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Review Article

Regulation of apoptosis by ubiquitination in liver cancer

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Abstract: Apoptosis is a programmed cell death process critical to cell development and tissue homeostasis in multicellular organisms. Defective apoptosis is a crucial step in the malignant transformation of cells, including hepatocellular carcinoma (HCC), where the apoptosis rate is higher than in normal liver tissues. Ubiquitination, a post-translational modification process, plays a precise role in regulating the formation and function of different death-signaling complexes, including those involved in apoptosis. Aberrant expression of E3 ubiquitin ligases (E3s) in liver cancer (LC), such as cellular inhibitors of apoptosis proteins (cIAPs), X chromosome-linked IAP (XIAP), and linear ubiquitin chain assembly complex (LUBAC), can contribute to HCC development by promoting cell survival and inhibiting apoptosis. Therefore, the review introduces the main apoptosis pathways and the regulation of proteins in these pathways by E3s and deubiquitinating enzymes (DUBs). It summarizes the abnormal expression of these regulators in HCC and their effects on cancer inhibition or promotion. Understanding the role of ubiquitination in apoptosis and LC can provide insights into potential targets for therapeutic intervention.

Keywords: Apoptosis, hepatocellular carcinoma, ubiquitin, E3s

Introduction

Apoptosis, or programmed cell death, is a tightly controlled process essential for maintaining tissue homeostasis and preventing the growth of abnormal cells [1, 2]. For instance, experiments using mouse models with impaired cell death pathways, such as deficient caspase activity or disrupted apoptosis regulators, have shown severe developmental abnormalities and embryonic lethality [3, 4]. Furthermore, elimination of unwanted or damaged cells through apoptosis helps regulate the balance between cell proliferation and cell death [5, 6].

Dysregulation of apoptosis is a hallmark of cancer, including liver cancer (LC) [7, 8]. Moreover, apoptosis evade is a critical mechanism contributing to the development, drug resistance and progression of hepatocellular carcinoma (HCC) [9-11]. Cancer cells in HCC acquire the ability to evade apoptosis, enabling their survival and uncontrolled proliferation [9-11]. In HCC, alterations in apoptotic pathways contribute to tumor development, progression, and resistance to therapy [12, 13]. Therefore, understanding the molecular mechanisms underlying the dysregulation of apoptosis in LC is crucial for developing effective therapeutic strategies.

In the context of LC, dysregulation of apoptotic proteins can occur through aberrant expression or activity of certain E3 ligases and deubiquitinating enzymes (DUBs). E3 ligases mediate the addition of ubiquitin molecules to proteins, while DUBs remove them, thereby modulating protein stability and function [14]. DUBs can either promote or inhibit apoptosis by deubiquitinating key apoptotic regulators (e.g., BimEL, Mcl-1, and XIAP) [15-19]. Several substrates involved in apoptotic pathways have been identified as targets of ubiquitination in LC. For example, proapoptotic factors like Bax, Noxa, p53, and several caspase family members [20-22], as well as antiapoptotic proteins like members of the Bcl-2 family (e.g., Mcl-1) [23, 24], undergo ubiquitination-mediated regula-

tion. This process influences their stability, subcellular localization, and interactions with other apoptotic regulators, ultimately impacting the apoptotic response in LC cells.

Ubiquitination modification system

Ubiquitination is a universal and multifunctional form of protein modification that covalently links the C-terminal glycine on 76-amino acid ubiquitin (Ub) protein to lysine residues on target proteins [25, 26]. The modification requires a multistep process mediated by three enzymes: ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3) [14, 26]. Activate and transfer ubiquitin to E2s in the presence of Mg^{2+} and ATP, and then E3s nonspecifically bind E2s and recruit substrate proteins for ubiquitin transfer from E2s to substrates [14]. There are two ways to transfer Ub: the first way is to directly connect the C-terminal of Ub to the lysine residues ε-amino of the substrates; the second way is to share Ub to E3, and then the C-terminal of Ub is connected to the lysine residues ε-amino of the substrates [27]. These Ub modifications can have different effects on the substrate, ranging from proteasome-dependent proteolysis to regulation of protein structure, function, assembly, and localization [28]. Hundreds of E3s have been identified, while E1 and E2 family members are relatively small, with 2 and 42 members, respectively [28, 29]. Ub contains seven lysine (Lys) sites (K6, K11, K27, K33, K48, and K63), one methionine (Met) site (M1) at the N-terminal, and one glycine (Gly) site (G76) at the C-terminal [30]. Single ubiquitin molecules can be conjugated to a target protein to form monoubiquitination, or ubiquitin chains can be created by linking individual ubiquitin molecules by seven Lys sites or M1 sites [31]. Different ubiquitin chains are recognized by specific ubiquitin-binding domains involving corresponding cellular processes [32]. The classic chains are the K48-linkage ubiquitin chains and the mixed K11/K48-linkage ubiquitin chains, which induce degradation of the modified protein via the proteasome [32]. Other ubiquitin chains, like K63 or M1-linkage ubiquitin chains, recruit related proteins to form signal complexes that regulate signal pathways [33, 34]. Besides, while not participating in protein degradation, monoubiquitination is crucial for regulating substrate activity, subcellular localization, protein-protein interactions, or endocytosis [35]. The ubiquitin modification generally regulates cellular physiological activities by degradative and non-degradative means [36].

Ubiquitination is reversible, and deubiquitination is also significant. Cellular ubiquitination events are counteracted by DUBs, which release conjugated ubiquitin from proteins to fine-control aspects of ubiquitin biology [37, 38]. DUBs are divided into seven subfamilies, either cysteine protease or metalloproteases. The only metalloproteinase subfamily is the Jad1/Pad/Mpn domain-containing metalloenzymes (JAMMs). The cysteine protease subfamilies include the ovarian tumor proteases (OTUs), ubiquitin specific proteases (USPs), Ub C-terminal hydrolases (UCHs), Machado-Joseph disease domain proteases (MJDs), Josephins motif interacting with Ub-containing novel DUB family (MINDYs), and the zinc-finger and UFSP domain protein (ZUFSP) [39, 40].

Ubiquitination is essential for apoptosis regulation

Apoptosis is a form of programmed cell death and involves the activation of catabolic enzymes (especially proteases) in signaling cascades, leading to the rapid destruction of cell structures and organelles [41]. In addition, apoptosis is tightly regulated and is essential for normal development and tissue homeostasis in all multicellular organisms [36]. Moreover, cell apoptosis has an effect against persistent viral infections, autoimmunity, and tumorigenesis [36, 42-44]. The apoptotic cell death program is triggered by the activation of caspases, a highly specific family of cysteine proteases essential for cell destruction [45]. Typically, caspase family member proteins are expressed as inactive enzymes activated in cascades of auto- and trans-stimulation [36, 46]. They are involved in the induction of apoptosis fall into two major classes: initiator and effector caspases, which function upstream and downstream of death signaling transduction, respectively [47, 48]. The amino terminal region of initiator caspases contains a caspase recruitment domain (caspase 1, 2, 4, 5, 9, and 11) or death effect domains (caspase 8 and 10), which facilitate their recruitment and activation in multiprotein complexes [46, 49, 50]. The

process of the initiator caspases zymogen into the active protease is driven by conformational changes induced by its dimerization [49, 51]. In contrast, effector caspases (caspase-3, -6, and -7) require cleavage by initiator caspases for their activation, thus breaking down cell proteins and acting as apoptotic effectors [49, 50].

Given the different initiation stages of apoptosis, it can be divided into three main branches, intrinsic pathways (mitochondrial pathway), extrinsic pathways (death receptor pathway), and apoptotic pathways induced by endoplasmic reticulum (ER) stress [52, 53]. Upon induction of mitochondrial apoptosis, mitochondrial outer membrane permeabilization (MOMP) is caused by the Bax/Bak activation, finely regulated by Bcl-2 family members [54, 55]. The MOMP process changes the permeability of the mitochondrial membrane and then releases cytochrome c and other proteins committing a cell to death [54]. Cytochrome c is released into the cytosol binding to apoptotic protease-activating factor 1 (Apaf-1) in the presence of ATP, forming a multimer named apoptosome [56, 57]. Then, the initiator caspase-9 in the cytoplasm was recruited and activated by the multimer through a caspase recruitment domain (CARD) at the N-terminal Apaf-1 [56, 57]. Activated caspase-9 cleaves downstream effector caspases such as caspase-3, -6, and -7 initiating the caspase cascade and inducing cell apoptosis [50, 58]. In ER stress-mediated apoptosis, extra-cellular environmental challenges such as reactive oxygen species (ROS), hypoxia, and nutrient deprivation could disturb cellular redox regulation of ER, leading to abnormal accumulation of unfolded or misfolded proteins and cell apoptosis [59-61]. ER's main function is to store Ca^{2+}, synthesize proteins, and perform post-translational modifications to achieve fidelity for synthesis and correct folding [62, 63]. Unfolded protein response (UPR), adaptive response of the cell and surveillance of ER proteostasis, is a crucial step for ER stress to mediate apoptosis [59, 64]. The UPR transmits information on protein folding status to the nucleus and cytoplasm to regulate the protein folding capacity of the cell or, in the case of chronic injury, to induce apoptotic death [62, 65]. In contrast, the extrinsic pathway is triggered by linking to specific cell-surface death receptors that initiate the assembly of the caspase-8 activation complex at the cell membrane [36]. Death receptor is a transmembrane protein belonging to the tumor necrosis factor receptor (TNFR) superfamily [66]. The extracellular portion contains a cysteine-rich region, and the cytoplasmic region has a death domain consisting of homologous amino acid residues that hydrolyze proteins [67-69]. There are five main death receptors, TFR-1 (also called CD120a or p55), Fas (CD95 or Apo1), DR3 (death receptor 3, also called Apo3, WSL-1, TRAMP, LARD), DR4 and DR5 (Apo2, TRAIL-R2, TRICK2, KILLER) [67]. The ligands corresponding to the first three receptors are tumor necrosis factor (TNF), Fas ligand (FasL), Apo-3L (DR3L), and the latter two are Apo-2L (TRAIL) [67, 70, 71].

Due to the potentially destructive effects of activated caspase, caspase activation and activity must be strictly regulated. The fine regulation of caspase is mainly determined by key antiapoptotic and proapoptotic molecules, which are accomplished by alteration of subcellular localization, change of protein synthesis, or Ub-dependent modification [36, 72]. Protein levels of many proapoptotic and antiapoptotic molecules are controlled by Ub-dependent degradation [36, 73]. In turn, during cell apoptosis, caspases destroy subunits of the 26S proteasome leading to the accumulation of ubiquitylated proteins, which might amplify or reduce the apoptosis signal [46, 74]. Besides, non-degradative ubiquitination events also play an essential role in regulating apoptosis levels in combination with DUBs.

The role of ubiquitination in apoptosis in LC

Increasing experimental evidence suggests cell death is the fundamental driving factor of HCC. Apoptosis is rare in normal liver tissues (only 2-4 apoptotic cells per 10,000 hepatocytes or biliary tract cells), but the rate is higher in HCC tissues [75, 76]. Still, their specific functions may differ or even reverse between the initiation of HCC and the later stages of tumor development [77]. In most malignant tumors, defective apoptosis is a critical step in the malignant transformation of cells, as apoptosis contributes to maintaining genome integrity [77-79]. Although evasion from cell death is an essential step in the malignant transformation process, the induction of cell death is also an important initiating factor in the early stages of

HCC [80]. Furthermore, many studies show that ubiquitination can precisely regulate the formation and function of different death-signaling complexes [73, 81]. The subsequent sections will delve into the effects of ubiquitination and deubiquitination on apoptosis and the aberrant expression of these E3 ubiquitin ligases LC, focusing on intrinsic and extrinsic apoptotic pathways.

Ubiquitination regulates TNFR1-induced apoptosis in HCC

Initially, newly synthesized TNF is expressed as a transmembrane protein and requires proteolytic cleavage by metalloproteinase ADAM17 (TNF-α converting enzyme) to release some soluble TNF [82-84]. TNF participates in various processes, including apoptosis and necroptosis, by binding to and activating TNF receptor 1 (TNFR1) and TNFR2 [81, 85]. The binding of TNF to TNFR1 triggers the rapid formation of the TNFR1 signaling complex (also called Complex I), which contains tumor necrosis factor receptor type 1 associated death domain (TRADD), receptor-interacting protein kinase 1 (RIPK1), TNF receptor-associated factor 2/5 (TRAF2/5), cellular IAPs (cIAP1/2), A20, linear ubiquitin chain assembly complex (LUBAC), and kappa B kinase (IKK) and transforming growth factor-beta-activated kinase 1 (TAK1) complexes [81, 86, 87]. The death domain of TNFR1 binds to another DD-containing adaptor TRADD, which contributes to stabilizing the binding of TRAF2 and recruits other molecules to complexes RIPK1 and cIAP1/2 [67]. The cIAP1/2 are members of the inhibitor of the apoptosis protein family that act as E3-ubiquitin ligases to mediate mixed-linkage ubiquitin chains of RIPK1 (K11, K48, and K63) [67, 88, 89]. The K63-linkage polyubiquitination of RIPK1 recruits other proteins, including a complex called LUBAC, which creates a linear ubiquitylation (M1) on RIPK1, and then the M1 recruits NEMO (NF-κB Essential Modulator) [67, 90, 91]. Consequently, the binding of NEMO (also known as IKKγ) recruits and activates the rest of the IKK complex (IKKα, IKKβ) and then activates the transcription factor nuclear factor-κB (NF-κB) [67, 92]. Besides, the K63-linkage polyubiquitination of RIPK1 also recruits TAB-TAK complexes and A20 [93-95]. Whereas, binding A20 to RIPK1 requires linkage between M1 and K63 [81, 96]. The ubiquitination of Complex I is a crucial regulator for activating MAPKs and NF-κB pathways. Then these pathways involve the production of proinflammatory cytokines and antiapoptotic proteins [81, 97, 98].

Complex II forms when a portion of Complex I (containing TRADD and RIPK1) separates from the receptor and recruits the adaptor protein Fas-associated death domain (FADD) from the cytoplasm [99]. FADD acts as a recruitment platform for caspase-8, leading to apoptosis, which is negatively regulated by the caspase-8-like molecule FLIP [81]. Because FLIP has a domain structure like caspase-8 and lacks enzyme activity, FLIP is similarly recruited for Complex II and inhibition of the caspase-8 mediated apoptosis [81, 99]. Furthermore, the ubiquitination or deubiquitination of Complex I affects its transformation into Complex II, regulating caspase-8 mediated apoptosis or/and RIPK1/3-mediated necroptosis [67]. For example, one of the DUBs, CYLD, removes K63 and M1-linkage ubiquitin chains from RIPK1, destabilizing the Complex I [100, 101]. In contrast, histidine-rich glycoprotein (HRG) overexpression promotes the formation of Complex II by upregulating K63 ubiquitination on TNFR1 [87]. Complex II contains RIPK1, RIPK3, FADD, mixed lineage kinase-like (MLKL), cFLIPL, cFLIPS, and caspase-8 [81]. It's worth noting that Complex II can trigger diverse types of cell death depending on the cell environment, especially the relative expression of caspase-8 and the cFLIPL and cFLIPS isoforms [81]. In contrast to the universal expression of TNFR1, TNFR2 is restrictively expressed in specific cell types, such as neurons, certain immune cell subsets, and endothelial cells, especially in cancer cells [102]. Although it lacks the death domain and thus cannot directly induce programmed cell death, TNFR2 is required for RIPK1-dependent cell death in the absence of cIAP1/2 and X chromosome-linked IAP (XIAP) [103, 104]. Both Complex I and Complex II are present in cells but do not induce apoptosis because Complex II is formed later than Complex I and Complex I induces rapid gene activation, leading to upregulation of many target genes, including antiapoptotic factors such as *Bcl-2*, *cIAP2*, and c*FLIPS* [99] (**Figure 1**).

Ubiquitination and deubiquitination of Complex I: Stimulated TNFR1 recruits RIPK1 and TRADD, and TRADD recruits TRAF2/5, which recruits

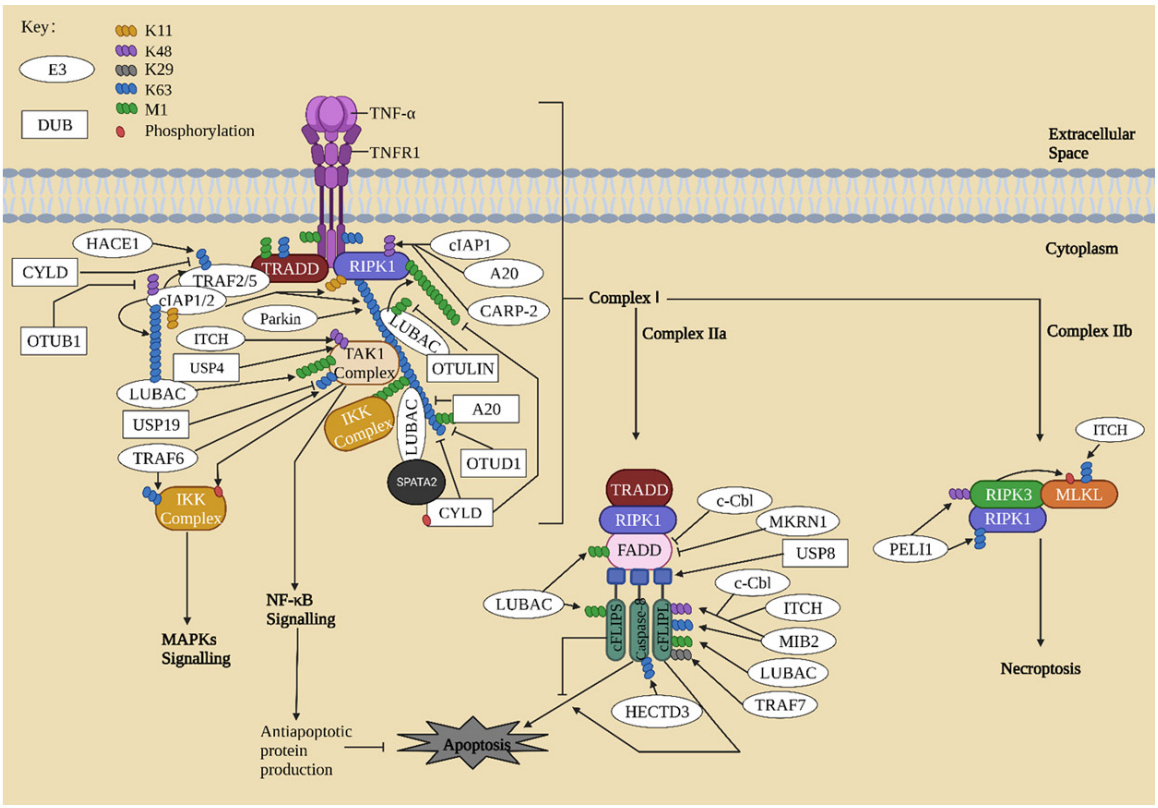

Figure 1. Overview of ubiquitin-mediated regulation of TNFR1-induced apoptosis. When trimer TNF-α binds to trimer TNFR1, Complex I is formed through interprotein and Ub chain-mediated interactions. Complex I is formed before Complex II and mainly activates the MAPKs and NF-κB pathways to produce inflammatory cytokines and antiapoptotic proteins. If RIPK1 or others major component is not ubiquitinated, they can dissociate from complex I and form complex IIa or IIb. Complex IIa (RIPK1/FADD/TRADD) and IIb (RIPK1/RIPK3/MLKL) mediate apoptosis and necroptosis, respectively. The TNFR1 signaling pathway is finely regulated by E3s and DUBs, and these regulators are abnormally expressed in LC (see **Table 1** for details).

cIAP1/2 [105-107]. As the first protein to be recruited to TNFR1, TRADD also directly interacts with TRAF2 and cIAP1/2 to promote K63-linkage ubiquitination of RIPK1 and regulate the stability of RIPK1 [108-110]. Enjoyably, RIPK1 could block TRADD recruitment to FADD to limit apoptosis [111]. Besides, the presence of RIPK1 is vital to protect TRAF2 from degradation by the proteasome [80]. An E3 ligase, HACE1, promotes the formation of K63-linkage chain on TRAF2, which in turn promotes recruitment of downstream components of Complex I to activate the NF-κB signaling [112]. Conversely, another E3 Siah2 introduces the ubiquitination and degradation of TRAF2, efficiently decreasing the activation of JNK and NF-κB signal [113]. Research shows that TRADD has proapoptotic and antiapoptotic functions [114, 115]. Previous studies have shown that TRADD can inhibit apoptosis in LC cells [116, 117] and is less positive in HCC tissues than in adjacent tissues [118]. While there are no specific E3 ligases known to target TRADD for degradation directly, it is known that TRADD degradation can be regulated by the ubiquitin-proteasome system (UPS) [119].

RIPK1 kinase activity is a potent trigger for hepatocyte apoptosis, which can lead to chronic liver disease and ultimately contribute to the development of HCC [120, 121]. RIPK1 contains an N-terminal kinase domain, an intermediate domain, and a C-terminal death domain [122]. RIPK1 kinase activity regulates the assembly of two death-inducing complexes, namely Complex IIa (RIPK1/FADD/TRADD), which drives apoptosis, and the Complex IIb (RIPK1/RIPK3/MLKL), resulting in necroptosis [81]. Conversely, RIPK1 functions as a scaffold to promote the recruitment of other Complex I

Table 1. Regulators of the ubiquitination in TNFR1 signaling

Regulator of theu-biquitination	Substrate Targeted protein Ubiquitination type	Impact on TNFR1-inducedcell death	Impact on TNFR1-in-ducedgene activation	Deregulation and role in liver cancer	Refs
cIAP1/2 (E3)	RIPK1 (K63)	Apoptosis↓ Necroptosis↓	NF-κB signaling↑ MAPKs signaling↑	Upregulation Cancer promotion	[105, 127]
	RIPK1 (K11)	Apoptosis↓	NF-κB signaling↑		[89]
	RIPK1 (K48)	Apoptosis↓ Necroptosis↓	ND		[88]
	TRAF2 (K48?)	Apoptosis↑	ND		[371, 372]
	cIAP1 (K63/K48/K11)	Apoptosis↑	ND		[53, 285, 373]
LUBAC (E3)	RIPK1 (M1)	Apoptosis↓ Necroptosis↓	NF-κB signaling↑ MAPKs signaling↑	Upregulation Cancer promotion	[34, 91, 137, 138]
	cFLIPL/S (M1)	Apoptosis↓ Necroptosis?	ND		[91, 171]
	NEMO (M1)	Apoptosis↓	NF-κB signaling↑		[137, 374]
	FADD (M1)	Apoptosis↓	ND		[172]
	TRADD (M1?)	Apoptosis↓	ND		[375]
Parkin (E3)	RIPK1 (K63)	Apoptosis↓ Necroptosis↓	NF-κB signaling↑ MAPKs signaling↑	Downregulation Cancer inhibition	[123, 150]
	TRAF2/6 (K48)	Apoptosis↑	NF-κB signaling↓		[150]
TRAF6 (E3)	NEMO (K63)	Apoptosis↓	NF-κB signaling↑ MAPKs signaling↑	Upregulation Cancer promotion	[142, 143]
	TAK1 (K63)		NF-κB signaling↑		[144]
TRAF7 (E3)	cFLIPL (K29/K33/K63)	Apoptosis↑ Necroptosis↑	ND	Upregulation Cancer promotion	[173, 174]
MIB2 (E3)	cFLIPL (K48/K63)	Apoptosis↓ Necroptosis↓	ND	ND	[180, 364]
ITCH (E3)	cFLIPL (K48)	Apoptosis↑ Necroptosis↑	ND	Upregulation Cancer inhibition	[176, 177, 179]
	MLKL (K63)	ND	ND		[193]
	TAK1 (K48)	Apoptosis↑	NF-κB signaling↓		[376]
HECTD3 (E3)	Caspase-8 (K63)	Apoptosis↓	ND	ND	[187]
c-Cbl (E3)	cFLIPS (K48?)	Apoptosis↑	ND	ND	[186]
PELI1 (E3)	RIPK1 (K63)	Apoptosis↓ Necroptosis↑	ND	ND	[190]
	RIPK3 (K48)	Necroptosis↓	ND		[191]
TRAF7 (E3)	cFLIPL (K29/K33/K63)	Apoptosis↓	JNK signaling↑	Upregulation Cancer promotion	[173, 174]
HACE1 (E3)	TRAF2 (K63)	Apoptosis↑ Necroptosis↓	NF-κB signaling↑	Downregulation Cancer inhibition	[112, 377]
Siah2 (E3)	TRAF2 (K48?)	ND	NF-κB signaling↓ JNK signaling↓		[113]
CARP-2 (E3)	RIPK1 (K48)	ND	NF-κB signaling↓	ND	[153]
RNF4 (E3)	TAB2 (K29?)	Apoptosis↑	NF-κB signaling↓	Upregulation Cancer promotion	[378, 379]
MKRN1 (E3)	FADD (K48?/K11?)	Apoptosis↓	ND	ND	[166]
A20 (E3)	RIPK1 (K48)	Apoptosis↓	NF-κB signaling↓	Upregulation Cancer inhibition	[156, 158, 159, 380, 381]
A20(DUB)	RIPK1 (K63)	Apoptosis↓	NF-κB signaling↓	ND	[156, 380]
CYLD(DUB)	RIPK1 (K63)	Apoptosis↑ Necroptosis↑	NF-κB signaling↓ MAPKs signaling↓	Downregulation Cancer inhibition	[101, 382, 383]
	RIPK1 (M1)	Apoptosis↑	NF-κB signaling↓ MAPKs signaling↓		[101]
	TNFR1 (K63)	ND	ND		[101]
	TNFR1 (M1)	ND	ND		[101]

	TRADD (K63)	ND	ND		[101]
	TRADD (M1)	ND	ND		[101]
	TRAF2/6 (K63)	Apoptosis↑?	NF-κB signaling↓		[384, 385]
USP8 (DUB)	cFLIPL (K48?/K11?)	Apoptosis↓ Necroptosis↓	ND	Upregulation Cancer inhibition	[182, 184, 364]
USP4 (DUB)	TAK1 (K63?)	Apoptosis↑	NF-κB signaling↓ JNK signaling↓	Upregulation Cancer promotion	[361, 362]
	TRAF2/6 (?)	ND	NF-κB signaling↓		[151]
	RIPK1 (K63)	Apoptosis↑	NF-κB signaling↓		[152]
USP11 (DUB)	IκBα	ND	NF-κB signaling↓	ND	[386]
USP19 (DUB)	TAK1 (K63/K27)	ND	NF-κB signaling↓	ND	[387]
OTULIN (DUB)	LUBAC (M1)	Apoptosis↓ Necroptosis↓	NF-κB signaling↓	Cancer inhibition	[388-390]
OTUD1 (DUB)	RIPK1 (K63)	ND	NF-κB signaling↓	ND	[90]
OTUB1 (DUB)	cIAP1 (K48)	Apoptosis↓	NF-κB signaling↑ MAPKs signaling↑	Upregulation Cancer promotion	[135, 391]
Usp27× (DUB)	cFLIPL (K48?)	Apoptosis↑	ND	Upregulation Cancer promotion	[181, 307]

components through the non-degradative ubiquitination of RIPK1, inducing the activation of NF-κB and MAPKs to promote cancer cell survival [123, 124]. In addition, the reduction or loss of ubiquitin chains of RIPK1 increases cell sensitivity to TNFα-induced apoptosis or necroptosis [125, 126]. Collectively, RIPK1-ubiquitin modifications finely regulated these two RIPK1-mediated opposite effects. In HCC cells, the protein and mRNA of cIAP1, cIAP2, and XIAP were significantly increased compared with normal liver tissue [127, 128] (**Table 1**). As the E3 ligase of RIPK1, cIAP1/2 contributes to enhancing the K11/K48/K63-linkage polyubiquitination of RIPK1 by its ubiquitin-associated (UBA) domain [88, 89, 105, 129, 130]. Besides, the UBA-mediated ubiquitination of RIPK1 could avoid immoderately activating RIPK1 kinase in response to TNF-α by inhibiting the releasing of RIPK1 from Complex I, therefore preventing RIPK1 kinase-mediated cell death and systemic inflammatory response syndrome [88, 99]. Previous studies have shown that cIAP1/2 promotes cell survival by acting as E3 ligases that promote RIPK1 ubiquitination and degradation [105, 131]. Conformably, loss of cIAP1/2, particularly cIAP1, can promote the production of TNF and sensitize cancer cell lines to TNF-induced necroptosis by promoting the formation of Complex IIb [126]. Intriguingly, RIPK1 ablation induces TNF-mediated hepatocyte apoptosis but not affects the NF-κB signal [80]. Another study also showed that RIPK1 ablation induced TNF-mediated hepatocyte apoptosis and liver tumors in liver parenchymal cells (NEMO-KO) [120]. Furthermore, the loss of RIPK1 leads to TNF-induced TRAF2 (an E3 involved in NF-κB activation) degradation in liver parenchymal cells [80]. The deficiency of both RIPK1 and TRAF2 leads to the over-activation of caspase-8. It impairs the activation of NF-κB and MAPKs, contributing to the dysregulation of hepatocyte apoptosis and promoting spontaneous HCC [80, 132]. Although cIAP1/2 degrades RIPK1 through the K48-linkage chain, the expression of cIAP1/2 did not change with the degradation of RIPK1. Still, the activity of cIAP1/2 can be regulated by auto-ubiquitination modulating their ability to ubiquitinate RIPK1, which may explain why RIPK1 expression is elevated in HCC compared with normal liver tissue [80, 88, 133]. Furthermore, a DUB (OTU domain aldehyde binding-1, OTUB1) reduced K48-linkage polyubiquitination of the cIAP1, thereby diminishing its degradation and avoiding hepatocyte death [134, 135]. In addition, the loss of RIPK1 in hepatocytes converts the function of RIPK3 from a mediator of necroptosis to a promoter of early hepatocyte apoptosis after TNF-α stimulation [80].

LUBAC acts as another E3 ligase complex of RIPK1 to add an M1-linkage chain on RIPK1 and is recruited by binding to the K63-linkage chain produced by cIAP1/2 [81, 136, 137]. The E3 ligase complex consists of HOIL-1 (heme oxidation IRP2 ubiquitin ligase 1), HOIP (HOIL-1 interacting protein), and SHARPIN, which can positively regulate the activation of NF-κB sig-

nal induced by TNF [81, 136, 137]. HOIP is the catalytic subunit of the complex, while HOIL-1 and SHARPIN serve as regulatory subunits. Studies have shown that LUBAC was significantly increased in HCC and promoted the progression of HCC, which may be partly dependent on the pro-survival effects of NF-κB [138, 139]. Notably, HOIL-1L interacts with HOIP and inhibits its ubiquitination and proteasome degradation, facilitating proliferation and metastasis in HCC [139]. Based on the M1-linkage chain generated by LUBAC, the RIPK1 recruits NEMO, subsequently phosphorylating IKKα/β and activating NF-κB [67, 90, 140]. In turn, phosphorylation of RIPK1 by IKKα/β reduces its kinase activity to inhibit TNF-induced Complex II formation and thus prevent cell death [141]. It is worth noting that the binding of K-63 or M1-linkage polyubiquitination to NEMO strongly triggers the creation of droplets with liquid-like properties, which activate IKKα/β [92]. Another E3 ligase responsible for K63-linkage NEMO polyubiquitination is TRAF6, which activates the IKK complex mediated NF-κB signal [142]. Significantly, TRAF6 increase was observed in LC, and TRAF6 knockdown induced apoptosis and activated caspase-3/7 activity [143]. Conformity, because TRAF6 also ubiquitin TAK1 with the k63-linkage chain, allows the TAK1 complex to phosphorylate and activate the IKK complex, thereby activating NF-κB signaling [144]. Similarly, NEMO can also recruit other kinases, such as TBK1 and IKKε, which are homologous to the canonical kinases IKKα and IKKβ, to inhibit RIPK1-dependent cell death by reducing RIPK1 kinase activity [145]. Phenotypically, a large proportion of NEMO expression decreased in HCC, and low NEMO expression is correlated with a poor 5-year overall survival in patients with HCC [146]. Recent studies have shown that NEMO prevents the occurrence of HCC independent of NF-κB mediated gene transcription function [120, 147]. Besides, NEMO prevents the degradation of cFLIPL, cIAP1, and TRAF2 from partly controlling spontaneous hepatocyte apoptosis and HCC development [120]. In short, NEMO is essential for normal cell survival and plays a particular role in inhibiting the occurrence and growth of HCC through NF-κB-dependent and -independent functions [148, 149].

Additionally, the K63-linkage ubiquitination of K376 on RIPK1 by Parkin in Complex I activates downstream pathways and regulates cell death, promoting cell survival via NF-κB signaling [123]. Conversely, Parkin directly mediates the K48-linkage chains of TRAF2/6, thereby impairing NF-κB activation and promoting LC cells apoptosis [150]. Similarly, USP4 directly deubiquitinates the TRAF2/6 to inhibit its activity, which negatively regulates TNFα-mediated gene expression [151]. Besides, USP4 directly interacts with RIPK1 and deubiquitinates K63-linkage ubiquitination of RIPK1 [152]. Moreover, direct binding between CARP-2 (E3 containing a RING domain) and RIPK1 kinase domains promotes K48-linkage ubiquitination and degradation of RIPK1 and negatively regulates the NF-κB pathway [153]. However, whether CARP-2 influences HCC progression by regulating RIPK1-mediated NF-κB has not been reported. Moreover, increased ubiquitination on RIPK1 hinders the transition from Complex I to Complex II, inhibiting the activation of caspase-8 [67]. The deubiquitination enzymes that target RIPK1 are not well-defined, but A20 and CYLD have been reported to interact with RIPK1 and remove M1, K48, and K63-linkage ubiquitin chains [154, 155]. Both A20 and CYLD have been implicated in the development and progression of LC. A20 is considered a ubiquitin editing enzyme, changing the chains on RIPK1 by removing K63-linkage ubiquitin and generating K48-linkage ubiquitin chains [156]. A20's deubiquitinating activity on RIPK1 can modulate the activity of downstream signaling cascades, such as the NF-κB and JNK pathways. Significantly, A20, as a molecular switch, discriminates TNF-induced NF-κB from JNK pathway activation in hepatocytes [157]. The mRNA and protein expression of A20 was significantly higher in HCC tissues than in adjacent nontumor tissues [158, 159]. Phenotypically, increased expression of A20 was negatively correlated with the tumor size, TNM stage, tumor thrombus formation, and capsular invasion [158]. Mechanistically, A20 has revealed its tumor-suppressive functions in LC cells partly by its A20-induced attenuation of NF-κB activity, inhibiting Twist1 expression [159]. Moreover, A20 inhibits apoptosis of hepatocytes and promotes proliferation through the NF-κB signaling pathway, suggesting its protection function on normal liver cells [160]. Besides, TAX1BP1 acts as a bridging protein of A20 and is required for A20-mediated deubiquitination of RIPK1 and inhibition of NF-κB [161]. Similarly, CYLD

has also been reported to have tumor-suppressive functions in LC cells [162, 163]. CYLD acts as an essential regulator of hepatocyte homeostasis, inhibits the uncontrolled NF-κB and MAPKs activation pathways, and initiates apoptosis by deubiquitinating several molecules of Complex I, including RIPK1, TRAF2, TAK1, and NEMO, thereby facilitating the formation of Complex II [162, 164]. Studies have shown that the expression of CYLD is frequently downregulated in LC, and this downregulation is associated with a poor prognosis [165]. A previous study showed that the mutation of *CYLD* exon9 can induce liver fibrosis and LC [165]. Significantly, CYLD regulates RIPK1 ubiquitination in the TNFα-induced Complex II but not Complex I [154]. Overall, the abnormal expression of A20 and CYLD in HCC is associated with the NF-κB and MAPKs signal, the Complex II formation, and the growth of HCC.

Ubiquitination and deubiquitination of Complex II: Deubiquitination of Complex I leads to decreased stability, and some components are dissociated from Complex I to form Complex II a and b, respectively. TRADD and RIPK1 contain a dead domain, and both interact directly with FADD to drive caspase-8 activation in cells [111]. During the transition of Complex I to Complex II, RIPK1 undergoes dimerization leading to its activation, then activated RIPK1 binds to FADD, which in turn binds to caspase-8 to mediate caspase activation and apoptosis [122]. FADD is an adaptor protein that mediates the recruitment of procaspase-8 and allows procaspase-8 to homodimerize, thus being activated. FADD contains two main domains: the death domain and the death effector domain. Other proteins, including the death domain (e.g., RIPK1, TRADD), interact with the death domain of FADD, which enables the recruitment of procaspase-8 to the Complex II via interactions between the death effector domain of FADD and procaspase-8. FADD is regulated by Makorin Ring Finger Protein 1 (MKRN1) E3 ligase-mediated ubiquitination and proteasomal degradation [166]. And MKRN1 knockdown leads to the FADD protein stabilization and formation of the rapid Complex II, promoting TNF-induced apoptosis [166]. The caspase-8's activation is known to be regulated by its paralog, FLIP, which is expressed as two splice variants, cFLIP Long (cFLIPL)and cFLIP Short (cFLIPS) [53]. cFLIPL/S can form heterodimers with procaspase-8 and be traditionally thought to inhibit caspase-8 activation. However, while the cFLIPS/procaspase-8 heterodimer has no catalytic activity and potently inhibits caspase-8 activation, the cFLIPL/procaspase-8 heterodimer does have catalytic activity (that is spatially restricted). cFLIPL can promote caspase-8 activation, depending on its relative levels to procaspase-8 [167].

Previous studies have shown that cFLIP is constitutionally expressed in all human HCC cell lines, and its expression is higher in human HCC tissues than in non-tumor liver tissues [168]. Significantly, downregulation of cFLIP has been shown to enhance cell apoptosis and thus limit the progression of LC [169, 170]. Several mechanisms, including the abnormal E3 ubiquitin ligase, regulate the abnormally high expression of cFLIP protein in LC. Existing studies show that HOIP could conjugate M1-linkage ubiquitination chains at Lys 351 and 353 of cFLIPL to stabilize cFLIPL, thereby protecting cells from TNFα-induced apoptosis [171]. Notably, HOIP is overexpressed in HCC and promotes the metastasis and growth of HCC cells [138], which may account for the abnormally high expression of cFLIP. Moreover, the N-terminal of HOIP binds with deubiquitinases, such as CYLD and OTULIN [172]. Furthermore, caspase-mediated cleavage of HOIP breaks critical functional regions of HOIP, regulating linear (de)ubiquitination of substrates upon apoptosis (e.g., FADD, NEMO) [172]. Another E3 ligase, TRAF7, can promote the polyubiquitination of cFLIPL, including K29, K33, and K63-linkage types, mainly promoting its degradation to enhance TNF-induced apoptosis [173]. Critically, previous studies have shown that TRAF7 is highly expressed in LC tissues and contributes to the progression of HCC by promoting ubiquitination and degradation of p53 [174, 175]. TRAF7 was less able to inhibit HCC progression by promoting cFLIPL degradation. Additionally, it was found that E3 ligase ITCH could induce the ubiquitination and degradation of cFLIPL via the K48-linkage chain [176, 177]. It was reported that ITCH could inhibit the progression of HCC by destabilizing several target substrates, such as TAK1 [178] and RORα [179]. Similarly, ITCH may promote HCC cell apoptosis by promoting the degradation of cFLIPL and exerting its anticancer effect. Interestingly, the E3 ligase Mind bomb 2 (MIB2)

forms K48- and K63-linkage polyubiquitin chains on cFLIPL, thus increasing its stability hence attenuating TNF-induced apoptosis [180]. Similarly, another E3 can destabilize cFLIPL via the ubiquitin proteasome system, enhancing cell apoptosis [181]. MIB2 also inhibits the kinase activity of RIPK1 and restricts the formation of Complex II but without RIPK1 [180]. A deubiquitylase ubiquitin-specific peptidase 8 (USP8) directly deubiquitylates and stabilizes cFLIPL, leading to TNF-mediated apoptosis suppression [182]. Besides, USP8 also indirectly contributes to cFLIPL degradation by directly deubiquitinating and stabilizing ITCH [183]. USP8 is more upregulated in HCC than in normal liver tissues [184]. Inhibition of USP8 can induce apoptosis of HCC cells, and USP8 is considered to have a tumor suppressor effect in HCC [184, 185]. At present, the only E3 ligase of cFLIPS reported is c-Cbl, which promotes proteasomal degradation of cFLIPS and, thus the activation of caspase-8 and apoptosis [186].

An E3 ligase HECTD3 interacts with caspase-8 death effector domains and ubiquitinates caspase-8 via K63-linkage chains that decrease the caspase-8 activation [187]. A high *HECTD3* mRNA expression level is associated with poor prognosis in HCC [188], which may be related to caspase-8 overactivation. When caspase-8 fails to be activated, the RIPK1/FADD/caspase-8 complex binds to RIPK3 to form complex IIb, which performs necroptosis by mediating MLKL activation and oligopolization [122, 189]. Upon the TNF-induced necroptosis process, an E3 ubiquitin ligase, PELI1 mediates K63 ubiquitination on K115 of RIPK1 promoting cell necroptosis [190]. Paradoxically, PELI1 mediates K48 ubiquitination on K363 of RIPK3 causing its degradation and effectively preventing cell death triggered by RIPK3 hyperactivation [191]. The major function of the RIPK3 is to phosphorylate MLKL, triggering MLKL oligomerization, membrane translocation, and membrane disruption [192]. This paradoxical role of PELI1 highlights its dual functions in regulating necroptotic signaling by promoting necroptosis through RIPK1 ubiquitination and inhibiting necroptosis by targeting RIPK3 for degradation. Another report shows that conjugation of K63-linkage polyubiquitin chains to distinct lysine residues in the N-terminal HeLo domain of phosphorylated MLKL (facilitated by the ubiquitin ligase ITCH that binds MLKL via a WW domain) results in the release of phosphorylated MLKL within extracellular vesicles [193].

Ubiquitination regulates TRAIL-induced apoptosis in HCC

A general overview of the protein recruitment events in TRAIL-R signaling: Ligand Binding and Receptor Trimerization: The TRAIL ligand binds to TRAIL-R1 or TRAIL-R2 receptors on the cell surface, leading to receptor trimerization [81, 194]. This ligand-receptor interaction initiates the signaling cascade [81, 194]. Formation of Death-Inducing Signaling Complex (DISC): Upon receptor trimerization, the death domains of TRAIL-R1 or TRAIL-R2 recruit the adaptor protein FADD to the receptor complex [195]. FADD serves as a scaffolding protein, facilitating the assembly of the DISC [196, 197]. Recruitment of Initiator Caspases: The DISC complex recruits procaspase-8 or procaspase-10, which are inactive forms of caspases [198]. Procaspase-8 or procaspase-10 undergoes a conformational change and is activated within the DISC complex [197]. Actived caspase-8 or caspase-10 serves as an initiator caspase, triggering downstream apoptotic events [49, 50]. Activation of Effector Caspases: Actived caspase-8 or caspase-10 cleaves and activates downstream effector caspases, such as caspase-3, caspase-6, and caspase-7 [49, 50]. Effector caspases cleave a variety of cellular substrates, leading to the characteristic morphological and biochemical changes associated with apoptosis.

TRAIL is known to interact with four distinct cell surface receptors that are named TRAIL-R1, TRAIL-R2, TRAIL-R3, and TRAIL-R4. Among these four receptors, only TRAIL-R1 and TRAIL-R2 contain cytoplasmic death domains that are capable of recruiting FADD to initiate the DISC [81]. TRAIL has gained a lot of attention in recent years due to its remarkable ability to selectively induce apoptosis in cancer cells while leaving normal cells unharmed. TRAIL plays its role in the apoptotic pathway by binding to death receptors (TRAIL-R1/2) on the surface of cancer cells, leading to the cancer cell's death [199]. However, several studies have shown that HCC exhibits inherent resistance to TRAIL-induced apoptosis [200, 201]. Upon binding to TRAIL-R1/2, TRAIL triggers the

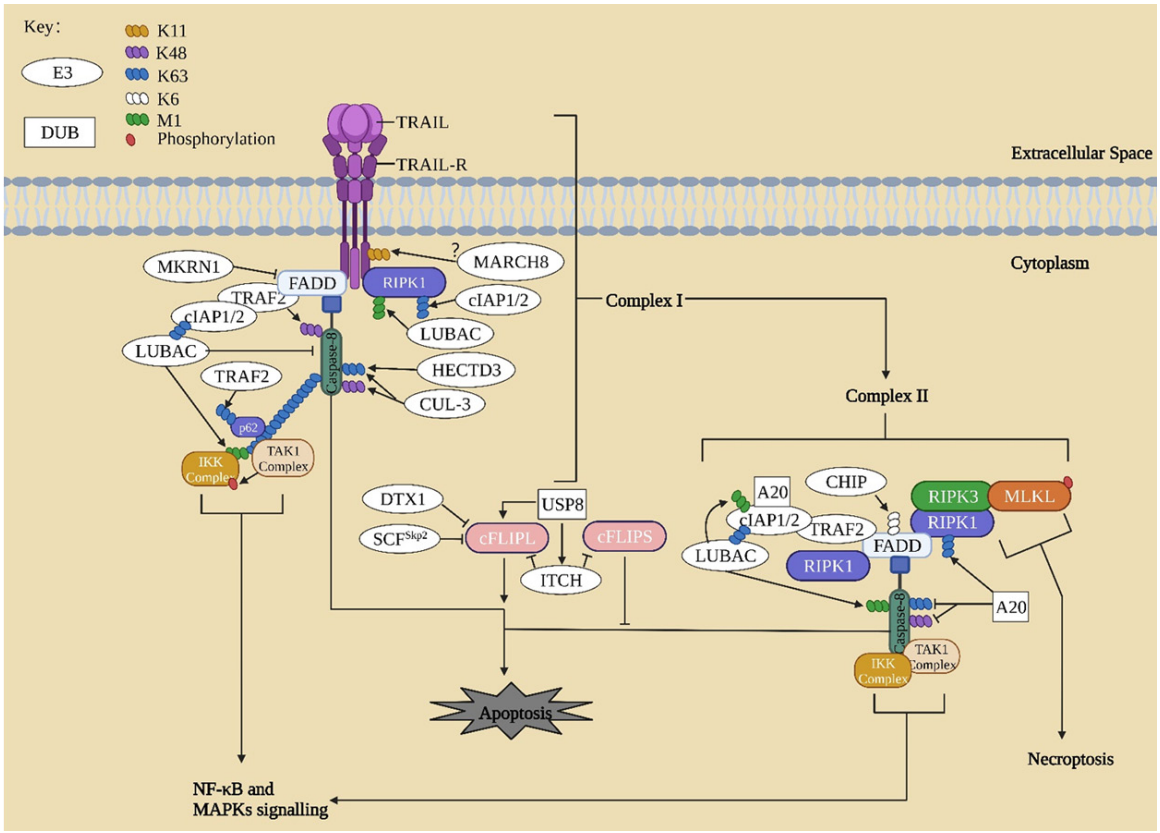

Figure 2. Overview of ubiquitin-mediated regulation of TRAIL-R-induced apoptosis. When trimer TRAIL binds to trimer TRAIL-R, Complex I is formed through interprotein and Ub chain-mediated interactions. The TRAIL signaling pathway is finely regulated by E3s and DUBs, and these regulators are abnormally expressed in LC (see **Table 2** for details).

formation of two complexes: the TRAIL-R-associated Complex I and a cytosolic Complex II that lacks TRAIL-Rs [81]. Previous studies have demonstrated that TRAIL-R simulation can induce the formation of complexes like TNFR1-induced complexes with a similar regulation mechanism via ubiquitination [53, 199]. Notably, the finding that Complexes I and II conduct apoptotic signals and pro-survival signals [81]. In TRAIL-R signaling, proapoptotic proteins (FADD and caspase-8) are initially recruited to TRAIL-R. They can serve as a scaffold for recruiting antiapoptotic proteins, including RIPK1, TRAF2, cIAP1/2, LUBAC, and the TAK1 and IKK complexes [81]. Importantly, LUBAC controls the TRAIL signaling outcomes of Complexes I and II since RIPK1 and caspase-8 as linearly ubiquitinated targets of LUBAC [202] (**Figure 2**).

Earlier studies have reported a prevalently low expression of TRAIL-R1 and -R2 in human HCC tissues and cell lines, negatively correlated with the survival rate of HCC patients [203, 204]. An E3 ligase, membrane-associated RING-CH-8 (MARCH8), targets TRAIL-R1 for lysosomal degradation and attenuates its cell surface expression [205] (**Table 2**). The high expression of MARCH8 in HCC is compared with that in normal tissues, and it can inhibit the apoptosis of HCC cells [206], suggesting that MARCH8 may exert its cancer-promoting effect by inhibiting TRAIL-R1/2-mediated apoptosis. When FADD binds to the trimerization of TRAIL-R1 and TRAIL-R2, it exposes the death effect domain (DED) of FADD, which contributes to interacting with caspase-8 and DED of cFLIPL/S. Caspase-8 will come together to form a homologous oligomerization, while caspase-8 and caspase-10 or cFLIPL/S will join forces in a hetero-oligomerization [81]. Stimulation with TRAIL has been shown to induce the ubiquitination of caspase-8, and this ubiquitination has been associated with the cullin3-based E3 ligase (CUL3) [207]. CUL3 can facilitate caspase-8 oligomerization and activation by medi-

Table 2. Regulators of the ubiquitination in TRAIL-R signaling

Regulator of the ubiquitination	Substrate Targeted protein Ubiquitination type	Impact on TRAIL-R induced cell death	Impact on TRAIL-R induced gene activation	Deregulation and role in liver cancer	Refs
MARCH8 (E3)	TRAIL-R1 (K11?)	Apoptosis↓	ND	Upregulation Cancer promotion	[205, 206]
MKRN1 (E3)	FADD (K48?/K11?)	Apoptosis↓	ND	ND	[166]
CUL-3 (E3)	Caspase-8 (K48/K63)	Apoptosis↑	ND	ND	[207]
HECTD3 (E3)	Caspase 8 (k63)	Apoptosis↓	ND	Upregulation	[187, 188]
TRAF2 (E3)	Caspase-8 (K48)	Apoptosis↓ Necroptosis↓	NF-κB signaling↑ JNK signaling↑	Downregulation Cancer inhibition	[80, 208, 209, 392]
	P62 (K63)	Apoptosis↓?			[210]
cIAP1/2 (E3)	RIPK1 (K63)	Apoptosis↓ Necroptosis↓	NF-κB signaling↑	Upregulation Cancer promotion	[127, 209, 393]
SCF^{Skp2} (E3)	cFLIPL (K48?)	Apoptosis↓	ND	ND	[217]
LUBAC (E3)	Caspase-8 (M1)	Apoptosis↓ Necroptosis↓	ND	Upregulation Cancer promotion	[393]
	RIPK1 (M1)	Apoptosis↓ Necroptosis↓	NF-κB signaling↑ ERK signaling↑		[393]
ITCH (E3)	cFLIPL/S (K48?)	Apoptosis↑	ND	ND	[183, 394]
CHIP (E3)	FADD (K6)	Apoptosis↓ Necroptosis↓	ND	ND	[260]
DTX1 (E3)	cFLIPL (K29?)	Apoptosis↑	ND	ND	[221]
A20 (DUB)	Caspase-8 (K48/K63)	Apoptosis↓	ND	ND	[207]
A20 (E3)	RIPK1 (K63)	Apoptosis↓	Apoptosis↓	ND	[395]
USP8 (DUB)	cFLIPL (K48?)	Apoptosis↓	ND	Upregulation Cancer inhibition	[182]

ating K48/K63 ubiquitination of caspase-8, which leads to the recruitment of the Ub-binding protein p62 to the DISC. This recruitment allows for p62-mediated aggregation and full activation of caspase-8, initiating the apoptotic cascade [207]. In contrast, the events were reversed by activating A20, which removes the ubiquitin chains from procapsase-8 [207]. Notably, CUL3 also promotes TNF - and FasL-induced caspase-8 activation. Additionally, the E3 ligase TRAF2 directly interacts with caspase-8 at Complex I and induces K48-linkage polyubiquitination of caspase-8, resulting in the proteasomal degradation of activated caspase-8 [208]. Besides, TRAF2 and cIAP1 mediate the K63-linkage ubiquitination of RIPK1, allowing NF-κB activation and cell survival [209]. Interestingly, TRAF2 also induces K63-linkage polyubiquitination on the K420 residue of p62 [210]. This may reduce the aggregation of p62 and prevent p62 from accumulating to caspase-8, thereby exerting its antiapoptotic effect. Previous studies have shown that decreased TRAF2 promotes spontaneous development of HCC via inducing overactivation of caspase-8 and impaired activation of NF-κB [80].

Besides, another E3 ligase, HECTD3, increases the ubiquitination of caspase-8 through the K63-linkage polyubiquitin chain [187, 188]. It should be noted that while CUL-3 activates caspase-8 through K63-linkage chain attachment, HECTD3 has the opposite effect by inhibiting caspase-8 activation. In addition, several other E3 ligases, WWP1, Siah2, and POSH, do not regulate the ubiquitination of caspase-8. However, inhibition of WWP1 increases the recruitment caspase-8 into Complex I, and silencing Siah2 and POSH enhances caspase-8 activity, ultimately sensitizing TRAIL-mediated apoptosis [211, 212]. In addition to caspase-8, caspase-10 is also recruited to the DISC, but its role in death receptor signaling is unclear. Previous study shows that expression of caspase-10 sensitizes MCF-7 breast carcinoma cells to TRAIL- but not TNF-induced apoptosis [213]. Importantly, caspase-10 was unable to compensate for the loss of caspase-8 in TRAIL or FasL-induced apoptosis of caspase-8-deficient Jurkat cells [167, 214]. Interestingly, cas-

pase-10 can act as a negative regulator of FasL-induced apoptosis [215], suggesting caspase-8 has opposite effects in several death receptor induced-apoptosis. Another study showed that FADD is modified by small ubiquitin-associated modifier 2 (SUMO2) on multiple lysine residues (K120/125/149), thereby recruiting caspase-10 to mitochondria for regulated necroptosis [216]. However, the ubiquitination modification of caspase-10 has not been clear yet. Therefore, gaining insight into how ubiquitination/deubiquitination affects the stability, oligomerization, and activation of caspase-10 could enhance our understanding of how it regulates death signaling.

In contrast to the inactive cFLIPS/caspase-8 heteropolymers, cFLIPL/caspase-8 heteropolymers exhibit spatially limited activity, enabling them to cleave RIPK1, RIPK3, and CYLD, thereby preventing necroptosis [217-219]. Importantly, the ratio of cFLIPL, cFLIPS, and caspase-8 also regulates the degree of caspase-8 activation via DED-mediated filament extension [81]. ITCH is thought to reduce the stability of cFLIPL and cFLIPS, thereby promoting TRAIL-induced apoptosis signaling [220]. Similarly, another E3, DELTEX1 (DTX1), binds cFLIPL and directs it into the endosome-lysosomal pathway for degradation, enhancing TRAIL-induced and FasL-induced apoptosis in T cells [221]. Enjoyable, Skp1-Cullin-1-F-box (SCF) Cullin-Ring E3 Ubiquitin Ligase complex containing Skp2 (SCF^{Skp2}) promotes ubiquitination and proteasome degradation of cFLIPL, thereby restraining TRAIL-R2-mediated apoptosis [217]. This suggests that cFLIPs are functionally different in TRAIL-R2/TRAIL-R1 mediated apoptosis. In contrast, USP8 interacts with cFLIPL through its caspase-like domain, resulting in its deubiquitination, thereby preventing the degradation of cFLIPL [171].

Ubiquitination regulates FasL-induced apoptosis in HCC

FasL is a type II transmembrane protein that belongs to the tumor necrosis factor family [222]. FasL plays a crucial role in inducing apoptosis, a form of programmed cell death, through binding to its receptor Fas on the surface of target cells [222]. FasL is mainly expressed in activated T lymphocytes and natural killer (NK) cells. When FasL binds to Fas, it induces the formation of DISC on the cytoplasmic side of the receptor [223]. Specifically, the death domain of Fas recruits FADD, then FADD binds procaspase-8 and cFLIP to form the DISC [224]. In mammals, two major cFLIP isoforms dominate, namely cFLIPL and cFLIPS. These two major isoforms are potent inhibitors of the caspase activity at the DISC [225, 226]. After the DISC is formed, oligomerization of procaspase-8 promotes its autocatalytic activation and the release of a mature tetramer to the cytosol, implementing apoptosis [224]. This apoptosis can be blocked by several mechanisms, including the production of soluble Fas (sFas) [227]; production of a soluble decoy receptor (DcR3) for FasL [228]; lack of Fas expression on the cell surface [229]; overexpression of inhibitory proteins in the signal transduction pathways such as Fas-associated phosphatase 1 (FAP-1) [230], Bcl-2 family members and FLICE inhibitory protein [231, 232]; and mutations in Fas's primary structure [233]. In addition, the activation of Fas can promote apoptosis by regulating the transcriptional activity of proapoptotic genes. FAS activation enhances the activity of LATS1, and LATS1-induced phosphorylation of YAP1 increases the affinity for p73, causing YAP1 to form a nuclear complex with p73, thereby inducing the transcription of the proapoptotic puma gene [234].

Remarkably, FasL/Fas activation also regulates pro-survival pathways such as NF-κB. For instance, the caspase-8-induced cleavage products of cFLIPL are conducive to stimulating NF-κB signaling [235, 236]. Moreover, cFLIPL requires a LUBAC-driven ubiquitination mechanism to activate NF-κB, presumably to generate a ubiquitinated substrate to interact with NEMO [237]. DISC also recruits caspase-10, which blocks caspase-8 activation and enhances the NF-κB response [238, 239]. Dysregulation of the FasL/Fas pathway has been implicated in the development and progression of cancer. In some cancers, overexpression of FasL in tumor cells can induce apoptosis of Fas-expressing tumor-infiltrating lymphocytes, thereby promoting immune evasion and tumor growth [240, 241]. Both Fas and FasL are expressed on the surface of LC cells, the Fas displaying while FasL is inhibiting compared with normal liver tissue, contributing to the anti-apoptosis for LC cells [242-244]. Significantly, the Fas/FasL pathway is finely regulated by ubiquitination,

including protein stabilization and localization changes. For example, the E3 ubiquitin ligase Hrd1 protected B cells from activation-induced cell death by degrading Fas [245]. Similarly, another E3 ligase MARCH8 directly interacts with Fas, promoting its ubiquitination and degradation [246]. Besides, the E3 ubiquitin ligase TRAF2 interacts with caspase-8 at the DISC, generating K48-linkage polyubiquitination in the large catalytic domain of caspase-8, ultimately promoting activated caspase-8 molecules to rapid proteasomal degradation [247]. Interestingly, KPC2 directly recognizes the Fas and serves as an adaptor to recruit p65 and KPC1, which acts as an E3 ubiquitin ligase promoting the cleavage of p105 into p50, eventually inhibiting NF-κB activation [248]. Moreover, another E3 ubiquitin ligase, AIP2, binds to and supports ubiquitin-mediated degradation of EGR2. This zinc finger transcription factor has been found to up-regulate FasL expression during activation-induced T-cell death [249]. Additionally, a role in the monoubiquitylation of FasL at Lys 72 and 73 is essential for correctly sorting FasL into the inner vesicles of secretory lysosomes [250].

The protein level of Fas is considerably decreased during the HCC transformation [244]. Notably, Fas expression was significantly higher in all the subtypes of tumor-infiltrating lymphocytes (CD3 positive, CD4 positive, CD8 positive, NK cells, and natural T cells) compared with normal liver tissues [251]. Therefore, Fas decreased significantly in HCC cells, and Fas expression increased in lymphocytes, contributing to the failure of HCC cells to be effectively recognized and killed by lymphocytes and the declined number of lymphocytes. There are many potential causes of abnormal changes in Fas-induced apoptosis in HCC, including transcriptional regulation and post-translational modification. In glioblastoma cells treated with temozolomide, E3-ubiquitin ligase Siah1 interacts with HIPK2 causing its degradation, and HIPK2 plays a role in the phosphorylation of p53 at serine 46, enhancing the activity of Fas promoter, which eventually inhibits the expression of Fas and Fas-induced apoptosis [252]. The tyrosine phosphatases family member PTEN, a tumor suppressor, promotes caspase-8 activation and Bcl-2 family member BID cleavage dependent on FADD, hence promoting Fas-induced apoptosis in prostate cancer cells [253]. Consistently, loss of PTEN led to the binding of phosphorylated PEA-15 to FADD, resulting in diminished DISC formation and decreased Fas-induced apoptosis in Jurkat-T cells [254]. PTEN also plays a proapoptotic role in HCC, and its expression is reduced or absent in almost half of HCC patients, which is closely associated with tumorigenesis [255, 256]. Previous studies have shown that the non-phosphorylated form of PTEN is destabilized through the ubiquitin-proteasome pathway [257-259] and that proper phosphorylation of PTEN is essential to protect the PTEN from ubiquitin-proteasome mediated degradation [258]. Recent studies show that FADD's Lys 149 and 153 residues are ubiquitinated by the E3 ligase CHIP in DISC, preventing cell death [260].

Ubiquitination of the intrinsic apoptotic pathway in LC

Intrinsic apoptosis senses a wide range of internal stress signals usually produced by cellular stresses, such as DNA damage, high levels of reactive oxygen species, ER stress, or nutrient starvation. All intracellular stress signals eventually converge at the mitochondria [261]. In the intrinsic apoptotic pathway, ubiquitination has been shown to influence the activation and function of key regulators (**Figure 3**). For instance, the E3 ubiquitin ligase MDM2 (mouse double minute 2) can ubiquitinate the proapoptotic protein p53, targeting it for degradation and suppressing its proapoptotic activity [262]. Conversely, DUBs such as USP7 proposed to stabilize MDM2 that promotes the proteasomal degradation of p53, leading to enhanced apoptosis [263]. Additionally, ubiquitination of Bcl-2 family proteins, which control mitochondrial membrane permeabilization and the release of apoptotic factors, can modulate their stability and activity, thereby impacting the intrinsic apoptotic pathway. Ubiquitination of Bax, a proapoptotic protein, has been shown to regulate its localization and function [264, 265]. Moreover, several studies have shown that intrinsic apoptosis defects have been observed in LC [266, 267]. In LC, mutations or inactivation of the *p53* gene are common, leading to the loss of its proapoptotic function and allowing cancer cells to evade apoptosis. Besides, alterations in the expression or activity of Bcl-2 family proteins have also been

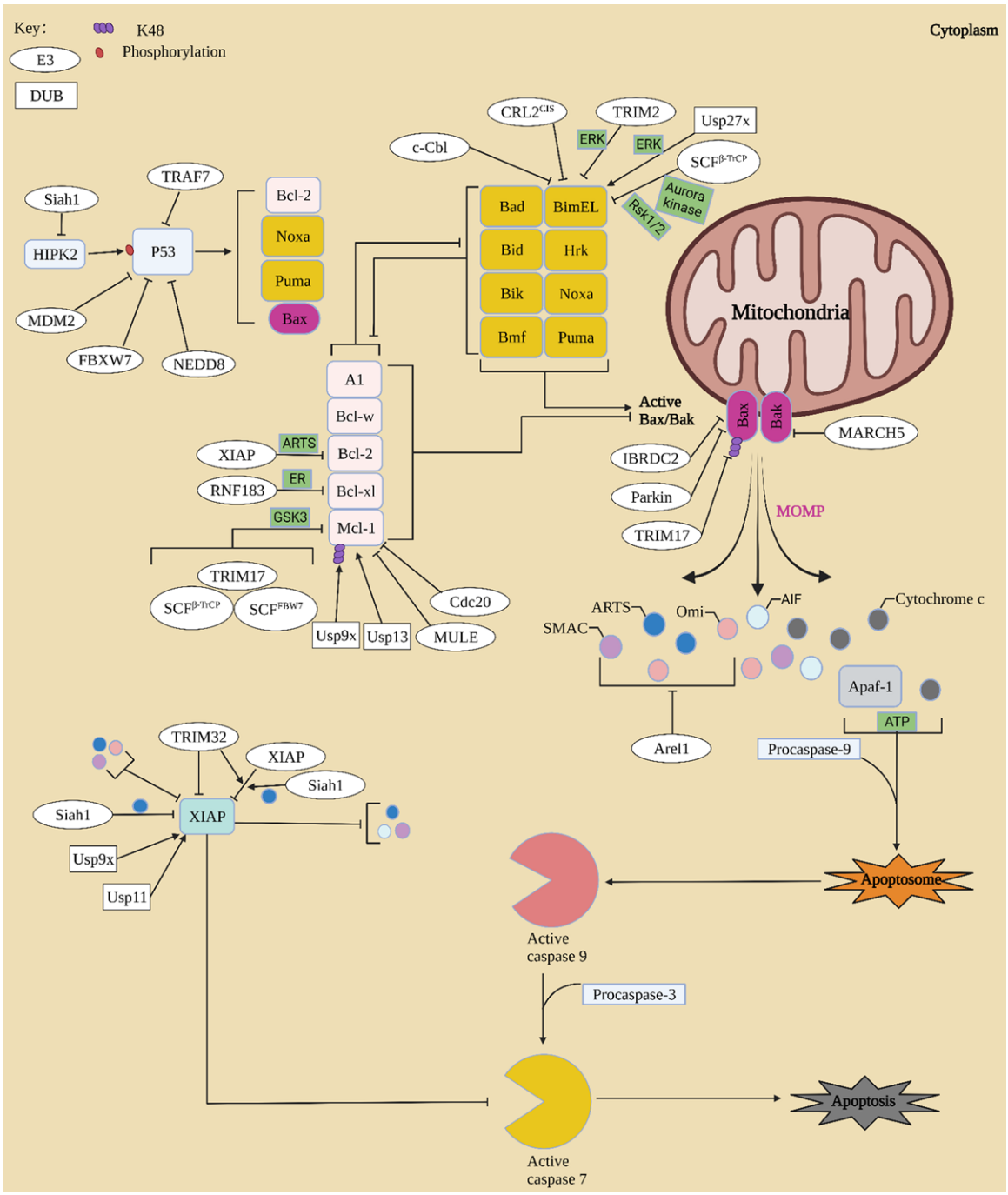

Figure 3. Overview of ubiquitin-mediated regulation of intrinsic apoptosis. The core of intrinsic apoptosis is the change of Mitochondrial Outer Membrane Permeabilization (MOMP) mediated by Bax/Bak. Upon MOMP, some cytokines like SMAC, AIF, Omi, and ARTS were released into the cytoplasm causing activation of caspases and sequent apoptosis. The activity of Bax/Bak is largely regulated by the proapoptotic BH3-only protein and the antiapoptotic Bcl-2 proteins. E3s and DUBs finely regulate the processes; these regulators are abnormally expressed in LC (see **Table 3** for details). Under certain conditions, such as phosphorylation and ER stress, the binding ability of E3s and DUBs to substrates is affected.

observed in LC. For example, decreased expression of proapoptotic proteins such as Bax and increased expression of antiapoptotic proteins such as Bcl-2 have been observed in HCC tissues, suggesting that HCC cells resist apoptosis [268]. Additionally, defects in other compo-

nents of the intrinsic apoptotic pathway, such as cytochrome c release from mitochondria and the activation of caspases, have also been reported in LC. These defects can disrupt the downstream apoptotic signaling cascade and contribute to the survival and proliferation of cancer cells. Therefore, abnormal or defective intrinsic apoptosis in LC is closely related to ubiquitination.

The ubiquitination of the Bcl-2 family executioners: Members of the Bcl-2 family can be both proapoptotic and antiapoptotic, and a balance between their protein levels determines whether apoptosis occurs or not [111, 269]. There are three subclasses of the Bcl-2 family: the proapoptotic executioners, the proapoptotic BH3-only proteins, and the antiapoptotic Bcl-2 proteins [111]. When activated, Bax and Bak are the main proapoptotic executioners that can oligomerize in the outer mitochondrial membrane, forming pores that induce MOMP [81]. The pro-survival Bcl-2 proteins, including Bcl-2, Bcl-xL, and MCL-1, which have four BH domains, are primary antagonists of Bax/Bak by preventing their outer mitochondrial membrane localization and activation [270, 271]. Enjoyably, these antagonists of Bax/Bak are distributed differently in LC. The Bcl-xL protein was expressed in HepG2, Hep3B, and Huh7 human hepatoma cell lines at high levels, but none of these cells expressed Bcl-2 [272]. Bcl-2 protein is constitutive expression in HCC-T cells, but not in HepG2 cells [231]. Moreover, Bcl-2 confers protection to HCC cells against Fas-mediated apoptosis [231]. Previous studies have demonstrated that the progression and tumorigenesis of LC is associated with decreased Bax protein [75, 273]. Specifically, the expression and mitochondrial translocation of Bax promote apoptosis of HCC cells, while translocation of Bax into the cytoplasm promotes survival of HCC cells. The E3 ligase IBRDC2 has been reported to target Bax for ubiquitin-mediated degradation, and, interestingly, IBRDC2 localizes to the mitochondria only when activated Bax emerges there [274] (**Table 3**). Similarly, mitochondrial Bax is also ubiquitinated by Parkin, causing targeted proteasome degradation [270]. Furthermore, Parkin-mediated ubiquitination of Bax in the cytoplasm inhibits the translocation of Bax to the mitochondria [275, 276]. Several studies have shown that E3 ubiquitin ligase Parkin acts as a tumor suppressor protein, and its protein expression was significantly decreased or absent in LC [150, 277]. Notably, the exon of the *Parkin* gene has a high-frequency mutation in HCC cell lines, suggesting the loss of function mutations may be associated with the occurrence and progression of LC [277]. Besides, recent reports have shown that another E3 TRIM17 is able to interact with Bax, promoting its K48-linkage polyubiquitin chains and proteasome degradation, leading to a deficiency in Bax-dependent apoptosis in gastric cancer cells in the absence and presence of apoptosis stimuli [265]. TRIM17 has not been studied in detail in LC, and whether it is related to the mechanism of LC cells escaping apoptosis in Bax-dependent needs further study. Rather than directly regulating Bax, most E3 ubiquitin ligases indirectly regulate Bax by regulating the stability or activity of their interacting partner. While Bak is also a crucial proapoptotic protein, its role in LC has not been extensively studied compared to Bax. Current studies have shown that LC tissues have higher Bax transcription levels, which are positively correlated with poor prognosis, compared with adjacent non-cancer tissue [278]. Recent studies have shown that the loss of E3 ubiquitin ligase activity of MARCH5 could drive Bax to adopt an activated conformation [279]. In addition, previous research has shown that high MARCH5 expression levels are correlated with improved survival of HCC patients [280], suggesting that MARCH5 may promote the apoptosis of LC cells by promoting the degradation of Bax.

Once activated Bak/Bax has induced MOMP, pro-apoptotic factors such as cytochrome c, AIF (apoptosis-inducing factor) and IAP antagonists (SMAC, Omi, ARTS) are released from the mitochondria into the cytosol [281]. In the presence of ATP, cytochrome c, Apaf-1, and procaspase-9 interact and oligomerize, forming a complex known as the apoptosome [281]. The apoptosome triggers procaspase-9 to form homodimers, which induces its enzymatic activity and autoproteolytic cleavage, activating it. Activated caspase-9 can then cleave the executioner caspases, procaspase-3/7, thereby promoting apoptosis. However, if the antiapoptotic protein XIAP is present, it can potently block caspase-3/7/9 activity [282]. Overexpression of XIAP has been observed in HCC and is strongly

Table 3. Regulators of the ubiquitination in intrinsic apoptosis

Regulator of the ubiquitination	Substrate Targeted protein	Impact on intrinsic apoptosis	Deregulation and role in liver cancer	Refs
IBRDC2 (E3)	Bax	Apoptosis↓	ND	[274]
Parkin (E3)	Bax	Apoptosis↓	Downregulation Cancer inhibition	[150, 270, 277]
TRIM17 (E3)	Bax	Apoptosis↓	ND	[265]
	Mcl-1	Apoptosis↑		[284]
MARCH5 (E3)	Bax	Apoptosis↓	Upregulation Cancer inhibition	[279, 280]
c-Cbl (E3)	BimEL	Apoptosis↓	Downregulation Cancer inhibition	[297, 396]
$CRL2^{CIS}$ (E3)	BimEL	Apoptosis↓	ND	[300]
TRIM2 (E3)	Bim	Apoptosis↓	ND	[301]
$SCF^{\beta\text{-}TrCP}$ (E3)	BimEL	Apoptosis↓	Upregulation Cancer promotion	[304, 305, 397]
	Mcl-1	Apoptosis↑		[316]
XIAP (E3)	Bcl-2	Apoptosis↑	Upregulation Cancer promotion	[283, 284, 289]
	SMAC, AIF, and ARTS	Apoptosis↓		[289-291]
Arel1 (E3)	SMAC, AIF, and Omi	Apoptosis↓	ND	[293]
RNF183 (E3)	Bcl-xl	Apoptosis↑	ND	[323]
SCF^{FBW7} (E3)	Mcl-1	Apoptosis↑	ND	[315, 398, 399]
MULE (E3)	Mcl-1	Apoptosis↑	ND Cancer promotion	[218, 400]
Cdc20 (E3)	Mcl-1	Apoptosis↑	Upregulation Cancer promotion	[267, 268, 320, 401]
Siah1 (E3)	XIAP	Apoptosis↑	Downregulation Cancer promotion	[292, 402, 403]
Usp11 (DUB)	XIAP	Apoptosis↓	Upregulation Cancer promotion	[16, 403]
Usp13 (DUB)	Mcl-1	Apoptosis↑	Upregulation Cancer promotion	[19, 404-406]
Usp9× (DUB)	Mcl-1	Apoptosis↑	Upregulation Cancer promotion	[309, 407, 408]
	XIAP	Apoptosis↓		[15]
Usp27× (DUB)	Bim	Apoptosis↓	Upregulation Cancer promotion	[17, 307]

associated with poor patient prognosis and increased resistance to chemotherapy and radiation therapy [283, 284]. XIAP is an E3 ligase and a potent inhibitor of both the intrinsic and extrinsic apoptotic pathways. In humans, the E3 ligase activity of XIAP does not appear necessary for its anti-apoptotic function, as its primary mechanism of inhibiting apoptosis involves direct binding to aspase-3/7/9. However, it's worth noting that the E3 ligase activity of XIAP plays a crucial role in its auto-ubiquitination, which is responsible for its degradation [285].

Previous studies have shed light on the regulation of XIAP via ubiquitination and deubiquitination. The E3 ligase TRIM32 has been shown to either stimulate XIAP's auto-ubiquitination or directly bind to and ubiquitinate it, leading to its degradation [286]. TRIM32 is significantly upregulated in LC and has been shown to promote cancer progression [287, 288], suggesting that it may weaken XIAP-mediated inhibition of apoptosis, contributing to the early growth of LC. In contrast, the deubiquitinases USP11 and USP9X exhibit the reverse effect by interacting with the BIR2 domain of XIAP and inducing XIAP

deubiquitination and stabilization [16], and USP9X deubiquitinate and stabilize XIAP to promote cell survival during the mitotic spindle assembly checkpoint, respectively [15]. XIAP has also been reported to function as an E3 ligase for several apoptotic-related proteins, including Bcl-2, SMAC, AIF, and ARTS [289-291]. To counteract XIAP's anti-apoptotic function, IAP antagonists such as SMAC, Omi, and ARTS are released from the inner mitochondrial membrane space following MOMP. In the case of ARTS, it is removed from the outer mitochondrial membrane preceding MOMP [282]. These IAP antagonists inhibit XIAP through various mechanisms. Of particular interest, ARTS can trigger the XIAP auto-ubiquitination and/or ubiquitination through the E3 ligase Siah1 [292]. However, the E3 ligase Arel1 (apoptosis-resistant E3 Ub protein ligase 1) has been reported to ubiquitinate and degrade SMAC, Omi, and ARTS under apoptotic conditions, likely due to its localization in the cytoplasm after MOMP and its proximity to XIAP antagonists [293].

The ubiquitination of the BH3-only proteins: Proapoptotic BH3-only proteins (Bid, Bim, Puma, Noxa, Bad, Bmf, Hrk, and Bik) induce Bax/Bak pore formation either directly by activating Bax/Bak or passively by isolating anti-apoptotic Bcl-2 proteins [294, 295]. Notably, only Bim has been reported to be regulated by several E3 ligases/DUBs, regulating its protein level. Bim protein was significantly expressed in HCC tissues compared to normal tissues [296]. Significantly, overexpression of Bim EL, L, S and all alpha isoforms induced apoptosis in HCC cells, while overexpression of Bim beta isoforms showed no effects on cell survival after 5-FU treatment [296].

Studies have shown that the ultra-long splicing variant (BimEL) of Bim is labeled degradable by the E3 ligase c-Cbl [297]. However, another study has shown that this is not the case in different cell lines [27], suggesting that the effects of c-Cbl on Bim may be cell type-specific. Previous studies have shown that ablation of Cbl-b and c-Cbl in dendritic cells causes spontaneous liver cirrhosis via altering multiple properties of CD103+ cDC1s [298]. Besides, other results imply that the Bim can be of importance in the livers of patients with primary biliary cirrhosis [299]. These studies suggest that c-Cbl may inhibit the occurrence of HCC by degrading Bim. In addition, BimEL is degraded by the E3 ligase complex $CRL2^{CIS}$, which contains Elongin B/C, Cullin-2, and CIS [300]. Another E3 ligase TRIM2 binds to Bim when it is phosphorylated by p42/p44 MAPK but does not interact with a Bim mutant (3ABim, loss of phosphorylation) [301]. Besides, ERK-mediated Bim phosphorylation at serine 69 induced BimEL degradation via ubiquitin-proteasome pathway [302]. These studies show that TRIM2 and Bim that are phosphorylated enhance their ability to interact with each other. Critically, the MAPK/ERK signaling pathway is activated in more than 50% of human HCC cases, suggesting TRIM2 may play a role in promoting cancer in HCC [303]. In addition, Rsk1/2 (Ribosomal protein S6 kinase 1/2) and Aurora kinase phosphorylated BimEL at Ser93/Ser94/Ser98, inducing ubiquitination and degradation via the $SCF^{\beta\text{-}TrCP}$ complex [304, 305]. Therefore, the phosphorylation-induced ubiquitination and degradation of BimEL by Rsk1/2, Aurora kinase, and the $SCF^{\beta\text{-}TrCP}$ complex can potentially impact the levels of BimEL in LC cells. For example, activating mutations, changes in protein expression, and phosphorylation patterns of Rsk1/2 and Aurora kinase in LC should be considered and further researched.

OTUD1 directly interacted with Bim and inhibited its ubiquitination at the lys 3 residue, stabilizing it [306]. LC cells often exhibit reduced apoptosis, allowing them to evade cell death and promote tumor growth. Stabilizing Bim through its deubiquitination by OTUD1 can potentially counteract this apoptosis resistance by restoring or enhancing its proapoptotic function. According to another study, Usp27x has the ability to decrease ERK-dependent Bim ubiquitination, while increasing its levels and stabilizing phosphorylated Bim [17]. However, Usp27× expression is increased in HCC and is positively correlated with poor prognosis [307], which may be related to the abnormal phosphorylation pathway in HCC.

The ubiquitination of the anti-apoptotic Bcl-2 proteins: The antiapoptotic Bcl-2 proteins (Bcl-2, Bcl-xL, Bcl-w, Mcl-1, and A1) can inhibit apoptosis either by the direct binding and inhibition of Bax/Bak or by sequestering BH3-only proteins that directly interact with Bax/Bak [308]. Several studies have shown that degradative types of ubiquitination regulate Mcl-1. The DUB

USP9X was reported to stabilize Mcl-1 by removing K48-linkage ubiquitin chains, promoting tumor cell survival [309]. Another DUB, USP13, was also shown to stabilize Mcl-1 by reducing its K48-linkage ubiquitin chains [19]. In the context of LC, the stabilization of Mcl-1 by USP9X and USP13 through deubiquitination has been implicated in promoting tumor cell survival and contributing to LC progression. Previous studies have shown that Mcl-1 is crucial for the survival and self-renewal of cancer stem-like cells in HCC [310]. Furthermore, Mcl-1 protein expression was considerably enhanced in human HCC tissue compared to adjacent non-tumor tissue [311]. Additionally, knockdown of *Mcl-1* efficiently enhanced apoptosis sensitivity towards combined treatment modalities [311, 312].

In neuronal cells, the E3 ligase TRIM17 was shown to mediate the ubiquitination and proteasomal degradation of Mcl-1 in a process dependent on GSK3 (Glycogen synthase kinase 3) induced phosphorylation of Mcl-1 [313]. The E3 ligase MULE was also shown to interact with Mcl-1, resulting in subsequent ubiquitination and degradation [218]; however, basal levels of Mcl-1 were not affected in MULE-deficient cells [314]. The $SCF^{\beta\text{-}TrCP}$ and SCF^{FBW7} E3 ligase complexes have been implicated in regulating the intrinsic apoptotic pathway via inducing Mcl-1 ubiquitination and degradation of Mcl-1 [315, 316]. GSK3-mediated phosphorylation of Mcl-1 at Ser159/Thr163 enhances the interaction between both $SCF^{\beta\text{-}TrCP}$ and SCF^{FBW7} association with Mcl-1, contributing to elevated ubiquitination and degradation [317]. Previous studies have shown that the presence of GSK3 inactivation in LC enhances the stability of Mcl-1 and inhibits HCC cell apoptosis, thus promoting liver carcinogenesis [318, 319], suggesting that these three E3 ligases may play an anticancer role in LC dependent on Mcl-1. Additionally, phosphorylation of Mcl-1 at Thr92 by CDK1/Cyclin B1, in response to mitotic arrest, was shown to induce APC/C (Cdc20) E3 ligase complex mediated ubiquitination and degradation of Mcl-1 [320]. However, another study shows that Cdc20-mediated degradation of PHD3 stabilizes HIF-1a and promotes tumorigenesis in HCC [267]. It's possible that a change of CDK1/Cyclin B1 activity and expression in LC weakens the anticancer impact of Cdc20, which is dependent on Mcl-1 [321, 322].

In addition to Mcl-1, a recent study has shown that Bcl-xL is also subject to regulation by ubiquitin-mediated degradation via the E3 ligase RNF183 in response to ER stress [323]. While RNF183 is typically localized to the ER and Bcl-xL to the mitochondria, it's worth noting that the mitochondria and ER often come into proximity and form membrane contact sites [324], indicating the plausibility of ER-located RNF183 being able to ubiquitinate mitochondria-located Bcl-xL. Bcl-xL is mainly present in the cytoplasm of hepatocytes, but in HCC cells Bcl-1xL is not only present in the cytoplasm but also in part of the nucleus [325]. This suggests that the redistribution of Bcl-xl may be involved in the evade of HCC cell apoptosis. After inducing apoptosis, ARTS introduced XIAP and Bcl-2 into the ternary complex so that XIAP promoted ubiquitination and degradation of Bcl-2 further enhancing apoptosis [289].

Other ubiquitin-involved apoptosis pathways in HCC

The tumor suppressor p53 plays a pivotal role in the cellular stress response (e.g., DNA damage, oxidative stress, or oncogene activation), which is closely associated with the process of cell death. When cells are under stress, p53 can activate a variety of proapoptotic target genes, ultimately leading to the elimination of the damaged cells via apoptosis. p53 can induce the expression of proapoptotic genes in the Bcl2 family, including *Bax* [326], *Puma* [327], and *Noxa* [328], among others. Furthermore, p53 promotes the expression of genes that target the death receptor, including Fas [329] and DR5 [330]. In non-stressed cells, the levels of p53 are maintained at a low level mainly due to its polyubiquitination by the E3 ubiquitin ligase MDM2 [331]. However, in LC, inactivation of p53 and overactivation of MDM2 are among the factors that contribute to the transformation of normal liver cells into cancer cells [331]. Moreover, p53 mutation is also involved in the proliferation and radiosensitivity of HCC cells through Bcl-2/Bax pathway [268]. Similarly, E3 ubiquitin ligases such as NEDD8 [332] and FBXW7 [333] directly target p53 to modulate its expression and thereby impede its transcriptional activity. Previous studies

have shown that the expression of FBXW7 is impaired in HCC tissues, and FBXW7 can act as a tumor suppressor to inhibit HCC by inducing apoptosis and growth arrest [334, 335]. This stands in contrast to the FBXW7-mediated degradation of p53, which can promote cancer cell survival [333], suggesting the involvement of other E2s or E3s in the intricate regulation of p53. Indeed, numerous E3 ubiquitin ligases also ubiquitinate the E3 ligases directly binding p53, leading to precise regulation of p53 activity [336].

Targeting specific components of the UPS for HCC therapy

Dysregulation of the UPS has been implicated in various diseases, including LC. Since proteasomes are responsible for the degradation of ubiquitinated proteins, inhibiting their function can impair cancer cell survival and promote apoptosis. Bortezomib and carfilzomib are proteasome inhibitors that have been approved for the treatment of multiple myeloma [337, 338]. In LC, bortezomib can be used for advanced HCC [339]. Bortezomib interferes with the 26S proteasome and inhibits proteasomal activity and promotes apoptosis by enhancing activities of the two major pathways (death receptor superfamily and intrinsic mitochondrial cell death pathway) involved in apoptosis-associated caspase activation [339]. Emerging evidence demonstrated that bortezomib performs its canonical functions in bortezomib-susceptible HCC, which has been associated with the accumulation of proapoptotic Bcl-2 proteins Bax and Noxa [340-342]. Moreover, treatment with MG132 (another proteasome inhibitor) suppressed the proliferation of LC cells and induced apoptosis in a dose-dependent manner [343]. MG132 treatment promotes the apoptosis of LC cells probably via increasing the accumulation of proapoptotic Bcl-2 proteins Bim and Bax [344].

E3 ligases are responsible for the transfer of ubiquitin to substrate proteins. By inhibiting specific E3 ligases, it may be possible to modulate the stability of oncogenic or tumor suppressive proteins. The IAPs (inhibitor of apoptosis proteins) family comprises several members, including NAIP, cIAP1/2, XIAP, Survivin, Apolon and ML-IAP. IAPs all contain one or more baculovirus IAP repeat motifs through which they interact with various other proteins [345]. Many IAPs also have another zinc-binding motif, the RING domain, which can recruit E2 ubiquitin-conjugating enzymes and catalyse the transfer of ubiquitin onto target proteins [345]. For example, cIAP1/2 can promote survival and inhibit apoptosis in LC cells by targeting RIPK1 for ubiquitination and degradation [120]. The E3 ligase activity of cIAP1 can be inhibited by D19 or promoted by SMAC mimics (LCL161 and birinapant) [346]. Inhibitors of IAPs, such as SMAC and LCL161, have been shown to induce apoptosis of LC cells both in *vitro* and in *vivo*, suggesting that targeting IAPs could be a promising strategy for the treatment of LC [128, 347]. SMAC is the best characterized inhibitor of IAPs that can increase the apoptosis of XIAP in HCC cells [348]. Small molecule SMAC mimetics can also inhibit IAPs function and lead to cell apoptosis [349, 350]. So far, SMAC mimics that are expected to inhibit the progression of HCC include LCL161 [128], SM-164 [347], APG-1387 [127, 351] and birinapant [352]. A phase I dose-escalation study of LCL161 in patients with advanced solid tumors has been published, indicating that LCL161 is tolerated and had significant pharmacodynamic activity [353]. In HCC cells, LCL161 is found to be effective in combination with paclitaxel to lead cancer cell apoptosis and depress cell proliferation [128]. Down regulating Bcl-2 overcomes drug resistance to LCL161 in HCC cells [354]. Although SM-164 induced complete cIAP1 degradation, it showed a weak inhibitory effect on HCC cell activity [347]. Nevertheless, SM-164 considerably potentiated TRAIL mediated apoptosis in HCC cells in combination with chemotherapeutic agents [347]. APG-1387 exhibits an antitumor effect on HBV-positive HCC with high expression of cIAP2 by inducing apoptosis [127]. Biinapant promotes apoptosis of LC cells and inhibits invasion of LC cells by activating cIAP1/TRAF3 axis [352]. SMAC mimics treatment alone significantly reduced the protein levels of IAPs, but had only a modest effect on the viability and apoptosis of HCC cells in *vitro.* However, these mimics in combination with TNF-α or TRAIL significantly reduced cell viability and proliferation, and induced cell apoptosis. All these results indicated IAPs inhibitors as promising drugs for HCC therapy, and further in *vivo* and in *vitro* studies in HCC are warranted. Besides, the E3 ubiquitin ligase MDM2 is over-

expressed in many tumors, including HCC, and promotes cell survival by targeting the tumor suppressor protein p53 for degradation. Nutlin-3 is a small molecule inhibitor of MDM2 that has been shown to induce apoptosis in HCC cells both in *vitro* and in *vivo* by stabilizing p53 and promoting its activity [355]. LUBAC, as a significant regulator of extrinsic apoptosis pathway, can significantly promote the survival of HCC cells. The administration of thiolutin inhibits catalytic activity of HOIP (a catalytic subunit of linear LUBAC), which impairs the propagation of myeloid leukemia [356]. While several inhibitors of E3 ubiquitin ligases have shown promising results in preclinical studies, further research is needed to determine their safety and efficacy in clinical trials.

DUBs remove ubiquitin from substrate proteins, potentially reversing the effects of ubiquitination. Inhibiting DUBs can increase the levels of ubiquitinated proteins, leading to their degradation by the proteasome. PR-619 is a broad-spectrum DUB inhibitor that has been investigated for its potential in various cancers via regulating cell apoptosis, including oesophageal squamous cell carcinoma [357] and metastatic bladder urothelial carcinoma [358]. But, PR-619 in LC is still under investigation. Given that cancer cells preferentially have TRAIL receptor overexpressed on their cell surface, TRAIL signaling can provide another therapeutic target for cancer treatment. The activation of NF-κB induced by TRAIL renders HCC resistant to TRAIL-mediated cell apoptosis. Notably, CYLD augmented the cytotoxicity of TRAIL in HCC cells by negatively regulating NF-κB activity since CYLD could reverse the ubiquitination of TRAF2 and interact with the NEMO [359]. Recent studies have shown that CAP-Gly domains (ubiquitin-binding domains) in CYLD are vital in determining CYLD activity [360], which raises the possibility of treating LC by controlling CYLD. USP4 can promote cell apoptosis and inhibit pro-survival signals, but it can promote the progression of HCC, which may be related to the occurrence of HCC [361, 362]. Degrasyn (WP1130) is a selective deubiquitinase (including USP4 and USP9X) inhibitor [362]. Furthermore, combined treatment with WP1130 sensitized HCC cells to doxorubicin via USP9X-depedent p53 degradation [363]. USP8 inhibits cell death by affecting cFLIPL/stability, and its protein expression is increased [182, 184, 364]. Of note, USP8 inhibition significantly enhanced doxorubicin or sorafenib's efficacy in HCC cells and mouse models [184]. Hence, inhibitors of USP8 such as HY50737, HY0736 and DC-U43-10 are expected to treat HCC [184].

Conclusion and perspectives

In conclusion, dysregulation of apoptosis is a crucial characteristic of LC, and targeting the ubiquitination pathway, particularly E3 ubiquitin ligases, represents a promising strategy for treating LC. The balance between proapoptotic and antiapoptotic proteins plays a pivotal role in maintaining the homeostasis of apoptosis. However, there are still limited knowledge about these pathways. (i.) The incompleteness of the death pathways: Although several core components of apoptosis have been identified, additional regulators and effectors likely remain undiscovered. For example, ferroptosis and cuproptosis have recently been viewed as new forms of programmed cell death processes [365-367]. (ii.) Limited understanding of cross-talk between pathways: There is little knowledge of how different apoptosis pathways interact with one another, as well as with other cellular processes like autophagy, necroptosis, and inflammation. For example, low levels of death signaling stimulate apoptosis, whereas high death signaling often result in necroptosis [368]. Nevertheless, autophagy significantly improves the fitness of metastatic cells under stressful conditions to counteract apoptosis and necroptosis [368]. Moreover, apoptosis and necroptosis also inhibited each other. (iii.) Species and cell-type specificity: Apoptosis pathways can vary between organisms and cell types. For example, compared to the normal cell, TNFR2 is mainly expressed on the tumor cell surface and inhibitory immune cells in the tumor microenvironment [369]. (iv.) In the death signaling, the expression, localization, and activation of essential regulator proteins still need further research, such as the discovery of related E3s. These limitations, among others, highlight the need for continued research and development of novel approaches to better understand and manipulate apoptosis pathways in a variety of biological contexts.

While several inhibitors of E3 ubiquitin ligases have shown promising results in preclinical

studies of LC, several challenges need to be addressed. These include the development of drug resistance, the potential toxicity of these agents, and identifying the most effective drug combinations and dosing regimens. Additionally, further research is needed to fully understand the mechanisms underlying the dysregulation of the ubiquitination modification in LC. One potential strategy to overcome these challenges is to develop more selective E3 ubiquitin ligase inhibitors/activators that target specific oncogenic substrates. For instance, recent studies have shown that STAT3 inhibitors 2-benzylmalonic acid derivatives inhibit tumor growth in HCC by upregulating β-TrCP E3 ubiquitin ligase [370]. This approach may reduce the potential toxicity of these agents and minimize the development of drug resistance. Another promising avenue of research is to identify biomarkers that can predict which patients are most likely to respond to E3 ubiquitin ligase inhibitors/activators, allowing for more personalized treatment approaches. Additionally, combining E3 ubiquitin ligase inhibitors/activators with other targeted therapies or immunotherapies may enhance their efficacy and reduce the likelihood of resistance. Overall, continued research into the role of the ubiquitin pathway involved death in LC and the development of novel therapeutic strategies is critical to improving clinical outcomes for patients with LC.

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Disclosure of conflict of interest

None.

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