively inhibit the proliferation of NSCLC cells. This anti-proliferation effect is particularly pronounced in AMG510-resistant KRAS-mutant NSCLC cells [34]. These findings indicate that USP7 may represent a potential therapeutic target for overcoming acquired resistance to KRAS inhibitors in NSCLC. These findings also provide a strong clinical rationale for the development of treatment regimens that combine USP7 inhibitors with existing KRAS-targeted therapies [34]. However, the study by Huang et al. only provides preliminary evidence supporting the synergistic anti-tumor effects of USP7 inhibitors and AMG510. The optimized treatment scheme, medication schedule, and treatment duration are yet to be optimized. Moreover, the potential for toxicity or drug-drug interaction also remains to be analyzed.

Nevertheless, evidence from other studies has been encouraging. For instance, He et al. elucidated the roles of USP7 and c-Abl in NSCLC, identifying USP7 as a deubiquitinase for c-Abl. They found that USP7 enhances the interaction between c-Abl and 14-3-3α/β while reducing the K48-linked polyubiquitination of c-Abl, thereby increasing its stability [35]. Moreover, the USP7/c-Abl axis was found to promote glycolysis and cell survival in NSCLC by directly phosphorylating and stabilizing hexokinase 2 (HK2) [35]. The knockdown of either USP7 or c-Abl was observed to inhibit glycolysis and decrease lactate production in NSCLC cells, suggesting that this signaling axis may represent a potential therapeutic target for the precision treatment of NSCLC [35]. Meanwhile, the study by Meng et al. further corroborated

the pivotal role of USP7 in NSCLC. Their study demonstrated that USP7 serves as a novel binding partner that deubiquitinates and stabilizes ERβ. This regulatory axis reduces reactive oxygen species (ROS) accumulation and enhances the interaction between mitochondrial ERβ and PRDX3, thereby promoting cellular resistance to the EGFR tyrosine kinase inhibitor (EGFR-TKI) osimertinib [36]. Notably, Meng et al. uncovered a novel mechanism by which the USP7-ERβ-PRDX3 signaling axis modulates ROS homeostasis and mediates osimertinib resistance in NSCLC. These findings suggest that targeting ERβ may represent a promising strategy for overcoming acquired osimertinib resistance in NSCLC [36].

Given the unclear biological function of USP7 in p53-deficient tumors, Huang et al. used CRISPR/Cas9-mediated gene editing technology to analyze the interaction network of USP7 in cancer cells [37]. Using this approach, they found that, in p53-deficient NSCLC, USP7 inhibits tumor progression by regulating the positive feedback loop of SMAD3. On a mechanistic level, USP7 mediates the removal of monoubiquitin from SMAD3, enabling unmodified SMAD3 to form heterodimers with SMAD4. These heterodimers bind to multiple super-enhancer (SE) elements located on the SMAD3 locus. Subsequently, this interaction enhances the transcriptional activity of SMAD3 and promotes its positive feedback regulation. This process regulates cell cycle progression and ultimately inhibits the malignant progression of p53-deficient lung cancer cells [37]. These findings highlight a previously unrecognized mechanism by which USP7 drives the SMAD/TGF-β signaling axis to inhibit the proliferation and growth of p53-deficient lung cancer cells [37].

Overall, the evidence shows that USP7 plays context- and environment-dependent dual regulatory roles and functions in lung cancer, acting as both a tumor promoter and a tumor suppressor. Specifically, its anti-cancer effect is mainly mediated through the targeting of substrates within the immune microenvironment, including core proteins such as PD-L1, Tim3, TGF-β, and SMAD3. In contrast, its tumor-promoting effects depend largely on the regulation of intracellular substrates, including c-Abl, ERβ, and KRAS.

Ubiquitin-specific protease 8 and ubiquitin-specific peptidase 32

Ubiquitin-specific protease 8 (USP8, also known as UBPY) and ubiquitin-specific peptidase 32 (USP32), both members of the USP subfamily, are frequently overexpressed in various human cancers [6, 38]. These deubiquitinases play crucial roles in regulating tissue homeostasis, cancer progression, ferroptosis susceptibility, and cell cycle progression, thus acting as potential targets for cancer therapy [6, 39].

By mediating deubiquitination, USP8 regulates the stability of multiple critical substrates and consequently influences tumor cell growth and malignancy. On a mechanistic level, USP8 antagonizes the melatonin-induced endocytosis and degradation of the MT1 receptor via deubiquitination, thereby facilitating the growth of lung cancer cells [40]. PTK7, a receptor tyrosine kinase, is highly expressed in NSCLC. USP8 enhances the stability of PTK7 via its deubiquitination, subsequently causing the activation of the PIK3CB/PI3K/AKT signaling cascade, which drives cell proliferation, invasion, and M2 macrophage polarization [41]. Collectively, the evidence thus demonstrates that USP8 exerts prominent pro-tumorigenic effects in lung cancer by modulating the degradation of essential receptors and activating downstream oncogenic signaling cascades.

Additionally, USP8 has been shown to contribute to immune evasion in lung cancer by altering the tumor immune microenvironment. Evidence demonstrates that USP8 enhances the stability of target oncoproteins by inhibiting Ub-dependent degradation. The long non-coding RNA SNHG12 facilitates immune escape by interacting with HuR, thereby increasing mRNA stability and upregulating the expression of both PD-L1 and USP8 [42]. USP8-mediated deubiquitination subsequently increases PD-L1 protein levels, thereby promoting immune evasion in NSCLC [42]. Compared with USP5, USP7, and USP51, USP8 appears to exhibit a distinct mode of PD-L1 regulation since it negatively modulates the expression of this protein. That is, USP8 selectively erases K63-linked Ub modifications from PD-L1, thereby rendering this protein accessible to E3 ubiquitin ligases. These ligases add K48-linked pol-

yubiquitin chains to PD-L1, accelerating its proteasomal degradation [38].

USP32, a newly characterized member of the USP subfamily, is an evolutionarily ancient and highly conserved gene located on chromosome 17q23 [43]. In recent years, accumulating evidence has revealed that USP32 governs the development and progression of multiple human tumors via its deubiquitinating function [6]. Existing studies on USP32 in the context of lung cancer have primarily focused on SCLC. However, the molecular mechanisms underlying USP32 function across diverse lung cancer subtypes, as well as its upstream regulatory factors and downstream substrates, remain largely uncharacterized and require systematic exploration. Therefore, USP32 represents a promising target with substantial research potential in the future. In line with this perspective, Jiao et al. demonstrated that the genetic knockdown of USP8 and USP32 inhibits MET receptor endocytosis and promotes MET receptor degradation under conditions of HGF overexpression. These effects ultimately reverse HGF-driven gefitinib resistance in EGFR-mutant LUAD cells with drug-sensitive backgrounds [44].

Ubiquitin-specific protease 9X

As an important member of the USP family, USP9X is involved in regulating a wide range of cellular processes, including cell proliferation and motility, programmed cell death (apoptosis), autophagy, immune regulation, and neurodevelopment [45].

In cancer biology, the abundance of proteins acts as a critical determinant of protein function and therefore warrants focused attention. Riley et al. demonstrated that USP9X facilitates the deubiquitination of both wild-type and mutant RIT1, thereby increasing RIT1 abundance and stability while suppressing RIT1-induced oncogenic phenotypes [46]. Moreover, USP9X has been shown to regulate pyrroline-5-carboxylate reductase 3 (PYCR3), a pivotal enzyme involved in proline metabolism, resulting in the suppression of the pentose phosphate pathway and impairment of mitochondrial respiratory function, ultimately promoting the growth and progression of lung cancer [47].

The regulatory role of USP9X in lung cancer drug resistance has become an important topic of research in the field of cancer biology. A CRISPR-based screening method was used to demonstrate that USP9X is required for RIT1-driven erlotinib and osimertinib resistance in RIT1 M90I mutant PC9-Cas9 cells [46]. Additionally, USP9X was found to activate the TGF-β2/Smad/ATM signaling pathway and promote radioresistance by stabilizing KDM4C in lung cancer cells [48]. Notably, Chen et al. demonstrated that USP9X mediates the deubiquitination of REV1, facilitates the binding of the E3 ubiquitin ligase Rad18 to CTH, and induces Gly/Ser/Thr metabolic remodeling [11]. These coordinated effects ultimately lead to radioresistance, rendering lung cancer cells insensitive to the effects of radiotherapy [11].

Therefore, KDM4C and REV1 represent promising therapeutic targets in lung cancer. The selective KDM4C inhibitor SD70 may serve as a valuable anticancer agent and radiosensitizer to prolong the overall survival of patients with lung cancer [48]. Likewise, the REV1 inhibitor JH-RE-06 may emerge as a novel radiosensitizer for future clinical treatments [11].

Ubiquitin-specific protease 10

Ubiquitin-specific protease 10 (USP10) is one of the most important DUBs in eukaryotic cells and has been shown to regulate numerous substrates. This enyzme deubiquitinates a variety of tumor-associated proteins, including MSH2, mTOR, Smad4, Raf-1, and NLRP7, thereby exerting either tumor-promoting or tumor-suppressive effects depending on the cellular context [49, 50]. Thus, USP10 is another USP family member that exhibits marked functional duality in lung cancer.

Compared with USP7, the dual functions of USP10 are more clearly reflected in its regulation of both tumor-suppressive and oncogenic substrates, with its overall biological effects depending on the selective deubiquitination of specific targets. From a tumor-promoting perspective, Guo et al. found that USP10 stabilizes histone deacetylase 7 (HDAC7) via deubiquitination, thereby activating the β-catenin-FGF18 signaling pathway and promoting NSCLC proliferation, metastasis, and epithelial-mesenchymal transition (EMT) [51]. On a mechanistic level, the interaction between HDAC7 and β-catenin was found to reduce the acetylation of HDAC7 at Lys49 and its phosphorylation at

Ser45, thereby promoting the nuclear translocation of HDAC7 and activating the expression of FGF18 [51]. This mechanism not only demonstrates the tumor-promoting effect of USP10 in NSCLC but also provides a theoretical and experimental basis for the further development of NSCLC treatment strategies [51]. In line with these findings, Li et al. found that USP10 stabilizes eukaryotic translation initiation factor 4 gamma 1 (EIF4G1) through deubiquitination and indirectly regulates *EIF4G1* mRNA expression through other substrates, thereby further increasing EIF4G1 stability. Elevated EIF4G1 expression promotes the proliferation, migration, and invasion of NSCLC cells, whereas USP10 knockout reverses this phenotype [52]. Notably, *in vitro* ubiquitination and functional experiments further confirmed that the inhibition of USP10 significantly suppresses tumor growth, suggesting that the USP10-EIF4G1 axis may represent a promising target for lung cancer treatment [52]. However, these findings require further validation in animal models and clinical samples [52].

From a tumor-suppressive perspective, Wang et al. found that USP10 regulates KLF4 stability in a $Kras^{G12D}$-driven LUAD model. Mechanistically, they found that USP10 removes K63-linked polyubiquitin chains from KLF4 via deubiquitination, thereby inhibiting the degradation of this protein. In turn, KLF4 directly activates the transcription of the metalloproteinase inhibitor TIMP3, which suppresses the proliferation and metastasis of lung cancer cells [53]. Clinical analyses show the positive correlations among USP10, KLF4, and TIMP3 expression in lung cancer tissues, with the low expression of these molecules being associated with poor prognoses [53]. These findings suggest that the USP10-KLF4-TIMP3 axis represents a promising therapeutic target in lung cancer [53]. Consistent with these findings, He et al. discovered that USP10 prevents the TRIM25-mediated K63-linked polyubiquitination of PTEN, thereby restoring the membrane localization and phosphatase activity of PTEN [54]. This process not only suppresses the activation of AKT/mTOR signaling but also reduces phosphatidylinositol (3,4,5)-trisphosphate [PI(3,4,5)P3] production, ultimately inhibiting the proliferation and migration of NSCLC cells [54].

Taken together, the functional duality of USP10 in lung cancer reveals that its final cancer-related effects depend on the selective deubiquitination of specific substrates. This dual role highlights the complexity of the DUB regulatory network. Nevertheless, current research on USP10 has primarily been limited to its upstream regulators and downstream substrates. Future studies are required to further analyze the substrate-specific regulatory mechanisms of USP10 in lung cancer.

Ubiquitin-specific protease 11

Ubiquitin-specific protease 11 (USP11), a DUB that is frequently overexpressed in various human cancers, has been reported to regulate multiple oncogenic processes [55, 56]. In SCLC, the expression of HK2 in cancer stem cells was reported to be significantly higher than that in differentiated tumor cells. The interaction between elevated non-mitochondrial HK2 and CD133 was found to promote the binding of USP11 to CD133, thus inhibiting its ubiquitination and enhancing the expression of renewal regulators, SCLC cell stemness, and tumor growth [57].

In addition, evidence has shown that USP11 plays a crucial role in regulating ferroptosis [15, 58]. In NSCLC cells, ROS-mediated stress causes USP11 activation. Subsequently, USP11 regulates cell proliferation and ferroptosis in NSCLC by stabilizing nuclear factor erythroid 2-related factor 2 (NRF2) [15].

USP11 lies at the core of the DNA damage response (DDR) pathway, modulating it through two distinct mechanisms. First, it stabilizes BRCA2 via deubiquitination to enhance homologous recombination (HR) repair. Second, it collaborates with RanBP9 to maintain p21 protein levels, which is critical for cell cycle arrest and the clearance of DNA lesions [59-61]. Beyond these functions, USP11 also participates in DNA-protein crosslink (DPC) repair and checkpoint signaling regulation [62]. Collectively, through these diverse functions, USP11 affects the sensitivity of lung cancer cells to DNA-damaging chemotherapeutic drugs, including platinum-based drugs and PARP inhibitors [63]. In contrast, ATXN3 (also a DUB) has a limited regulatory effect on DNA double-strand break (DSB) repair and mainly promotes single-strand DNA damage repair through PNKP [64, 65].

Ubiquitin-specific protease 12

In recent years, research on USP12 in lung cancer has been limited, with only a few studies reporting its dual effects on cell proliferation [6, 66-68]. However, investigations into the role of USP12 in other cancers, such as renal cell carcinoma, breast cancer, prostate cancer, and myeloma, have been more extensive. Nevertheless, elucidating the mechanistic relationship between USP12 and lung cancer remains of notable significance from a clinical standpoint [16, 69]. In a key study, Chen et al. identified USP12 as a critical regulator of ribonucleotide reductase M2 (RRM2), demonstrating that USP12 directly interacts with RRM2 and mediates its deubiquitination, thereby stabilizing RRM2 protein levels. In line with these findings, elevated USP12 expression was also significantly associated with poor prognoses in patients with NSCLC under physiological conditions [6].

Matrix metalloproteinase 14 (MMP14) has been identified as a regulatory factor in multiple cancers. Additionally, circular RNAs (circRNAs) have been found to play crucial roles in the biology of LUAD cells. Interestingly, one study suggested that Circ-ADRM1 recruits USP12 to promote the deubiquitination of MMP14 and subsequently induces macrophage M2 polarization through exosomal transfer. As such, the targeted inhibition of USP12 activity effectively prevents the deubiquitination of MMP14, thereby influencing the progression of LUAD [66]. Specifically, the downregulation of USP12 contributes to the activation of convergent downstream regulators, which create an immunosuppressive TME. From a mechanistic standpoint, USP12 deubiquitinates and stabilizes PPM1B, leading to the suppression of NF-κB-dependent signaling and chemokine expression, thereby promoting tumor survival [67]. Within the bidirectional regulatory network that links the mTOR/AKT signaling axis and the USP family, USP5 and USP12 act as downstream effectors that are passively activated by mTOR-driven signals. In contrast, USP10 and USP14 function as upstream regulators that actively initiate and amplify pathway signaling, positively promoting pathway activation [67]. Interestingly, USP12 has been demonstrated to modulate the response of tumors to anti-PD-1 therapy [67]. While this mechanism has been validated through preliminary studies, whether it engages in upstream/downstream crosstalk or functional redundancy with DUBs that directly stabilize PD-L1 (such as USP5, USP7, and USP51) remains poorly understood due to a lack of robust molecular evidence and in vivo studies. Answering this question should be a priority for future studies.

Ubiquitin-specific protease 13

The DUB USP13 is a member of the cysteine-dependent protease superfamily [70] and regulates the ubiquitination of multiple substrates [71]. Studies have shown that USP13 is involved in cancer metabolism and metastasis, DNA repair, autophagy, metabolism, antiviral response, and drug tolerance [72]. NFE2L2S, a major transcriptional regulator, is in turn regulated by the USP system [73]. In LUAD, USP13 overexpression has been linked to the increased expression of NFE2L2. Meanwhile, research has shown that in KRAS-mutant tumor tissues, USP13 promotes ferroptosis and autophagy by activating the NFE2L2-SQSTM1-KEAP1 axis. Moreover, USP13 appears to possess dual and context-dependent functions, acting on both oncoproteins and tumor suppressors to modulate their stability, which in turn modulates the activity of key oncogenic signaling pathways [73].

USP13 plays a key role in cell lineage reprogramming and the regulation of lineage plasticity in lung cancer. Research has shown that USP13 can promote the interaction between NKX2-1 and SOX2. This effect influences the fate of alveolar type II epithelial cells and promotes their transformation into squamous cell carcinoma cells [74]. In the context of KRAS mutations and TP53 deletions, USP13-mediated deubiquitination leads to the upregulation of MYC expression and SOX2 levels. This process regulates the development and transdifferentiation of lung squamous cell carcinoma [74]. In SCLC, USP13 prevents the ubiquitin-dependent degradation of fatty acid synthase (FASN) to enhance the stemness and lipid synthesis capacity of cancer cells. Evidence has demonstrated the potential of the FASN inhibitor TVB-2640 as a combination chemotherapeutic drug for SCLC [75]. Notably, Guo et al. found that in NSCLC carrying KRAS

mutations, USP13 specifically removes K63-linked polyubiquitin chains from lysine 508 (K508) of the β-catenin protein to strengthen the binding of β-catenin and TCF4. This interaction further activates the expression of downstream target genes, ultimately promoting tumor invasion and metastasis [76].

Ubiquitin-specific protease 14

Ubiquitin-specific protease 14 (USP14) plays an important role in tumorigenesis and the pathogenesis of various cancer types and has become an important target of clinical research. Clinical evidence consistently shows that this enzyme is highly expressed in a variety of malignant tumors, including colorectal cancer, pancreatic cancer, lung cancer, and gastric cancer [77-80]. Recent studies have revealed that USP14 affects the progression of lung cancer by regulating multiple signaling pathways. Notably, ceramide zygase 1 (CERS1) interacts with USP14 and thus inhibits the brain metastatic potential of NSCLC cells by downregulating the PI3K/AKT/mTOR signaling pathway. On a molecular level, CERS1 and USP14 can form an immune complex and co-localize within the cytoplasm [81]. USP14 is a metamorphic proteasome-associated regulatory factor that can regulate the DDR pathway. This protein can modulate the two major DNA DSB repair pathways: HR and non-homologous end joining (NHEJ). USP14 can alter the radiosensitivity of cancer cells, thus helping to improve treatment effects in patients with NSCLC [82]. Previously, Zhao et al. developed an aptamer-siRNA nanodelivery system that could accurately deliver siRNA targeting USP14 within DDP-resistant lung cancer cells. This approach effectively alleviated chemotherapeutic resistance in these cells, inhibiting tumor growth [8]. Meanwhile, Moghadami et al. discovered a novel mechanism in which the inhibition of USP14 leads to the accumulation of ubiquitinated proteins, triggering endoplasmic reticulum (ER) stress and subsequently activating the unfolded protein response (UPR). This mechanism was found to specifically upregulate the PERK, IRE1α, and JNK1 signaling pathways, ultimately promoting autophagy without inducing apoptosis in lung cancer cells [83]. Furthermore, USP14 was demonstrated to enhance the migratory potential of NSCLC cells by deubiquitinating and stabilizing actin crosslinking factor 7 (ACF7) [84].

Ubiquitin-specific protease 15

Ubiquitin-specific protease 15 (USP15) has been implicated in the regulation of a wide range of cellular and tumor-related processes, exhibiting dual functions as both an oncogene and a tumor suppressor under different conditions [85, 86]. Recent studies have indicated that USP15 expression is markedly reduced in patients with LUAD and is inversely associated with tumor migration and invasion. Evidence shows that USP15 can interact with the N-terminal domain of BECN1, facilitating its deubiquitination and thereby inhibiting the induction of autophagy. Conversely, TRAF6, an E3 ubiquitin ligase, interacts with BECN1 to enhance autophagy activation. Overall, USP15 suppresses the TRAF6-BECN1 signaling pathway, thereby hindering the progression of lung cancer [87]. Das et al. discovered that both USP15 and USP4 modulate the expression of the functional full-length SRSF1 protein, which shows increased endogenous expression in lung cancer cells and promotes their proliferation and migration [88]. Furthermore, USP15 has been found to be overexpressed in NSCLC cells, with its knockdown leading to the downregulation of MMP3 and MMP9, resulting in decreased cell growth and invasion [89]. The long non-coding RNA ABHD11-AS1 demonstrates increased expression across various stages of lung carcinogenesis, from early to advanced phases, and its expression levels show a positive correlation with tumor malignancy [90]. Notably, ABHD11-AS1 promotes the binding of USP15 to pre-mRNA processing factor 19 (PRPF19) by interacting with SART3. Subsequently, the expression of CD44v6 is upregulated, and the Wnt/β-catenin signaling pathway is activated. This process promotes the malignant transformation of healthy cells and the development of lung tumors [90].

Ubiquitin-specific protease 18

Ubiquitin-specific protease 18 (USP18), formerly known as UBP43, is a multifunctional protein. It was initially identified as a specific decoupling enzyme for interferon-stimulated gene 15 (ISG15) [91-93]. In lung cancer cell lines, increased expression levels of USP18, ATGL, and UCP1 were found to promote cell proliferation and thus potentially contribute to a poor patient prognosis. On a mechanistic

level, USP18 has been shown to regulate fatty acid metabolism by modulating the expression of ATGL and UCP1, thereby accelerating the malignant progression of tumors [92]. Knocking down USP18 disrupts the steady-state balance of 14-3-3ζ protein, thereby inhibiting the proliferation, migration, and invasion capacity of lung cancer cells [94]. SHANK1 is highly expressed in NSCLC tissues and cells resistant to Paclitaxel (PTX). USP18 enhances paclitaxel resistance in NSCLC cells by regulating the deubiquitination of SHANK1 [95]. POU4F1 is a member of the POU domain transcription factor family and exhibits unique oncogenic characteristics in many types of cancer [96, 97]. In LUAD, USP18 regulates the POU4F1-PRKAA2 signaling axis. It inhibits cell apoptosis and ferroptosis while promoting cell proliferation and migration, thereby playing a key role in tumor progression [97]. Consequently, USP18 could serve as a promising therapeutic target for lung cancer treatment.

Ubiquitin-specific protease 22

Ubiquitin-specific protease 22 (USP22), a histone-modifying enzyme, has been increasingly recognized for its upregulation and its role in modulating the tumor immune microenvironment in various cancers [98-100]. Han et al. discovered a USP22-centered gene module pathway network, demonstrating its contribution to LUAD progression via ubiquitination-mediated immune suppression [101]. In addition, evidence has shown that USP22 facilitates the progression of LUAD by enhancing the secretion of myosin IB (MYO1B)-enriched extracellular vesicles (EVs) and upregulating the expression of KDEL endoplasmic reticulum protein retention receptor 1 (KDELR1) [102]. Similarly, LINC01426 recruits USP22 to mediate the deubiquitination of the Sonic Hedgehog (SHH) protein, thereby activating the Hedgehog signaling pathway and promoting LUAD progression [103]. Interestingly, Chen et al. demonstrated that COL17A1 can counteract the inhibitory effects of USP22 silencing on LUAD cell growth, invasion, and migration *in vitro* while concurrently promoting apoptosis and ferroptosis. Their findings confirm that USP22-stabilized COL17A1 exhibits oncogenic properties in LUAD [104]. Beyond these studies, additional research has shown that the transcription factors AP2, ATF3, c-Myc, NF-YA, and SP1 are crucial for regulating USP22 mRNA expression in lung cancer cells. USP22 expression is transcriptionally activated by AP2 and c-Myc but suppressed by SP1 and ATF3, underscoring its significant role in the pathogenesis of lung cancer [99].

In the context of lung cancer, USP22 is co-overexpressed with USP7. Together, these enzymes contribute to immune suppression by stabilizing the immune checkpoint protein PD-L1 and FOXP3 in regulatory T cells (Tregs). Additionally, USP7 inhibitors trigger the degradation of SP1, which alleviates the transcriptional repression of USP22 and leads to its upregulation. These inhibitors also decrease H2Bub1 levels in USP22-knockout cells, enhance p53 activation in USP22-expressing cells, and exacerbate the malignancy of cancer cells. Targeting USP7 further inhibits cell growth and increases sensitivity to cisplatin in USP22-knockout lung cancer cells [105]. USP22 has also been implicated in chemoresistance across various human cancers. Specifically, this enzyme stabilizes murine double minute 2 (MDM2) through deubiquitination, thereby enhancing resistance to gefitinib and protecting NSCLC cells against ferroptosis [100]. Moreover, circFAT1(e2) is overexpressed in NSCLC cells, where it acts as an miRNA sponge to sequester miR-30e-5p, thereby relieving the repression of its downstream target USP22 and ultimately promoting tumor cell growth and metastasis [106].

Ubiquitin-specific protease 28

Ubiquitin-specific protease 28 (USP28) was first identified in 2001 [107, 108]. Since then, numerous studies have shown that USP28 plays important roles in physiological processes such as cell migration, apoptosis, and protein homeostasis [108-110].

Sterol regulatory element-binding transcription factor 2 (SREBF2) is a basic helix-loop-helix leucine zipper transcription factor [111]. This transcription factor is crucial for the expression of most enzymes involved in the mevalonate pathway (MVP) [107]. USP28 can bind to mature SREBP2, deubiquitinating and stabilizing it, and thereby regulating the expression of MVP-related enzymes. In NSCLC cells, LINC01426 and USP28 are upregulated. LINC01426 promotes cell proliferation, migration, invasion, autophagy, and glycolysis by acting as a sponge

for miR-143-3p and subsequently regulating USP28 expression [112]. Previously, Meng et al. reported that the upregulation of FOXK1 expression can significantly enhance the radioresistance of lung cancer cells and promote tumor development. Their research found that FOXK1 is deubiquitinated and stabilized by USP28. The biological effects of this process are mediated by the activation of the Hippo signaling pathway [113]. Furthermore, USP28 plays a critical role in deubiquitinating and stabilizing ΔNp63 by removing K48-linked ubiquitin chains, which highlights its potential as a therapeutic target for the treatment of lung squamous cell carcinoma (LSCC) [114]. In LUAD, the deletion of the USP28 gene can recapitulate TP53-deficient phenotypes and affects tumor progression through this mechanism [115].

Because USP28 and USP25 are structurally similar, inhibitors of these enzymes tend to have an inhibitory effect on both. At present, most highly effective compounds exert dual inhibitory effects [116, 117]. The dual-inhibition strategy against USP28/USP25 has shown remarkable anti-tumor outcomes in preclinical models, particularly in overcoming chemoresistance and restoring metabolic sensitivity. Current translational research focuses on the development of compounds that induce cell cycle arrest, trigger mitochondrial-dependent apoptosis, and enhance the therapeutic efficacy of cisplatin. Studies have shown that the combination of simvastatin and USP28/USP25 dual inhibitors can reduce the survival rate of SCC cells and restore sensitivity to statin-mediated MVP inhibition [107]. Furthermore, the USP28 inhibitor AZ1 can induce G1 cell cycle blockade, mitochondrial-dependent apoptosis, and DNA damage in lung cancer cells. In NSCLC, these effects are further enhanced following combined treatment with cisplatin [116, 117]. Ruiz et al. were the first to demonstrate that the inhibition of USP28 using compound FT206 led to the significant regression of human LSCC xenograft tumors [117]. However, even though USP28 monotherapy could induce tumor regression in certain models, combination therapy could perhaps be more feasible in clinical settings. Notably, evidence shows that USP28 inhibitors can reverse ΔNp63-mediated chemoresistance and enhance the DDR pathway; therefore, clinical trials should focus on employing combination regimens to reduce toxicity and enhance efficacy. At present, the next steps in the clinical development of USP28 inhibitors include pharmacokinetic optimization, the validation of in vivo selectivity, and long-term toxicity assessments. More in-depth in vivo studies are needed to confirm their safety and effectiveness.

Ubiquitin-specific protease 35

Extensive evidence indicates that the deubiquitinase ubiquitin-specific protease 35 (USP35) is significantly overexpressed in human lung cancer tissues and cell lines [118], highlighting its broad functional significance [119, 120]. After confirming the significant upregulation of USP35 in NSCLC tissues, studies have found that FUS interacts with USP35, thereby enhancing mRNA stability. Subsequently, USP35 stabilizes VEGFA protein levels through its deubiquitinating activity, promoting tumor growth, invasion, and angiogenesis [121]. Additionally, USP35 plays an important role in the development of chemoresistance in NSCLC cells. It mediates the K48-linked polyubiquitination of BIRC3 and thereby stabilizes this protein. This process inhibits cisplatin-induced cell apoptosis, thus reducing cellular sensitivity to cisplatin [122]. Further research has shown that USP35 knockdown can enhance the sensitivity of lung cancer cells to DDP and PTX chemotherapy. Mechanistic analyses indicate that USP35 directly interacts with the iron transporter FPN to prevent iron overload and ferroptosis in lung cancer cells. USP35 can also alleviate iron steady-state imbalances and the ferroptosis induced by erastin/RSL3, thereby promoting cancer cell proliferation and tumor progression [118]. An important study by Wang et al. identified RRBP1 as a novel substrate of USP35. USP35-mediated upregulation of RRBP1 was found to reduce oxaliplatin-induced cell apoptosis. Therefore, USP35 has now emerged as a potential therapeutic target for NSCLC [123]. Research has shown that USP35 does not directly bind to or stabilize mutant KRAS. Instead, it primarily stabilizes key downstream effectors of RAS signaling, thereby indirectly promoting the development of KRAS-driven NSCLC. This is an example of a classic "downstream pathway-mediated regulatory mechanism".

Ubiquitin-specific protease 51

A growing body of evidence indicates that ubiquitin-specific protease 51 (USP51) plays a crucial role in cancer progression [124, 125]. Among patients with NSCLC, elevated levels of USP51, PD-L1, and ITGB1 are closely associated with poor clinical prognosis. USP51 shares high homology with USP5. Mechanistically, USP51 activates the ITGB1/NF-κB signaling pathway by deubiquitinating PD-L1, thus promoting resistance to chemotherapy. The flavonoid compound dihydromyricetin (DHM) has been identified as a potential inhibitor of USP51, providing a new therapeutic strategy for tumor treatment and risk prevention and control [126]. TWIST1 is significantly overexpressed in NSCLC tissues and cell lines. USP51 stabilizes TWIST1 through deubiquitination and enhances tumor stem cell characteristics, thereby promoting tumor proliferation [125]. In patients with LUAD, elevated USP51 expression can predict poor clinical prognosis. Further research has shown that USP51 is phosphorylated by CDK4/6 at the Ser26 site, which promotes epithelial-mesenchymal transition (EMT) and tumor metastasis by regulating ZEB1 [127]. Additionally, USP51 is also involved in mediating drug resistance. It can reduce the levels of γ-H2AX and enhance the phosphorylation of checkpoint kinase 1 (CHK1), thereby regulating the DDR in cisplatin-sensitive lung cancer cells [128]. Notably, the knockdown of USP51 reduces cisplatin resistance in lung cancer cells by disrupting its interaction with ZEB1 [129].

CYLD

CYLD was first isolated more than 20 years ago and has been linked to a rare familial disease, cylindromatosis. This enzyme has been confirmed to act as a key tumor suppressor [130-132]. In NSCLC tissues and cells, the CYLD gene is also a downstream target of miR-135b and miR-587. Its dysfunction is associated with poor prognosis in patients with lung cancer [133, 134]. Studies have shown that the interleukin-6 (IL-6)/STAT3 signaling pathway can activate miR-135b. miR-135b directly targets the 3'-untranslated region (3'-UTR) of CYLD. This interaction inhibits CYLD expression, thereby activating NF-κB signaling and its downstream effectors, which in turn affects processes such as cell proliferation, migration, invasion, apoptosis, and angiogenesis [133]. Meanwhile, miR-587 promotes cell proliferation and migration by targeting CYLD, thereby contributing to the malignant progression of NSCLC [134].

A study conducted by Wang et al. showed that YTHDC2 is downregulated in lung cancer tissues and cells exposed to cigarette smoke. YTHDC2 is associated with smoking and stabilizes the CYLD protein through m6A modification, thus inhibiting the progression of lung cancer [135]. In PC-9 and PC-9/GR cells, CYLD expression can enhance sensitivity to gefitinib. This affects the proliferation and apoptosis of lung cancer cells as well as the inflammatory response of tumor-associated endothelium (TAE) [131]. In LUAD, CYLD regulates the activity of dendritic cells (DCs) and the NF-κB signaling pathway. As a result, it can promote the proliferation of CD4+ T cells and play a role in tumor suppression [136].

Other USPs involved in lung cancer

Beyond the USPs mentioned above, several other USPs linked to lung cancer have recently been identified, including USP1, USP2, USP4, USP19, USP25, and USP41. Notably, USP1 has been identified as a key gene in SCLC. Its overexpression has been shown to inhibit the immune response mediated by natural killer (NK) cells and promote tumor proliferation [137]. According to the latest research, the expression of USP2 is significantly downregulated in cisplatin-resistant NSCLC cells. On a mechanistic level, USP2 promotes ferroptosis in lung cancer cells and attenuates cisplatin resistance by deubiquitinating p53 at the K305 site [138]. In contrast, USP4 enhances the stemness, proliferation, and metastasis of LUAD cells by regulating the expression of tumor-related factors. Accordingly, it significantly affects the overall survival and prognosis of patients with LUAD [139, 140]. USP4 interacts with the Twist1 protein, deubiquitinating and stabilizing it, and subsequently promoting tumor stemness. These effects are closely associated with adverse clinical outcomes in patients with LUAD [139]. Previously, Wei et al. systematically analyzed the multiple functions of USP4 in LUAD. They discovered that USP4 promotes lymphatic vessel genera-

tion and lymph node metastasis by upregulating the expression of VEGF and MMP2. At the same time, it also regulates the cell cycle and apoptosis through the p53 signaling pathway and enhances the migratory and invasive abilities of LUAD cells by promoting EMT processes [140].

Research has confirmed that Tianmaxin can interfere with the interaction between USP19 and survivin. It can promote the ubiquitination and degradation of survivin, thus exerting antitumor effects [141]. USP25 inhibits RNF31-mediated linear ubiquitination of KRAS mutants. This process plays an important role in the development of KRAS G12-mutant NSCLC, providing key insights into tumor biology [142]. Within the regulatory network of KRAS-mutant lung cancer, USP25 shows both shared and unique characteristics when compared with USP5 and USP7. USP25 displays a high degree of mutation specificity and mainly targets KRAS G12 mutants. Moreover, it selectively interferes with the linear ubiquitination modification mediated by RNF31, rather than the classical lysine-linked ubiquitination, thus promoting the development of NSCLC [142]. Additionally, USP41 is overexpressed in lung cancer tissues and USP41 knockdown inhibits cell proliferation and migration and induces cell apoptosis of lung cancer [143].

JAB1/MPN/MOV34 metalloenzymes (JAMMs)

The JAB1/MPN/Mov34 metalloenzyme (JAMM) family represents a category of DUBs characterized by DUB metalloprotease activity and has emerged as a pivotal molecular nexus connecting the TME with immune-inflammatory responses at various levels [144, 145]. To date, only 12 members of the JAMM family within the human genome have been identified. Of these, seven are classified under the MPN+ subfamily, including STAM-binding protein (STAMBP, also known as AMSH), STAMBP-like 1 (STAMBPL1, also known as AMSH-LP), BRCC3 (also known as BRCC36), eIF3h, PSMD14 (also known as RPN11 or POH1), COP9 signalosome subunit 5 (CSN5), and MYSM1 [144, 146]. Notably, eight members of the JAMM family - namely, PSMD14, STAMBP, EIF3H, EIF3F, CSN6, CSN5, PSMD7, and BRCC3 - have been implicated in lung cancer.

PSMD14 functions as a non-ATPase regulatory subunit of the 26S proteasome and is a structural component of the 19S regulatory particle lid complex [145, 147]. Previous research has demonstrated that PSMD14, a protein-coding gene, can act as a potential prognostic biomarker across multiple types of cancer [148]. For instance, Lei et al. conducted immunohistochemical analyses of 184 NSCLC tissue samples and corresponding adjacent non-cancerous tissues and found that the cooverexpression of USP14 and PSMD14 was associated with increased disease severity and progression in patients with NSCLC [145]. Notably, both PSMD7 and PSMD14 have been found to act as integral components of the 26S proteasome but exhibit functional interdependence [149]. PSMD7 influences the proliferation and apoptosis of LUAD cells via the activation of the p53 signaling pathway [149].

Meanwhile, STAMBP is overexpressed in human NSCLC tumors and facilitates the recycling of epidermal growth factor receptor (EGFR) to the cell membrane. It achieves this by deubiquitinating and stabilizing EGFR both *in vitro* and in xenograft models [150].

The eukaryotic translation initiation factor 3 (EIF3) complex, one of the largest complexes found in mammalian cells, contains EIF3F and EIF3H, which are members of the JAMM-domain protease family of DUBs. These proteins play pivotal roles in gene regulation and disease progression by modulating the expression and activity of cancer-related targets [151-153]. For instance, research has shown that EIF3H is markedly upregulated in esophageal cancer, where its levels show a positive correlation with Snail expression [152]. In contrast, in lung invasive adenocarcinoma, the expression of miR-496 is negatively correlated with that of eIF3H, thus influencing tumor progression [154]. This negative regulatory mechanism warrants further investigation in future studies. In LSCC, EIF3F has been confirmed to upregulate the expression of several key proteins, including ribosomal proteins [151]. Meanwhile, in lung neuroendocrine tumors (lung-NETs), PRPF8 has been proven to affect cell proliferation and colony formation. These findings highlight the dysregulation of the transcriptional splicing mechanism in the context of malignant progression [155]. Furthermore, PRPF8 is also

known to play a pivotal role in modulating cellular responses to cisplatin [156].

CSN6 is overexpressed in various malignant tumors and is evolutionarily conserved across different organisms (including humans, mice, plants, and even viruses). In the tumor-promoting inflammatory microenvironment, alveolar type II (AT-II) cells secrete TNF-α. This increases the expression of CSN6, which subsequently enhances the expression of PD-L1 in monocytic macrophages (MoMs) [157]. This process promotes the formation of an immunosuppressive microenvironment that is conducive to the progression of lung cancer [157].

Numerous studies have confirmed that CSN5 is a multifunctional protein that has been highly conserved during evolution and contributes to cell cycle regulation in cancer cells. A key function of CSN5 is to mediate protein degradation by regulating the ubiquitination process [158-160]. In the context of lung cancer, most studies on CSN5 indicate that PD-L1 is an important downstream effector of this protein. A study by Liu et al. showed that in NSCLC, BBR can inhibit the deubiquitinating activity of CSN5 at the Glu76 site. This can reduce the expression of PD-L1 and enhance anti-tumor T-cell immunity [160]. Meanwhile, menin can promote the instability and degradation of PD-L1 by downregulating the expression of CSN5 [161]. USP22 interacts with CSN5 and stabilizes it through deubiquitination. Subsequently, both USP22 and CSN5 show enhanced interaction with PD-L1, thus synergistically regulating PD-L1 expression. This coordinated mechanism enables PD-L1 to promote immune escape in lung cancer [162]. Moreover, docosahexaenoic acid (DHA) can show enhanced immunomodulatory function and demonstrate anti-tumor activity by promoting CSN5-mediated ubiquitination of PD-L1 [163]. Interestingly, Wang et al. confirmed the interaction between MALT1 and CSN5. They showed that CSN5 stabilizes MALT1 through the E3 linkase FBXO3, subsequently activating the NF-κB pathway to promote the malignant progression of NSCLC [164]. However, these above-mentioned regulatory mechanisms all rely on the selective recognition of specific ubiquitin chain linkages by CSN5, highlighting the substrate specificity of JAMM family enzymes. Because CSN5 is a key regulator of PD-L1 in lung cancer and also participates in the regulation of multiple signaling pathways, the development of CSN5 inhibitors faces the dual challenge of achieving selectivity while minimizing off-target effects. The systemic inhibition of CSN5 may cause a wide range of off-target effects and potential toxicity, significantly limiting its clinical application.

In cancer cells with elevated Snail expression, tumor-derived exosomes are enriched in miR-21, which can inhibit the expression of PTEN and BRCC3 in macrophages. This suppression leads to the phosphorylation and K63-linked polyubiquitination of NLRP3, resulting in the disassembly and inactivation of the NLRP3 inflammasome. Ultimately, these molecular events reduce chemotherapy-induced inflammation and immunogenic cell death (ICD) [165].

Machado-Joseph disease proteases

Machado-Joseph disease (MJD) domain-containing proteases represent the smallest family of DUBs, consisting of only four members: JOSD1, JOSD2, Ataxin-3, and Ataxin-3L. These enzymes exhibit dual roles in cancer biology, functioning as both tumor promoters and tumor suppressors [166-168].

Accumulating evidence indicates that JOSD1 is involved in various types of cancer, and its upregulation is associated with unfavorable clinical outcomes. Ma et al. were the first to demonstrate that JOSD1 interacts with the Snail protein, causing its deubiquitination and subsequently promoting the EMT process in LUAD, leading to enhanced metastasis, migration, and invasion [168]. In contrast, JOSD2 has also been shown to serve as a pivotal oncogenic factor that paradoxically suppresses the progression of NSCLC, whereas LKB1 is a well-established tumor suppressor. JOSD2 interacts with LKB1 and removes its K6-linked polyubiquitin chains, resulting in the destabilization of the LKB1-STRAD-MO25 complex and the inhibition of LKB1 kinase activity. Thus, HY041004, a novel small-molecule inhibitor targeting JOSD2, has emerged as a promising therapeutic strategy for NSCLC patients with inactivated LKB1 [169]. Additionally, JOSD2 promotes NSCLC progression by modulating the DDR pathway. The inhibition of JOSD2 significantly increases sensitivity to doxorubicin and olaparib [170].

Using a CRISPR-based screening platform, Wang et al. identified ATXN3 as a positive transcriptional regulator of PD-L1. On a mechanistic level, ATXN3 was found to enhance immune evasion in tumors by stabilizing HIF-2α, IRF1, STAT3, and JunB, thus protecting them from ubiquitin-mediated degradation in response to IFNγ stimulation [171].

Ubiquitin C-terminal hydrolases

In recent years, ubiquitin has been increasingly recognized for its indispensable roles in numerous regulatory pathways. The ubiquitin C-terminal hydrolase (UCH) family, a critical subgroup of DUBs, consists of four members: UCHL1, UCHL3, UCHL5, and BRCA1-associated protein-1 (BAP1) [172, 173].

UCHL1 is a unique DUB with a dual expression pattern. It is physiologically expressed in normal tissues (such as the brain and nervous system) but is also frequently overexpressed in a variety of malignant tumors, including NSCLC [173, 174]. Multiple studies have confirmed that the overexpression of UCHL1 can serve as a biomarker for predicting poor clinical prognosis in cancer [174-176]. This overexpression has been linked to a smoking history, larger tumor size, and a high degree of atypical proliferation [174]. On a mechanistic level, UCHL1 confers resistance to pemetrexed (PEM) in NSCLC cells by upregulating thymidylate synthase (TS). This reduces DNA damage and prevents the expression of PD-L1 and cell cycle blockage [176]. This enables immune escape in NSCLC tumors, making UCHL1 a key target for cancer immunotherapy [177]. Notably, UCHL1 enhances PD-L1 expression by activating the AKT-p65 signaling pathway, which leads to impaired T-cell function and oncogenic effects [177]. Aberrant TGF-β signaling is associated with cancer development because TGF-β activates the SMAD pathway to regulate protein expression [178, 179]. Under hypoxic conditions, the overexpression of UCH-L1 amplifies the TGF-β/Smad signaling pathway. This negatively regulates Dauer formation in *Caenorhabditis elegans* and promotes the occurrence of lung tumors [179]. Previously, Yao et al. demonstrated that UCHL1 may serve as both a diagnostic biomarker and a therapeutic target in LUAD. In LUAD, this DUB promotes tumor migration, invasion, and metastasis by inhibiting cell apoptosis [175].

UCHL1 and UCHL3 share up to 53% sequence homology, indicating that they have significant structural similarity and comparable molecular weights [180, 181]. UCHL3 can affect the radiosensitivity of NSCLC through a unique molecular pathway. Experimental data show that LINC00665 acts as a sponge for microRNA (miR)-582-5p. It promotes UCHL3-dependent deubiquitination and stabilizes the aryl hydrocarbon receptor (AhR), maintaining its activity. This process promotes the expression of PD-L1, reduces radiosensitivity in tumor cells, and facilitates immune escape [182]. In addition, the knockdown of UCHL3 interferes with the recruitment of RAD51 to DSBs, thus reducing the efficiency of HR repair [183].

Ubiquitin C-terminal hydrolase L5 (UCHL5/UCH37) is a paralog of BAP1 [180]. In LUAD cells, the knockdown of UCHL5 inhibits cell proliferation and decreases the mRNA and protein levels of the critical cell cycle regulators cyclin D1 and CDK4 [184]. Interestingly, BAP1 was initially identified as the primary histone deubiquitinase for histone H2A ubiquitinated at lysine 119 (H2AK119ub) in *Drosophila* [185]. Since then, numerous studies have demonstrated that the BAP1/ASXL3/BRD4 epigenetic axis is essential for maintaining transcriptional activity in SCLC cells [185, 186]. Importantly, iBAP-II has been identified as a novel inhibitor of BAP1 that targets its catalytic activity, disrupts the BAP1/ASXL3/BRD4 axis, and promotes the degradation of the ASXL3 protein [185].

Ovarian tumor domain-containing proteases

The OTU DUB subfamily consists of 16 members, which can be classified into four distinct subclasses based on their catalytic protein structures and domains: the Otubains subfamily (OTUB1 and OTUB2), the OTUD subfamily (OTUD1, OTUD2, OTUD3, OTUD4, OTUD5, OTUD6A, OTUD6B, and ALG13), the A20-like OTUs subfamily (A20, OTUD7A, OTUD7B, Trabid, and VCPIP1), and the OTULIN subfamily [187, 188].

Within the OTUD subfamily, the proteins OTUD1, OTUD3, OTUD4, OTUD5, and OTUD6B have been experimentally shown to mediate Ub-dependent pathways in lung cancer. Substantial evidence demonstrates that OTUD1 possesses tumor-suppressive properties across various types of cancer, with its expres-

sion significantly downregulated in lung cancer cell lines when compared with normal cells [189-191]. Furthermore, OTUD1 levels are positively correlated with KLF4 expression and inhibit the progression of NSCLC by stabilizing and deubiquitinating KLF4 [189]. The overexpression of OTUD1 inhibits the nuclear translocation of YAP1, thereby diminishing its activity. This exclusion of YAP1 from the nucleus leads to the inactivation of the SOX9/SPP1 axis, subsequently suppressing resistance to erlotinib in NSCLC cells [190]. Additionally, FHL1 exhibits immune-related expression characteristics in lung cancer, while OTUD1 stabilizes FHL1 through deubiquitination, thereby inhibiting tumor proliferation and migration. Notably, one study identified VE-822 as an OTUD1 agonist that mitigates lung cancer progression [191]. Collectively, these findings suggest that OTUD1 is a tumor suppressor and can act as a promising therapeutic target in lung cancer.

OTUD3 is a key deubiquitinase in the OTU family and has multifaceted biological functions [188, 192, 193]. Zhang et al. showed that CHIP mediates the downregulation of OTUD3 by interacting with this protein, thereby promoting its polyubiquitination and subsequent degradation. This, in turn, reduces GRP78 levels in lung cancer cells, thereby inhibiting cell invasion and metastasis [192]. On a mechanistic level, rolapitant directly targets the OTUD3-GRP78 axis and induces ER stress-mediated apoptosis in lung cancer cells through the CHOP-DR5 pathway [193]. In LUAD, the expression of OTUD4 is positively correlated with that of NRF2. NRF2 enhances OTUD4 transcription by binding to its promoter region. This, in turn, promotes the deubiquitination of EGFR and improves its protein stability [194].

OTUD5 has been identified as a crucial regulator of tumor progression [195]. PDCD5 is a highly conserved protein associated with apoptosis [196, 197]. Functional studies have shown that knocking out OTUD5 can inhibit the activity of p53 and PDCD5, thus enhancing the proliferation, metastasis, and invasion of NSCLC cells and increasing their resistance to doxorubicin and cisplatin [197]. From a regulatory perspective, microRNA-652-3p was found to directly target and inhibit OTUD5 expression, leading to an increase in the level of PTEN ubiquitination, thus driving the proliferation, invasion, and migration of NSCLC cells [198]. Notably, Bai et al. found that CacyBP, as a negative regulatory factor of OTUD5, is highly expressed in LUAD tissues [199]. The overexpression of CacyBP promotes the ubiquitination and degradation of OTUD5, which in turn promotes tumor development [199]. Moreover, evidence indicates that OTUD6B is markedly overexpressed in human LUAD, where it interacts with RIPK1 to promote disease progression [195].

In the A20-like OTU subfamily, A20 (i.e., tumor necrosis factor α-induced protein 3, TNFAIP3) and OTUD7B both play a negative regulatory role to inhibit the growth of lung cancer. A20 plays a key role in maintaining inflammatory homeostasis. Studies have shown that the downregulation or deletion of A20 in LUAD tumors promotes immune escape by activating the TBK1-STAT1-PD-L1 axis, thus driving disease progression. The inhibition of A20 through the autocrine interferon signaling pathway also leads to the abnormal proliferation of LUAD [200]. These findings indicate that A20-mediated PD-L1 regulation does indeed exist in lung cancer. However, its primary mechanism appears to be indirect, mediated by the inhibition of upstream signaling pathways, rather than through the direct regulation of substrate protein degradation. A20 also promotes ferroptosis in lung cancer cells through the specific protease 1 (SENP1)-mediated regulation of its SUMOylation status. Additionally, A20 influences ferroptosis by directly regulating two critical ferroptosis-related proteins, acyl-CoA synthetase long-chain family member 4 (ACSL4) and solute carrier family 7 member 11 (SLC7A11) [201].

Intriguingly, OTUD7B has been identified as a pivotal factor in inhibiting LCL161-induced invasion and migration in lung cancer cells. On a mechanistic level, OTUD7B interacts with and deubiquitinates TRAF3, leading to the suppression of NIK and the subsequent inhibition of non-canonical NF-κB activation, which is responsible for promoting cancer cell invasion and migration [202]. Hyperthermia, a clinical antitumor strategy, induces apoptosis in lung cancer cells by increasing the temperature of tumor tissues. Importantly, the upregulation of OTUD7B enhances the antitumor efficacy of hyperthermia treatment [203]. OTUD7B interacts with and deubiquitinates endogenous mitochondrial Smac protein resulting in mitoch-

Table 2. The list of JAMMS, MJD, UCH, OTU involved in lung cancer

DUBs	Upstream Regulatory Events	Substrate(s)	Detailed mechanisms	Biological Effects On LC	Ref.
JAMMS					
STAMBP	Not mentioned	EGFR	STAMBP knockdown suppresses LUAD tumor growth and metastasis by modulating EGFR-mediated ERK activation.	+	[150]
CSN6	Not mentioned	PD-L1	In vitro inhibition of CSN6 reduces PD-L1 expression in TNF-α-activated macrophages and suppresses lung tumorigenesis.	+	[157]
CSN5	BBR	PD-L1	BBR suppresses PD-L1 expression and enhances anti-tumor immunity in NSCLC by inhibiting CSN5's deubiquitinase activity.	+	[160]
	Not mentioned	MALT1	CSN5 promotes NSCLC malignant progression by stabilizing MALT1 through the E3 ligase FBXO3.	+	[164]
	USP22	PD-L1, USP22	USP22 regulates PD-L1 protein levels via the USP22-CSN5-PD-L1 axis to mediate immune evasion.	+	[162]
	DHA	PD-L1	DHA induces PD-L1 ubiquitination and degradation by inactivating CSN5, thereby enhancing anti-tumor immunity.	+	[163]
	Menin	PD-L1	Menin promotes PD-L1 destabilization and degradation by suppressing CSN5 expression.	+	[161]
EIF3H	miR496	eIF3h	The expression of miR-496 is negatively correlated with eIF3h.	Not mentioned	[154]
PSMD7	Not mentioned	p53 pathway	PSMD7 downregulation suppresses lung cancer progression by modulating the p53 pathway.	+	[149]
BRCC3	miR-21	NLRP3	miR-21 suppresses PTEN and BRCC3 to promote NLRP3 phosphorylation and K63-linked ubiquitination, thereby inhibiting NLRP3 inflammasome assembly.	+	[165]
MJD					
JOSD1	Not mentioned	Snail	JOSD1 promotes tumor cell proliferation and metastasis by deubiquitinating and stabilizing Snail protein.	+	[168]
JOSD2	Not mentioned	LKB1	JOSD2 suppresses LKB1 kinase activity by deubiquitinating LKB1 in NSCLC.	+	[169]
		DDR	JOSD2 promotes malignant progression of NSCLC by regulating DNA damage repair pathways.	+	[170]
ATXN3	Not mentioned	IRF1, STAT3, HIF-2α, JunB	ATXN3 enhances tumor immune evasion.	+	[171]
UCH					
UCHL1	Not mentioned	Ki-67	UCHL1 expression is positively correlated with Ki-67 and promotes tumor proliferation.	+	[175]
	Not mentioned	Not mentioned	UCHL1 overexpression is associated with smoking, larger tumor size, and high-grade dysplasia, which are typically linked to poor prognosis and unfavorable survival outcomes.	+	[174]
	Not mentioned	TS	UCHL1 promotes pemetrexed resistance in non-small cell lung cancer by upregulating thymidylate synthase.	+	[176]
	Not mentioned	R-Smad	UBH1/UCH-L1 enhances DAF7/TGF-β signaling, suppresses dauer formation, and promotes pulmonary tumorigenesis.	+	[179]

	Not mentioned	PD-L1	UCHL1 promotes PD-L1 expression in NSCLC cells.	+	[177]
UCHL3	miR-582-5p	AhR	LINC00665 stabilizes AhR protein through the miR-582-5p/UCHL3 axis, thereby enhancing immune evasion of NSCLC cells both in vitro and in vivo.	+	[182]
	Not mentioned	RAD51	UCHL3 knockdown enhances radiosensitivity in NSCLC cells by increasing IR-induced DNA damage and impairing HR repair.	+	[183]
UCHL5	Not mentioned	Cyclins	UCHL5 knockdown significantly inhibits cell proliferation through modulation of cyclins.	+	[184]
BAP1	iBAP-II	ASXL3, ASCL1	Pharmacological inhibition of BAP1's catalytic activity disrupts the BAP1/ASXL3/BRD4 epigenetic axis by inducing degradation of the scaffolding protein ASXL3, which bridges BRD4 and BAP1 at active enhancers.	+	[185]
	Not mentioned	ASXL3	ASXL3 bridges BRD4 to the BAP1 complex and controls enhancer activity in small cell lung cancer.	+	[186]
OTU					
OTUD1	Not mentioned	KLF4	OTUD1 suppresses NSCLC progression by deubiquitinating and stabilizing KLF4.	-	[189]
	Not mentioned	YAP1	OTUD1 confers erlotinib sensitivity in NSCLC by inhibiting YAP1 nuclear translocation.	-	[190]
	VE-822	FHL1	VE-822 upregulates the deubiquitinase OTUD1 to stabilize FHL1, thereby suppressing lung adenocarcinoma progression.	-	[191]
OTUD3	CHIP	GRP78	The ubiquitin ligase CHIP regulates OTUD3 stability in lung cancer and suppresses tumor metastasis.	+	[192]
	Rolapitan	GRP78	Rolapitant suppresses human lung cancer growth by inhibiting the OTUD3-GRP78 axis, thereby inducing ER stress and DR5-mediated extrinsic apoptosis.	+	[193]
OTUD4	NRF2	EGF	NRF2 regulates EGF stability in lung adenocarcinoma through OTUD4.	-	[194]
OTUD5	miR-652-3p	PTEN	miR-652-3p promotes NSCLC cell proliferation, invasion and migration by inhibiting OTUD5-mediated deubiquitination and stabilization of PTEN.	-	[198]
	CacyBP	Not mentioned	CacyBP promotes lung adenocarcinoma progression by downregulating OTUD5.	-	[199]
	Not mentioned	PDCD5	OTUD5 is downregulated in NSCLC tissues and suppresses malignant phenotypes of NSCLC cells by regulating p53 and PDCD5.	-	[197]
OTUD6B	Not mentioned	RIPK1	OTUD6B promotes lung adenocarcinoma progression by stabilizing RIPK1.	+	[195]
A20	Not mentioned	TBK1	Downregulation of A20 promotes immune evasion in lung adenocarcinoma.	-	[200]
	SENP1	ACSL4, SLC7A11	SENP1 inhibition suppresses lung cancer cell growth by activating A20-mediated ferroptosis.	-	[201]
OTUD7B	Not mentioned	TRAF3	OTUD7B inhibits Smac mimetic-induced lung cancer cell invasion and migration by deubiquitinating TRAF3.	-	[202]
	miR-491-5p	VEGFA	miR-491-5p suppresses vasculogenic mimicry in NSCLC by inhibiting OTUD7B and enhancing VEGFA ubiquitination.	+	[204]

	Not mentioned	Smac	OTUD7B potentiates heat therapy-induced suppression of lung cancer progression by enhancing Smac-mediated mitochondrial dysfunction.	-	[203]
OTUB1	Not mentioned	CHK1	OTUB1 promotes lung cancer progression and radioresistance by deubiquitinating and stabilizing CHK1.	+	[207]
	Not mentioned	OXPHOS	OTUB1 governs lung cancer cell fitness by regulating proteostasis of OXPHOS proteins.	-	[206]
	Crizotinib	STAT3	Targeting the Otub1/p-STAT3 axis suppresses non-small cell lung cancer progression.	+	[209]
	Not mentioned	Aiolos	OTUB1-mediated deubiquitination explores the oncogenic potential of Aiolos in lung cancer.	-	[208]

+: promote;-: inhibit.

ondrial dysfunction, which inhibits lung cancer cell proliferation and invasion [203]. Notably, Chen et al. identified OTUD7B as a novel target gene of miR-491-5p. By suppressing OTUD7B and promoting the ubiquitination of vascular endothelial growth factor A (VEGFA), miR-491-5p was found to facilitate vasculogenic mimicry (VM) [204].

Within the Otubain subfamily, which includes OTUB1 and OTUB2, OTUB2 appears to mediate PD-L1 degradation, thereby exerting tumor-suppressive effects. However, the specific regulatory network of OTUB2 in lung cancer remains largely unexplored at present [205]. Under normoxic conditions, OTUB1 interacts with oxidative phosphorylation (OXPHOS) proteins to regulate cellular respiration. Furthermore, OTUB1 modulates the interaction network of mitochondrial proteins, thereby influencing the adaptive capacity of lung cancer cells [206]. Research indicates that OTUB1 deubiquitinates and stabilizes CHK1, thereby regulating DDR pathways. This mechanism enhances the efficacy of radiotherapy during lung cancer treatment [207]. The overexpression of Aiolos (IKZF3), a zinc finger transcription factor, significantly enhances the migratory and invasive capacities of lung cancer cells. OTUB1 can specifically bind Aiolos and reduces its ubiquitination, thereby regulating key oncogenic behaviors in lung cancer cells [208]. In NSCLC, OTUB1 binds to phosphorylated STAT3 (pSTAT3-Y705) and selectively removes K48-linked ubiquitin chains. This enhances the transcriptional activity of STAT3, preventing its proteasomal degradation and promoting cancer cell survival. Recent studies have shown that crizotinib specifically targets the OTUB1/pSTAT3-Y705 axis within the proteasome system, thereby inhibiting the proliferation and colony-forming ability of NSCLC cells without inducing apoptosis [209].

Conclusion and perspectives

In recent years, research on DUBs and lung cancer signaling networks has advanced considerably, with remarkable progress being made, particularly in elucidating molecular regulatory mechanisms. This article systematically summarizes the latest research on the roles of DUBs in the occurrence and progression of lung cancer. As summarized in **Tables 1** and **2**, although most DUBs exhibit tumor-promoting activities in lung cancer, some exert antitumor effects in specific molecular contexts, highlighting the dual nature of their functions. For instance, the functional diversity of the USP family of DUBs in lung cancer is mainly determined by substrate preference and the overall pattern of intracellular signaling. Therefore, clarifying the mechanisms by which the same DUB exerts opposite biological effects owing to differences in substrate abundance, lung cancer subtype, and the immune microenvironment has become a key scientific question that must be answered to advance precision medicine for lung cancer. As we move toward the future, techniques such as single-cell transcriptomics, spatial transcriptomics, and other multi-omics technologies should be comprehensively leveraged to systematically analyze these environment-dependent regulatory mechanisms. Accurately defining the critical conditions that determine whether DUBs exert tumor-promoting or tumor-suppressive effects

will provide a rational basis for targeted therapeutic interventions.

In addition, this review systematically classifies and analyzes the regulatory networks of the five major DUB subfamilies (USP, JAMMs, MJDs, UCH, and OTU) in the context of lung cancer. However, it should be noted that significant gaps remain in our understanding of the DUB family, particularly with respect to the MINDY and ZUP1 subfamilies, whose mechanisms of action are still at an early stage of investigation and remain far from fully understood. Therefore, further exploration of the therapeutic potential of DUBs in lung cancer is of great scientific significance for the development of novel treatment strategies.

The current pipeline of DUB inhibitors exhibits a clear polarization trend, and the vast majority of therapeutic strategies for lung cancer remain at the preclinical stage. Drugs such as the USP7 inhibitor P5091 and the USP14/UCHL5 inhibitor b-AP15 have failed to advance to clinical development because of insufficient selectivity or poor drug-like properties. Indeed, substantial mechanistic evidence has accumulated for targets such as USP22 and USP25. For example, USP22 has been shown to stabilize EGFR and promote TKI resistance. However, corresponding inhibitors have not yet been adequately optimized [210-212]. Among the many strategies targeting DUBs, the USP1 inhibitor KSQ-4279 is currently the only representative with practical clinical translational potential, having advanced to phase I/II clinical trials. Its core mechanism is based on synthetic lethality, thereby shifting the therapeutic window from reliance on the absolute biochemical selectivity of the compound to the inherent genetic vulnerabilities of tumor cells. For example, in tumors harboring BRCA mutations, KSQ-4279 provides a feasible strategy for USP1-targeted therapy and serves as an important proof of concept for DUB-targeted therapeutic approaches [213].

The clinical data obtained from existing DUB-targeting drugs indicate that the main cause of clinical failure is dose-limiting toxicity rather than insufficient target validation. This problem is primarily attributable to the lack of selectivity among DUB family members and between DUBs and non-target cysteine proteases [214]. Almost all DUB inhibitors exhibit some degree of hematological toxicity, which is consistent with the essential role of DUBs in the hematopoietic system [215]. It is worth noting that there are significant methodological limitations in the preclinical efficacy data obtained from lung cancer models. Most *in vivo* efficacy studies rely on subcutaneous xenograft models and lack parallel evaluation of the key physiological functions of DUBs in normal lung tissue. Existing evidence strongly supports the use of DUB inhibitors as enhancers in combination therapy rather than as monotherapy. For example, from a mechanistic perspective, USP22 stabilizes EGFR to promote TKI resistance, USP18 stabilizes PD-L1 to facilitate immune escape, and USP14/UCHL5 regulates MHC I antigen presentation. Together, these findings provide a strong theoretical basis for combining DUB inhibitors with TKIs or immunotherapy.

Overall, the field of lung cancer treatment faces five major converging challenges: selectivity, toxicity, biomarkers, disease models, and medicinal chemistry. Among these, the interaction between selectivity and toxicity constitutes a fundamental obstacle. The highly conserved catalytic domains and broad substrate spectrum of DUBs make low-selectivity inhibitors extremely susceptible to dose-limiting toxicity. At the same time, the lack of predictive biomarkers, the limited ability of existing disease models to simulate clinical conditions, and challenges in medicinal chemistry further hinder the clinical translation of antitumor therapies [213, 214, 216]. The key to overcoming these challenges is to develop highly selective interventions for specific genetic backgrounds and redefine the clinical value of DUB inhibitors within the framework of combination treatment regimens [142].

Although some progress has been made, several limitations remain. This review outlines key issues that should be addressed in future research. First, although numerous studies have explored the upstream regulators and downstream effectors of DUBs, their precise molecular mechanisms have not been fully elucidated. For example, the specific mechanism by which USP1 regulates NK-cell responses and how USP14 regulates the NHEJ and HR pathways still require further investigation. Second, the limited sample sizes and insufficient follow-up data of existing studies restrict the

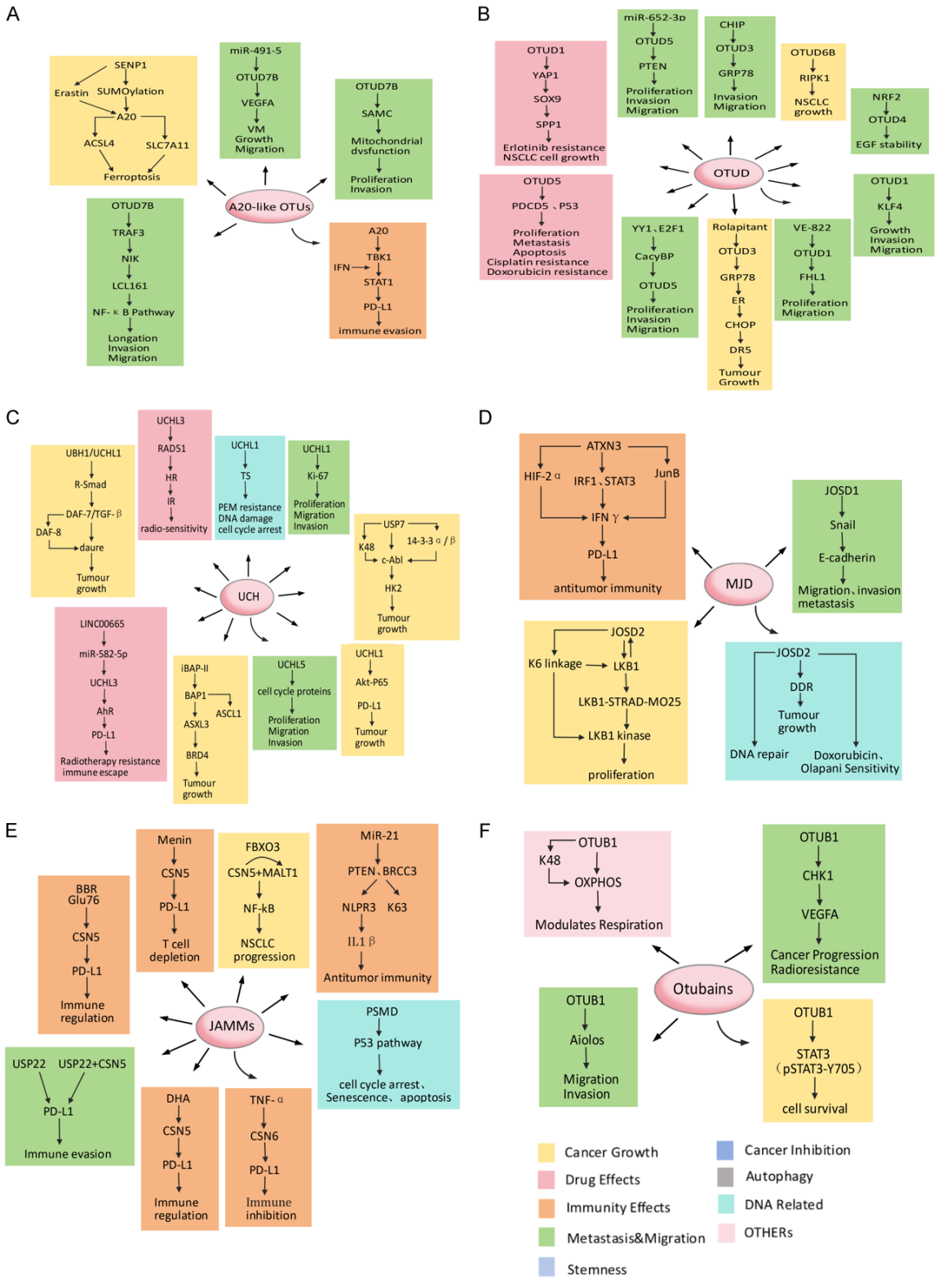


Figure 5. The mechanistic pathways associated with the JAMMS, MJD, UCH, OTU in the pathogenesis of lung cancer. The DUBs presented in the figure - OTUB (A), MJD (B), A20-Like OTUs (C), JAMMs (D), UCH (E), OTUD (F) - demonstrate significant potential as therapeutic targets for innovative lung cancer treatments.

reliability and generalizability of their conclusions. Future studies should include larger cohorts and longer follow-up periods to improve the robustness of the research data. Third, the specific E3 ubiquitin ligases responsible for regulating ubiquitination at different sites and mediating proteasomal degradation have not been systematically identified. To date, only a limited number of studies have comprehensively characterized these E3 ligases, highlighting the need for more extensive investigation.

In conclusion, this comprehensive review identifies critical nodal points connecting various DUBs to the pathogenesis of lung cancer (**Figures 4** and **5**). As discussed above, we also compare the similarities and differences among these regulatory mechanisms in detail. Specifically, we discuss how USP5, USP7, USP8, USP22, USP51, CSN5, CSN6, UCHL1, and A20 collectively influence lung cancer progression through their interactions with PD-L1. Additionally, both STAMBP and USP14 facilitate lung cancer cell growth through distinct EGFR-mediated pathways. Furthermore, USP5 and USP12 influence lung cancer progression by regulating the mTOR signaling pathway. Overall, this review not only provides novel conceptual frameworks for understanding the mechanistic roles of DUBs in lung cancer but also lays a theoretical foundation for accelerating the identification of therapeutic targets and the development of targeted drugs.

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Disclosure of conflict of interest

None.

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