Review Article The roles of KLHL family members in human cancers

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Abstract: The Kelch-like (KLHL) family members consist of three domains: bric-a-brac, tramtrack, broad complex/ poxvirus and zinc finger domain, BACK domain and Kelch domain, which combine and interact with Cullin3 to form an E3 ubiquitin ligase. Research has indicated that KLHL family members ubiquitinate target substrates to regulate physiological and pathological processes, including tumorigenesis and progression. KLHL19, a member of the KLHL family, is associated with tumorigenesis and drug resistance. However, the regulation and cross talks of other KLHL family members, which also play roles in cancer, are still unclear. Our review mainly explores studies concerning the roles of other KLHL family members in tumor-related regulation to provide novel insights into KLHL family members.

Keywords: Kelch-like family member, E3 ubiquitin ligase, ubiquitination, degradation, human cancer

Introduction

Ubiquitin is a small protein composed of 76 amino acids with highly conserved sequences: it is widely present in all eukaryotic cells and is involved in ubiquitination modification [1]. Ubiquitination, an important post-translational modification type, links ubiquitin to target a protein and then triggers protein degradation by the 26S proteasome complex or regulates the biological functions of substrates [2, 3]. This type of regulation is catalyzed by the sequential enzymatic reactions of ubiquitinactivating enzyme (E1), ubiquitin-binding enzyme (E2) and ubiquitin-ligase enzyme (E3). First, the ATP-dependent activation of ubiquitin occurs when the cysteine residues of E1 connect to the C-terminal lysine residues of ubiquitin. Second, activated ubiquitin is transferred and binds E2. Finally, through the action of E3, ubiquitin is transferred to a substrate's lysine via a covalent bond; the transfer results in the ubiquitination of a target protein [4]. Notably, a ubiquitin molecule has seven lysine (K) residues (K6, K11, K27, K29, K33, K48, and K63) and one methionine residue (M1). And a variety of linkages can be formed in poly-ubiquitin chains; the linkage type determines the ultimate fate of target proteins [5, 6] and affects various biological functions, including DNA damage repair [7, 8], cell cycle regulation [9], autophagy [10], and immune response [11, 12]. The main destination of ubiquitinated proteins is degradation by the ubiquitin-proteasome system (UPS), which is the main pathway of more than 80% of intracellular protein turnovers and plays significant roles in regulation of cellular proteins' activities and functions [13, 14]; thus, the aberrant regulation of the UPS is associated with various types of cancer [15].

A total of 2 species of E1, 40 species of E2, and over 600 species of E3 are found in mammals [16]. E3 ligases, which transfer ubiquitin to substrates, determine the fate of substrate proteins and regulate biological functions [17-19]. According to structural features and functional mechanisms, E3 ligases can be divided into three categories: the really interesting new gene (RING) family, homologous to the E6AP carboxyl terminus (HECT) family, and RINGbetween-RING (RBR) family [17]. At least one catalytically active cysteine residue is present in the HECT and RBR families and binds with the C-terminal amino acid residues of ubiquitin through thioester bonds, and E3 specifically

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Figure 1. A: The Diagram of 42 KLHL family members with Amino acid numbers are listed on the right. B: The structural components of the Cullin3-RING-KLHLs complex and its ability to regulate tumor occurrence and development. A. Kelch-like protein family members (KLHLs) consist of the bric-a-brac, tramtrack, broad complex (BTB)/ poxvirus and zinc finger (POZ) domain, the BACK domain and the Kelch repeated domain, the BTB/POZ domain is responsible for binding cullin3, the Kelch domain determines substrates recruitment, and the BACK domain forms a linker between BTB domain and Kelch domain. Data comes from the Uniprot and the Smart databases. B. The Cullin3-RBX1-KLHLs complex consists of three components, including the Cullin3 protein functioning as the scaffold protein, the KLHLs protein responsible for identifying the targeted substrates and binding the Cullin3 protein, and the RING-box protein crucial to recruitment to E2. The KLHLs have the abilities of triggering several substrates ubiquitination modification to influence its stability and localization, thereby taking part in the regulation of tumor occurrence and development.

recognizes its substrates and facilitates ubiquitin-substrate conjugation. However, the RING family has no active cysteine; E2 is necessarily involved in the combination of ubiquitin and then completes conjugation with E3 and substrates [20, 21].

The Cullin-RING E3 ligases (CRLs) constitute the largest E3 ligase family, including CRL1, CRL2, CRL3, CRL4A, CRL4B, CRL5, CRL7 and CRL9, and are responsible for the ubiquitination of substrate proteins [22]. A CRL consists of four components: a Cullin protein functioning as a scaffold protein, a substrate-recognizing receptor that is vital to the identification of target substrates, an adaptor protein linking a Cullin protein to adaptor proteins, and one RING-Box (RBX) protein, which is crucial to recruitment to E2 [17]. CRL3 is a highly conserved member of the CRL family, consisting of a Cullin3 protein, an RBX1 protein, and a bric-abrac tramtrack, broad complex (BTB) protein which serves as the roles of both the adaptor protein and the substrate-recognizing receptor [23, 24].

Kelch-like (KLHL) family members (KLHLs), regarded as the substrate-binding subunits of CRL3, commonly possess a BTB/poxvirus and zinc finger (POZ) domain, a BACK domain, and Kelch domain with 4-6 Kelch repeated motifs [25]. In a Cullin3-RBX1-KLHLs complex, the BTB/POZ domain is responsible for binding Cullin3, the Kelch domain determines substrate specificity, and the BACK domain forms a link between the BTB and Kelch domains. To date, 42 kinds of KLHLs in mammals have been identified [26] (**Figure 1**). Among these,

KLHL19, also called Kelch-like-ECH-associated protein 1 (KEAP1), has been the most extensively studied, which is the substrate adaptor protein of the Cullin3 ubiquitin ligase complex, consisted of an N-terminal region, a BTB domain, an intermediate region (IVR), a doubleglycine repeat (DGR) domain/Kelch domain with six repeated Kelch motifs, and a C-terminal region. The BTB domain is responsible for the dimerization of KLHL19 and promotes its binding to Cullin3 ligase. The Kelch repeated domain contains important binding sites interacting with specific substrates, such as nuclear factor E2-related factor 2 (NRF2) and P62. The IVR contains nuclear export-signals that regulate the cytoplasmic localization of KLHL19 [27]. A growing body of research has focused on other family members involved in regulating several biological functions, such as cell division, brain development, and blood pressure regulation [28-30]. A detailed classification of KLHLs and substrates are shown in Tables 1, 2 and Figures 2.3.

Ubiguitination is closely involved in the physiological and pathological regulation of cancer, particularly through epithelial-to-mesenchymal transition (EMT) [31], stemness maintenance [32, 33], resistance to radiotherapy [34, 35], chemotherapy [36, 37], endocrine therapy [38], and tumorigenesis, metastasis, and invasion [39-41]. Interestingly, the abnormal levels of KLHLs are tightly related to tumorigenesis and progression [42-44], and KLHLs are engaged in many signal pathways, including phosphatidylinositol 3-kinase (PI3K)/the protein kinase B (AKT), Wnt/ β -catenin signaling, mammalian target of rapamycin (mTOR) signaling, hippo signaling, nuclear factor kappa-B (NF-kB) signaling and autophagy-lysosome pathway (Figure 2). Therefore, identifying the underlying mechanisms of KLHLs may be of great significance to tumor prevention, screening, precise treatment, prognosis assessment, and drug development.

PI3K/AKT signaling

The PI3K/AKT pathway is a signaling pathway activated by various growth factors, cytokines and insulin, and regulates normal physiological and pathological events, including glucose metabolism, lipid metabolism, biosynthesis, tumorigenesis, and tumor progression [45, 46].

In addition, it is widely aberrantly upregulated in human cancer [47, 48] and involved in the regulation of tumor metabolism, cell cycle, and angiogenesis [49].

PI3K is an intracellular phosphatidylinositol kinase activated by a series of upstream signals. Activated PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) into phosphatidylinositol 3,4,5-triphosphate (PIP3). Then, PIP3 facilitates the membrane recruitment of AKT and promotes its phosphorylation at T308 [50, 51]. Further, phosphorylated-AKT (p-AKT) activates downstream signaling [52, 53], including mTOR [46], VEGF [54], MAPK [55] and NF-kB [56] signaling. PIK3CA, the gene encoding PI3K, is usually genetically dysregulated by amplification and somatic point mutations in various human cancer types [57]. At the protein modification level, the E3 ligase TRAF6 degrades P85 α (the regulatory subunit of PI3K) through UPS, which promotes prostate cancer (PCa) migration [58].

In addition, the phosphatase and tensin homolog (PTEN) is a tumor suppressor that can antagonize the PI3K phosphorylation effect by dephosphorylating PIP3 into PIP2, thereby strictly regulating PIP3 levels and AKT signaling in normal cells [59, 60]. *PTEN* (gene) loss or its decreased expression has been detected in a range of human cancer types [13], which is related to poor prognosis [61] and chemotherapy resistance of lung cancer (LC) [62].

Ubiquitination plays significant roles in various modes of signal transduction, including PI3K/ AKT signaling, which participates in tumorigenesis, cell proliferation, invasion, apoptosis and chemotherapy resistance [55, 63-66]. Currently, several studies have observed that KLHL38 and KLHL18 are involved in LC-related processes through ubiquitination degradation to associated substrates (PI3K and PTEN, respectively).

KLHL38-PTEN

As a member of the KLHL family, KLHL38 was found to be involved in heart failure formation due to its-mediated excessive degradation of myocardin, one protein essential in the differentiation and development of myocardium and smooth muscle [67]. In tumor-related research, KLHL38 is an oncogenic protein that partici-

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KLHLs	Substrates	Degraded or not	Roles	References
KLHL2	WNK4	Yes	Anti-hypertension effect	[306]
	WNK3	Yes	Anti-hypertension effect	[331]
	NPCD	No	Regulation of neuronal development	[332]
KLHL3	WNK1	Yes	Anti-hypertension effect	[333]
	WNK4	Yes	Anti-hypertension effect	[334-338]
	cMyBP-C	Yes	Regulation of heart development	[339]
	Claudin-8	Yes	Anti-hypertension effect	[340]
	NCC	Yes	Anti-hypertension effect	[28]
KLHL6	HBXIP/Lamtor5	No	Inhibition of B cell maturation	[341]
KLHL7	TUT1	Yes (K48)	Maintaining nucleolar integrity	[342]
KLHL8	Rapsyn	Yes	Regulation of neuromuscular junction	[343]
KLHL9	Aurora B	No	Regulation of Mitotic progression	[284]
	IRS1	Yes	Insulin resistance	[283]
KLHL10	dBruce	Yes	Regulation of spermiogenesis and male fertility	[344, 345]
KLHL12	DVLs	Yes	Inhibition of Wnt pathway	[140, 141, 147]
	Lunapark	Yes	Regulation of neurodevelopment	[144]
	DRD4	No	-	[346-348]
	SEC31	No	Promotion of collagen secretion	[142, 143]
	KHSRP	No	Inhibition of enterovirus ires-mediated translation	[349]
KLHL13	Aurora B	No	Regulation of mitotic progression	[284]
	IRS1	Yes	Insulin resistance	[283]
KLHL15	DCX, DCLK1 and DCLK2	Yes	Regulation of neurogenesis	[350]
	PP2A	Yes	Regulation of cellular dephosphorylation events	[351]
	CTIP	Yes	DNA-end resection and DSB repair	[352]
KLHL16	MAP1B-LC	Yes	Regulation of neuronal function	[161]
	ATG16L1	Yes (K48)	Regulation of autophagosomes production	[353]
	MAP8	Yes	Regulation of neuronal function	[354]
	GFAF	Yes	Regulation of neuronal function	[162]
	TBCB	Yes	Regulation of neuronal function	[355]
	IFs	Yes	Regulation of neuronal function	[356]
KLHL17	GluR6	Yes	Maintaining synaptic normality among neurons	[357]
KLHL18	Aurora-A	Yes	Regulation of mitotic entry	[73]
	UNC119	Yes	Protection of cells from light damage	[358]
KLHL19	MCM3	No	Maintaining the stability of cell cycle	[359, 360]
	PGAM5	Yes	Regulation of oxidative stress	[361]
	PALB2	No	Regulation of cell cycle	[362]
	P62	No	Promotion of anti-oxidant response and autophagy	[363, 364]
	MIRO-2	Yes	Regulation of mitochondrial transport	[365]
	NRF1	Yes	Cellular oxidative stress response	[237]
	NRF2	Yes	Cellular oxidative stress response	[237]
	PGAM5, BCL2L1	Yes	Promotion of cell apoptosis	[366]
	BCL2	Yes	Promotion of cell apoptosis	[367]
KLHL20	Coronin 7	No (K33)	Protein Trafficking	[368]
	PDZ-RhoGEF	Yes	Neurite outgrowth	[369]
	DAPK, PML	Yes	Inhibition of apoptotic and autophagic death	[281]
KLHL21	EB	No	Promotion of cell migration	[370]
	Aurora B	No	Regulation of mitosis	[371]
KLHL22	PLK1	No	Regulation of mitosis	[98, 372-374]
KLHL24	KRT14	Yes	Regulation of skin integrity	[375]
	Keratin 14, 15	Yes	Regulation of hair maintenance	[376]

Table 1. The biological functions of interactions between KLHLs and different substra	ates
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KLHL25	4E-BP1	Yes	Promotion of translational activity	[377]
	ACLY	Yes	Promotion of iTreg cell differentiation	[264]
KLHL31	FLNC	Yes	Maintenance of muscle function	[378]
KLHL38	Myocardin	Yes	Promotion of heart failure	[67]
KLHL40	DP	Yes	Regulation of skeletal muscle myogenesis	[379]
KLHL41	Nebulin	No	Maintenance of muscle function	[380]
	NRAP	Yes	Maintenance of muscle function	[381]
KLHL42	PPP2R5	Yes	Promotion of connective tissue fibrosis	[382]
	P60/Katanin	Yes	Regulation of mitosis	[383]

Abbreviations: WNK1: WNK Lysine Deficient Protein Kinase 1; WNK3: WNK Lysine Deficient Protein Kinase 3; WNK4: WNK Lysine Deficient Protein Kinase 4; NPCD: Neuronal Pentraxin with Chromo Domain; cMyBP-C: Myosin Binding Protein C3; NCC: Na⁺-CI: Cotransporter; HBXIP/Lamtor5: Late Endosomal/Lysosomal Adaptor; TUT1: Terminal Uridylyl Transferase 1; IRS1: Insulin Receptor Substrate 1; dBruce: One of the Inhibitor of Apoptosis Family of Proteins Family; DVLs: Disheveled Family Members; DRD4: Dopamine D4 Receptor; SEC31: Protein Transport Protein SEC31; KHSRP: KH-Type Splicing Regulatory Protein; DCX: Doublecortin; DCLK1: Doublecortin-Like Kinase 1; DCLK2: Doublecortin-Like Kinase 2; PP2A: Protein Phosphatase 2A; CTIP: Carboxy-Terminal Binding Protein 1 Interacting Protein; DSB: DNA Double Strand Breaks; MAP1B-LC: The Light Chain (LC) of Microtubule-Associated Protein 1B (MAP1B); ATG16L1: Autophagy Related 16 Like 1; MAP8: Microtubule-Associated Protein 8; GFAF: Glial Fibrillary Acidic Protein; TBCB: Tubulin Folding Cofactor B; IFs: Intermediate Filaments; GluR6: Glutamate Ionotropic Receptor Kainate Type Subunit 2; UNC119: Unc-119 Lipid Binding Chaperone; MCM3: Minichromosome Maintenance Complex Component 3; PGAM5: Phosphoglycerate Mutase Family Member 5; PALB2: Partner and Localizer of BRCA2; RHOT2/MIRO-2: Ras Homolog Family Member T2; NRF1: Nuclear Factor Erythroid-2-Related Factors 1; NRF2: Nuclear Factor Erythroid-2-Related Factors 2; BCL21: BCL2 Like 1; BCL2: BCL2 Apoptosis Regulator; PDZ-RhoGEF: Rho Guanine Nucleotide Exchange Factor 11 (also called ARHGEF11); DAPK: Death Associated Protein Kinase; PML: Promyelocytic Leukemia Protein; EB: End Binding Protein; PLK1: Polo Like Kinase 1; KRT14: Filamin-C (FInC) Keratin 14; 4E-BP1: Eukaryotic Translation Initiation Factor 4E Binding Protein 1; ACLY: ATP-Citrate Lyase; iTreg: Inducible Regulatory T Cells; FLNC: Filamin C; DP: Dimerization Protein; NRAP: Nebulin-Related Anchoring Protein; PPP2R5: Phosphatase 2 Regulatory Subunit B'.

KLHLs	Substrates	Degraded or not	Roles	References
KLHL2	ARHGEF7	Yes	Inhibition of ccRCC progression	[322]
	UCK1	Yes	Promotion of AML progression and 5-AZA resistance	[313]
KLHL6	CDK2	Yes	Inhibition of AML progression	[305]
	Roquin2	Yes	Inhibition of DLBCL progression	[191]
KLHL7	p53	Yes	Promotion of BC progression	[42]
KLHL9	C/EBPβ, C/EBPδ	Yes	Inhibition of GBM progression	[289]
KLHL12	DVL1	Yes	Inhibition of HCC progression	[147]
KLHL14	BCR	Yes	Inhibition of DLBCL progression	[156]
KLHL16	NF-κΒ	Yes	Maintaining chemotherapy sensitivity of HNC	[155]
KLHL18	PI3K	Yes	Inhibition of LC progression	[72]
KLHL19	ΙΚΚβ	Yes	Inhibition of tumorigenesis	[154]
	Myosin 9b	Yes	Inhibition of NSCLC progression	[256]
	SOX9	Yes	Inhibition of tumorigenesis	[263]
KLHL20	ULK1	Yes (K48)	Maintaining chemotherapy sensitivity of CML	[236]
	PML	Yes	Promotion of PCa progression	[44]
	DAPK, PML	Yes	Promotion of CRC progression	[282]
KLHL22	DEPDC5	Yes (K48)	Promotion of BC progression	[103]
	PD-1	Yes	Inhibition of CRC progression	[99]
KLHL25	ACLY	Yes	Maintaining lipid metabolism balance to suppress LC progression	[273]
KLHL37	LATS1/2	Yes	Promotion of radio-resistance of BC	[34]
KLHL38	BECN1	Yes	Promotion of BC and OC progression	[68]
	PTFN	Yes	Promoting of NSCI C progression	[71]

Table 2	The	interaction	hetween	KIHIS	and	snecific	substrates	about c	ancers
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Abbreviations: ARHGEF7: Rho Guanine Nucleotide Exchange Factor 7; ccRCC: Clear Cell Renal Cell Carcinoma; UCK1: Uridine-Cytidine Kinase 1; AML: Acute Myeloid Leukemia; 5-AZA: 5-Azacytidine; CDK2: Cyclin-Dependent Kinase 2; DLBCL: Diffused Large B-Cell Lymphoma; BC: Breast Cancer; C/EBP: CCAAT Enhancer Binding Protein; GBM: Glioblastoma; DVL1: Dishevelled Segment Polarity Protein 1; HCC: Hepatocellular Carcinoma; BCR: B Cell Receptor; NF-*k*B: Nuclear Factor Kappa-B; HNC: Head and Neck Cancer; PI3K: Phosphatidylinositol 3-Kinase; LC: Lung Cancer; IKK*β*: IkB Kinase *β*; NSCLC: Non-Small Cell Lung Cancer; SOX9: Sex-Determining Region Y (SRY)-Box Transcription Factor 9; ULK1: UNC-51-Like Kinase 1; CML: Chronic Myelogenous Leukemia; PML: Promyelocytic Leukemia Protein; PCa: Prostate Cancer; DAPK: Death Associated Protein Kinase; CRC: Colorectal Cancer; DEPDC5: Dishevelled, EgI-10 and Pleckstrin Domain-Containing 5; PD-1: Programmed Death-1; ACLY: ATP-Citrate Lyase; LATS1/2: Large Tumor Suppressor Kinase 1/2; BECN1: Beclin1; OC: Ovarian Cancer; PTEN: Phosphatase and Tensin Homolog.



Figure 2. The Role of KLHLs in signaling pathways in cancer. The abnormity of signaling pathways is always closely related to tumor occurrence and development. KLHLs, as substrate adaptor proteins of Cullin3 E3 ligases, are involved in the occurrence and development of several types of cancers and regulates various signal pathways, including the PI3K/AKT pathway, mTOR signaling, Wnt/ β -catenin signaling, NF- κ B signaling, hippo signaling and autophagy-lysosome pathway.



Figure 3. The Role of KLHLs in cancers. KLHLs are involved in the occurrence and progression of a variety of tumors via promoting ubiquitination of a series of substrate proteins, including NRF2, Myosin 9b, SOX9, ACLY, PD-1, PML, DAPK, C/EBPs, p53, CDK2, UCK1 and ARHGEF7.

pates in the regulation of the autophagy pathway and promotes tumor progression in breast cancer (BC) and ovarian cancer (OC) [68]. PTEN was recently found to be a substrate of KLHL38 in one LC-associated study.

One of the most common cancer types and the leading cause of death due to cancer [69], LC can be divided into non-small cell lung cancer (NSCLC) and small cell lung cancer, which account for approximately 85% and 15% of LC cases, respectively [70]. Xu *et al.* [71] showed a negative relationship existed between the survival times of patients with NSCLC and KLHL38 protein levels. They found that the mRNA and protein levels of KLHL38 in clinical LC tissues were dramatically higher than those in normal bronchi and alveoli, and also discovered that KLHL38 promoted the ubiquitination and proteasome degradation of PTEN to activate AKT signaling. Specifically, KLHL38 overexpression promoted LC cell proliferation by positively regulating *CYCLIN D1*, *CYCLIN B*, and *C-MYC*, simultaneously downregulating *P21*, and stimulated LC migration and invasion by upregulating *RHOA* and *MMP9* and downregulating *E-CADHERIN* [71]. In general, KLHL38 acts as an oncoprotein facilitating LC occurrence and progression by degrading PTEN and activating the PI3K/AKT pathway. However, another research confirmed KLHL18 as a tumor suppressor inhibiting the PI3K/AKT pathway [72].

KLHL18-PI3K

KLHL18 was shown to interact with Aurora-A. a mitotic serine/threonine kinase essential to the regulation of mitosis and cell cycle progression, and promote its ubiquitination and proteasome degradation [73]. Moreover, it was suggested that KLHL18 inhibited LC progression by degrading PI3K [72]. Jiang et al. [72] have found that the expression of KLHL18 in LC tissues is much lower than that in normal bronchial epithelial tissues, and negatively correlated with tumor size, differentiation level, lymph node metastasis and TNM stage. A series of experiments in vivo and in vitro have indicated that KLHL18 inhibits NSCLC cells proliferation, migration and invasion by promoting the ubiquitination and proteasome degradation of P85 α , an essential regulatory subunit of PI3K, thereby inhibiting the activity of PI3K/AKT pathway. In addition to this, KLHL18 is negatively correlated with the programmed death-1 ligand 1 (PD-L1) level.

PD-L1 is a transmembrane protein frequently expressed in human tumor cell membranes and interacts with programmed death-1 (PD-1), a co-inhibitory receptor expressed on immune cells, contributing to tumor immune escape [74]. The PI3K/AKT/mTOR pathway plays an essential role in carcinogenesis [75] and enhances the protein levels of PD-L1 by inhibiting the autophagy pathway, thus facilitating tumoral immune escape [76]. KLHL18 might suppress the PI3K/AKT pathway, which attenuates such pathway-induced inhibitory effects on PD-L1's autophagy lysosomal degradation. Overall, KLHL18 is a tumor suppressor in LC and its low protein levels are closely relevant to high invasion, metastasis, immune tolerance and poor prognosis.

MTOR signaling

The mTOR is an atypical serine/threonine kinase in the PI3K-related kinase family [77]. It is the catalytic subunit existing in two complexes: mTOR complex 1 (mTORC1) and mTOR complex 2. mTORC1 is a trimer protein kinase composed of three core components: mTOR, Raptor,

and mammalian lethal with Sec13 protein 8 [78], and plays a critical role in promoting anabolism processes (lipid synthesis, glycolysis, angiogenesis, and mitochondrial biogenesis) and inhibiting catabolism processes (autophagy and lysosome biogenesis). The mTOR is regulated by a series of upstream signals, which include growth factor, energy state, oxygen, and amino acid [79], and then signals to various downstream transcription factors, such as hypoxia-inducible factor-1 (HIF-1), peroxisome proliferators-activated receptor α/β , C-MYC, and transcription factor EB, which regulates physiological and pathological processes, including protein translation, cell proliferation, and normal cell cancerization [80-83].

Rag GTPases (Rags), heterodimers composed of RagA/RagB and RagC/RagD, can be activated and bind with the Raptor of mTORC1 to accelerate the activation of mTORC1 in response to amino acid stimulus [84, 85]. GTPaseactivating protein (GAP) activity toward Rags 1 complex (GATOR1) is composed of three proteins: dishevelled, Egl-10, and pleckstrin domain-containing 5 (DEPDC5); nitrogen permease regulator 2-like (NPRL2); and NPRL3 [86]. GATOR1, as one of the upstream-inhibiting regulators of Rags, has GAP activity and inactivates Rags [87, 88], which further suppresses the mTORC1's aggregation and activation as well as downstream pathways. Even so, the structure of GATOR1 and its specific forms that inhibit Rags are still unknown.

DEPDC5 is an integral component of GATOR1 involved in the inhibition of the mTOR pathway and plays an important role in maintaining embryonic and brain development [89]. DEPDC5 mutations are tightly associated with brain dysplasia and epilepsy occurrence [90]. Moreover, the aberrant activation of the mTOR pathway induced by DEPDC5 mutation is responsible for tumor occurrence and progression, including gastrointestinal stromal tumors [91] and hepatocellular carcinoma (HCC) [92]. Regarding the inhibition modes between DEPDC5 and mTORC1, scientists previously believed that DEPDC5 exerts its effect by promoting GTP hydrolysis to turn RagA/B into its inactive GDP state [93]. However, a recent study by Shen et al. revealed that at least two binding modes between Rag GTPases and a GATOR1 complex are required in the inhibition

of mTORC1 in amino acid deficiency. A strong direct inhibiting interaction has been found between RagA and the SHEN domain of DEPDC5, and a weak interaction exists between the NPRL2-NPRL3 heterodimer and RagA, which stimulates GAP activity [94].

The mTORC1 signaling pathway is closely correlated with tumor occurrence and progression and is hyper-activated in many kinds of human cancer types, including BC [87, 95, 96] and renal carcinoma [97]. It has been shown that KLHL20 and KLHL22 promote the ubiquitination and degradation of promyelocytic leukemia protein (PML) and DEPDC5, respectively, thereby enhancing the mTOR signaling and accelerating cancer progression.

KLHL22-DEPDC5

As the substrate-specific adaptor of the Cullin3 E3 ligase, KLHL22 interacts with substrates and promotes its ubiquitination in mitosis [98] and tumor immunity [99]. It has been shown that KLHL22 can inhibit colorectal cancer (CRC) metastasis and invasion by suppressing the Wnt/ β -catenin signaling [100] and promote malignant melanoma (MM) growth by activating the PI3K/AKT/mTOR signaling [101]. Moreover, KLHL22 promotes BC progression by activating the mTOR signaling.

BC is the most common malignant carcinoma in women worldwide, posing a considerable threat to women's health and their lives: its incidence increases annually in aging populations [102]. At the protein level, Chen et al. observed that KLHL22 expression in human BC tissues was obviously higher than those in adjacent normal tissues. Their experiments at the cellular level showed that the depletion of KLHL22 negatively influenced BC cell proliferation [103]. Their research revealed that KLHL22 might be an oncogene of BC, promote its encoding protein aggregation on the lysosome surface, and initiate DEPDC5 K48-linked ubiguitination and proteasome degradation, thus activating the mTORC1 signaling pathway to promote BC growth [103].

KLHL20-PML

As an adaptor of CRL3, KLHL20 can promote Unc-51-like autophagy activating kinase 1 (ULK1) ubiquitination and proteasome degradation, a serine/threonine-protein kinase, which emerges as a regulator of autophagy termination [104, 105]. In addition, KLHL20 is involved in regulation of tumor hypoxia environment [44] and tumor progression [106] through promoting specific substrates ubiquitination and proteasome degradation.

Clear cell renal cell carcinoma (ccRCC) is the most common kidney cancer [107]. The Von Hippel-Lindau (VHL) is a substrate-binding subunit of Cullin2 ubiquitin ligase and targets HIF1/2 α for degradation. In clinical practice, *VHL* is lost or inactivated in the vast majority of ccRCCs, and this effect increases the expression level of HIF1/2, which in turn promotes angiogenesis and renal tumor growth [108, 109]. PML inhibits neovascularization by inhibiting the activation of mTOR and downstream synthesis of HIF-1 α [110].

First identified in patients with acute promyelocytic leukemia (APL) [111], PML is a tumor suppressor. Under normal conditions, it usually accumulates in the nucleus and forms PML nuclear bodies, which participates in the repair of DNA damage and regulation of protein synthesis, gene transcription and other biological functions [112]. In the regulation of the pathways, such as PTEN/AKT [113] and mTOR [110] signaling pathway, PML is essential to antitumor function, such as inhibition of tumor cell proliferation, invasion, migration and angiogenesis as well as activation of tumor cell apoptosis [110, 114, 115]. PML is downregulated in a range of tumors [116], and ubiquitination is key to PML's dysregulation in tumors [117]. Intriguingly, with regard to PCa, Yuan et al. found that KLHL20 can promote PCa growth by degrading PML [44].

By investigating the relationship between PML and ccRCCs, Chen *et al.* observed that the small C-terminal domain phosphatases (SCPs) dephosphorylated PML at S518, blocking PML ubiquitination and proteasome degradation mediated by the prolyl isomerase 1 and KLHL20. They also found that the SCP1 expression was significantly downregulated compared with those in normal tissues, and the dephosphorylation effect of SCP1 can promote PML degradation, alleviate the inhibitory effect of PML on mTOR activity and increase the levels of downstream HIF1. Maintaining PML stability by suppressing KLHL20-mediated degradation can inhibit the mTOR-HIF1 pathway and ccRCC cell proliferation, migration, invasion and angiogenesis [106].

Wnt/ β -catenin signaling

Wnt signaling is mainly divided into two types [118]: the canonical Wnt/ β -catenin-dependent signaling cascade and noncanonical Wnt signaling cascades (Wnt/PCP and Wnt/Ca²⁺ pathways). The classic Wnt/ β -catenin signaling pathway has been a focus of research in the areas of tumorigenesis, and the abnormal expression or activation of β -catenin is essential to tumorigenesis [119] and metastasis [120]. β-catenin in its inactivated state forms a degradation complex with Axin protein, casein kinase-1 (CK1), the kinases glycogen synthase kinase-3, and adenomatous polyposis coli protein, which induces the β -catenin phosphorylation [121-123] and β -TrCP-mediated ubiquitination and proteasome degradation [124, 125]. Conversely, this signaling pathway is activated by the secretory glycoprotein, Wnt, which binds to the heterodimeric receptor complex consisting of frizzled (FZD) receptor and low-density-lipoprotein-related (LRP5/6) protein to stabilize β -catenin in the cytoplasm [126, 127] and promote β -catenin nuclear translocation and the subsequent activation of T cell factor/lymphoid enhancer binding factor (TCF/LEF) transcription factors, thus regulating the expression of downstream target genes [128, 129]. The Wnt/ β -catenin signaling pathway is closely involved in the regulation of cell proliferation, differentiation and migration [130], and its dysregulation promotes carcinogenesis and progression in almost all human cancer types, including BC [131, 132].

The three homologs of dishevelled (DVL) family members have been described: DVL1, DVL2 and DVL3, which all contain three domains: the N-terminal dishevelled, axin (DIX) domain responsible for DVL aggregation and interaction with Axin1 [133], the central postsynaptic density 95, disc large, zonula occuldens-1 domain responsible for interacting with the FZD receptor [134] and C-terminal Dvl, Egl-10, pleckstrin (DEP) domain responsible for DVL dimerization [122]. Upon stimulation by the Wnt protein, DVLs are rapidly phosphorylated and recruited to the FZD receptor, which inhibits the formation of degradation complex [126, 127], thereby blocking the ubiquitination and proteasome degradation of β -catenin and promoting its nuclear translocation. DVLs are involved in tumorigenesis and are highly expressed in many human cancer types [135, 136]. Several E3 ligases, such as SMURF2 [137], ITCH [138], and NEDD4L [139], perform DVLs ubiquitination and proteasome degradation. KLHL12 interacts with DVLs through the β -propeller regions of Kelch domains and triggers DVL1 ubiquitination and proteasome degradation, thereby suppressing the Wnt signaling [140, 141].

KLHL12-DVL1

As an adaptor of CRL3 in KLHL family, KLHL12 regulates collagen secretion [142, 143], neurodevelopment [144], and the Wnt signaling pathway [141] by ubiquitinating and degrading target substrates.

The sixth most common cancer, and the third leading cause of cancer death worldwide, primary liver cancers mainly consist of HCC (75%-85%) and intrahepatic cholangiocarcinoma (10%-15%) [145]. Abnormal spindle microtubule assembly (ASPM) is regarded as an oncoprotein highly expressed in HCC tissues. Its overexpression in HCC cells is associated with the activation of the Wnt signaling, which facilitates cell proliferation, invasion, migration, and induces EMT [146]. Kelvin et al. found that ASPM was upregulated in superpotent cancer stem cells (spCSCs) in HCC. They screened cancer stem cells (CSCs) from HCC cells with knockdown of ASPM and found that protein expression levels of β -catenin, DVL1 and CK1 were significantly downregulated compared with those in the control group. Furthermore, through co-immunoprecipitation and a series of experiments, they confirmed that ASPM regulated the Wnt pathway by modulating the stability of DVL1 rather than β -catenin and CK1. Finally, they demonstrated that ASPM and KLHL12 competitively bind with DVL1, which inhibited its degradation and activated the Wnt pathway in spCSCs to actively regulate its stemness and tumorigenic potential, thus leading to the progression of HCC [147].

NF-*k*B signaling

The NF-*k*B pathway is involved in regulating a variety of biological processes, including innate

and adaptive immunity to infection, inflammation, stress responses, B cell development, lymphoid organogenesis, tumorigenesis and tumor progression [148-150]. The mammalian NF-kB family consists of five members: RelA/ P65, C-REL, RelB, P50 (NF-κB1) and P52 (NF- κ B2), which can form a variety of heterodimers or homologous dimers. The P50/P65 dimer (commonly referred to as NF- κ B) is the most common dimer and exists in almost all cells. In mammals, the inhibitory proteins of κB family (ΙκΒ) consists of ΙκΒα, ΙκΒβ, ΙκΒγ, ΙκΒδ, ΙκΒε, P100 and P105, which inhibits the NF-*k*B activity in the cytoplasm. Under resting conditions, IkB binds to the NF-kB dimer and forms a trimeric complex, which maintains its inactivated state [151]. The NF- κ B signaling pathway can be divided into classical or nonclassical signaling cascades [152]. In mammalian cells, the classical pathways can be activated upon a variety of stimuli, such as tumor necrosis factor α (TNF α), lipopolysaccharide, and interleukin 1β (IL- 1β). When the conformation of receptors, such as IL-1R, toll-like receptor (TLR) and TNFR, changes upon the binding of upstream signaling factors, it delivers the signals into IKB kinase (IKK), which induces the phosphorylation and ubiquitination of IkB, and dissociates IkB from trimers [153]. Subsequently, NF-kB rapidly enters nucleus from the cytoplasm and binds to specific sequences on the nuclear DNA, and further promotes the transcription of associated genes, including CYCLIN D1, C-MYC, and VEGF.

Under physiological conditions, NF- κ B can promote cell apoptosis and inhibit tumorigenesis. Conversely, when the NF- κ B is aberrantly activated, it can promote cell carcinogenesis by accelerating cell cycle evolution and inhibiting cell apoptosis. KLHL19 exerts adverse effects on LC and HCC progression by inhibiting the NF- κ B signaling pathway [154]. Meanwhile, KLHL16 maintains chemotherapy sensitivity to head and neck cancer (HNC) by inhibiting the NF- κ B signaling pathway [155]. Besides, several studies have demonstrated that KLHL14 [156] and KLHL6 [157] can suppress the NF- κ B signaling pathway and then inhibit the progression of diffused large B-cell lymphoma (DLBCL).

KLHL19-IKKβ

IKK β , as a serine/threonine kinase, contains four domains, including kinase domain (KD),

scaffold/dimerization domain, ubiquitin-like domain and C-terminal NEMO binding domain [158]. It acts as a critical regulator in the NF- κ B cascade. IKK β undergoes phosphorylation and activation in response to multiple proinflammatory stimuli, which promotes the nuclear translocation of NF- κ B and induces downstream gene transcription, playing an important role in the regulation of tumor invasion, metastasis and EMT. In addition, IKK β is considered an oncogenic kinase promoting tumorigenesis and progression [159].

KLHL19 acts as a substrate-specific adaptor to IKK β , inhibiting tumor progression by downregulating the NF-kB signaling [154]. During the physiologic motion, the Kelch domain of KLHL19 is primarily responsible for IKKB KD domain binding, which promotes its K48-linked ubiquitination and proteasome degradation [160]. KLHL19 mutations occur frequently in tumors, and its abnormal mutation-induced IKKB dysregulation has been also demonstrated in a variety of tumors. KLHL19 Kelch domain mutants (S404X and D479G) in liver cancer and Kelch domain mutants (G333C, G364C, G430C and R413L) in NSCLC can attenuate binding affinity and inhibit subsequent IKKB ubiquitination and proteasome degradation, thereby activating NF-kB signaling to promote tumor progression [154]. In conclusion, KLHL19 may act as a tumor suppressor, inhibit IKKB ubiquitination and proteolysis to suppress NF-*k*B signaling, and subsequently curb tumor progression.

KLHL16-NF-кВ

Multiple studies have shown that KLHL16 (Gigaxonin) is critical for neuronal maintenance and survival [161, 162]. *KLHL16* mutations occur frequently in various tumors, including bone tumors, CRCs and hematopoietic/lymphocytic tumors [163]. Research has also suggested that *KLHL16* mutations enhance NF-*κ*B signaling in HNC cells and result in chemotherapy resistance [155].

HNC is the seventh most common type of cancer in the world and has many different histological types, the most common of which is squamous cell carcinoma (SCC) [164]. So far, platinum-based drugs remain the mainstays of chemotherapy regiments for HNC [165]. *P16* is a tumor suppressor gene that plays a role in cell cycle regulation, and its mutations are associated with tumor progression and chemotherapy resistance [166, 167]. In addition, cisplatin inhibits head and neck squamous cell carcinoma growth through *P16*-mediated cell cycle arrest, and reduction in *P16* expression is associated with cisplatin resistance [168]. In HNC, Veena *et al.* have found that the inhibition of IKK β leads to arrested tumor growth, and cisplatin treatment reduces NF- κ B nuclear expression. Cisplatin treatment leads to the nuclear translocation of *P16*, which induces the recruitment of KLHL16 and promotes the ubiquitination and degradation of NF- κ B.

KLHL14-BCR

KLHL14 is critical to cortical development by regulating the axon extension of corticospinal neurons [169]. In addition, KLHL14 has been found upregulated in OC and endometrial carcinoma (EC) tissues, and high KLHL14 expression in OC and EC patients is associated with poor prognosis [170, 171]. Notably, KLHL14 is highly expressed in B cells and crucial to its differentiation and development [172]. Moreover, its encoded gene *KLHL14* has been identified frequently mutated in mature B-cell malignancies [173].

DLBCL is the most common histological type of non-Hodgkin's lymphoma, which is mainly divided into three subtypes: germinal center B-cell-like, activated B cell-like (ABC) and unclassified subgroups. Many patients still experience drug resistance or relapse during or after treatment [174] despite the rapid progress in DLBCL treatment. The B cell receptor (BCR) is a molecule on the surface of B cells responsible for specific recognition and conjugation to antigens. The BCR signaling pathway is closely associated with the pathogenesis and development of B cell malignancies and plays a significant role in DLBCL progression [175, 176]. TLR, an important protein in nonspecific immune responses, is involved in the activation of NF- κ B by binding myeloid differentiation factor 88 (MYD88), an important adaptor protein essential to innate immune responses and inflammatory response signal transduction [177]. In DLBCL-ABC cells, the BCR combines with MYD88 and TLR9 to form MyD88-TLR9-BCR (My-T-BCR) supramolecular complex, which facilitates the NF- κ B signaling into the nucleus [178]. NF- κ B activation is a principal feature of the DLBCL-ABC subgroup, which depends on constitutive NF- κ B signaling to decrease tumor cell apoptosis and maintains its viability, called "chronic active" BCR signaling [179]. Blocking the BCR signaling pathway can inhibit NF- κ B signaling and result in cell cycle arrest and apoptosis, thereby suppressing DLBCL progression [180, 181].

George *et al.* have demonstrated that KLHL14, as a tumor suppressor, promotes the ubiquitination and degradation of BCR subunits, CD79A, CD79B and IgM, thus inhibiting My-T-BCR complex formation to block NF- κ B signaling. In 574 DLBCL biopsy samples, *KLHL14* mutations were most common in DLBCL-ABC (10.8%). They confirmed that the deletion of *KLHL14* induced DLBCL resistance to brutinib, a bruton tyrosine kinase inhibitor that inhibits the degradation of BCR subunits and promotes the assembly of a My-T-BCR super complex, thereby promoting NF- κ B activation and DLBCL progression [156].

KLHL6-Roquin2

KLHL6 is highly expressed in gastric cancer (GC) cells and tissues, promoting GC cell growth and lymphangiogenesis [182]. KLHL6 disrupts the formation of germinal centers in chronic lymphocytic leukemia (CLL) and its high level predicts poor clinical prognosis [183]. The recurrent mutations of *KLHL6* have been found in CLL [184] and other mature B-cell malignancies, including DLBCL. The high frequency of *KLHL6* mutations facilitated the proliferation of DLBCL-ABC cells [185].

Roguin2 is an RNA-binding protein in the Roguin family [186] and composed of a RING domain, conserved ROQ domain and zinc finger domain [187]. Roquin2 decays target mRNAs by binding with the conserved stem-loop motif in the 3'UTR of mRNA and its ROO domain [187]. The tumor necrosis factor- α -inducible gene 3 (TNFAIP3) is a tumor suppressor gene in DLBCL [188, 189], and its encoding protein, $TNF\alpha$ induced protein 3 (TNFAIP3/A20), is a key NF-*k*B regulator and inhibits IKKy activation [190]. Zhou et al. have shown that Roquin2 can induce the mRNA decay of TNFAIP3 and then suppress the accumulation of TNFAIP3. It has been shown that roquin2 is one of the substrates of KLHL6 which mediating roguin2 degradation through UPS [191]. Under physiologi-

cal conditions, KLHL6 is upregulated during antigen-induced BCR/NF-KB activation and induces roquin2 degradation, which inhibits mRNA decay of TNFAIP3 and further leads to TNFAIP3 accumulation. Further, TNFAIP3 inhibits the IKK complex, which negatively regulates BCR signaling to maintain the homeostasis of the NF-*k*B signaling. By contrast, the high-frequency mutations of KLHL6 in DCLBC cells suppress the roquin2 degradation, accelerate TNFAIP3 decay and attenuate the inhibitory effect of TNFAIP3 on the IKK complex, which in turn induces the abnormal activation of NF-KB pathways. In conclusion, Zhou et al. suggested that the KLHL6-Roquin2 axis was of great importance to the regulation of B lymphoma cell proliferation, and regulated the mRNA decay and NF-kB activity [191, 192].

Hippo pathway

The hippo pathway is composed of a series of conserved kinases and is involved in the regulation of several biological processes, including tumorigenesis [193-196]. The core components of the pathway in mammals include mammalian STE20-like protein kinase (MST1/2), cofactor human salvadorhomology 1, large tumor suppressor kinase 1/2 (LATS1/2) and its cofactor MOB kinase activator (MOB1) [197, 198]. Under normal conditions, an extracellular growth signal induces a series of phosphorylation reactions of kinases: the phosphorylated MST1/2 (p-MST1/2) promotes LATS1/2 phosphorylation, and p-LATS1/2 induces the phosphorylation of downstream effector factors, Yes-associated protein (YAP) [199] and Tafazzin (TAZ) [200]. Then, p-YAP and p-TAZ interact to form a complex and stabilizes in the cytoplasm by binding 14-3-3 proteins and promote the β -TrCP-dependent proteasome degradation. which inhibits β -TrCP nuclear translocation and downstream transcription activation function [201-204]. A series of missense mutations in the hippo pathway appear in the early stage of tumor [205], which inhibits this pathway by affecting the phosphorylation cascade of key components and attenuating YAP/TAZ proteasome degradation. The accumulative unphosphorylated YAP/TAZ in the cytoplasm is transported to the nucleus and binds with TEAD transcription factors, thereby modulating the transcriptional activity of downstream oncogenes to facilitate cell proliferation and inhibit cell apoptosis [206].

Several E3 ligases have been suggested associated with tumor-related processes *via* regulating the hippo signaling pathway. For example, E3 ligase PARK2 can promote YAP K48-linked ubiquitination and proteasome degradation to inhibit esophageal squamous cell carcinoma procession [207]. E3 ligase ITCH can ubiquitinate and degrade LATS1 to promote BC progression [208]. Likewise, KLHL37 can induce radio-resistance in BC by ubiquitinating and degrading the key protein, LATS.

KLHL37-LATS1/2

KLHL37 is involved in various pathophysiologic processes, acting a vital role in nervous system development [209] and tumorigenesis and progression [210-212], LATS [213], YAP [213, 214] and TAZ [215-217] are closely associated with the regulation about BC progression. Li et al. have clarified that the overexpression of KLHL37 results in the hyperactivation of the hippo pathway in RaR (radio-resistant) BC cells. They found the expression of KLHL37 in BC samples from patients resistant to radiotherapy were significantly higher than those from patients sensitive to radiotherapy. In line with the histological outcome, the expression of KLHL37 are significantly higher in RaR BC cells compared with in non-RaR BC cells [34]. Specifically, they observed that the overexpression of KLHL37 degraded LATS1/2 through UPS and suppressed YAP/TAZ phosphorylation, promoting its nuclear translocation, further increasing the expression of the downstream anti-apoptotic genes GLI1, CTGF and FGF1, and enhancing radio-resistance in BC cells [34].

Autophagy-lysosome pathway

Autophagy is a tightly regulated pathway that plays an important role in basic metabolic functions and cellular homeostasis [218], and its dysregulation is closely related to tumor occurrence and progression [219, 220]. The ULK1 complex and VPS34 complex are vital to autophagic processes and regulate autophagy initiation [221, 222]. Under several types of autophagic stress, such as starvation, hypoxia and DNA damage, the ULK1 complex is activated and transmits signals that activate the VPS34 complex, which promotes autophagic protein localization to the phagophore [223]. The Beclin1 (BECN1), a protein of the VPS34 complex, plays a key role in autophagy regulation involved autophagosome formation, extension and maturation [224]. Several E3 ligases, such as HUWE1 [225] and WWP1 [226], promote the ubiquitination and proteasome degradation of crucial proteins in the autophagy pathway, affecting tumor progression. Among KLHL family, KLHL38 induces BECN1 degradation and promotes BC progression, and KLHL20 is vital to chemotherapy sensitivity by regulation of ULK1 degradation.

KLHL38-BECN1

As mentioned above, KLHL38 often acts as an oncoprotein and promotes tumor progression. It has been suggested that protein levels of BECN1 in tumor tissues are significantly lower than those in normal tissues, and its deficiency is closely related to tumorigenesis and tumor progression [227, 228]. Xuan et al. analyzed 817 BC samples from the TCGA database and found the inconsistency between protein and mRNA expression levels of BECN1 in BC samples. They hypothesized that the reduced expression of BECN1 in tumor is due to posttranslational modification, and discovered an obvious increase of BECN1 expression in BC cells after treatment with proteasome inhibitors. Through the TCGA database, they discovered elevated expression of KLHL12 and KLHL38 in triple-negative breast cancer (TNBC) tissues, and observed that BECN1 was significantly elevated only when KLHL38 was knocked down. Through a series of confirmatory experiments, they revealed that KLHL38 interacted with BECN1 and induced its K48-linked ubiquitination and proteasome degradation, thereby inhibiting autophagy and inducing BC progression [68].

KLHL20-ULK1

It has been established that KLHL20 can promote ULK1 ubiquitination and proteasome degradation to regulate autophagy termination [104]. ULK1 is a serine/threonine-protein kinase necessary for phagophore formation, which is directly regulated by mTOR and AMPactivated protein kinase and negatively correlates with the bone metastasis of BC [229].

Chronic myelogenous leukemia (CML) is an acquired clonal disease originating from pluripotent hematopoietic stem cells [230], and the inhibition of autophagy may increase therapeutic efficacy and improve patient prognosis [231]. Imatinib is a tyrosine kinase inhibitor widely used to treat CML and has a good therapeutic effect. However, a small number of patients still acquire therapeutic resistance to imatinib in the treatment process [232, 233]. Autophagy dysregulation can result in imatinib resistance in CML therapy [234]. Grancalcin (GCA) is a cytoplasmic protein translocated to the cytoplasmic membrane when neutrophils are activated [235]. Seung et al. found that GCA was upregulated in peripheral blood mononuclear cells from patients with CML and imatinib resistance at the mRNA and protein levels [236] and showed that GCA can inhibit the imatinib-induced apoptosis of CML cells. They further confirmed that GCA facilitated the dimerization and activation of ULK1 by inducing the K63-linked ubiquitination of TRAF6 and inhibited the KLHL20-mediated proteasome degradation of ULK1, thus synergistically promoting the autophagy pathway to induce imatinib resistance.

Others

KLHL19-NRF2

NRF2, encoded by NFE2L2, belongs to the Cap'n'collar basic leucine zipper transcription factor family and can be divided into seven conserved functional domains (Neh1-Neh7). The Neh2 domain is located in the N-terminus and contains two important conserved regions (DLG and ETGE) responsible for the binding between NRF2 and KLHL19, which can induce NRF2 degradation and inhibit its transcriptional activity [237]. NRF2 is an important regulator of many antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase, and heme oxygenase-1, and interacts with the antioxidant response elements (AREs) of antioxidant and cell-protective genes, maintaining intracellular redox equilibrium [238].

Discovered in 1999, KLHL19 is an important negative regulator of NRF2 [239]. Under normal physiological conditions, NRF2 is strictly regulated by KLHL19. Through its N-terminal BTB domain, KLHL19 dimerizes and forms an E3 ligase complex with Cullin3 and RBX1, which promotes NRF2 ubiquitination and degradation to maintain NRF2 steady state. In the presence of multiple redox stimuli, the highly reactive cysteine residues of KLHL19 are immediately

modified, and this effect inhibits the binding of KLHL19 to Cullin3 and facilitates NRF2 stabilization. And then, accumulative NRF2 is transported to the nucleus and binds to AREs located within the promoter region of a specific target gene, inducing the expression of a large number of cell-protective proteins with antioxidant and detoxification effects [27]. In recent years, the regulation of the KLHL19-NRF2 axis has attracted considerable interest. In addition to the crucial role in cell physiology and stress response, the abnormal regulation of the KLHL19-NRF2 axis has been confirmed involved in the progression of various cancer types, specifically promoting tumor progression, metastasis formation, drug resistance and radiotherapy resistance [240-242]. In the last few years, many scholars have extensively explored the KLHL19-NRF2 signaling pathway [240, 242-248]. In this review, we mainly describe the regulation of KLHL proteins on specific substrates (other than NRF2) related to cancer progression.

KLHL19-myosin 9b

Myosin is a motor molecule based on actin with ATPase activity. The myosin family has fourteen distinct classes (1-14), which all contain a head (motor) domain containing ATP and actin binding sites, a neck domain containing one or more light chain binding sites, and a tail domain varying in size and structure [249]. Myosin 9 is an unconventional member of the myosin family because its tail domain contains a Rho-GTPaseactivating protein and is closely associated with the regulation of cell motility [250]. Yang et al. found that the inhibition of myosin 9 can enhance LC cell migration [251]. Wang et al. discovered that tissue factor pathway inhibitor 2. a tumor suppressor, may inhibit the proliferation and invasion of BC cells partially by interacting with myosin 9 [252]. In neoplastic hematologic disorders, the expression levels of myosin 9 are positively correlated with the percentage of apoptosis in acute myeloid leukemia (AML) and CML cells [253].

RhoA, a member of the Rho-GTPase family, plays a significant role in the regulation of actin cytoskeleton dynamics and is crucial to the regulation of malignant transformation and cell migration [254]. The DGR domain of KLHL19 is responsible for interaction with the actin cytoskeleton [255]. KLHL19 promotes F-actin formation and inhibits the conversion of focal adhesion by enhancing RhoA activity. Zhou et *al.* have demonstrated that KLHL19 overexpression significantly inhibits the migration and invasion of LC cells, they have observed that its overexpression not only promotes the formation of stress fibers, but also inhibits the conversion of focal adhesion. Their study has indicated that KLHL19 triggers myosin 9b ubiquitination and proteasome degradation, which indirectly upregulates RhoA activity to stabilize the F-actin cytoskeleton, thereby inhibiting the migration and invasion of NSCLC [256].

KLHL19-SOX9

Sex-determining region Y-box transcription factor 9 (SOX9) is one of the transcription factors playing key roles in chondrocyte differentiation and bone development [257]. Ubiquitination modification is essential to the regulation of the activity, expression levels, and localization of SOX9 [258, 259]. In recent years, the association among its abnormal protein levels, tumor development and progression have been investigated, particularly in HCC [260] and LC [261]. In addition, SOX9 is a potential therapeutic target based on human cancers [262].

Liu et al. found that KLHL19 negatively regulated the stability of SOX9 through UPS. In databases (https://cancer.sanger.ac.uk/cosmic and http://www.cbioportal.org/), at least fifty different mutations in *KLHL19* have been recorded in a variety of cancer types and are largely concentrated in the BTB and Kelch domains. To explore the action mechanisms between KLHL19 and SOX9, they carried out a series of experiments and demonstrated that KLHL19 triggered SOX9 ubiquitination and degradation through the Kelch domain. In summary, they found that tumor-related KLHL19 mutations may impair the substrate recruitment function of the Kelch domain and thereby inhibit the oncoprotein SOX9 ubiquitination and degradation, which accelerates the progression of LC and HCC [263].

KLHL25-ACLY

KLHL25 is involved in the regulation of transition from fatty acid synthesis to fatty acid oxidation through the ubiquitination and degradation of ATP-citrate lyase (ACLY), which facilitates inducible regulatory T cell differentiation [264].

ACLY, a key enzyme in de novo lipid synthesis, links glucose metabolism to de novo lipid synthesis [265, 266], is frequently overexpressed and activated in many types of cancer, including LC, and promotes lipid synthesis in cancer [267, 268]. Abnormal lipid metabolism is a hallmark of cancer cells, which plays an important role in cancer progression [269-271], including LC [272]. To explore the relationship between KLHL25 and ACLY in LC progression, Zhang et al. conducted a series of experiments and revealed that KLHL25 can target ACLY and induce its ubiquitination and proteasome degradation to maintain lipid metabolism balance, thus suppressing LC cell proliferation and tumor progression [273].

KLHL22-PD-1

KLHL22 is involved in the regulation of the occurrence and progression of many tumors, including BC, MM and CRC. CRC is a high-incidence disease, ranking third among all diseases in terms of incidence and second in terms of mortality. PD-1 is an important immune-suppressive molecule expressed on the surfaces of activated T cells, suppresses T cell proliferation and function, and prevents the immune system from killing cancer cells [274]. The regulation of the PD-1/PD-L1 axis is significant for tumor occurrence, progression and therapy, and PD-1 inhibitors benefit a subset of patients with CRC [275].

PD-1 is regulated by post-translational modification, including a series of E3-mediated ubiquitination, which may influence immunosuppression effects [276]. Albert et al. have determined that KLHL22 is a major PD-1 interacting protein and maintains the homeostasis of PD-1 through UPS before PD-1 is transported to the cell surface [99]. In vitro cell experiments showed that KLHL22 knockdown increased the expression of PD-1 and leaded to excessive T cell suppression. And, the nude mouse tumorigenicity assays showed that nude mice injected subcutaneously with KLHL22 knockout CRC and MM cells have stronger tumor-forming abilities and shorter survival times compared to control group. In conclusion, their research showed that KLHL22 can regulate PD-1 expression through ubiquitination and maintain proper levels of PD-1 and T cell homeostasis, thereby inhibiting tumorigenesis and progression.

KLHL20-KLHL39

KLHL39 has been traditionally known as "influenza virus NS1A binding protein" in the past, which antagonizes the primary host anti-viral response by binding to the ubiquitin-like ISG15 protein and inhibiting its binding to a range of proteins [277]. In tumor-associated research, KLHL39 is considered a tumor suppressor inhibiting tumor invasion and migration [278]. It interacts with KLHL20 and inhibits the ubiquitination and degradation of the target substrates by KLHL20, which inhibits CRC progression.

The death-associated protein kinase (DAPK) is a calmodulin-regulated associated serine/threonine kinase that transmits apoptosis or autophagy death signals in presence of various cellular stress signals [279]. It acts as a suppressor protein and is downregulated in a variety of tumors [280]. PML, as mentioned above, is a pleiotropic tumor suppressor protein downregulated in many tumors [116]. KLHL20, as an adaptor of E3 ligase, promotes DAPK [281] and PML [44] ubiquitination and degradation, thus promoting tumor progression.

Hatano et al. showed that highly expressed KLHL39 inhibits the migration and invasion of colon cancer cells, and mice inoculated with colon cancer and melanoma cells with overexpressed KLHL39 tended to exhibit low rates of lung and liver metastasis and long survival periods [278]. To explore the underlying mechanisms of the anticancer effects of KLHL39, Chen et al. confirmed the interaction between KLHL20 and KLHL39 by yeast two-hybrid screening and co-immunoprecipitation. Interestingly, they have shown that KLHL39 interacts with the Kelch domain of KLHL20, is not a substrate for CRL3-KLHL20 ubiquitin ligase, and is not degraded through KLHL20-mediated ubiguitination modification. They hypothesized that KLHL39 might act as a pseudo-substrate preventing target substrate recruitment to the KLHL20 complex. Consistent with this hypothesis, a series of in vitro and in vivo experiments have demonstrated that KLHL39 overexpression can inhibit the binding of KLHL20 with its substrates, PML, and DAPK and mediated ubiguitination degradation, thereby suppressing CRC cell migration and invasion. Additionally,

they observed that KLHL39 overexpression disrupted the formation of the Cullin3-RBX1-KLHL20 complex. In summary, their research indicated that KLHL39 not only blocked the binding of KLHL20 to its substrate but also disrupted the formation of E3 ligase complex, thereby inhibiting CRC progression [282].

KLHL9-C/EBPs

KLHL9 induces insulin receptor substrate 1 (IRS1) ubiquitination and proteasome degradation, therefore leading to insulin resistance [283], and regulates mitotic progression *via* inducing Aurora degradation [284]. In addition, the linkage between KLHL9 and brain tumor progression has been found, recently.

Glioblastoma (GBM) is the most common malignant tumor of the human brain and has a poor prognosis even after a series of aggressive treatments [285]. The mesenchymal subtype of GBM (MES-GBM) has the worst prognosis, and the regulation of the transition of GBM to a mesenchymal state is largely unknown. The CCAAT/enhancer binding protein (C/EBP) family consists of six transcription factors: C/EBPa, C/EBPB, C/EBPy, C/EBPo, C/EBPE, and CHOP, which contain three structural regions: a C-terminal leucine-zipper, basic DNA-binding region, and N-terminal transactivating region [286]. C/EBPo promotes the metastasis of pancreatic cancer [287], and C/EBPß and C/EBPδ are necessary for the transition to mesenchymal-like states in GBM [288]. Michael et al. found that GBM cells with KLHL19 knockdown tended to have enhanced tumorigenicity ability. They confirmed C/EBPß and C/EBPδ were substrates for KLHL9, and KLHL9 induced their degradation through UPS, which inhibited mesenchymal characteristics and reduced tumorigenesis in vitro and in vivo [289].

KLHL7-p53

KLHL7 plays crucial roles in maintaining nucleolar integrity by inducing terminal uridylyl transferase 1 ubiquitination and proteasome degradation [290]. Additionally, it has been observed that the tumor protein p53 is a substrate of KLHL7 and undergoes KLHL7-mediated ubiquitination and proteasome degradation, which promotes BC progression.

Tumor suppressor protein p53 participates in the coordination of multiple responses, includ-

ing cell cycle arrest, DNA repair, antioxidant effects and anti-angiogenesis, thereby preventing tumor occurrence and progression [291]. The p53 mutations are in more than 50% tumors and provide selective advantages to tumor cells, enabling them to prevent apoptosis and senescence, and maintain proliferation when normal cells cannot proliferate [292]. Its role in the dysregulation of ubiquitination in tumor cells has been explored [293]. Two E3 ligases, MDM2 [294] and CRL4A [295], can promote BC progression by degrading p53, and E3 ligase TRIM47 can facilitate renal cell carcinoma (RCC) progression by degrading p53, [296]. Kurozumi et al. showed that patients with high KLHL7 levels tended to have shorter survival times despite that the mRNA levels of KLHL7 were not highly expressed in most BC specimens. They also found that KLHL7 protein expression increased in high histologic grade. ER (-) or HER-2(+) tumors and TNBC [42], and patients with higher expression of KLHL7 in BC tissues often have shorter survival times. Overall, their study indicated that KLHL7 might function as an adaptor protein and induce p53 ubiquitination and proteasome degradation, thereby boosting BC procession [42].

KLHL6-CDK2

KLHL6 is involved in the regulation of the formation of germinal centers about CLL, and the high expression of its encoded gene *KLHL6* is considered a poor prognostic indicator [183]. Many studies have demonstrated the association between KLHL6 and hematological malignancies, including AML.

The disorder of hematopoietic stem cell differentiation is one of the principal hallmarks of AML, and altering differentiation stasis may be a potential treatment for AML. For example, alltrans retinoic acid (ATRA) functions as a differentiation-inducing drug and significantly improves the prognoses of patients with APL [297]. Cyclin-dependent kinase 2 (CDK2) is a serine/threonine-protein kinase and is essential to cell cycle regulation [298] and involved in DNA damage [299], intracellular material transport [300], protein degradation [301]. The overexpression of CDK2 is directly related to cancer progression and is considered a potential cancer therapeutic target [302, 303]. It has been suggested that CDK2 in AML is specifically degraded during ATRA differentiation therapy [304]. Ying *et al.* found that CDK2 in AML cells was specifically degraded during intramedullary differentiation progression and this degradation can be blocked by proteasome inhibitors. Peroxiredoxin 2 (PRDX2) is one of the mercaptan-specific peroxidases, and its inhibition may promote the differentiation of AML cells [303]. They hypothesized the existence of E3 ligases interacting with CDK2, and identified that KLHL6 induced CDK2 ubiquitination and proteasome degradation to inhibit PRDX2 activation, promote AML cell differentiation [305] and suppress AML progression.

KLHL2-UCK1

As an adaptor of Cullin3-E3 ligase, KLHL2 promotes WNK kinase ubiquitination and proteasome degradation to regulate electrolyte balance in kidneys [306]. KLHL2 inhibits ccRCC progression by targeting a specific substrate and triggering its degradation.

AML is a malignant disease of the myeloid hematopoietic stem or progenitor cells. Currently, 5-azacytidine (5-AZA) is the first-line therapy and has a significant efficacy for AML, but the challenge of chemotherapy resistance remains persistent. [307-309]. Uridine-cytidine kinase 1 (UCK1) is an important member of the UCK family and phosphorylates uridine and cytidine into uridine monophosphate and cytidine monophosphate [310]. UCK1 is essential for the activation and metabolism of 5-AZA [311] with a low level in mononuclear cells from 5-AZA-resistant AML patients [312]. Huang et al. identified that KLHL2 and USP28 (one deubiguitinating enzyme) participated in the regulation of the ubiquitination of UCK1 in AML cells. In vitro, they observed that silencing KLHL2 not only inhibited the proliferation of AML cells but also enabled AML cells to be sensitive to 5-AZA. Overall, they revealed that KLHL2, as an oncoprotein, can facilitate AML cell proliferation and inhibit 5-AZA-induced cell apoptosis via inducing UCK1 ubiquitination and proteasome degradation [313].

KLHL2-ARHGEF7

Rho guanine nucleotide exchange factor 7 (ARHGEF7) is a guanine nucleotide exchange factor for Rho GTPases and plays a significant role in cell migration [314, 315], cell spreading [316], cytoskeletal rearrangements [317], and

protein polymerization in the trans-Golgi network [318]. In many types of cancer, such as BC and CRC, it acts as an oncoprotein and is highly expressed [319-321]. Zhang *et al.* found that ARHGEF7 levels in ccRCC tissues were significantly higher than that in normal tissues, in contrast to the low KLHL2 expression in ccRCCs. This result suggested that the protein expression levels of KLHL2 were negatively correlated with ARHGEF7 in ccRCCs. Further, they confirmed that ARHGEF7 was a substrate to KLHL2, promoted ubiquitination and proteasome degradation, and inhibited ccRCC cell growth, migration and invasion [322].

Discussion

KLHL family members, as the significant substrate-recognizing proteins of CRL3, play important biological functions, particularly in immune response, skeletal muscle maintenance and brain development [25, 323]. Notably, emerging evidence has suggested the maladjustment of KLHLs in a series of human tumors [42-44, 324]. Among the KLHL family, KLHL19 has been a subject of interest in research for several years, and many reviews have systematically introduced its association with tumor occurrence and progression [27, 244, 248, 325]. Otherwise, the dysregulation of other KLHL family members may be also associated with tumorigenesis and progression by dysregulating the specific substrates, thus affecting their stability and localization. As mentioned earlier in this review, several signaling pathways are involved in tumor-associated regulation by KLHLs. Exploring the underlying mechanisms involved in tumor occurrence and progression may be of great significance to the precise treatment of malignancy. Our review mainly focuses on the role of KLHLs and their target substrates in tumorigenesis and progression, providing the potential insight for the discovery of diagnostic and prognostic markers as well as the development of KLHLs-targeted drugs.

Even though the members of the KLHL family have similar structural domains, their biological functions are varied due to the specificity of substrate selection. It has been found that the different or even same members recognize varied substrates, which exerts disparate effects on different tumor contexts. A better understanding of KLHLs molecular structures and their substrate selection mechanisms will be beneficial in finding more undetected substrates and further comprehending tumor pathogenesis and therapy. To date, only the crystal structure of KLHL19 has been elucidated. The Kelch domain of KLHL19 consists of six Kelch repeated motifs that form a highly conserved β -propeller structure. Specifically, each Kelch motif forms a β -fold structure consisting of four anti-parallel chains, and the loop structure between the four anti-parallel chains is complex and varies [326]. This variation may partly account for the specificity of the substrate. And, mountainous research has been devoted to KLHL19 not only due to its relatively lucid structure but also due to the discovery of a "star substrate", NRF2. As noted above, NRF2, as a crucial substrate, is tightly associated with a series of physiological and pathological processes, including tumor occurrence, progression and metastasis [242]. This may provide us some hints and may be useful in determining whether other substrates with vital biological significance remain undiscovered.

Before this study, limited number of research explored the relationship between KLHL14 and tumor, one study first determined that KLHL14 induced BCR ubiquitination and proteasome degradation, which inhibited the NF-KB signaling to suppress DLBCL progression [156]. Moreover, KLHL37 was previously considered essential to nervous system development [209], and recent studies revealed that it not only inhibited the hippo signaling by ubiquitinating and degrading LATS1/2 to induce BC radiotherapy resistance [34], but also activated the Wnt/ β -catenin signaling to facilitate BC growth, migration and invasion [327]. The activation mechanism of the Wnt/ β -catenin signaling by KLHL37 is not yet fully understood, therefore, we raise a question: is there an unknown KLHL37 target-substrate which is closely involved in regulating the Wnt/ β -catenin signaling in BC? No doubt, a large number of KLHLs target-substrates involved in tumor-associated regulations are waiting to be found, which may bring benefits to the tumor treatment.

With the rapid development of molecular biology in the past two decades, molecular targeted therapy has widely applied in tumor clinical therapy. Conventional one-target therapy has shown its advantages for tumor treatment indeed, however, there still exists many problems such as suboptimal therapy efficacy and drug resistance. Multi-target combination treatment, as a future direction, is one of the most promising approaches in tumor therapy, thus, discovering more promising therapeutic targets is of great urgency [328]. Several key proteins, such as ULK1, CDK2, PD-1 and p53, have been demonstrated to be the substrates targeted by a series of KLHLs and also the target molecules of various molecular-targeted drugs [302, 329, 330]. KLHLs function as their upstream regulators influencing their stability, structure, localization and function. Is it possible that KLHLs play roles as potential targets in development of molecular targeted drugs? There are still numerous unknown questions waiting to be answered. With further research and technological development, KLHLs may become markers or therapeutic targets in the near future.

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Disclosure of conflict of interest

None.

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