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Advances of E3 ligases in lung cancer

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ABSTRACT

Lung cancer is a leading cause of cancer-related death, and the most common type of lung cancer is non-small cell lung cancer, which accounts for approximately 85 % of lung cancer diagnoses. Recent studies have revealed that ubiquitination acts as a crucial part of the development and progression of lung cancer. The E1-E2-E3 three-enzyme cascade has a core function in ubiquitination, so targeted adjustments of E3 ligases could be used in lung cancer treatment. Hence, we elucidate research advances in lung cancer-related E3 ligases by briefly describing the structure and categorization of E3 ligases. Here, we provide a detailed review of the mechanisms by which lung cancer-related E3 ligases modify substrate proteins and regulate signaling pathways to facilitate or suppress cancer progression. We hope to show a new perspective on targeted precision therapy for lung cancer.

1. Background

1.1. Lung cancer

Being one of the most common types of malignant cancers in the world, lung cancer emerges as a leading cause of cancer-related deaths [1,2]. Due to its continuously rising incidence and mortality rates, lung cancer poses a significant threat to human health and life expectancy [3]. According to the global cancer statistics from the World Health Organization's International Agency for Research on Cancer, lung cancer was responsible for approximately 2.2 million new cases and 1.8 million deaths, accounting for 11.4 % of all cancer cases and 18.0 % of all cancer deaths on a global scale [4]. Lung cancer, characterized by its molecular diversity, originates from the lung's bronchial epithelium or glandular structures. The development of lung cancer is a complex process, deeply intertwined with factors such as tobacco smoking, environmental exposures and genetic predispositions. In the current therapeutic landscape, a multifaceted approach is employed to combat this disease, including chemotherapy, radiotherapy, surgical interventions, and immunotherapeutic strategies [5]. For early-stage lung cancer patients, those with tumors classified as Stage I-IIIA, the standard treatment often involves a combination of surgical resection and chemotherapy. In contrast, patients with advanced-stage lung cancer, who lack targetable genomic mutations and are not candidates for surgical intervention, typically receive conventional chemotherapy [6]. However, these chemotherapy treatments are often associated with significant side effects and toxicity. The introduction of targeted drugs has marked a significant advancement in the treatment of lung cancer, leading to improved patient survival rates and a more optimistic prognosis. Despite these advancements, there is an urgent need to identify clinical biomarkers that can aid in the diagnosis, prognosis, and treatment of lung cancer, to ensure more effective and personalized therapeutic strategies for patients [7]. In recent years, numerous evidence has shown that post-translational modifications (PTM), especially ubiquitination modifications, are involved in the progression of many types of cancers.

1.2. Classification of lung cancer

According to different histopathological characteristics, lung cancer can be categorized into multiple subtypes based on distinct cellular features. The two most prevalent subtypes are small cell lung carcinoma (SCLC) and non-small cell lung cancer (NSCLC). Notably, NSCLC accounts approximately for 85 % of all cases [8]. NSCLC is a subtype collection originating from lung epithelium [9], based on the difference in characteristics and treatment measures, NSCLC can be subdivided into three categories, including lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and large cell lung carcinoma. Meanwhile, according to the expression of the putative transcription factor, SCLC has been divided into four molecular subgroups since 2019,

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including *ASCL1*/SCLC-A, *NEUROD1*/SCLC-N, *POU2F3*/SCLC-P, and SCLC-I [10].

2. Ubiquitination

Ubiquitination is one of the most common PTM types, which involves a wide range of essential eukaryotic cellular biochemical processes [11], such as gene transcription and silencing, DNA damage repair, cell signaling, cell cycle regulation, immune response, etc [12]. Ubiquitination modification most regularly leads to regulation of activity of various essential downstream proteins and their degradation. This intricate process necessitates the coordinated function of several cellular systems, including the ubiquitin-proteasome-autophagy system, which collectively facilitate the proper management of protein homeostasis within the cell [13]. Ubiquitination is a process of attaching ubiquitin (Ub), a 76-amino acid polypeptide chain, to the specific sites on substrate proteins, while deubiquitination is the reverse of the above action [14]. Ubiquitination involves three-step catalysis by the cascade of Ub-activating enzymes (E1s), Ub-conjugating enzymes (E2s) and Ub ligases (E3s) [15]. Firstly, E1s bind with and activate Ub through acyl-adenylation of the *C*-terminus of the Ub, then E1s transmit the activated Ub to the E2s by forming a thioester linkage with ATP providing energy. After that, E3s transfer the Ub from E2s to substrates [15]. Usually, single Ub molecules or Ub-Ub chains can be conjugated to any of seven different lysine residues (K6, K11, K27, K29, K33, K48 and K63) [16] or *N*-terminal methionine residue (M1) [15]. Compared to normal tissues, some PTM levels of specific proteins, including ubiquitination, may be altered in cells at the site of disease. Ubiquitination modification most regularly leads to regulation of activity of various essential downstream proteins and their degradation and difference in protein abundance, so targeting ubiquitination mechanisms in tumor cells is beneficial in the search for tumor-associated pathological mechanisms [17].

3. Classification of E3 ligases

Within the realm of enzymes that participate in the ubiquitination process, E3 ubiquitin ligases stand out as the most abundant, with their numbers exceeding 700 distinct members [18]. These E3 ligases exhibit a diversity in their structure and function; they can exist as single polypeptide chains or operate as part of larger protein complexes. Categorized based on their structural characteristics, E3 ubiquitin ligases can be divided into three notable families: HECT (homologous to E6-associated protein carboxyl terminus) family, RING (really interesting new gene) family and RBR (RING between RING-RING) family [19]. Each family member within these groups possesses unique functional attributes that set them apart, often due to the presence of specific protein interaction domains, as highlighted in. This specialization allows for the precise and varied regulation of ubiquitination across a wide array of cellular processes [20].

As the E3 family with the widest variety of members, RING family contains over 340 types in humans. The RING family is most typically characterized by ring finger domains, each of which is linked to two Zn^{2+} ions. RING E3s rely on their ring finger domains to bind to E2s to function as E3s [19]. On this basis, due to the different structural domains, RING E3s can be divided into several subfamilies: The Membrane-associated RING-cysteine-histidine (MARCH) subfamily, protease-associated (PA)- multiple transmembrane (TM)-RING subfamily, tripartite motif (TRIM) subfamily and RING-Ub interacting motif (UIM) subfamily [21]. In addition, based on the form in which it functions, RING E3 ligases can be further categorized into monomeric RING, homodimeric RING, heterodimeric RING, cullin-RING (CRLs), and other multisubunit RING [19].

HECT E3s remain the second largest family of E3s, this family usually contains 3 domains, including an *N*-terminal C2 lobe, a flexible chain domain and a *C*-terminal C2 lobe (Fig. 1) [22]. Three subfamilies with 28 types of HECT E3s are identified in humans, including neuronally expressed developmentally downregulated 4 (NEDD4) subfamily, HECT and RLD domain-containing (HERC) subfamily and "Other HECTs" subfamily [23]. Over the past few years, extensive researches have demonstrated the importance of HECT E3s in lung cancer [24].

There are 14 RBR E3 ligases found in humans, the member of this family has typically a characteristic of owning a triple-RING/zinc finger motif, including 2 RING domains (RING1, RING2) and an in-between-RING (IBR) domain (Fig. 1) [19]. To date, 4 subfamilies have been identified: the Ariadne subfamily which contains Ariadne domain, Parkin, heme-oxidized IRP2 ubiquitin ligase 1L (HOIL-1L) and HOIL-1-interacting Protein, also called RNF31 (HOIP) contain other domains. Recent reports have shown that RBR family participates in degenerative diseases, cancer, inflammation and other diseases [25].

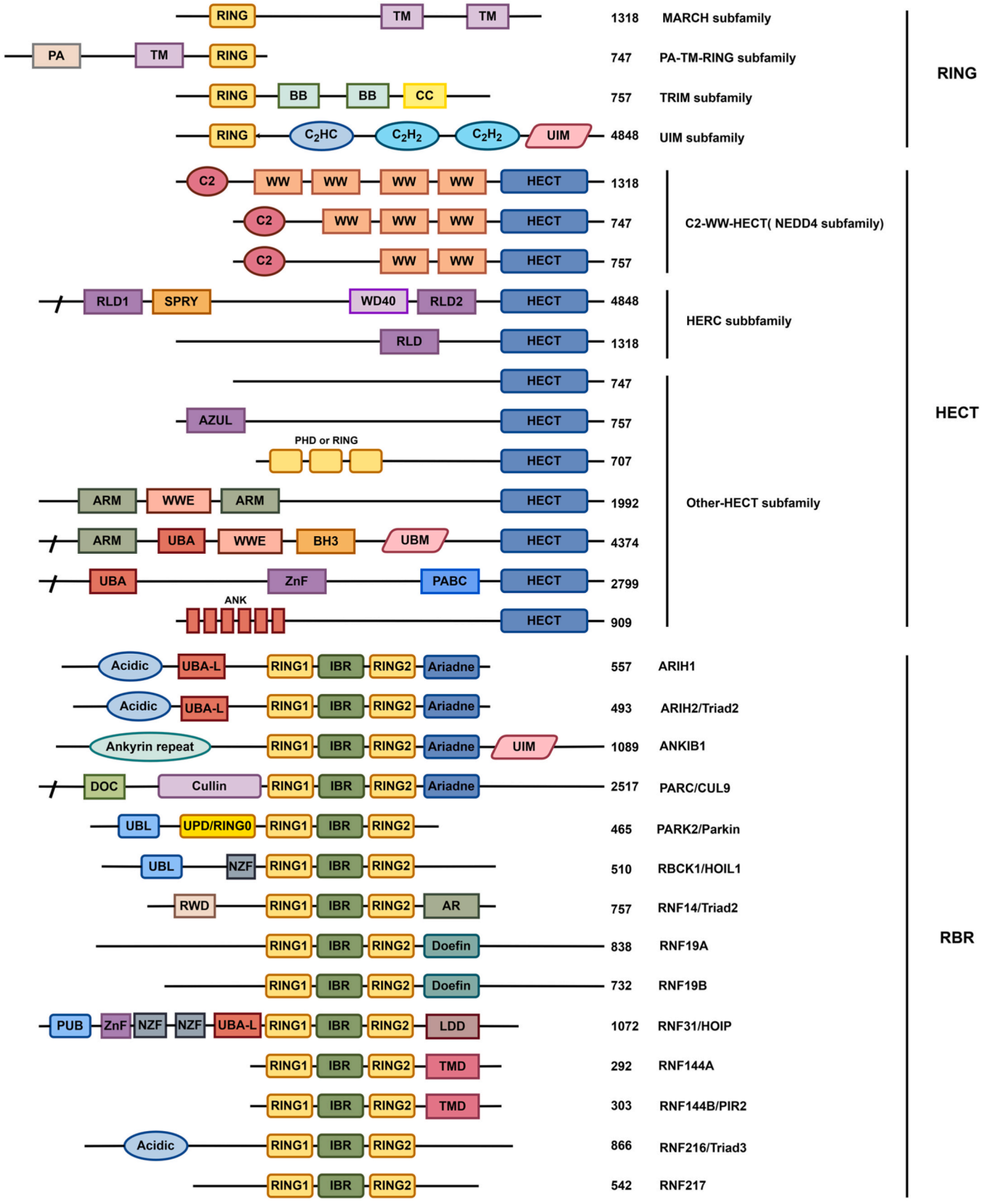
4. Advanced researches on the functions of E3 ligases in lung cancer progression

This review concentrates on the advances in mechanisms of lung cancer-associated E3s in the last few years. E3 ligases play a crucial role in regulating lung cancer progression by targeting and promoting the degradation of substrates that are abnormally accumulated or hyperactivated within key signaling pathways. In turn, they are involved in lung cancer tumorigenesis and progression, regulating the malignant phenotype of lung cancer cells and remodeling the immune microenvironment of lung cancer [26], so focusing on how E3 ligases regulate ubiquitination of substrate proteins and followed degradation process or apoptosis makes a crucial point in the diagnosis and treatment of lung cancer (Fig. 2). Due to space constraints, some of the E3s whose molecular mechanisms are not clearly defined will be listed in Table 1.

4.1. E3 ligases affecting a single phenotype of lung cancer

4.1.1. Cell proliferation

Therapeutic strategies for lung cancer, especially chemotherapy and targeted therapies, are often aimed at inhibiting the proliferation of cancer cells. Studying the molecular mechanisms of E3 ligases affecting proliferation can help develop targeted drugs in lung cancer, thereby improving therapeutic efficacy and reducing side effects. The CRLs family is the largest subfamily of E3s, and is deeply involved in the regulation of lung cancer progression. Cullin-3 (CUL3) can form as an E3 that ligates kelch like ECH associated protein 1 (KEAP1), and the KEAP1-CUL3 complex ubiquitinates and degrades nuclear factor erythroid2-related factor 2 (NRF2), thus inhibiting proliferation in NSCLC cells [27]. The Ring finger protein (RNF) family is also an important component of monomeric RING E3s. Ring finger protein 20 (RNF20), also called BRE1, regulates H2Bub1-specific monoubiquitination with the association of RNF20-RAD6, which causes promotion of the cell growth in NSCLC [28]. Rad18, also called ring finger protein 73 (RNF73), can promote the monoubiquitination of proliferating cell nuclear antigen (PCNA), which will cause downregulation of SERTA domain containing 2 (SERTAD2) and promotion of proliferation in NSCLC cells ultimately [29,30]. Casitas B lineage lymphoma (c-Cbl) interacts with EGFR on Y1045, induces K48-linked polyubiquitination and degradation of EGFR. Hence, c-Cbl acts as a negative regulator of proliferation and tumor growth in NSCLC [31]. One of members of homodimeric RING family, X-linked inhibitor of apoptosis protein (XIAP), owning a RING domain, can form homodimer and self-ubiquitinate, which will cause its proteasomal degradation, and ultimately facilitate cell growth and tumorigenesis in LUAD. This process can be promoted by formation of dimerized monoglyceride lipase (MGL) through interacting with XIAP, inducing homodimerization and autoubiquitination degradation of two XIAP molecules [32]. Seven in absentia homolog 1 (Siah1) interacts with, ubiquitinates and stabilizes notch receptor 1 (Notch1) via proteasome-related signaling, therefore activating Akt pathway and promoting proliferation in NSCLC cells [33].



(caption on next page)

Fig. 1. Schematic diagram of the domain structures of E3 ubiquitin ligases. Approximate domain positions and molecular weights are provided. E3 ligases are usually divided into three main families: RING, HECT and RBR family. Members of RING family can be further divided into four subfamilies, including MARCH, PA-TM-RING, TRIM and UIM subfamily. HECT E3s are classified into three subfamilies: C2-WW-HECT, HERC, and 'other' HECT E3 ligases. TM, multiple transmembrane; PA, protease-associated domain; UIM, ubiquitin-interacting motif; BB, B-box domain; CC, coiled-coil domain; HECT, homologous to E6AP *C*-terminus; C2, Ca^{2+} domain; WW, tryptophan–tryptophan domain; RLD, regulator of chromatin condensation 1-like domain; SPRY, SPIA and ryanodine receptor domain; WD40, WD dipeptide domain; ZNF, zinc finger; DOC, APC10/DOC domain; ARM, armadillo repeat-containing domain; UBA, ubiquitin-associated domain; WWE, WWE domain; BH2, Bcl-2 homology 3 domain; BH3, Bcl-2 homology 3 domain; ANK, ankyrin-repeat domain; SUN, SAD1/UNC domain; PABC, Mademoiselle/PABC domain; AZUL, Zn-binding *N*-terminal domain; PHD, plant homeodomain-type zinc finger; AR, androgen receptor; IBR, in-between-RING; LDD, linear ubiquitin chain-determining domain; NZF, NPL4 zinc finger domain; PUB, PNGase/ubiquitin-associated domain; RBR, RING-in-Between-RING; RWD, RING finger and WD repeat-containing; TMD, transmembrane domain; UBA-L, ubiquitin associated-like domain; UBL, ubiquitin-like.

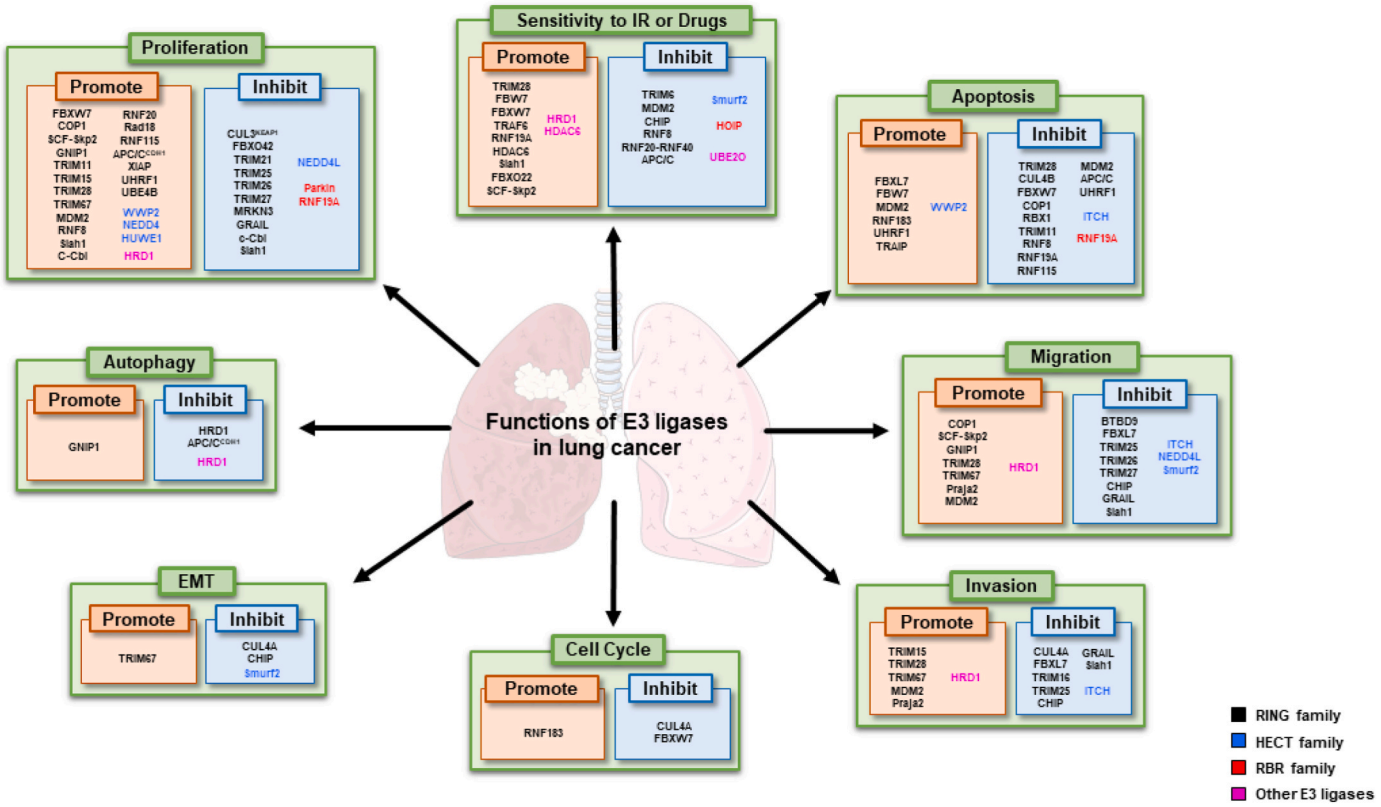


Fig. 2. The roles of E3 ubiquitin ligases in lung cancer. E3 ligases play an important role in the occurrence and progression of lung cancer and are involved in a variety of cellular biochemical processes including, thus having different functions and influence in cell proliferation, migration, cell cycle, invasion, apoptosis, autophagy, EMT and sensitivity to IR or drugs in lung cancer.

NEDD4 can degrade ATP citrate lyase (ACLY) through K48-linked ubiquitination, which in turn inhibits lung cancer cell proliferation [34]. NEDD4 also ubiquitinates and induces degradation of phosphorylated 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCL), which will result in the promotion of proliferation and tumorigenesis in NSCLC [35]. HECT, UBA and WWE domain containing E3 ubiquitin protein ligase 1 (HUWE1) can decrease the stability of PCF11 cleavage and polyadenylation factor subunit (PCF11) by ubiquitination, which promotes the proliferation of LUSC cells [36].

Parkin, as a tumor suppressor, is a member of RBR family, and participates in numerous diseases, particularly Parkinson's disease. Parkin can interact with and ubiquitinate phosphoglycerate dehydrogenase (PHGDH) at Lys 330, which causes its degradation and serine synthesis suppression. As a result, Parkin inhibits proliferation and tumorigenesis in NSCLC [37].

In lung cancer, aberrant activity of certain E3 ubiquitin ligases may lead to uncontrolled cell proliferation and promote tumorigenesis and progression. With further research, more novel anticancer drugs targeting E3 ligases may emerge in the future, providing more therapeutic options for lung cancer patients. However, the clinical application of these drugs is still subject to rigorous clinical trials and safety assessments [38].

4.1.2. *Migration*

In lung cancer, especially small cell lung cancer, cell migration is a key feature of tumor metastasis and is a critical link in the process of lung cancer metastasis [39]. By developing small molecule inhibitors targeting specific E3 ubiquitin ligases, it is possible to intervene in the migration and metastasis of tumor cells and provide new strategies for lung cancer treatment. BTB domain containing 9 (BTBD9), a specific adaptor component of the Cul3-ROC1 (CRL3) complex, can bind to and promote TNFAIP1 ubiquitination and degradation. By this way, BTBD9 suppresses NSCLC cell migration [40]. A small-molecule inhibitor of NEDD8 activating enzyme E1 (NAE), MLN4924, can block the activity of CRLs, cause the accumulation of TNFAIP1. Besides, chromobox 4 (CBX4) can regulate the sumoylation status of B-cell-specific moloney murine leukemia virus insertion site 1 (BMI1), recruit BMI1 to the DNA damage sites in mammalian cells, and upregulate cell migration-related proteins including matrix metallopeptidase 2 (MMP2), MMP9 and *C*-X-C motif chemokine receptor 4 (CXCR4) via BMI1 [41].

Table 1
Summary of E3 ligases in lung cancer.

Family	Subfamily	E3 ligase	Substrates in lung cancer	The way E3 ligases affect substrates	Function in lung cancer	Reference
RING	Monomers	TRIM6	SLC1A5	Degradation	Inhibit sensitivity to drugs	[51]
		GNIP1	14-3-3ζ	Degradation through K48-linked ubiuqitination	Promote autophagy, proliferation, migration	[70]
		TRIM11	DUSP6		Promote proliferation, inhibit apoptosis	[71]
		TRIM15	KEAP1	Degradation through K48-linked ubiuqitination	Promote proliferation, invasion	[77]
		TRIM16	Vimentin	Degradation through K48-linked ubiuqitination	Inhibit invasion, metastasis	[42]
		TRIM21	GAC	Activity affected by K63-linked ubiquitination	Inhibit proliferation	[78]
			PFKP	Proteasomal degradation	Inhibit glycolysis	[64]
		TRIM25	IGF2BP	Proteasomal degradation	Inhibit proliferation, migration, invasion	[79]
		TRIM26	PBX1	Degradation	Inhibit proliferation, migration	[81]
			PI3K p85	Proteasomal degradation	Inhibit proliferation	[80]
			AKT			
		TRIM27	SIX3	Degradation	Inhibit proliferation, migration	[127]
		TRIM28	RLIM	Proteasomal degradation	Promote proliferation, migration, invasion, sensitivity to drugs, inhibit apoptosis	[83]
			IRF5		Inhibit TIME	[128]
			IRF8			
		TRIM29	E-cadherin	Autophagy degradation	Promote proliferation, migration and invasion	[85]
		TRIM67			Promote the proliferation, migration, invasion	[129]
		MID1	PP2A		Inhibit apoptosis, proliferation and cell cycle arrest	[130]
		Praja2	HOXB9	Proteasomal degradation	Promote migration, invasion	[88]
		CNOT4			Promote T lymphocyte infiltration	[131]
		A20			Inhibit immune escape	[132]
		MKRN3	PABPC1		Inhibit proliferation	[133]
		RNF8	Akt	Phosphorylation through K63-linked ubiquitination	Promote cell growth, inhibit apoptosis and sensitivity to drugs	[99]
		RNF20	H2B	Phosphorylation of H2B through ubiquitination	Promote cell growth	[52]
		Rad18	PCNA	Degradation	Promote proliferation	[29,30]
		TRAF6	STAT3	Phosphorylation through K63-linked ubiquitination	Promote sensitivity to drugs	[61]
		RNF115	APC	Proteasomal degradation	Promote proliferation, metabolism, inhibit apoptosis	[86]
		GRAIL	STAT3		Inhibit proliferation, migration, invasion	[134]
			c-Myc			
		RNF183	SHP2	Proteasomal degradation	Promote apoptosis, cell cycle	[100]
		MARCH8	PD-L1			[135]
		UHRF1			Promote cell proliferation, inhibit apoptosis	[136]
		DZIP/ hRUL138	Cyclin D1	Interacts at 3′UTR of substrate mRNA and stabilizes substrate	Promote cancer progression	[57]
		UBE4B	p53	Proteasomal degradation	Promote proliferation	[137]
		c-Cbl	EGFR	Degradation	Inhibit proliferation, tumor growth	[31]
		TRAIP	IκB		Promote apoptosis	[138]
	Homodimers	CHIP	CIB1	Proteasomal degradation through K48-linked ubiuqitination	Inhibit migration, EMT, tumor metastasis	[95]
			MAST1	Degradation	Inhibit sensitivity to IR	[96]
			SMAD3	Proteasomal degradation	Inhibit migration, invasion, cell adhesion, vasculogenic mimicry	[97]
			OTUD3	Proteasomal degradation	Inhibit invasion, metastasis	[98]
		XIAP	XIAP	Proteasomal degradation	Promote cell growth	[139]
		Siah1	Notch1	Degradation	Promote proliferation	[33]
			HMGCR	Proteasomal degradation	Promote sensitivity to drugs, inhibit proliferation, migration, invasion	[87]
		MDM2	p53	Degradation	Inhibit apoptosis, sensitivity to drugs	[101]
			Klotho		Promote migration, invasion, inhibit apoptosis	[105]
	Heterodimers	BMI1	NLRC5	Degradation	Promote immune escape	[58,62]
		RNF20-RNF40	H2B	Phosphorylation of H2B through ubiquitination	Inhibit sensitivity to IR	[52]
	CRLs	BTBD9	TNFAIP1	Degradation	Inhibit migration	[40]
		$CUL3^{KEAP1}$	NRF2	Degradation	Inhibit proliferation	[27,140]
		FBXO22	BACH1	Degradation	Promote sensitivity to IR and drugs	[141]
			PD-L1	Degradation		
		FBXO42	SUMO1	Proteasomal degradation	Inhibit proliferation	[142]
		CUL4B	*p*-FOXO3A	Proteasomal degradation	Inhibit apoptosis	[66]
		βTrCP	YAP	Proteasomal degradation	Promote tumor growth	[60]
		FBW7	Mcl-1	Degradation	Promote apoptosis	[49]
			PD-1	Proteasomal degradation	Promote sensitivity to immunotherapy	[50]
		FBXW7	HSF1	Degradation	Promote sensitivity to drugs	[72]
			ENO1	Proteasomal degradation	Promote proliferation, inhibit cell cycle	[73]

(*continued on next page*)

Table 1 (*continued*)

Family	Subfamily	E3 ligase	Substrates in lung cancer	The way E3 ligases affect substrates	Function in lung cancer	Reference
			c-Myc	Degradation	Inhibit macrophage polarization	[75]
			ERK3	Proteasomal degradation	Promote proliferation	[74]
		FBXL7	PFKFB4	Degradation	Promote apoptosis, inhibit migration, invasion, glucose metabolism	[67]
		COP1	c-Jun	Proteasomal degradation	Promote proliferation	[89]
			p-IκBα	Proteasomal degradation	Promote proliferation, migration, inhibit apoptosis	[90]
			p53			
			STAT3			
			β-catenin			
			p27			
			C/EBPα			
		RBX1	UBE2F	Proteasomal degradation	Inhibit apoptosis	[45]
		SCF-Skp2	p27	Proteasomal degradation	Promote proliferation, migration	[91]
			E-cadherin			
			MLKL	Proteasomal degradation	Inhibit sensitivity to drugs	[92]
	Other multisubunit E3s	APC/C	securin	Proteasomal degradation	Inhibit premature senescence, apoptosis, sensitivity to drugs	[106]
			cyclin B1			
		APC/C^{CDH1}	DEPTOR	Degradation	Promote proliferation, inhibit autophagy	[93]
HECT	NEDD4	NEDD4	ACLY	Proteasomal degradation	Promote proliferation	[34]
			p-HMGCL	Degradation	Promote proliferation	[35]
		NEDD4L	β-catenin	Proteasomal degradation	Inhibit proliferation, metastasis	[107]
			Notch2	Proteasomal degradation	Inhibit proliferation	[108]
			UBE2T	Degradation	Inhibit proliferation	[109]
		WWP2	PTEN		Promote proliferation, inhibit apoptosis	[110]
			BMPR1A	lysosomal degradation	Promote metastasis	[111]
		ITCH	TXNIP	Proteasomal degradation	Inhibit migration, invasion, ROS generation, inflammation and apoptosis	[112]
		Smurf2	KRAS	Degradation	Inhibit sensitivity to drugs	[113, 114]
			L858 R/T790 M EGFR	Degradation	Inhibit sensitivity to drugs or IR	[114]
			TβRI	Proteasomal degradation	Inhibit migration, EMT, extravasation	[115]
	Other HECTs	HUWE1	PCF11	Proteasomal degradation	Promote proliferation	[36]
		HACE1	RAC	Proteasomal degradation	Inhibit ROS generation, DNA damage	[65]
		TRIP12	NFATc1	Proteasomal degradation	Promote immune cell infiltration	[64]
RBR		Parkin	PHGDH	Proteasomal degradation	Inhibit proliferation	[37]
		HOIP	PTEN	Degradation through K48-linked ubiuqitination	Inhibit sensitivity to drugs	[53]
		RNF19A	p53	Proteasomal degradation	Promote proliferation, inhibit apoptosis	[117]
Other E3 ligases		HRD1	SIR2	Proteasomal degradation	Promote proliferation, invasion	[116]
			ATG3	Proteasomal degradation	Inhibit autophagy	[143]
		HDAC6	Chk1	Degradation	Promote sensitivity to IR	[54]
		UBE2O	Mix1	Proteasomal degradation	Inhibit sensitivity to IR	[55]

Abnormal activity of E3 ligases may lead to enhanced and migration of lung cancer cells. E3 ligases regulate a variety of proteins associated with cell migration through the ubiquitination pathway, including cytoskeletal proteins, cell adhesion molecules, and signal transduction molecules. Therefore, drug development targeting E3 ligases, including small molecule inhibitors, may provide new strategies for lung cancer treatment [40].

4.1.3. Invasion

Cell invasion is another key feature of tumor metastasis in lung cancer. Tripartite motif containing 16 (TRIM16), plays a key role in the transcription and apparent modification of mRNA. Through K48-linked polyubiquitination of Vimentin, TRIM16 binds to Vimentin and decreases expression level of Vimentin via ubiquitin-proteasome pathway, which causes the half-life of Vimentin to be shortened to less than 12 h. Hence, TRIM16 acts as an inhibitor of invasion and metastasis in LUAD [42].

The role of E3 ligases in lung cancer cell invasion and their potential as drug targets are being continuously explored. E3 ligases regulate many proteins associated with cell invasion and affects extracellular matrix remodeling, resulting in increased invasiveness of lung cancer cells [43].

4.1.4. Apoptosis and autophagy

Apoptosis is a programmed cell death process, while autophagy is the process of recycling and degradation of intracellular material, both of which play important roles in maintaining cellular homeostasis and tumor development [44]. Ring-box protein 1 (RBX1), a key component of CRLs, interacts with and promotes the proteasomal degradation of ubiquitin conjugating enzyme E2 F (UBE2F), thus suppressing evasion of platinum-induced apoptosis in NSCLC cells [45].

The development of drugs that target E3 ligase opens up new possibilities for lung cancer treatment. By restoring the normal regulation of apoptosis and autophagy, drugs target E3s slow down tumor progression. In addition, the combination of these drugs with existing radiotherapy, chemotherapy or immunotherapy may produce a synergistic effect and improve the therapeutic efficacy [46].

4.1.5. Sensitivity to ionizing radiation (IR) or drugs

E3 ligases can modulate chemotherapeutic drug target proteins, such as DNA repair proteins and transcription factor through ubiquitination modifications, thereby affecting the sensitivity of cancer cells to radiotherapy or specific chemotherapeutic drugs [46,47]. F-box protein 22 (FBXO22), which is another member of CRLs, can promote the degradation of BTB domain and CNC homolog 1 (BACH1) in lung cancer cells [48]. Besides, FBXO22 induces polyubiquitination and degradation of programmed cell death 1 ligand 1 (PD-L1), leading to upregulation of

sensitivity to ionizing radiation (IR) and cisplatin in NSCLC cells [47]. Deguelin can enhance F-BOX and WD repeat domain-containing 7 (FBW7)-mediated myeloid cell leukemia-1 (Mcl-1) ubiquitination and degradation [49]. It was reported that FBW7 can also interact with programmed cell death 1 (PD-1), promote its K48-linked polyubiquitination on Lys 233 residue and degradation in a phosphorylation-dependent manner, which causes cytotoxic lymphocytes infiltrating the tumor microenvironment and increasing sensitivity to anti-PD-1 blockade therapy in NSCLC [50]. Tripartite motif containing 6 (TRIM6) interacts with, induces ubiquitination and degradation of solute carrier family one member five (SLC1A5), which leads to suppression of the import of glutamine, glutaminolysis, lipid peroxidation and ferroptosis in lung cancer cells and impairment of chemotherapeutic effects of cisplatin and paclitaxel [51]. Studies have shown that the RNF20-RNF40 complex can mediate monoubiquitination of histone H2B at Lys 120, inhibiting IR-induced cell death sensitivity in SCLC cells [52].

HOIP can interact with PTEN, promoting K48-linked polyubiquitination and degradation of PTEN, facilitating chemotherapy-related inhibition in lung cancer [53]. With the DAC1 domain which contains E3 ligase activity, Histone Deacetylase 6 (HDAC6) ubiquitinates and promotes the degradation of checkpoint kinase 1 (Chk1) at K436. Meanwhile, depletion of HDAC6 increases IR sensitivity in NSCLC cells [54]. Ubiquitin conjugating enzyme E2 O (UBE2O), which has E3 ligase activity, can interact with and degrade MAX interactor 1 (Mix1) through K46-linked polyubiquitination, and enhance tumorigenesis and radio-resistance in lung cancer [55].

Limited options for target therapy and IR- and drug-resistance still block the development of clinical treatment of lung cancer [56]. In the future, the E3 ligase targets mentioned in this section are expected to be used in combination with existing chemotherapy drugs to improve treatment efficacy and delay or overcome the development of drug resistance.

4.1.6. Cell cycle

E3 ligases are involved in regulating key proteins in the cell cycle through the ubiquitination pathway, such as cell cycle dependent kinase inhibitors (CKIs), cyclins, and cyclin dependent kinases (CDKs). The ubiquitination and subsequent degradation or activation of these proteins directly affect the progression of the cell cycle, including G1/S transition, G2/M transition, and cell division [15]. DAZ interacting zinc finger protein 3 (DZIP3, also called hRUL138) interacts with and ubiquitinates Cyclin D1 on Lys 63, then upregulates stability of Cyclin D1 mainly in the G1 phase of the cell cycle. Overall, DZIP3 promotes cancer progression in NSCLC [57].

Small molecule inhibitors of E3s have a significant impact on cell cycle regulation. Future study will focus on the clinical application potential of these inhibitors, giving further therapeutic choices for lung cancer patients.

4.1.7. Immune-related functions

E3 ligases can influence immune cell function, including the expression and stability of immune checkpoint molecules, leading to regulating tumor immune escape and anti-tumor immune responses [58,59]. Beta-transducin repeat containing E3 ubiquitin-protein ligase (βTrCP), also known as FBW1A, promotes LUAD tumor growth by interacting with, ubiquitinating and mediating proteasomal degradation of YAP [60]. It's been reported that TNF receptor associated factor 6 (TRAF6), also known as ring finger protein 85 (RNF85), could induce phosphorylation and K63-linked polyubiquitination of STAT3. By this way, TRAF6 improves the immunosuppressive effects of myeloid-derived suppressor cells (MDSCs) [61]. As a heterodimers RING E3, BMI1 can induce H2A ubiquitylation at Lys 119. BMI1 can induce ubiquitination and degradation of NLR family CARD domain containing 5 (NLRC5), given that BMI1 can facilitate immune escape in NSCLC [58,62]. Thyroid Hormone Receptor Interacting Protein 12 (TRIP12), a HECT E3, also known as Ubiquitin Ligase for ARF (ULF) [63], ubiquitinates and degrades nuclear factor of activated T cells 1 (NFATc1), thereby downregulating PD-1 expression, resulting in increasing cancer infiltrating $CD8^+$ T cells and inhibition in LLC growth in mice [64].

4.1.8. Other functions

HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1 (HACE1) ubiquitinates and promotes proteasomal degradation of active AKT serine/threonine kinase 1 (AKT1, also called RAC) proteins, thus suppressing ROS generation, DNA damage and tumorigenesis in NSCLC [65].

4.2. E3 ligase affecting multiple phenotypes of lung cancer

In fact, only a minority of E3 ligases affect a single phenotype of lung cancer cells, the majority of E3 ligases are capable of affecting a variety of cellular functions through PTM of substrates, such as simultaneously affecting cell proliferation, migration, and invasion, while promoting or inhibiting apoptosis, autophagy, or ferroptosis. In this section, the functions of E3 ligases are described according to their family classification.

Cullin 4 B (CUL4B) suppresses cell apoptosis via the Ub-proteasome degradation pathway of ERK-induced phosphorylation of FOXO3A in LUSC and SCLC cells [66]. F-box and leucine rich repeat protein 7 (FBXL7) ubiquitinates and degrades PFKFB4, thus inhibiting glucose metabolism, migration, invasion and inducing apoptosis in NSCLC cells [67]. The glycogen-interacting protein (GNIP) gene, also called trim 7, encodes more than four distinct isoforms of GNIP protein, including glycogen-interacting protein 1 (GNIP1), glycogen-interacting protein 2 (GNIP2), glycogen-interacting protein 3 (GNIP3), and tripartite motif containing 7 (TRIM7) [68]. As the longest isoform, GNIP1 promotes the degradation of 14-3-3ζ (also called tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta (YWHAZ) through K48-linked ubiquitination. Based on that, GNIP1 can promote autophagy, proliferation and migration in NSCLC cells [69,70]. Tripartite motif containing 11 (TRIM11) ubiquitinates dual-specificity phosphatase 6 (DUSP6), subsequently promotes proliferation, and inhibits apoptosis in NSCLC cells by regulating DUSP6-ERK1/2 pathway [71]. Skp-1-Cull-F-box (SCF) ubiquitin ligase complex (FBXW7), a CRL E3, targets many key regulators in lung cancer. FBXW7 interacts with phosphorylated-heat shock transcription factor 1 (pHSF1) at Ser 303/307 and induces degradation of HSF1. This process affects drug resistance development in paclitaxel- and doxorubicin-resistant by ERK1/2 activation NSCLC cells [72]. FBXW7 can inactivate cell cycle signaling in LUAD either by direct degradation of enolase 1 (ENO1) protein or by degradation of c-Myc to inhibit the binding between c-Myc and the ENO1 promoter [73]. Moreover, inactivation of FBXW7 causes accumulation of p53, and increases p53 transacivating p21 and inhibiting transcription of cell cycle genes, which leads to cell senescence [73]. Also, FBXW7 ubiquitinates and promotes degradation of ERK3 through binding between C34 domain of ERK and the WD40 domain of FBXW7, thus promoting proliferation in lung cancer cells [74]. Besides, FBXW7 interacts with c-Myc, inhibits M2-like tumor-associated macrophages (TAM) polarization by catalyzing K48-linked polyubiquitination of c-Myc via ubiquitin-proteasome system, and acts as a suppressor factor in tumor progression in Lewis lung carcinoma cells (LLCs) [75]. In addition, m^6A methylation induced by methyltransferase 3 (METTL3) or miR-92a-mediated reduction in FBXW7 expression could downregulate the inhibitory effect of FBXW7 on lung cancer [76]. Tripartite motif containing 15 (TRIM15) enhances degradation of KEAP1 via K48-linked ubiquitination, which is the principal regulator of NRF2 degradation, causing NRF2 to escape from KEAP1-mediated degradation, and thus promoting antioxidant response, cell proliferation and invasion in NSCLC [77]. Tripartite motif containing 21 (TRIM21) can interact with GAC, leading to K63-linked ubiquitination and downregulation of protein activity, thus inhibiting proliferation and tumorigenesis in NSCLC

cells [78]. Also, TRIM21 polyubiquitinates and induces proteasomal degradation of phosphofructokinase platelet (PFKP), which can be inhibited by AKT-mediated phosphorylation and F-action bundling and stress-fibre formation spatial sequestration, causing the downregulation of glycolysis in NSCLC cells [64]. Tripartite motif containing 25 (TRIM25) is also an RNA-binding protein and can catalyze polyubiquitin chains adding to insulin-like growth factor 2 mRNA-binding protein (IGF2BP) proteins for degradation in a manner dependent on proteasome-mediated signalings in NSCLC cells, which enables TRIM25 to have an inhibitory effect on proliferation, migration and invasion in NSCLC cells and activating antitumor immunity [79]. Tripartite motif containing 26 (TRIM26) suppresses phosphorylation of PI3K p85 and AKT, leading to inhibition of proliferation in NSCLC cells [80]. Besides, TRIM26 can interact with and induce K48-linked polyubiquitination and proteasomal degradation of Pre-B cell leukemia transcription factor 1 (PBX1), leading to inhibition of proliferation and migration in NSCLC cells [81]. Tripartite motif containing 28 (TRIM28) induces cisplatin resistance by promoting proliferation and suppressing apoptosis in NSCLC cells [82], TRIM28 also polyubiquitinates and induces proteasome-mediated degradation of E3 ring finger protein, LIM domain interacting (RLIM, also called RNF12) while promoting the stability of murine double minute 2 (MDM2), causing degradation of p53 and upregulation of proliferation, migration and invasion in NSCLC cells [83]. Tripartite motif containing 29 (TRIM29) is reported to be a potential molecular target for NSCLC treatment [84], which can promote proliferation, migration and invasion by regulating autophagolysosomal degradation of E-cadherin in LUSC cells [85]. With BCA2 zinc-finger domain, ring finger protein 115 (RNF115) ubiquitinates β-catenin regulator adenomatous polyposis coli (APC), leading to downregulation of apoptosis and upregulation of proliferation and metabolism by modulating Wnt/β-catenin pathway in LUAD cells [86]. However, it is proved that Siah1 interacts, ubiquitinates and degrades 3-hydroxy-3--methylglutaryl-CoA reductase (HMGCR) through ubiquitin-proteasome pathway, subsequently upregulating cholesterol synthesis, cisplatin sensitivity and downregulating NSCLC tumor development such as proliferation, migration and invasion [87]. An essential E3 in monomeric RING, praja ring finger ubiquitin ligase 2 (Praja2) can interact with homeobox B9 (HOXB9). Praja2 induces degradation of HOXB9 by polyubiquitination and promotes migration and invasion of LUAD cells [88]. COP1, also called RFWD2, decreases expression of c-Jun via ubiquitination, thus increasing histone H3 acetylation of PD-L1 promoter, which improves proliferation of T cells in cisplatin-resistant NSCLC [89]. In contrast, COP1 ubiquitinates and induces the degradation of *p*-IκBα, p53, signal transducer and activator of transcription 3 (STAT3), β-catenin, p27 and C/EBPα in the proteasome-mediated pathway, which promotes proliferation and migration but inhibits apoptosis in NSCLC [90]. SCF-Skp2 is an E3 ligase complex belonging to CRLs and can induce the degradation of p27 and E-cadherin through ubiquitination, which will upregulate proliferation and migration in NSCLC cells. The above process can be reversed by a plant-derived Skp2 inhibitor, betulinic acid (BA), and pRb [91]. Another study notes that Skp2 induces proteasomal degradation of mixed-lineage kinase domain-like (MLKL) through K48-ubiquitination, knockdown of Skp2 induces p27 expression and cell cycle arrest which may enhance the anti-tumor effect of cisplatin by DNA damage in NSCLC cells [92]. APC/C^{CDH1} ubiquitinates and degrades DEP domain containing MTOR interacting protein (DEPTOR), causing activation of mTOR signaling, which promotes proliferation and inhibition of autophagy in NSCLC cells [93]. Another important member of homodimeric RING family is carboxyl-terminus of hsp70-interacting protein (CHIP), also known as STIP1 homology and U-Box containing protein 1 (STUB1) [94]. CHIP can cause proteasomal degradation of calcium and integrin binding 1 (CIB1) via promoting polyubiquitination of CIB1 at Lys 10 and Lys 65. CHIP-mediated CIB1 ubiquitination can suppress EMT, tumor metastasis and migration of LUAD [93] which also means a better prognosis [95]. CHIP ubiquitinates and downregulates stability of microtubule associated serine/threonine kinase 1 (MAST1). In this way, CHIP inhibits tumorigenic ability and radiation resistance in NSCLC stem cells [96]. CHIP interacts with MH2 domain of SMAD family member 3 (SMAD3), ubiquitinates and induces proteasome degradation of SMAD3, leading to inhibition in migration, invasion, cell adhesion and vasculogenic mimicry in NSCLC [97]. Besides, CHIP interacts with OTU deubiquitinase 3 (OTUD3) and induces polyubiquitination and degradation of OTU3, thereby inhibiting OTUD3-glucose regulated protein 78 (GRP78) signaling, and impairing invasion and metastasis in NSCLC [98]. Ring finger protein 8 (RNF8) mediates DNA-damage-induced activation of Akt through K48-linked ubiquitination, which facilitates cell growth, inhibits apoptosis and causes chemoresistance in NSCLC [99]. Ring finger protein 183 (RNF183) interacts and ubiquitinates protein tyrosine phosphatase non-receptor type 11 (PTPN11, also called SHP2), leading to activation of STAT3 pathway and promotion of apoptosis and cell cycle in LUAD cells [100]. MDM2 is an important member of the homodimeric RING family. It has been proved that MDM2 is strongly related to p53 level in lung carcinogenesis [101], and overexpression of MDM2 can induce primary resistance to EGFR-tyrosine kinase inhibitors (TKIs) [102]. MDM2 can ubiquitinate and degrade p53, thus preventing apoptosis in NSCLC cells [103]. However, mutant p53 reduces susceptibility to MDM2-mediated degradation instead of nonsense-mediated decay (NMD) [104]. MDM2 can also interact with and ubiquitinate Klotho, leading to promotion of migration and invasion but inhibition of apoptosis in NSCLC [105]. Anaphase-promoting complex/cyclosome (APC/C) can degrade securin and cyclin B1, causing the exit of anaphase and mitosis, thus suppressing premature senescence, apoptosis [106] and chemotherapeutic drug-induced NSCLC cell death [106].

One member of NEDD4 subfamily, NEDD4 like E3 ubiquitin protein ligase (NEDD4L), can be upregulated by β, β-dimethyl-acryl-alkannin (ALCAP2), thus facilitating the binding of ubiquitin molecules to β-catenin, which ultimately affects the WNT-triggered transcription of genes including surviving, cyclin D1 and MMP9, and ultimately inhibit the proliferation and metastasis of LUAD cells [107]. NEDD4L ubiquitinates and induces proteasomal degradation of notch receptor 2 (Notch2), downregulating Notch signaling activation and proliferation in LUAD cells [108]. Besides, NEDD4L is also reported to inhibit mTOR pathway activity and can be deregulated by EGFR [108]. Also, NEDD4L ubiquitinates and degrades ubiquitin conjugating enzyme E2 T (UBE2T), and subsequently inhibit PI3K/AKT pathway, which finally causes repression of proliferation in LUAD cells [109]. WW domain-containing E3 ubiquitin protein ligase 2 (WWP2) can interact with and be downregulated by etomidate, a small molecule inhibitor, thus WWP2 overexpression promoting the expression of PTEN and proliferation, and reducing apoptosis in NSCLC cells [110]. WWP2 also polyubiquitinates bone morphogenetic protein receptor type 1 A (BMPR1A) and induces its lysosome-mediated degradation, thus promoting lung-specific metastasis [111]. Another member of NEDD4 family, itchy E3 ubiquitin protein ligase (ITCH) interacts and promotes proteasomal degradation of thioredoxin interacting protein (TXNIP), based on that, ITCH acts as a negative stimulus to migration, invasion, ROS generation, inflammation and apoptosis in lung cancer cells [112]. It has been reported that SMAD Ubiquitination Regulatory Factor 2 (Smurf2), a HECT E3, can regulate the Ub-mediated degradation of oncogenic KRAS [113, 114]. Smurf2 can also induce polyubiquitination and downregulate stability of L858 R/T790 M EGFR, resulting in tolerance to TKIs or IR in lung cancer cells [114]. Smurf2 promotes polyubiquitination and proteasomal degradation of transforming growth factor beta receptor 1 (TβRI), this process can be involved by LncRNA LITATS1, which can interact with both TβRI and Smurf2 and upregulate the cytoplasmic retention of Smurf2 and finally leads to inhibition of EMT, migration and extravasation in NSCLC cells [115].

E3 ubiquitin ligase 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase degradation 1 (HRD1), can interact with sirtuin 2 (SIR2), promote its ubiquitination and degradation through proteasome

pathway, thus promoting cell migration, invasion and tumorigenesis in NSCLC [116]. The ring finger protein 19 A (RNF19A) downregulates p53, p21, and B-cell lymphoma-2 (BCL2) associated X, apoptosis regulator (BAX) expression but upregulates Cyclin D1, cyclin dependent kinase 4 (CDK4), cyclin dependent kinase 6 (CDK6) and BCL2 expression in NSCLC cells. Moreover, RNF19A promotes proliferation and reduces apoptosis in NSCLC cells by interacting with, ubiquitinating and inducing proteasomal degradation of p53 [117] (see Fig. 3).

5. E3 ligase in clinical applications

In the contemporary landscape of oncology, the utilization of precision-targeted inhibitors and agonists that are specific to E3 ligases remains a relatively uncommon practice within cancer clinics. The primary focus of such clinical applications has been on the prominent E3 ligases, notably MDM2 and Skp2, which are known for their significant roles in the pathogenesis of various cancers. While the clinical use of inhibitors directed at these star E3 ligases is more established, the exploration of inhibitors that target a broader spectrum of E3 ligases is an emerging field. Several inhibitors have been identified that are designed to target E3 ligases beyond MDM2 and Skp2, although these are less frequently discussed in the clinical context. When it comes to the therapeutic targeting of MDM2, the strategy often involves the disruption of the critical interaction between the MDM2 protein and the tumor suppressor p53. This interaction is pivotal as it can lead to the degradation of p53, thereby attenuating its tumor-suppressive functions. A variety of small molecule inhibitors have been developed to interfere with this interaction, with the aim of stabilizing the p53 protein and restoring its tumor-suppressive activity. Notable examples include: Nutlin and its analogues, RG7112, idasanutlin, AMG-232, APG-115, BI-907828, CGM097, milademetan and siremadlin inhibitors [44,118]. Among them, Nutlin-3a has been proved to induce KRAS mutant/p53 WT lung cancer specific methuosis-like cell death [119], and Nutlin-3 can cause NSCLC stem cells to axitinib-induced apoptosis [120]. However, most of drugs targeting MDM2 are still being investigated in clinical trials, and there are even fewer small molecule inhibitors available for targeted lung cancer therapy. Moreover, some MDM2 inhibitors also have the defect of being unable to target mutant p53. So currently, combination therapies with MDM2 inhibitors and chemotherapeutic agents or other targeted therapy drugs such as EGFR-TKIs and mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors were found to have efficacy in multiple lung cancer models [103,121].

Other E3 inhibitors, such as SMIP004, an inhibitor of Skp2, which was found to downregulate cell proliferation of breast cancer [122]. ARV-825, an inhibitor of bromodomain and extra terminal (BET) proteins, which used proteolysis-targeting chimera (PROTAC) technology to recruit BET proteins to the E3 ligase for degradation. ARV-825 treatment was shown to cause proliferative suppression, cell cycle arrest, and apoptosis in neuroblastoma [123]. Taken together, the above drugs targeted E3s are expected as a potential therapeutic strategy for the treatment of lung cancers. As our understanding of the molecular underpinnings of cancer continues to evolve, so too will the precision and effectiveness of these targeted therapeutic strategies.

5.1. Prospect

Due to the high recurrence rate and metastatic nature, lung cancer remains one of cancers with the lowest cure rate. Although there are significant advances in lung cancer immunotherapy and targeted therapies, many patients still experience side effects and harmful effects of drug or radiation resistance, which can lead to recurrence and metastasis of lung cancer. There are numerous carcinogens involved in the occurrence and progression of lung cancer [117]. Also, oncogene mutation or inactivation may lead to lung cancer. Emerging evidence proved that E3s have been essential functions in oncogenesis and tumor progression in lung cancer for ubiquitin modification. In this process, E3s can modify some key proteins to regulate their activity or expression, thus influencing the downstream signaling in lung cancer. By this way, E3s regulate cell cycle, DNA repair, cell death and many other tumor malignant phenotypes [124]. Through ubiquitination, E3s target substrates to proteasomal degradation, therefore, binding site mutation or abnormally interruptions to the target recognition process can both cause accumulation of some oncogenic substrates. However, molecular mechanisms other than ubiquitin-proteasome-system (UPS), including selective autophagy programmed cell death of E3 ligases still lack in-depth study, so the exact interaction between E3 ligases and their substrates urgently need investigation [19]. Besides, drug targets, inhibitors and biomarkers for E3 ligases are still hard to meet needs of clinical diagnosis and treatment of lung cancer [14,24], which should be a key focus of future research. Protein-protein interaction inhibitors, PROTACs, molecular glues and related molecules are the most common small molecule drugs to target E3s. PROTACs can ubiquitinate and degrade the substrate protein through their unique structures, which

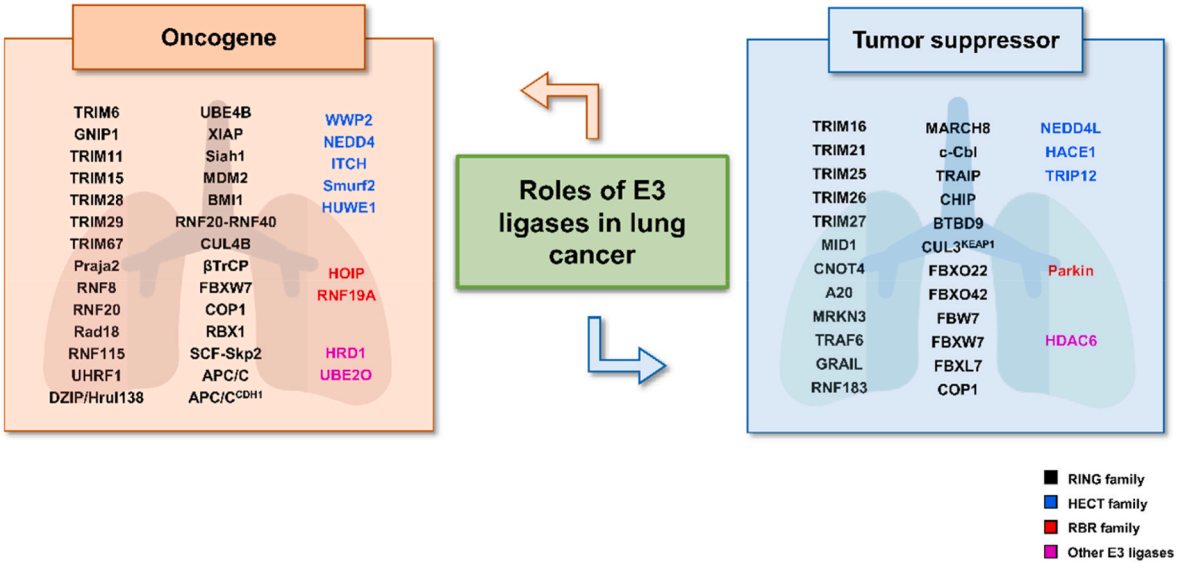


Fig. 3. Classification of E3 ligases in lung cancer according to oncogenic/tumor suppressor gene type.

consists of two ligands connected by a linker, with one ligand binding to a target protein and another one binding to an E3 ubiquitin ligase [25]. Compared to standard catalytic inhibition, PROTACs may produce more potent effects on select signaling pathways. PROTACs have been developed against many cancer targets, leading to promising therapeutic opportunities for advanced lung cancer, such as EGFR-, ALK- and KRAS-targeting PROTACs [125], however, the substrate specificity of E3s, poor cellular permeability and subpar pharmacokinetic profiles greatly limit their drug-forming property. Molecular glues exhibit lower molecular weight, greater cell permeability, and better pharmacokinetic and pharmacodynamic profiles as compared to PROTACs. However, most known molecular glues are identified serendipitously, such as IMiDs, auxin and rapamycin, and the understanding of their interaction modes is limited [56,126]. Researches on E3s on lung cancer are still focused on a few members of the RING family, especially MDM2, while little research has been done on other E3s. As a result, researchers have found very few remarkable drugs to target HECT and RBR E3 ligases until now, so expansion of knowledge in this area will be both a notable opportunity and a challenge.

CRediT authorship contribution statement

Jingwen Yu: Writing – review & editing, Writing – original draft. **Yiqi Zhao:** Writing – review & editing. **Yue Xie:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

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