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Ubiquitination in hepatocellular carcinoma immunity

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Abstract

Hepatocellular carcinoma (HCC) is the sixth most prevalent malignancy worldwide, and represents a major global health challenge. While surgical resection at early stages offers favorable prognosis with 5-year survival rates exceeding 70%, the clinical reality in China reveals a contrasting scenario, where over 60% of patients present with advanced disease, resulting in a dramatic decline in 5-year survival to below 12.5%. The immunological landscape plays a pivotal role in HCC pathogenesis and progression, comprising two complementary arms: the innate immune system's rapid-response mechanism for immediate tumor surveillance and the adaptive immune system's antigen-specific targeting with immunological memory capabilities. Emerging evidence has highlighted ubiquitination, a sophisticated post-translational modification system, as a critical regulator of immune homeostasis in HCC pathogenesis. This molecular process exerts precise control through three primary mechanisms: (1) Modulation of immune cell activation thresholds via proteasomal degradation of signaling proteins, (2) Orchestrating immune cell differentiation through stability regulation of transcriptional factors, and (3) Maintenance of immune tolerance by dynamic modification of checkpoint regulators. Such multifaceted regulation affects both innate immune recognition pathways (e.g., NF-κB and STING signaling) and adaptive immune effectors (particularly T cell receptor signaling cascades). This comprehensive review establishes a threefold Objective: First, to elucidate the mechanistic interplay between ubiquitination networks and HCC-related immune dysregulation; Second, to systematically analyze how innate immune-associated ubiquitination events drive hepatocarcinogenesis through chronic inflammation modulation; and third, to critically evaluate recent clinical advances combining ubiquitination-targeted therapies (e.g., proteasome inhibitors and E3 ligase modulators) with immunotherapeutic regimens. Our synthesis revealed that strategic manipulation of ubiquitination pathways can potentiate PD-1/PD-L1 blockade efficacy while mitigating therapeutic resistance, particularly through modulation of tumor-associated macrophages and exhausted T cell populations. By integrating fundamental mechanistic insights with translational clinical data, this review provides a conceptual framework for the development of next-generation diagnostic biomarkers and rational therapeutic combinations. The proposed strategy of ubiquitination-immune axis modulation holds significant potential to transform current HCC management paradigms, offering new avenues for precision immunotherapy for this challenging malignancy.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world. Early detection of HCC can provide a good prognosis with surgical resection, with a 5-year survival rate of >70%. However, most patients are diagnosed with advanced disease, and the 5-year survival rate in China is less than 12.5%. There are various risk factors for HCC, including hepatitis B virus infection, hepatitis C virus infection, obesity, and non-alcoholic steatohepatitis (NASH) [1]. A follow-up study found that approximately 33% of HCC patients had long-term liver cirrhosis [2, 3], 50% of HCC cases had HBV infection, and the rest of patients with HCV infection [4]. The biological processes involved in HCC development are complex. Abnormal activation of molecular signaling pathways and viral infection could lead to disruption of the balance between inactivation and/or activation of tumor suppressor genes and/or oncogenes.

In HCC, the immune system serves as a double-edged sword. On one hand, it can act as a formidable bulwark against tumors, deploying a multi-faceted defense mechanism. However, under certain circumstances, tumors can cunningly co-opt the immune system, subverting their normal functions to foster their own growth and metastasis [5, 6]. There is a balance between immune defense and tolerance, and once this balance is disrupted, it is possible for the body to enter a pathological state with an unbalanced immune response [7, 8]. The immune system is akin to a meticulously engineered defensive citadel, primarily comprising two major components: innate and adaptive immunity. Innate immunity, which functions as the body's first line of defense, is analogous to the ever-vigilant vanguard troops. It responds instantaneously and comprehensively to the emergence of tumors. Without delay, it can rapidly recognize the presence of abnormal cells and initiate a preliminary defense cascade, providing an immediate, albeit non-specific, response to the tumor threat. In contrast, adaptive immunity is like an elite, specially trained, and special force unit. It is characterized by a high degree of specificity and long-term memory. During the protracted battle against tumors, adaptive immunity gradually deciphers the unique molecular signatures of tumor cells, enabling it to launch highly targeted assaults, precisely tailored to neutralize tumor cells. Moreover, it has a remarkable ability to retain the memory of these tumor-specific antigens. As a result, upon subsequent encounters with the same tumor cells, they can mount a much more rapid and efficient immune response. In-depth exploration of the distinct mechanisms underlying innate and adaptive immunity in the context of HCC is key to unlocking novel therapeutic strategies. By understanding the crosstalk between these two immune systems in HCC cells, we can develop more effective immunotherapeutic approaches, which are crucial for ultimately conquering this pernicious disease [9].

The ubiquitin-proteasome system(UPS) is the main pathway of intracellular protein degradation, which mediates the cell cycle, apoptosis [10] and lysosomal proteolytic pathways [11, 12]. Ubiquitin is a polypeptide chain consisting of 76 amino acids, with an N-terminal and C-terminal linked to other proteins. Under the condition of ATP energy, E1 adheres to the tail of ubiquitin molecules (Cys) and mutates Cys into Ala to activate ubiquitin molecules and transfers ubiquitin molecule to E2, which recognizes the target protein together with E3 and then mediates its subsequent ubiquitination. There are two E1 ubiquitin ligases, approximately 38 E2 ubiquitin ligases, and more than 600 E3 ubiquitin ligases [13] in human cells, which are most specifically responsible for the recognition of different target proteins. Notably, numerous kinds of E3 are found mutations occurred in HCC patients, and dysregulated expression that is involved in the occurrence and development of HCC [14].

In HCC, some transducers of the signaling pathway are dysregulated by the abnormal expression of certain E3 ligases, which transmit carcinogenic signals downward and accelerate HCC progression [15, 16]. Therefore, targeting the aberrant signaling pathways induced by dysregulated E3 ligases opens new possibilities for HCC treatment [17, 18]. In conclusion, this study aimed to provide a broader perspective on HCC immunotherapy by elucidating the abnormal ubiquitination in the signaling pathway of immunity systems during the development of HCC and the carcinogenic process of ubiquitination during viral infection.

Innate immune/pathways

Innate immunity, which functions as the body's primary line of defense, serves as a rapid-acting and broad-spectrum response system that safeguards against pathogen incursions. It is instantaneously activated upon pathogen detection and plays a pivotal role in curbing infections during the early stages of an infectious episode. Signaling pathways are integral to innate immunity. Acting as the molecular "circuitry" they endow innate immune cells with the capacity to perceive pathogens, communicate intercellularly, and mount a potent defensive response. The relationship between ubiquitination and signaling pathways is characterized by a high degree of interconnection and dynamism. Ubiquitination modification exerts a critical regulatory role in signaling pathways by

modulating the fate and functionality of effectors. Conversely, signaling pathways govern the ubiquitination process, thereby establishing a complex regulatory network. In the following sections, we examine the underlying mechanisms of HCC development, focusing on the relationships between various signaling pathways and aberrant ubiquitination modification (Table 1).

PI3K/AKT/mTOR pathway

Inositol-3-kinase (PI3K)/AKT/mTOR signaling pathway is a common physiological signal transduction pathway that is essential for many aspects of cell growth, survival, and cycle progression and is activated in many cancer types through the role of maladjusted receptor tyrosine kinase (RTK). Overexpression of the PI3K/AKT/mTOR signaling pathway is very common in HCC, exhibiting a promising target for the treatment of HCC [19].

The impacts of the PI3K/AKT/mTOR pathway on the innate immune pathway are manifested primarily in two aspects including suppression of immune cell activity, and inhibition of immune cell development and differentiation. Activation of the PI3K/AKT/mTOR pathway has the capacity to dampen the activity of innate immune cells. For instance, activation of this pathway can drive their polarization towards the M2 phenotype in macrophages, leading to a reduction of their antigen-presenting and phagocytic capabilities, along with a decrease in the production of inflammatory cytokines [20]. In natural killer (NK) cells, abnormal activation of this pathway may result in a decline of their cytotoxicity, thereby impairing their ability to eliminate tumor cells [21, 22]. Moreover, Activation of the PI3K/AKT/mTOR pathway can curtail the production of inflammatory cytokines by innate immune cells. For example, through the inhibition of PI3K-Akt-mTOR signaling pathway, the production of key inflammatory cytokines such as interleukin-1β/8/11/(IL-1β/8/11) and interferon gamma (IFN-γ) is diminished, consequently attenuating the intensity of the inflammatory response [22, 23]. Additionally, this pathway may impede the inflammatory response by modulating the activation of inflammasomes. Specifically, it can inhibit the activation of the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome, leading to a reduction in the release of inflammatory cytokines like IL-1β [24]. Besides, NLRP1 is immunoprecipitated with mTOR, abolishing NLRP1 inflammasome-driven inflammatory reactions [25]. Notably, activation of the PI3K/AKT/mTOR pathway can induce changes in the metabolic state of immune cells, which in turn impacts their functional capabilities. By promoting metabolic pathways such as glycolysis and arginine metabolism which supply energy for the rapid proliferation and activation of immune cells [20, 26]. Nevertheless, in some situations, this can cause an imbalance in immune cell energy metabolism, thereby affecting their normal functions. In addition, activation of this pathway may influence the

Table 1 Different E3 ligases in signal pathways and virus infection

E3 ligases	Substrates	Degraded or not	Site	Level in HCC	Refs	Pathways or virus-related
NEDD4	PTEN	YES	Unknow	UP	[35, 36]	PI3K/AKT/mTOR
TRAF6	Akt	NO	K8, K14	UP	[37]	PI3K/AKT/mTOR
SPOP	PDK1	YES	Unknow	DOWN	[38]	PI3K/AKT/mTOR
MDM2	P53	YES	Unknow	UP	[43, 44]	PI3K/AKT/mTOR
FBXW7	mTOR	YES	K631, K635	DOWN	[30]	PI3K/AKT/mTOR
RNF173(MARCH3)	GRB2	YES	Unknow	DOWN	[51]	Ras/Raf/MAPK
TRIM71	RAF1	YES	K48	DOWN	[52]	Ras/Raf/MAPK
LZTR1	Ras	YES	K48, K63, K33	DOWN	[54]	Ras/Raf/MAPK
β-TrCP	β-catenin	YES	Unknow	DOWN	[63]	WNT/β-catenin
TRAF6	GSK-3β	YES	K183	UP	[67]	WNT/β-catenin
ZNRF3	Frizzled	YES	Unknow	DOWN	[69]	WNT/β-catenin
TRIM65,RNF146	Axin	YES	Unknow	UP	[70, 71]	WNT/β-catenin
Prickle-1	Dishevelled	YES	K669, K707	DOWN	[72, 73]	WNT/β-catenin
β-TrCP	p100	NO	K856	UP	[77]	NF-κB
TRAF6	CARMA3	NO	Unknow	UP	[79]	NF-κB
TRAF2	RIP	NO	K63	UP	[81]	NF-κB
ITCH	TAK1	YES	Unknow	DOWN	[83]	NF-κB
TRAF6,TRAF3	TAK1	NO	Unknow	UP	[83]	NF-κB
NEDD4	HBx	YES	K48	DOWN	[85]	HBV-related
UHRF2	DHX9	YES	K63	UP	[88]	HBV-related
TRIM29	HMMR	YES	Unknow	DOWN	[93]	HBV-related
PRC1	H2A	NO	K119	UP	[97, 98]	HCV-related
LUBAC	NEMO	YES	K285, K309	DOWN	[101]	HCV-related

uptake and utilization of nutrients by immune cells, thus restricting their functional performance within specific microenvironments.

Activation of the PI3K/AKT/mTOR pathway can affect the maturation and differentiation processes of immune cells. In dendritic cells, for example, activation of this pathway may suppress their maturation and antigen-presenting abilities, thereby undermining the initiation and maintenance of the immune response [27]. Moreover, this pathway may modulate the lineage determination and functional specialization of immune cells by regulating the activities of transcription factors and signaling molecules. For instance, mTORC1 activation promotes Th1 and Th17 cell differentiation by upregulating the expression of transcription factors like T-bet and RORγt, while mTORC2 signaling is essential for the development of Th2 cells [28, 29]. As a result, PI3K/AKT/mTOR pathway can alter the type and magnitude of the immune response. It has previously been reported that the disturbance of PI3K/AKT/mTOR pathway in HCC is involved in ubiquitin modification [30, 31]. Therefore, it is conceivable that the overactivation of the PI3K/AKT/mTOR pathway caused by the disturbance of ubiquitination modification is closely related to the innate immune cells in HCC.

RTK monomers are high-affinity cell surface receptors of growth factors, cytokines, and hormones, which are activated and dimerized after ligand binding. Each monomer phosphorylates itself, thus activating the PI3K/Akt/mTOR pathway. Activated RTK recruits PI3K, PI3K then phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-triphosphate (PIP3). PIP3 interacts with and recruit inositol-3-phosphate-dependent protein kinase 1 (PDK1) and Akt to the plasma membrane. PDK1 phosphorylation partially activates Akt by activating Thr308, and indirectly increases mTORC2 activity, thus completely activating AKT by activating Ser473. The homologous phosphatase-tensin gene (PTEN) can negatively regulate activated AKT, and PTEN can dephosphorylate PIP3 to produce PIP2, which prevents the activation of ATK. Complete activation of AKT can cause AKT shedding and activate or inhibit targeted downstream proteins, including mammalian rapamycin target (mTOR), Rab guanosine triphosphatase activating protein (AS160), fork box O protein (FOXO), MDM2, BRCA1, and nuclear factor-kappa B (NF-kB), thus regulating glycogen uptake, cell survival and differentiation, protein synthesis, and DNA repair [19, 32] (Fig. 1).

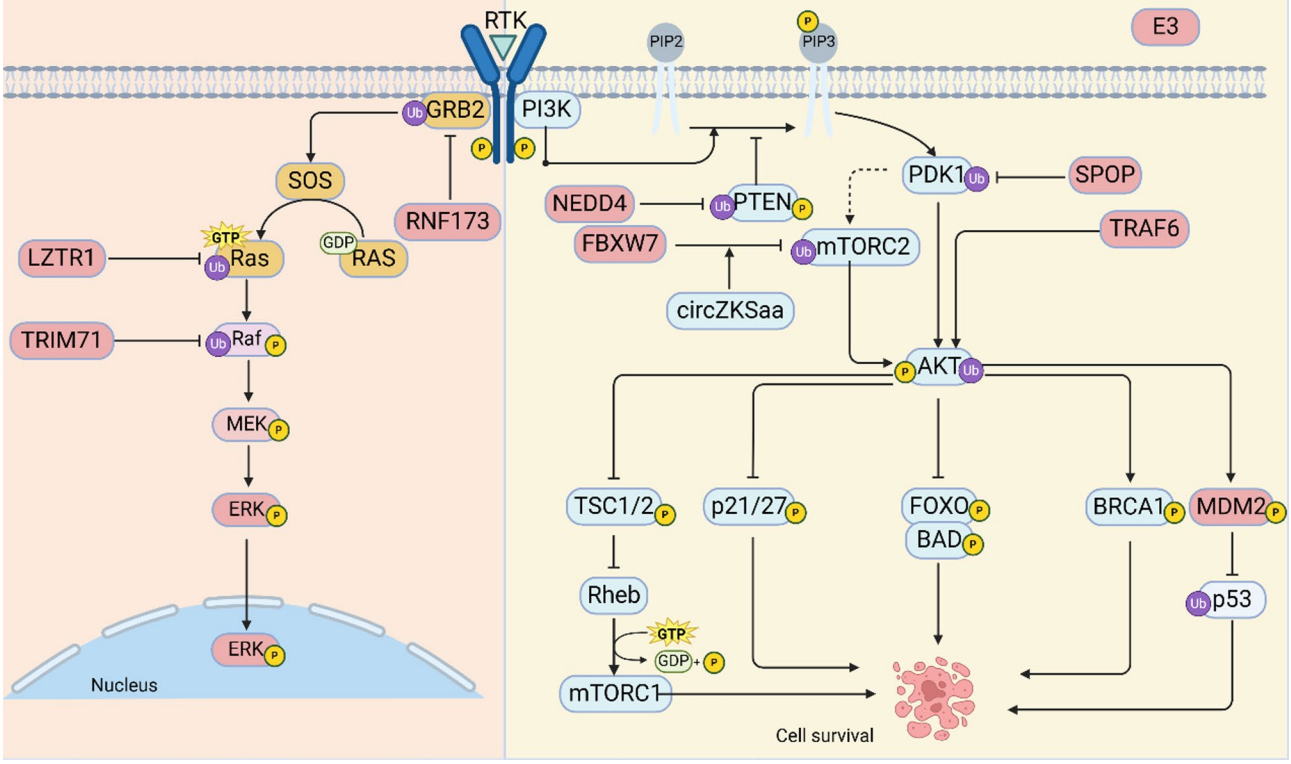

Fig. 1 PI3K/Akt and Ras/MAPK signaling pathway processes and associated ubiquitination. Phosphorylated RTK can activate upstream proteins of the PI3K/Akt pathway and Ras/MAPK pathway, resulting in downstream Ras/Raf/MAPK cascade reaction and activation of the key protein Akt, ultimately leading to abnormal cell behavior and the occurrence of HCC. In this process, many transducers can be activated or degraded by different E3 ubiquitin ligase ubiquitination, accelerating the disorder and abnormal activation of the pathway

Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is a common tumor suppressor gene that is inactivated in HCC. PTEN is a central negative regulator of PI3K-Akt signal transduction, dephosphorylates PIP3, and inhibits downstream signaling and carcinogenesis [33]. Neural precursor cell-expressed developmentally downregulated gene 4 (NEDD4), a member of the HECT family, is an E3 ligase overexpressed in HCC [34]. Some studies have shown that NEDD4 can mediate the ubiquitination and degradation of PTEN to reduce its stability, affecting the phosphorylated activation of downstream proteins such as AKT and ERK, resulting in enhanced invasion and metastasis of HCC cells [35, 36].

Tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6), an E3 ubiquitin ligase, is a member of the tumor necrosis factor receptor-associated factor (TNFR) family. TRAF6-mediated K63-linked ubiquitination of Akt does not affect Akt stability but improves Akt signaling activation. Previous studies have shown that Akt ubiquitination occurs at K8 and K14 within the PH domain of Akt, and mutations at these sites(from K to R) abrogate Akt phosphorylation and activation, highlighting the critical role of Akt ubiquitination in Akt signaling activation [37]. Subsequently, excessive activation of AKT leads to PI3K/AKT/mTOR pathway disorders and activation or inhibition of downstream proteins, which leads to the occurrence and development of cancer.

In the PI3K/AKT/mTOR pathway, 3-phosphoinositide-dependent protein kinase 1 (PDK1) plays a critical role in activating AKT, modulating the tumor microenvironment, and markedly influencing tumor immunotherapies. Recent studies have shown that increased PDK1 contributes to the promotion of tumorigenesis in different types of cancer, including HCC [38, 39]. SPOP is an E3 ubiquitin ligase junction based on cullin 3, which is frequently mutated in a series of cancers and is associated with therapeutic drug resistance. SPOP recognizes phosphorylated PDK1 and induces its ubiquitination and degradation of PDK1. Hypoxia reduces the phosphorylation of PDK1, contributing to its escape of PDK1 from SPOP-mediated ubiquitination and degradation. Simultaneously, SPOP can degrade the tumor suppressor PTEN under hypoxia and indirectly inhibit the activity of PDK1 kinase. Together, these molecular events could lead to overexpression of PDK1, which induces an imbalance in the PI3K/AKT/mTOR pathway and accelerates liver cancer progression [40].

As a tumor suppressor, p53 plays a key role in inhibiting tumor growth [41]. Under normal physiological conditions, p53 has a short half-life and is maintained at relatively low levels. However, when cells are subjected to DNA damage and oxidative stress, p53 ubiquitination is inhibited, resulting in a rapid increase in p53 protein levels and leading to cell cycle arrest or apoptosis [42]. MDM2, an E3 ubiquitin ligase that induces ubiquitination and degradation of p53, can inhibit the anti-tumor function of p53 and help DNA-damaged cells escape immune surveillance and continue to proliferate, leading to tumor formation and progression. Moreover, under conditions of cellular homeostasis, MDM2 directly inhibits its p53 activity by binding to the transcriptional activation domain. Simultaneously, p53 enhances MDM2 transcription through p53-specific response elements in the MDM2 promoter, thus forming an autoregulatory feedback loop that is essential for controlling the balance between p53 and MDM2 [43]. Previous studies have found that when HCC occurs, the homeostasis of the MDM2-p53 axis is always destroyed, and the overactivation of the main kinase AKT in the PI3K/AKT/mTOR pathway leads to the overexpression of the downstream MDM2 protein, which directly inhibits the transcriptional activity of p53 and promotes the growth of tumorigenic cells by evading cell cycle checkpoint control [44].

mTOR is an atypical serine/threonine protein kinase that belongs to the phosphatidylinositol kinase-associated kinase (PIKK) protein family. PI3K/AKT/mTOR pathway promotes downstream pathways by partially activating AKT. circZKSCAN1 has been reported to be a tumor-associated circRNA by sponging microRNAs, which encodes a secretory peptide circZKSaa in the liver [45]. FBXW7 is an SCF E3 ubiquitin ligase that inhibits tumor growth by interacting with circZKSaa to promote mTOR ubiquitination and ultimately inhibit the proliferation of HCC. Physiologically, circZKSaa binds to key sites 631 and 635 on mTOR to induce FBXW7 to recognize the specific sites on mTOR to ubiquitinate and degrade mTOR to inhibit the PI3K/AKT/mTOR pathway. In the early stages of HCC, overexpression of circZKSaa in cancer cells leads to an increase in mTOR ubiquitination. However, with the progression of HCC, mutations often occur at key sites of mTOR, which leads to a decrease in the level of ubiquitination, ultimately inducing tumor development [30].

Ras/Raf/MAPK pathway

Mitogen activated protein kinase (MAPK) pathway is a highly conservative three-stage kinase cascade participating in a variety of physiological and pathological processes, including cell proliferation, migration, inflammation and cell differentiation, and is inextricably related to HCC. The starting point of the Ras/MAPK pathway is the stimulation of the cell, where growth factor (GF) activates RTK, auto-phosphorylated RTK produces the site of the binding protein GRB2, and SOS protein is recruited to the cell membrane. The SOS protein promotes Ras to release GDP, binds GTP to activate itself, and changes the Ras protein from an inactive to an active

state. Subsequently, activated Ras binds to the serine/threonine kinase Raf and locates Raf on the membrane, which leads to activated Raf (MAPKKK) phosphorylation, activating MEK(MAPKK) and MEK phosphorylation, activating downstream ERK (MAPK) proteins [46]. Finally, activated ERK enters the nucleus to regulate downstream transcription factors that respond to stimulation, including proliferation, anti-apoptosis and differentiation [47]. Under normal physiological conditions, some inhibitors, such as the Ras inhibitor RASSF1A and ERK inhibitor DUSP1, regulate the Ras/MAPK pathway. However, in HCC, a large amount of clinical data has found that the tumor suppressors RASSF1A and DUSP1 can undergo SKP2/CKS1-dependent ubiquitination and degradation, which contributes to abnormal activation of the Ras signaling pathway, resulting in HCC tumorigenesis [48] (Fig. 1.).

Growth factor receptor-bound protein 2(GRB2) is a junction protein that connects the surface receptor to downstream targets of the Ras/MAPK pathway. RNF173(MARCH3), a member of the MARCH family, functions as an E3 ligase associated with immune responses and transmembrane transport [49]. Recent studies have shown that RNF173 is an inhibitor of GRB2 that can specifically bind to GRB2 and promote its ubiquitination and degradation, thereby inhibiting the Ras/MAPK pathway and preventing abnormal epithelial-mesenchymal transition (EMT) and metastasis in HCC [50]. Previous studies have shown that the expression of RNF173 in tumor samples is dramatically decreased, reducing the ubiquitination and degradation of GRB2, thus enhancing the proliferation, invasion, and metastasis of HCC [51].

RAF1 is a member of the serine/threonine protein kinase family. As a key shuttle enzyme, it transmits stimulating signals of the growth factor receptor and protein kinase C from the cell membrane to target proteins to regulate the expression of genes involved in cell growth, differentiation, and survival. TRIM71 is an E3 ubiquitin ligase that binds to RAF1 for K48-ubiquitination and degradation, and negatively regulates the Ras/MAPK pathway in the liver. HDLBP (Viglin) is a member of the lipid family, and its dysregulation is associated with lipid disorders and is an important factor in the pathological progression of HCC. Mechanistically, increased expression of HDLBP competes with TRIM71 to inhibit the ubiquitination and degradation of RAF1 to activate the Ras/MAPK pathway, thus contributing to sorafenib resistance, with RAF1 as the main therapeutic target [52].

The Ras protein is a member of the GTP enzyme family, which binds guanosine nucleotides (GTP and GDP) and GTP and is periodically converted to active and inactive states through internal GTP enzyme activity [53]. The Leucine Zipper Like Post Translational regulator 1 (LZTR1) protein is the ligator of the Cullin 3 (CUL3) ubiquitin ligase complex and is considered to be a tumor suppressor. It mediates the polyubiquitination and degradation of Ras by K48, K63, and K33-linkage ubiquitination chains, thereby inhibiting activation of the Ras/MAPK pathway and HCC [54, 55]. Notably, several studies have found that the expression of LZTR1 in HCC cells is decreased, which leads to stabilization of the Ras protein and exerts its signal transduction function to activate the Ras/MAPK pathway, resulting in HCC development and resistance to lenvatinib [56, 57].

Wnt/β-catenin pathway

The Wnt/β-catenin pathway is one of the major signaling pathways that regulates liver regeneration, homeostasis, and tumorigenesis. Recent genomic studies have shown that 30–40% of HCC tumors demonstrate aberrant activation of the Wnt/β-catenin pathway [58–60]. Therefore, targeting this signaling cascade is an attractive therapeutic strategy for the treatment of HCC. Several molecules have been studied and screened for targeted Wnt signaling components, including small-molecule inhibitors that block the interaction between β-catenin and TCF, or the binding of β-catenin to cAMP-binding proteins, and therapeutic monoclonal antibodies against the binding of Wnt ligands to Frrizled receptors. Moreover, some clinically used drugs, such as indomethacin, aspirin, and celecoxib, have been proven to have activity against the Wnt pathway, such as indomethacin, aspirin and celecoxib [61]. In the absence of Wnt ligands, β-catenin forms complexes with glycogen synthase kinase 3β (GSK-3β), casein kinase 1α (CK1α), adenomatous polyposis coli (APC), and Axin-1 proteins that mediate N-terminal phosphorylation of β-catenin. This leads to ubiquitination of β-catenin by E3 ubiquitin ligase β-transducer repeat sequence protein (β-TRCP), followed by proteasome degradation and prevention of β-catenin translocation into the nucleus. Wnt signaling begins when the Wnt ligand binds to the Frizzled receptor which crosses the plasma membrane seven times to form a unique family of G protein-coupled receptors (GPCR). At the same time, coreceptor LDL receptor-related protein (LRP) interacts with the Wnt-Frizzled protein complex to promote Wnt signal transduction. Subsequently, the Dishevelled (Dvl/Dsh) protein is phosphorylated to recruit Axin-1 and GSK-3β from the adjacent plasma membrane, preventing the formation of degradation complexes. Dephosphorylated β-catenin escapes the recognition of β-TRCP and translocates to the nucleus, where it interacts with T cytokines (TCF) and lymphoenhancer binding protein family (LEF) transcription factors, leading to the activation of downstream target genes, including c-myc, c-jun, cyc D, and fra-1, to accelerate tumorigenesis [62] (Fig. 2.).

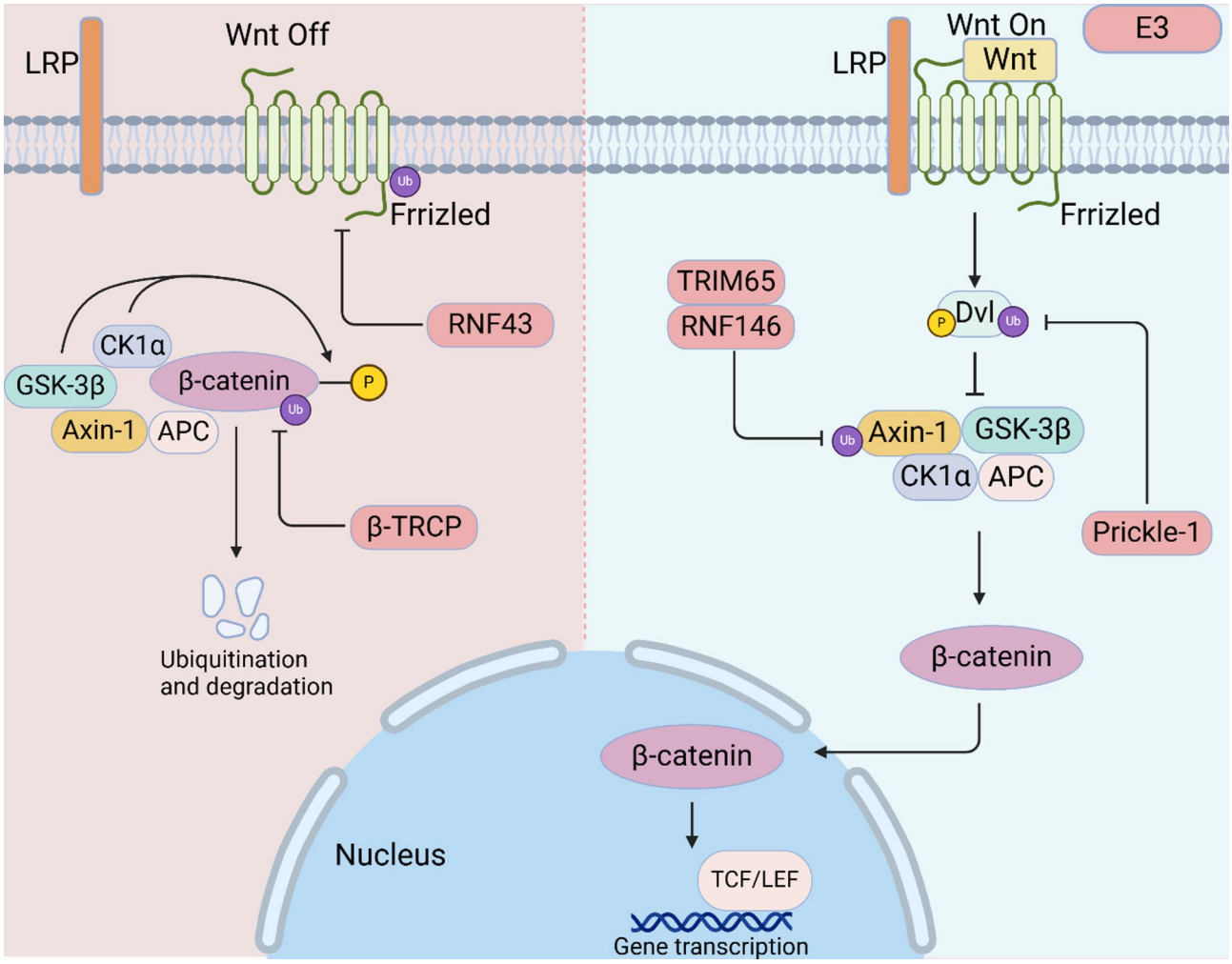

Fig. 2 Wnt/β-catenin signaling pathway processes and associated ubiquitination. Under normal conditions (Wnt Off), β-catenin binds to the degradation complex and is phosphorylated, subsequently recognized by E3 ubiquitin ligase (β-TrCP) and undergo ubiquitination and degragdation. The Wnt/β-catenin signaling pathway is initiated by binding of Wnt ligand protein to transmembrane protein FZD receptor (Wnt On), Dvl protein will be recruited to the cell membrane to bind FZD, and then Dvl protein interacts with Axin to recruit a protein complex composed of Axin, GSK-3β and APC. This progress allows the β-catenin protein to enter the cell and direct downstream gene transcription. Most E3 ubiquitin ligases protect against Wnt signaling pathway transduction and eventual oncogene transcription through ubiquitining and degrading related proteins, but are underexpressed in HCC

β-catenin is a glycoprotein with dual functions. On the one hand, it binds to cadherin to form a complex that participates in intercellular junctions, and on the other hand, it participates in the Wnt signaling pathway to regulate embryonic development and tumorigenesis. In the absence of Wnt signaling, β-catenin, an intercellular adhesion junction protein, is phosphorylated under the coordination of APC/Axin/GSK-3β/CK1 α and forms a complex as a target that is recognized by β-TrCP/Skp1/Cul1 and other E3 ligases entering proteasome-mediated degradation. Moreover, p53 could help some E3 ligases, including Siah-1, Skp1, and TBL1, to degrade dephosphorylated β-catenin and regulate β-catenin protein levels. The upstream regulation of β-catenin prevents it from entering the nucleus to bind with transcription factors, avoiding the activation of downstream proteins and promoting tumor occurrence and development [63].

TRAF6 is a member of the tumor necrosis factor receptor-associated factor (TRAFs) family and is involved in many physiological processes, including innate immunity, adaptive immunity, and inflammatory responses. When Wnt signaling decreases, GSK-3β binds to and phosphorylates β-catenin; thus, phosphorylated β-catenin is recognized by β-TrCP and subsequently degraded. Previous studies have shown that HBV X protein (HBX) plays a key role in HCC induced by chronic hepatitis B virus (HBV) [64–66]. Non-muscle myosin heavy chain IIA (MYH9) is a new HBX-related protein that enhances TRAF6-mediated ubiquitination and degradation of GSK-3β at the K183 site. Thus, β-catenin can avoid phosphorylation, escape β-TrCP recognition, enter

the nucleus to bind to transcription factors, and accelerate tumorigenesis [67].

The frizzled (FZD) receptor is the main receptor involved in Wnt signal transduction. It is a type of seven transmembrane protein, similar to G protein-coupled receptors or GPCR. When the Wnt protein, seven transmembrane coreceptor FZD proteins, and a single transmembrane receptor (LRP 5/6) combine to form the Wnt/FZD/FZD complex, the C-terminal tail of FZD recruits dishevelled protein (Dvl/Dsh) and downstream proteins at the plasma membrane to promote the activity of the Wnt signaling pathway. Both ring finger protein 43 (RNF43) and zinc and ring finger 3 (ZNRF3) have E3 ligase activities and high structural homology. They not only have the cytoplasmic region of the RING finger domain, but also have the iconic N-terminal extracellular domain and transmembrane domain, so both can inhibit the Wnt signaling pathway through ubiquitination of FZD receptors. According to previous studies, Dvl is necessary for ZNRF3/RNF43-mediated ubiquitination and degradation of FZD [68]. Dvl binds to Fzd through the DEP-C domain to help ZNRF3/RNF43 target FZD for ubiquitination. Under physiological condition, the expression of RNF43 is very limited. As a negative regulator of FZD, its surface level is reduced by ubiquitination and degradation. Notably, RNF43 is often mutated and expressed at low levels in HCC, leading to an increase in FZD levels and an enhancement of the initiation signal intensity of the Wnt pathway [69].

Axin exists as a scaffold protein in two subtypes of the Wnt signaling pathway. In the absence of Wnt signaling, Axin1 directly interacts with GSK-3β, CK1α, APC, and β-catenin to promote the formation of a β-catenin degradation complex in which Axin1 is a rate-limiting protein. Axin2 is a direct target of TCF/LEF transcription factors. When the Wnt pathway is activated, β-catenin enters the nucleus and binds to transcription factors TCF/LEF to increase Axin2 mRNA expression. The RNA product of Axin2 is a marker of Wnt pathway activity, which helps increase the stability of the β-catenin degradation complex and downregulate β-catenin transcription, thus forming a negative feedback loop [70]. TRIM65 and RNF146 are members of the triple domain protein (TRIM) and Ring Finger Protein families, respectively, and both have E3 ligase activity. Clinical data from many patients with HCC show that the expression levels of TRIM65 and RNF146 are abnormally high. Previous studies have shown that the overexpression of TRIM65 and RNF146 leads to ubiquitination of Axin protein, which leads to homeostasis of Axin protein turnover and promotes the transduction and transcription of the Wnt signaling pathway, resulting in the development of HCC [71].

When the Wnt ligand binds to the Frizzled receptor and the coreceptor LPR5/6, Dishevelled (Dvl) in the cytoplasm is phosphorylated. Subsequently, DVL stabilized free β-catenin in the cytoplasm by inhibiting the function of the complex formed by APC, Axin, and GSK-3β. Prickle-1 is a Dvl-related protein with E3 ligase activity and is a negative regulator of the Wnt/β-catenin signal transduction pathway [72]. There are two conserved D-boxes in the sequence of Prickle-1, including D-box 1(amino acid residues–557–565) and D-box 2 (699–707) are associated with binding to the DEP domain of Dvl, promoting the ubiquitination of Dvl in a β-catenin-dependent manner. Previous studies have shown that low Prickle-1 expression is a hallmark of HCC and contributes to tumorigenesis [73].

NF-κB pathway

According to the latest statistics, cirrhosis caused by chronic liver inflammation is present in approximately 80–90% of HCC cases. The IKK/NF-κB(NF-κB) signaling pathway participates in the injury-inflammation-regeneration reaction in HCC, which accelerates the occurrence and development of liver cirrhosis, leading to HCC tumorigenesis. As the most important members of the IKK/NF-κB signaling pathway, the NF-κB family has five members: p50, p52, RelA(p65), RelB, and c-Rel. The RelA and p50 subunits form the NF-κB1 dimer protein, while the RelB and p52 subunits form the NF-κB2 dimer protein, which participate in canonical and non-canonical NF-κB pathways, respectively [74].

Activation of the NF-κB1 dimer in the canonical NF-κB signaling pathway is caused by the degradation of IκBα through the phosphorylation and ubiquitination of K32 and K36, mediated by the IKK kinase complex (IKKγ). IKKγ can be activated through two pathways: one is down-transduced by TCR/BCR to activate the phospholipase C (PLC)-DAG/IP3-PKC pathway, and finally PKC can phosphorylate the CARMA-BCL 10-MALT1 (CBM) complex to activate IKKγ, and the other is stimulated by pro-inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) to activate the tumor necrosis factor receptor-associated factor (TRAF) complex with E3 ligase activity, and finally ubiquitin to activate TAK1 and IKKγ. When the NF-κB1 dimer enters the nucleus and is activated, it regulates the transcription of a series of anti-apoptotic genes and inflammation-related genes to promote the occurrence of HCC [75]. The non-canonical NF-κB signaling pathway mainly exists in B cells, and its activation is mainly induced by members of the tumor necrosis factor receptor (TNFR) superfamily, such as CD 40 L and BAFF. The TRAF family, mainly TRAF2 and TRAF3, is recruited to prevent NF-κB inducing kinase (NIK) from ubiquitination and then phosphorylates IKKα. Subsequently, IKKα phosphorylates

ubiquitin P100 to produce p52, which then binds with RelB to form the NF- κ B2 dimer, enters the nucleus, and regulates downstream genes [76] (Fig. 3.).

The non-canonical NF-κB signaling pathway requires the activation of the p52/RelB (NF-κB2) dimer, while NF-κB2 depends on the hydrolytic processing of p52 precursor protein p100 [77, 78]. p100 is a member of the NF-κB protein family, and its C-terminus can respond to NIK elements so that NIK and IKKα can induce phosphorylation at the K866 and K870 sites of p100. Previous studies have shown that after the activation of the non-canonical NF-κB signaling pathway and the phosphorylation of p100 caused by the increase in NIK protein, it could be recognized by β-TrCP, which is an E3 ligase that regulates signal transduction, cell cycle, and DNA damage repair response [76]. Subsequently, β-TrCP mediates non-degradative ubiquitination of p100 via K856-phosphorylation. After phosphorylation and ubiquitination, p100 is transformed into p52 to form NF-κB2 and enter the nucleus, thus activating downstream gene transcription and leading to tumorigenesis. In normal mammals, p100 is barely converted to p52; thus, endogenous NF-κB2 exists mainly as a precursor p100/RelB. When liver injury or inflammation occurs, there is often a dramatic increase in the number of members of the TNFR family, which induces the development of HCC.

The caspase recruitment domain and membrane-associated guanosine kinase-like protein 3 (CARMA3) are members of the CARMA family and are expressed in many tissues, especially in the liver. CARMA3 is a novel scaffold protein with a CARD domain at the N-terminus, which can recruit Bcl-10 and MALT1 to form a CBM complex and activate the downstream IKKγ complex, resulting in activation of the NF-κB pathway. Chemotherapies, such as doxorubicin and other drugs, are often used to treat locally advanced or locally recurrent primary and metastatic liver cancers [79]. However, previous studies have found that DNA damage triggers the association between CARMA3 and TRAF6, and that TRAF6 activates the CBM complex by binding to CARMA3 and mediating non-degradative ubiquitination, which results in the resistance of cancer cells to

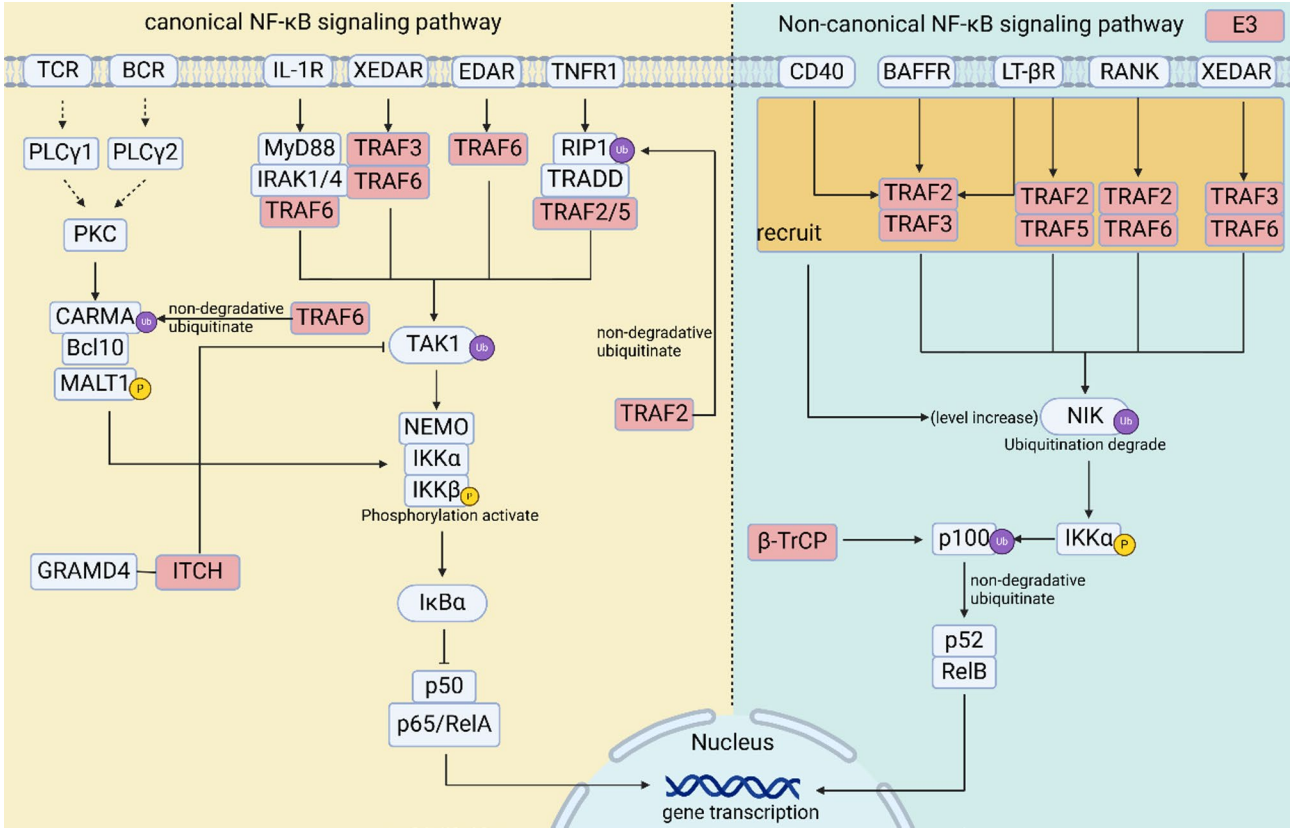

Fig. 3 NF-κB signaling pathway processes and associated ubiquitination. The NF-κB signaling pathway is classified into canonical and non-canonical pathways. The classical pathway relies primarily on the activation of the IκB kinase complex β (IKKβ) and the phosphorylation and degradation of IκB by the inflammatory immune response, leading to nuclear transcription of NF-κB (primarily p50/RelA dimer) molecules. The non-classical pathway is stimulated by a cytokine (CD40L, BAFF), which leads to the activation of NIK and IKKα, then partial degrading p100 to p52 and forming NF-κB molecules with RelB. A large number of E3 ubiquitin ligases are involved in this pathway, some acting as transducers and others activating or inhibiting the NF-κB signaling pathway by ubiquitinating and degrading related proteins

chemotherapeutic drugs through activation of the NF-κB pathway [80].

The receptor-interacting protein (RIP) family is a group of threonine/serine protein kinases that are important mediators of cell stress and integrate extracellular stimulation from various cell surface receptors and intracellular pattern recognition receptor signals. TNFR is expressed in all human tissues and is one of the main receptors in the TNF-α-mediated NF-κB pathway. Under the pro-inflammatory effects of TNF-α, TRAF2, TNFR1-related death domain (TRADD), and RIP1 are recruited into TNFR to form a complex, and the E3 ligase TRAF2 mediates K63-linkage non-degradative ubiquitination of RIP1,which could bind IKKγ (NEMO) to stabilize the binding of TNFR and IKK, thus activating the NF-κB pathway [81, 82].

TAK1 is a key intermediate kinase in the NF-κB pathway that can transmit upstream signals from the complex to IKKγ, and plays a key role in the growth and metastasis of HCC. GRAMD4 (glucosyltransferase Rab-like GTPase activator and myotubularin domain containing 4) is a newly discovered death-inducing protein (DIP). Under normal physiological conditions, GRAMD4 recruits TAK1-specific E3 ligase ITCH at the N-terminus to mediate the K48-ubiquitination and degradation of TAK1. However, in the cellular tissues of patients with HCC, the expression of GRAMD4 is often decreased, and thus, TAK1 is overexpressed with a shorter OS [83]. The decreased GRAMD4-mediated ubiquitination and degradation of TAK1 and the increased TRAF family mediated non-degradative ubiquitination and activation of TAK1 induced by inflammatory factors lead to the activation of the NF-κB pathway, ultimately accelerating the progression of HCC.

Virus infection and ubiquitination

When a virus breaches the host's defenses, innate immunity is activated. Pattern recognition receptors (PRRs) that are nestled on the surface of innate immune cells act as vigilant sentinels and swiftly detect virus-associated molecular patterns. This detection sets in motion a cascade of precisely choreographed signaling events that are intricately regulated by ubiquitination modification. Ubiquitination plays a dual-faceted role in this dynamic scenario. It serves as an indispensable link for the seamless operation of innate immune signaling pathways. By tagging signaling proteins downstream of PRRs with ubiquitin molecules, ubiquitination facilitates activation of crucial transcription factors. These activated transcription factors act as master regulators, orchestrating the production of cytokines and interferons with the body's potent antiviral weapons. Conversely, viruses, through continuous evolution, have a remarkable ability to subvert ubiquitination for their own nefarious purposes. Certain viruses possess the capacity to manipulate the host ubiquitination machinery with astonishing precision. They may engineer an increase in the ubiquitination of pivotal innate immune proteins, leading to their subsequent degradation, thereby evading the surveillance of the immune system. Alternatively, they can hijack the ubiquitination process altogether, co-opting it to fuel their replication and dissemination within host cells, thus furthering the pathogenic agenda.

Ubiquitination associated with HBV infection

Upon HBV infection, it disrupts the host's immune recognition and activation processes via diverse mechanisms. Among these, ubiquitination modification assumes a pivotal role. For instance, the X protein of HBV (HBx) is capable of inducing the ubiquitination - mediated degradation of several critical immune signaling molecules within host cells. HBx forms a complex with ubiquitin ligases, leading to the ubiquitination of essential adapter proteins or transcription factors in immune signaling pathways. Subsequently, these ubiquitinated molecules are degraded by the proteasome. This effectively blocks the transmission of immune signals, impeding the efficient activation of both the host's innate and adaptive immune responses, thereby enabling the virus to elude host immune clearance. Furthermore, HBV can exploit ubiquitination modification to modulate the presentation of its own antigens. Ordinarily, viral antigens must be processed by antigen - presenting cells and then presented to T cells to trigger an immune response. Nevertheless, HBV can induce abnormal ubiquitination of molecules associated with antigen presentation. This aberrant ubiquitination interferes with the normal antigen processing and presentation processes, diminishing the ability of T cells to recognize HBV antigens, thus facilitating immune escape.

HBV X protein (HBx) is a multifunctional regulatory molecule encoded by the HBV genome that directly or indirectly affects the replication and proliferation of HBV by affecting signaling pathways and protein degradation, thus playing an important role in the occurrence and development of chronic liver cirrhosis and HCC [84]. Neural precursor cells express developmentally downregulated gene 4 (NEDD4), a member of the HECT family that has E3 ligase activity and acts as an oncogenic factor in a variety of tumors, including HCC [35]. However, NEDD4 also plays a different role in HBV-related HCC. For example, NEED4 acts as an E3 ligase that mediates ubiquitination and degradation of HBx, thereby inhibiting HCC progression. Moreover, clinical data show that HCC patients with HBV infection exhibiting elevated NEDD4 levels have a better prognosis and higher survival rates [34, 85] (Fig. 4.).

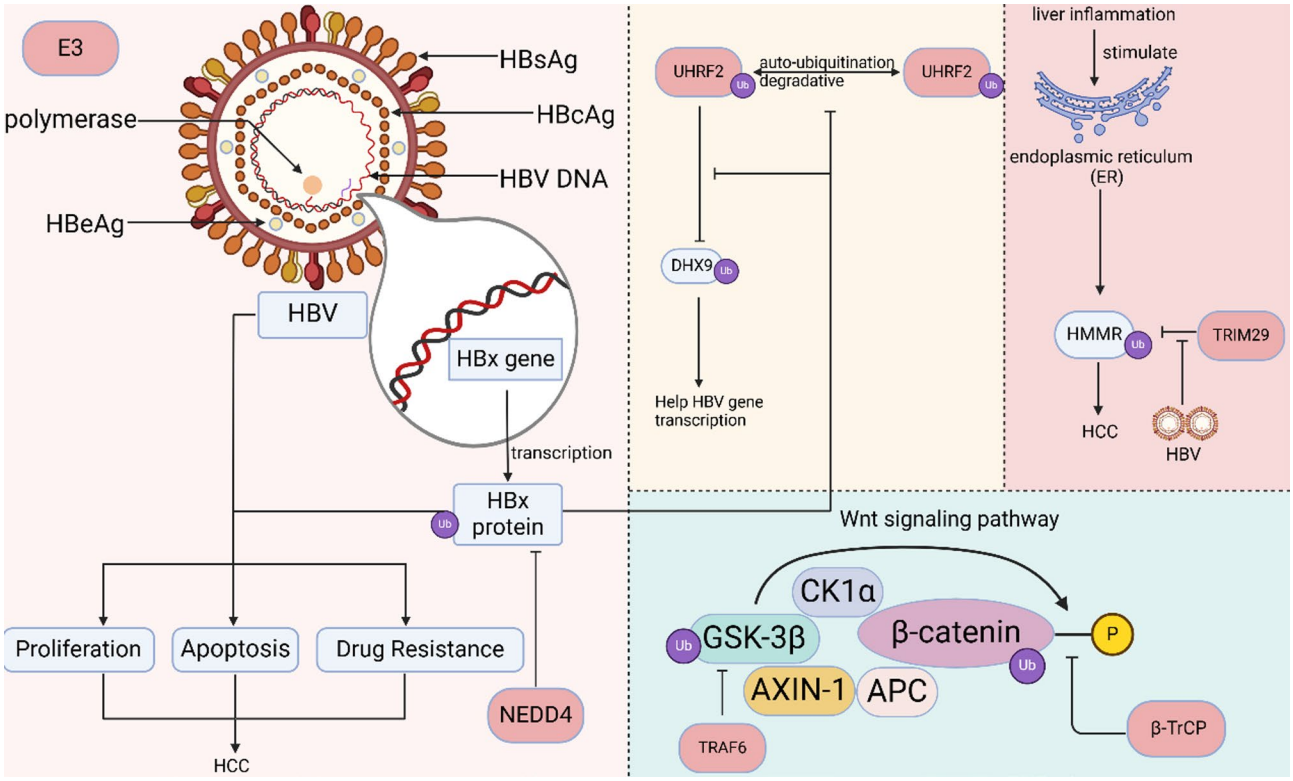

Fig. 4 HBV virus structure and related immune ubiquitination process involving HBx protein. HBx protein in HBV is involved in ubiquitination of endoplasmic reticulum related proteins and Wnt pathway related proteins, leading to immune disorders, abnormal cell proliferation, apoptosis and other physiological function resulting in HCC

DHX9 is an RNA helicase that can unspin DNA and RNA double strands, thereby contributing to HBV DNA replication. Previous studies have shown that DHX9 is often elevated in HCC and is considered a carcinogenic gene that promotes cell proliferation, invasion, and metastasis in HCC [86]. Ubiquitin-like with PHD and Ring finger domain 2(UHRF2), a ubiquitin E3 ligase, has been identified as an oncogenic protein associated with poor prognosis, immune infiltration, and metastasis in HCC. In HBV-negative HCC, UHRF2 is often downregulated in an auto-ubiquitination degradative manner, which may be caused by the interaction of two RING domains in UHRF2, one recognizing the substrate and the other acting as an E3 ligase to form a K63-linkage ubiquitination chain [87]. In contrast, in HBV-positive HCC, the autoubiquitination degradation ability of UHRF2 is inhibited by HBx through K643-phosphorylation of UHRF2, which increases its stability of UHRF2. Moreover, UHRF2-mediated ubiquitination and degradation of DHX9 are decreased, resulting in poor prognosis in patients with high UHRF2 expression. Additionally, previous studies have shown that UHRF2 can promote HBV replication in HBV-related HCC, contributing to poor clinical efficacy [88, 89].

Chronic HBV infection often contributes to genomic instability of the host by integrating its own DNA into the host chromosome, which is associated with a high risk of HCC. For example, mutations in the HBV surface antigen (HBsAg) lead to HBsAg accumulation in the endoplasmic reticulum (ER), contributing to the pathological characteristics of ground-glass hepatocytes (GGH) and ER stress [90]. ER stress can directly regulate the transcription of the hyaluronan-mediated motility receptor (HMMR), which is considered to be an oncogene in many studies, regulating cell migration, growth, and cell cycle physiological processes, and its high expression is associated with poor prognosis in many tumors [91, 92]. The three-motif protein family (tripartite motif, TRIM) is a large group of proteins with E3 ubiquitin ligase activity that is involved in different cellular functions and plays an important role in the antiviral immune response. TRIM29 is related to the Wnt pathway in HCC and can mediate ubiquitination and degradation of HMMR under ER stress. The mRNA expression of TRIM29 in HBV hepatitis is increased, but the level of TRIM29 in HBV-positive HCC is decreased, which may be due to an increase in HMMR expression by regulating the activity of autophagosomes and lysosomes to alleviate ER stress [93].

Ubiquitination associated with HCV infection

HOX regulates processes involved in organ maturation and tissue differentiation. Previous studies have shown that abnormal HOX expression often occurs in various cancers, including HCC [94, 95]. HCV is an enveloped RNA virus in which the core proteins E1 and E2 form virions that wrap around the viral genome, serving as a direct transcriptional activator of HOX genes. H2A, a member of the histone protein family, often undergoes non-degradative mono-ubiquitination mediated by PRC1, which is composed of RNF2, RNF1, and BMI1 E3 ligases, at the K119 site under healthy conditions(H2Aub). This site is widely distributed in the genome and exists at the transcriptional initiation site, silencing the transcription of downstream target genes, especially the HOX gene [96, 97]. Moreover, in HCV-positive HCC, the HCV core protein can degrade RNF2 and downregulate PRC1 by regulating proteasome activity. This reduces the K119-mono-ubiquitination of H2A and disrupts the inhibition of PRC1-H2Aub pathway regulation, leading to the occurrence of HCC [98].

The NS3 protein is a nonstructural HCV protein. It is a bifunctional protein with a protease domain at the N-terminus and a helicase domain at the C-terminus, contributing to viral replication [99]. LUBAC is a dimer complex composed of HOIL-1 L (RBCK1) and HOIP (RNF31), which have E3 ligase activity. In HCV-negative hepatitis, LUBAC mediates the ubiquitination and degradation of K285 and K309 sites in NEMO as an immune response that inhibits the occurrence and development of the NF-κB signaling pathway stimulated by the inflammatory factor TNF-α [100, 101]. However, in HCV-positive hepatitis or HCC, an increase in the level of TNF-α is not accompanied by an immune response. This is because the NS3 protein interacts with HOIP through the N-terminal protease domain and competes with NEMO for binding to LUBAC, thereby inhibiting the activation of the subsequent NF-κB pathway to avoid an immune response and enhance the survival of the virus, leading to chronic hepatitis, cirrhosis, and even HCC [102].

Adaptive immunity and ubiquitination

Another inherent natural immune mechanism is the adaptive immune response. In the tumor immune microenvironment (TME), there exist various adaptive immune cells such as CD8 + T [103], CD4 + T [104], B cells [105], and regulatory T cells (Treg cells), which are closely associated with the malignant behavior of HCC. During the development of HCC, the adaptive immune system can timely identify malignant cells, and different types of adaptive immune cells begin to accumulate around tumor cells. They are activated and differentiated into effector T cells and plasma cells by antigenic foreign substances, initiating a clearance program against HCC cells. However, as HCC progresses, T and B cells enter a state of functional fatigue and exhaustion. Meanwhile, HCC cells begin to recruit immunosuppressive cells such as Tregs to disrupt immune homeostasis and remodel the vascular system to invade the surrounding tissues, resulting in deterioration of the immune microenvironment and HCC metastasis. The ubiquitination system is extensively involved in this process. Different E3 ligases regulate the TME by mediating ubiquitination of key effectors in adaptive immune cells, such as B cells, promoting the early occurrence of immune escape in HCC cells (Table 2).

Ubiquitination related to T cells

T Cell-Mediated Immunity and Ubiquitination Networks in HCC (Fig. 5.).

The anti-tumor efficacy of T lymphocytes in HCC is fundamentally dependent on the precise recognition of tumor-associated antigens through T cell receptor (TCR)-peptide/MHC interactions [106]. Within the complex immune checkpoint network, the PD-1/PD-L1 axis has emerged as a pivotal therapeutic target, and multiple clinical trials have confirmed its critical role across malignancies [106, 107]. Mechanistically, the Cullin 3-SPOP E3 ligase complex orchestrates PD-L1 ubiquitination and proteasomal degradation under physiological conditions, thereby constraining tumor immune evasion. Notably, BCLAF1, a multifunctional protein initially characterized as an apoptosis regulator, has been identified as a novel oncogenic driver in HCC via HIF-1α-mediated angiogenesis and chemoresistance [108]. Crucially, BCLAF1 competitively binds SPOP to stabilize PD-L1 by impeding its ubiquitination, resulting in suppressed T-cell activation (evidenced by reduced CD3+/CD8 + T-cell infiltration) and enhanced immune escape [109]. This discovery has spurred clinical exploration of CDK4/6 inhibitors, which disrupt the PD-L1/SPOP interaction by targeting cyclin D-CDK4 complexes, thereby synergizing with α-PD-1/

Table 2 Different E3 ligases in daptive immunity

E3 ligases	Substrates	Degraded or not	Site	Level in HCC	Refs	Related-Pathway
SPOP	PD-L1	YES	K48	DOWN	[109]	Cullin 3 - SPOP
MARCHF3	PARP1	YES	K48	DOWN	[111]	cGAS-STING
TRIM21	CNOT4	YES	K48/K6	Unknow	[113]	JAK2/STAT3
TRIM32	STING	YES	K63	DOWN	[115]	STING - IFN
PRP19	DDX5	YES	Unknow	UP	[119]	Ras/Raf/MAPK

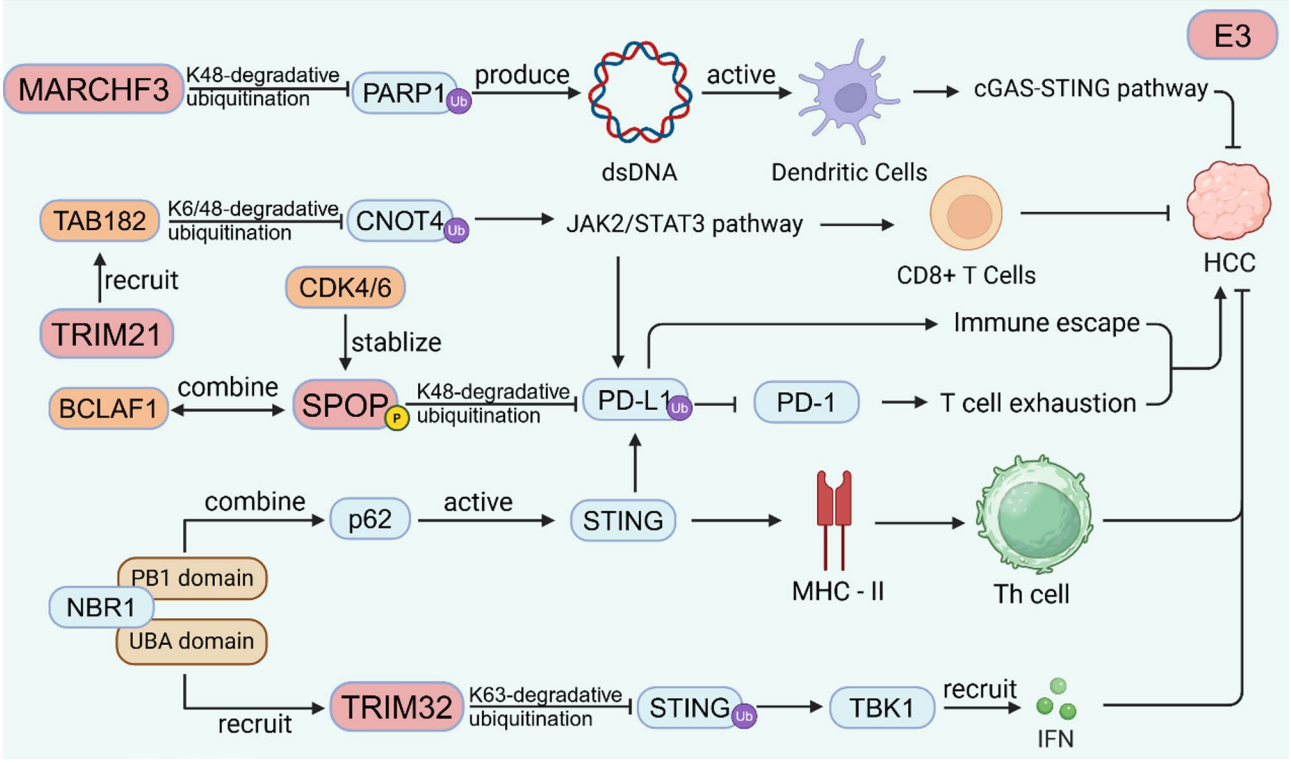

Fig. 5 Diverse E3 ligases participate in the modulation of multiple signaling pathways via the ubiquitination process, playing crucial roles in either immunological activation or immune evasion through specific mechanisms. For instance, MARCHF3 - PARP1 - dsDNA complex activates the cGAS - STING pathway in dendritic cells, which is essential for initiating innate immune responses. NBR1 - associated activation of STING impacts Th cells, thereby influencing the balance of the adaptive immune response. TRIM32 recruits TBK1, leading to the induction of IFN, which is a key cytokine in antiviral and antitumor immunity. TAB 182 - CNOT4 interaction affects CD8 + T cells, potentially altering their cytotoxic function and tumor - killing ability. Moreover, SPOP - PD - L1/PD − 1 axis causes T - cell exhaustion, a major mechanism of tumor immune evasion. Evidently, numerous T - cell immune regulation processes are intricately associated with PD - L1. Consequently, targeted immunotherapy in combination with anti - PD - L1 treatment has emerged as a promising approach in the clinical management of HCC, offering new prospects for improving patient outcomes

PD-L1 therapies to reverse immunosuppression in HCC [108].

E3 ligase MARCHF3: a dual-faceted regulator of tumor immunity

MARCHF3, an E3 ubiquitin ligase in the MARCH family, plays a context-dependent tumor-modulatory role. Although it suppresses colon carcinogenesis via IL-6 receptor ubiquitination [110] and inhibits HCC progression by targeting GRB2 in the Ras/MAPK/ERK pathway [51], its function in immunotherapy resistance reveals paradoxical dynamics. Recent studies have demonstrated that MARCHF3 overexpression during anti-PD-1 therapy induces K48-linked polyubiquitination and PARP1 degradation, a key DNA damage sensor. This process generates cytosolic dsDNA fragments that activate dendritic cell (DC)-mediated cGAS-STING signaling, enhancing antigen cross-presentation and CD8 + T cell priming to remodel the tumor immune microenvironment (TME) [111]. Translational studies have leveraged this mechanism by combining PARP inhibitors (e.g., olaparib) with immune checkpoint inhibitors (ICIs), successfully re-sensitizing patients with ICI-resistant HCC, and revitalizing cytotoxic T cell responses. This combinatorial strategy offers a paradigm shift for overcoming immunotherapy resistance across malignancies.

TAB 182-mediated immune reprogramming via ubiquitin-dependent signaling

TAB 182 (TNKS1BP1), a radiosensitization-associated protein, has recently been implicated in HCC immune evasion via JAK2/STAT3/PD-L1 axis regulation [112]. Mechanistic investigations revealed that TAB 182 recruits TRIM21 to catalyze the K48/K6-linked ubiquitination of CNOT4, a CCR4-NOT complex subunit, leading to its proteasomal degradation [113]. This process disrupts JAK2/STAT3 signaling, thereby suppressing PD-L1 expression and enhancing cytotoxic T lymphocyte (CTL) infiltration. Conversely, TAB 182 knockdown stabilizes CNOT4, which phosphorylates JAK2/STAT3 to upregulate PD-L1 while paradoxically amplifying CTL effector functions, a duality suggesting context-dependent therapeutic targeting. These findings position TAB 182 as a molecular rheostat for optimizing PD-L1

blockade efficacy with potential utility in patient stratification for combination therapies.

NBR1-p62-sting crosstalk: balancing autophagy and anti-tumor immunity

As a selective autophagy receptor, NBR1 plays a dichotomous role in HCC pathogenesis. While promoting oncogenesis through STING pathway modulation [114], its functional domains mediate critical interactions: [1] The PB1 domain facilitates p62 binding to form a regulatory complex for STING trafficking, and [2] The UBA domain recruits TRIM32 to inhibit K63-linked STING ubiquitination, thereby blocking TBK1 recruitment and suppressing IFN production [115]. Conversely, tumor-suppressive p62 enhances STING activation, driving IFNγ-dependent upregulation of PD-L1 and MHC-II in macrophages to remodel the TME. This intricate balance highlights NBR1 as a promising therapeutic node-strategic inhibitor that could amplify STING signaling to synergize with PD-L1 blockade while mitigating autophagy-mediated immune suppression. Preclinical models suggest that the dual targeting of NBR1 and PD-L1 may overcome resistance mechanisms in HCC immunotherapy.

Ubiquitination related to B cells

To date, research related to tumor immunotherapy has mainly focused on T cells. The role of T cells in antitumor immunotherapy is indisputable [116]. However, increasing evidence indicates that tumor-infiltrating B lymphocytes (TIL-Bs) play a crucial synergistic role in tumor control [117]. DEAD-Box Helicase 5 (DDX5) is colocalized in the nucleus with C-X-C Motif Chemokine Ligand 12 (CXCL12). As an RNA-binding protein, DDX5 maintains CXCL12 levels in the nucleus by stabilizing CXCL12 mRNA transcription. C-X-C motif chemokine receptor 4 (CXCR4) is the target of CXCL12. After the DDX5 binds with CXCL12 and activate with each other, on the one hand, B cells are activated to promote their differentiation into immature plasma cells and produce IGg to inhibit colorectal liver metastases. In contrast, B cells overexpressing CXCR4 and CXCL12 jointly promoted the infiltration of NK cells and M1 macrophages in HCC and reshaped the TME to inhibit the occurrence of HCC. Pre-mRNA processing factor 19 (PRP19) is an evolutionarily conserved essential E3 ubiquitin ligase that helps proteins avoid replication-transcription conflicts by facilitating processes such as mRNA splicing [118]. PRP19 has three domains: a central crimp helix, C-terminal WD-40 repeat domain, and N-terminal U-box. Through these domains, it can interact with DDX5 and promote the ubiquitination and degradation of DDX5 [119], disrupting the transcriptional stability of CXCL12 and reducing its expression, thus weakening B-cell function in the HCC TME and reducing tumor immunosuppression. Therefore, CXCL12 can be used as an immune target. Local administration of CXCL12 may reduce TME heterogeneity, tumor immune tolerance, and drug side effects. However, a large number of clinical trials are needed to determine the feasibility of this treatment.

Discussion and perspective

HCC is a malignant tumor that seriously endangers human health. Low early diagnosis rate and high recurrence rate are key factors that affect the survival rate of patients with HCC. The environment for the occurrence and development of HCC is complex, and innate immunity is particularly important to inhibit the occurrence of tumors. Many signaling pathways (such as PI3K/Akt, Ras/MAPK, Wnt/β-catenin, and NF-κB) participate in innate immunity, which seem to be independent of each other but always mutually influence each other. HBV and HCV infections are major risk factors for HCC. During viral infections, the body uses a series of immune responses to resist the adverse reactions. In these two immune processes, E3 ligase, as an important regulator, participates in the regulation of various signal transduction proteins and viral infection-related proteins to resist or promote the occurrence of HCC, playing an extremely important role.

Research on the ubiquitination of innate and adaptive immunity in HCC has extremely broad prospects. First, delving deeper into the molecular mechanisms underlying the ubiquitination-mediated regulation of immune cell functions is highly likely to unearth a plethora of more specific ubiquitination targets. For instance, by precisely identifying the key ubiquitination sites that govern macrophage polarization or T-cell activation, we can design and develop targeted small-molecule inhibitors or activators. This would enable precise modulation of immune cell functions, thereby significantly enhancing their anti-tumor activities. Second, considering the profound impact of the Tumor Microenvironment (TME) on ubiquitination and the immune response, the development of novel therapies capable of remodeling the immunosuppressive state of the TME, in combination with ubiquitination-targeted therapies, may emerge as an effective strategy for treating HCC. Such an integrated approach could potentially break the tumor immune evasion mechanisms and restore the immune system's ability to recognize and eliminate cancer cells. Moreover, with recent advancements in single-cell sequencing technology, proteomics, and gene-editing technologies, it has become feasible to conduct in-depth investigations into the effects of ubiquitination on immune cell subsets at the single-cell level and during dynamic physiological and pathological changes [120, 121]. This will provide a more accurate theoretical foundation for personalized

immunotherapy. By leveraging the ubiquitination profiles of immune cells within patient tumor tissues, individualized treatment regimens can be formulated, ultimately leading to a substantial improvement in the therapeutic efficacy for HCC.

From the vantage point of basic research, while a diverse array of E3 ligases have been identified as influencing the immune microenvironment of HCC, the comprehensive landscape of the ubiquitination modification network in the initiation, progression, and immune evasion of HCC still demands further elucidation. In the time to come, it is imperative to conduct in - depth investigations into the dynamic alterations of distinct ubiquitination modifications, such as monoubiquitination and polyubiquitination, within diverse signaling pathways in HCC cells. Additionally, it is essential to explore how these changes interact with tumor - associated immune cells and to identify more potential ubiquitination enzymes and substrates that play pivotal regulatory roles. This will furnish a more comprehensive molecular foundation for understanding the mechanism underlying HCC immune escape. Regarding clinical translation, the discovery of ubiquitination - related targets has paved a novel way for HCC immunotherapy. For instance, the inhibitor of DTX2 has demonstrated the ability to inhibit tumor growth and render liver cancer cells more sensitive to programmed death protein 1 (PD − 1) antibody treatment [122]. In the future, it is anticipated that, based on such research, more specific drugs targeting diverse ubiquitination targets will be developed. Moreover, large - scale clinical trials will be carried out to assess the efficacy and safety of these drugs when used either alone or in combination with existing immunotherapies, like immune checkpoint inhibitors and adoptive cell immunotherapy, in HCC patients at different stages and with various molecular subtypes. Through this approach, the patient subgroups that can derive the most benefit from specific ubiquitination - targeted therapy will be screened out, thereby achieving precise immunotherapy.

In summary, the in-depth exploration of innate and adaptive immune ubiquitination in HCC is anticipated to blaze a new trial for the treatment of this disease, thereby bringing more hope to patients with HCC.

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References

1. Norero B, Dufour JF. Should we undertake surveillance for HCC in patients with MAFLD? Ther Adv Endocrinol Metab. 2023;14:20420188231160389.
2. Sangiovanni A, et al. The natural history of compensated cirrhosis due to hepatitis C virus: A 17-year cohort study of 214 patients. Hepatology. 2006;43:1303–10.
3. Ioannou GN, et al. Incidence and predictors of hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol. 2007;5:938–e945934.
4. Maucort-Boulch D, de Martel C, Franceschi S, Plummer M. Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. Int J Cancer. 2018;142:2471–7.
5. Hao X, et al. Targeting immune cells in the tumor microenvironment of HCC: new opportunities and challenges. Front Cell Dev Biol. 2021;9:775462.
6. Donne R, Lujambio A. The liver cancer immune microenvironment: therapeutic implications for hepatocellular carcinoma. Hepatology. 2023;77:1773–96.
7. Chen Y, Tian Z. HBV-Induced immune imbalance in the development of HCC. Front Immunol. 2019;10:2048.
8. Milosevic I et al. HCV and HCC Tango-Deciphering the intricate dance of disease: A review Article. Int J Mol Sci 2023;24.
9. Ruf B, Heinrich B, Greten TF. Immunobiology and immunotherapy of HCC: spotlight on innate and innate-like immune cells. Cell Mol Immunol. 2021;18:112–27.
10. Li Y, et al. Regulation of apoptosis by ubiquitination in liver cancer. Am J Cancer Res. 2023;13:4832–71.
11. Xia SW, et al. Endoplasmic reticulum stress and protein degradation in chronic liver disease. Pharmacol Res. 2020;161:105218.
12. Yu Z, Li H, Zhu J, Wang H, Jin X. The roles of E3 ligases in hepatocellular carcinoma. Am J Cancer Res. 2022;12:1179–214.
13. Park JS, Ma H, Roh YS. Ubiquitin pathways regulate the pathogenesis of chronic liver disease. Biochem Pharmacol. 2021;193:114764.
14. Chen YJ, Wu H, Shen XZ. The ubiquitin-proteasome system and its potential application in hepatocellular carcinoma therapy. Cancer Lett. 2016;379:245–52.

15. Yin J, Zhu JM, Shen XZ. The role and therapeutic implications of RING-finger E3 ubiquitin ligases in hepatocellular carcinoma. Int J Cancer. 2015;136:249–57.
16. Lu K, et al. TRIM proteins in hepatocellular carcinoma. J Biomed Sci. 2022;29:69.
17. Miao Y, et al. Strategic advancement of E3 ubiquitin ligase in the management of hepatocellular carcinoma. Med Oncol. 2024;41:178.
18. Llovet JM, et al. Immunotherapies for hepatocellular carcinoma. Nat Rev Clin Oncol. 2022;19:151–72.
19. Tian LY, Smit DJ, Jücker M. The role of PI3K/AKT/mTOR signaling in hepatocellular carcinoma metabolism. Int J Mol Sci 2023;24.
20. Sun Y, et al. Spermine synthase engages in macrophages M2 polarization to sabotage antitumor immunity in hepatocellular carcinoma. Cell Death Differ. 2025;32:573–86.
21. Howe MK, et al. Patients with natural killer (NK) cell chronic active Epstein-Barr virus have immature NK cells and hyperactivation of PI3K/Akt/mTOR and STAT1 pathways. J Infect Dis. 2020;222:1170–9.
22. Wang Y et al. Inhibition of TIGIT on NK cells improves their cytotoxicity and HIV reservoir eradication potential. mBio 2025;16:e0322624.
23. Kahraman DC, Kahraman T, Cetin-Atalay R. Targeting PI3K/Akt/mTOR pathway identifies differential expression and functional role of IL8 in liver Cancer stem cell enrichment. Mol Cancer Ther. 2019;18:2146–57.
24. El Tabaa MM, El Tabaa MM, Elgharabawy RM, Abdelhamid WG. Suppressing NLRP3 activation and PI3K/AKT/mTOR signaling ameliorates amiodarone-induced pulmonary fibrosis in rats: a possible protective role of nobiletin. Inflammopharmacology. 2023;31:1373–86.
25. Zhu Y-J, et al. Autophagy dysfunction contributes to NLRP1 inflammasome-linked depressive-like behaviors in mice. J Neuroinflammation. 2024;21:6.
26. Li X, et al. Enhanced glucose metabolism mediated by CD147 contributes to immunosuppression in hepatocellular carcinoma. Cancer Immunol Immunother. 2020;69:535–48.
27. Zhang Q, et al. Itaconate attenuates autoimmune hepatitis via PI3K/AKT/mTOR pathway-mediated Inhibition of dendritic cell maturation and autophagy. Heliyon. 2023;9:e17551.
28. Eleftheriadis T, et al. Differential effects of the two amino acid sensing systems, the GCN2 kinase and the mTOR complex 1, on primary human alloreactive CD4$^+$ T-cells. Int J Mol Med. 2016;37:1412–20.
29. Lee K, et al. Mammalian target of Rapamycin protein complex 2 regulates differentiation of Th1 and Th2 cell subsets via distinct signaling pathways. Immunity. 2010;32:743–53.
30. Song R, et al. A novel polypeptide encoded by the circular RNA ZKSCAN1 suppresses HCC via degradation of mTOR. Mol Cancer. 2023;22:16.
31. Pellegrino R, et al. EEF1A2 inactivates p53 by way of PI3K/AKT/mTOR-dependent stabilization of MDM4 in hepatocellular carcinoma. Hepatology. 2014;59:1886–99.
32. Sun EJ, Wankell M, Palamuthusingam P, McFarlane C, Hebbard L. Targeting the PI3K/Akt/mTOR pathway in hepatocellular carcinoma. Biomedicines 2021;9.
33. Xu Y, Zhang D, Ji J, Zhang L. Ubiquitin ligase MARCH8 promotes the malignant progression of hepatocellular carcinoma through PTEN ubiquitination and degradation. Mol Carcinog. 2023;62:1062–72.
34. Zheng H, et al. NEDD4 promotes cell growth and motility in hepatocellular carcinoma. Cell Cycle. 2018;17:728–38.
35. Hang X, et al. NEDD4 depletion inhibits hepatocellular carcinoma growth via targeting PTEN. Cell Physiol Biochem. 2016;39:768–79.
36. Huang ZJ, Zhu JJ, Yang XY, Biskup E. NEDD4 promotes cell growth and migration via PTEN/PI3K/AKT signaling in hepatocellular carcinoma. Oncol Lett. 2017;14:2649–56.
37. Yang WL, Wu CY, Wu J, Lin HK. Regulation of Akt signaling activation by ubiquitination. Cell Cycle. 2010;9:487–97.
38. Bamodu OA et al. Elevated PDK1 expression drives PI3K/AKT/MTOR signaling promotes Radiation-Resistant and dedifferentiated phenotype of hepatocellular carcinoma. Cells 2020;9.
39. Vanhaesebroeck B, Alessi DR. The PI3K-PDK1 connection: more than just a road to PKB. Biochem J 346 Pt. 2000;3:561–76.
40. Jiang Q, et al. SPOP-mediated ubiquitination and degradation of PDK1 suppresses AKT kinase activity and oncogenic functions. Mol Cancer. 2021;20:100.
41. Muller PA. Vousden, p53 mutations in cancer. Nat Cell Biol. 2013;15:2–8.
42. Bensaad K, Vousden KH. p53: new roles in metabolism. Trends Cell Biol. 2007;17:286–91.
43. Meng X, Franklin DA, Dong J, Zhang Y. MDM2-p53 pathway in hepatocellular carcinoma. Cancer Res. 2014;74:7161–7.
44. Cao H, et al. The role of MDM2-p53 axis dysfunction in the hepatocellular carcinoma transformation. Cell Death Discov. 2020;6:53.
45. Zhu YJ, et al. Circular RNAs negatively regulate cancer stem cells by physically binding FMRP against CCAR1 complex in hepatocellular carcinoma. Theranostics. 2019;9:3526–40.
46. Ito Y, et al. Activation of mitogen-activated protein kinases/extracellular signal-regulated kinases in human hepatocellular carcinoma. Hepatology. 1998;27:951–8.
47. Delire B, Stärkel P. The Ras/MAPK pathway and hepatocarcinoma: pathogenesis and therapeutic implications. Eur J Clin Invest. 2015;45:609–23.
48. Calvisi DF, et al. SKP2 and CKS1 promote degradation of cell cycle regulators and are associated with hepatocellular carcinoma prognosis. Gastroenterology. 2009;137:1816–e18261811.
49. Cao J, et al. Comprehensive analysis of the clinical significance, immune infiltration, and biological role of MARCH ligases in HCC. Front Immunol. 2022;13:997265.
50. Dongre A, Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. Nat Rev Mol Cell Biol. 2019;20:69–84.
51. Zhou J, et al. RNF173 suppresses RAF/MEK/ERK signaling to regulate invasion and metastasis via GRB2 ubiquitination in hepatocellular carcinoma. Cell Commun Signal. 2023;21:224.
52. Yuan J, et al. HDLBP promotes hepatocellular carcinoma proliferation and Sorafenib resistance by suppressing Trim71-dependent RAF1 degradation. Cell Mol Gastroenterol Hepatol. 2023;15:307–25.
53. Rajalingam K, Schreck R, Rapp UR, Albert S. Ras oncogenes and their downstream targets. Biochim Biophys Acta. 2007;1773:1177–95.
54. Abe T, et al. LZTR1 facilitates polyubiquitination and degradation of RAS-GTPases. Cell Death Differ. 2020;27:1023–35.
55. Bigenzahn JW, et al. LZTR1 is a regulator of RAS ubiquitination and signaling. Science. 2018;362:1171–7.
56. Ye G, et al. Low protein expression of LZTR1 in hepatocellular carcinoma triggers tumorigenesis via activating the RAS/RAF/MEK/ERK signaling. Heliyon. 2024;10:e32855.
57. Nacak TG, Leptien K, Fellner D, Augustin HG, Kroll J. The BTB-kelch protein LZTR-1 is a novel golgi protein that is degraded upon induction of apoptosis. J Biol Chem. 2006;281:5065–71.
58. Giles RH, van Es JH, Clevers H. Caught up in a Wnt storm: Wnt signaling in cancer. Biochim Biophys Acta. 2003;1653:1–24.
59. Suzuki T, Yano H, Nakashima Y, Nakashima O, Kojiro M. Beta-catenin expression in hepatocellular carcinoma: a possible participation of beta-catenin in the dedifferentiation process. J Gastroenterol Hepatol. 2002;17:994–1000.
60. Fujie H, et al. Frequent beta-catenin aberration in human hepatocellular carcinoma. Hepatol Res. 2001;20:39–51.
61. He S, Tang S. WNT/β-catenin signaling in the development of liver cancers. Biomed Pharmacother. 2020;132:110851.
62. Wang W, Smits R, Hao H, He C. Wnt/β-Catenin signaling in liver cancers. Cancers (Basel) 2019;11.
63. Xu C et al. β-Catenin signaling in hepatocellular carcinoma. J Clin Invest 2022;132.
64. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology. 2012;142:1264–e12731261.
65. Hou L, et al. Restriction of hepatitis B virus replication by c-Abl-induced proteasomal degradation of the viral polymerase. Sci Adv. 2019;5:eaau7130.
66. Liu X, et al. Interaction between tobacco smoking and hepatitis B virus infection on the risk of liver cancer in a Chinese population. Int J Cancer. 2018;142:1560–7.
67. Lin X, et al. Silencing MYH9 blocks HBx-induced GSK3β ubiquitination and degradation to inhibit tumor stemness in hepatocellular carcinoma. Signal Transduct Target Ther. 2020;5:13.
68. Jiang X, Charlat O, Zamponi R, Yang Y, Cong F. Dishevelled promotes Wnt receptor degradation through recruitment of ZNRF3/RNF43 E3 ubiquitin ligases. Mol Cell. 2015;58:522–33.
69. Farnhammer F, Colozza G, Kim J. RNF43 and ZNRF3 in Wnt Signaling - A master regulator at the membrane. Int J Stem Cells. 2023;16:376–84.
70. Callow MG, et al. Ubiquitin ligase RNF146 regulates tankyrase and Axin to promote Wnt signaling. PLoS ONE. 2011;6:e22595.
71. Yang YF, Zhang MF, Tian QH, Zhang CZ. TRIM65 triggers β-catenin signaling via ubiquitylation of Axin1 to promote hepatocellular carcinoma. J Cell Sci. 2017;130:3108–15.

72. Gubb D, et al. The balance between isoforms of the prickle LIM domain protein is critical for planar Polarity in Drosophila imaginal discs. Genes Dev. 1999;13:2315–27.
73. Chan DW, Chan CY, Yam JW, Ching YP, Ng IO. Prickle-1 negatively regulates Wnt/beta-catenin pathway by promoting dishevelled ubiquitination/degradation in liver cancer. Gastroenterology. 2006;131:1218–27.
74. Chen L, et al. Aerobic Glycolysis enhances HBx-initiated hepatocellular carcinogenesis via NF-κBp65/HK2 signalling. J Exp Clin Cancer Res. 2022;41:329.
75. He G, Karin M. STAT3 - key players in liver inflammation and cancer. Cell Res. 2011;21:159–68.
76. Sun SC. The noncanonical NF-κB pathway. Immunol Rev. 2012;246:125–40.
77. Xiao G, Harhaj EW, Sun SC. NF-kappaB-inducing kinase regulates the processing of NF-kappaB2 p100. Mol Cell. 2001;7:401–9.
78. Betts JC, Nabel GJ. Differential regulation of NF-kappaB2(p100) processing and control by amino-terminal sequences. Mol Cell Biol. 1996;16:6363–71.
79. Zhang S, Lin X. Scaffold protein involved in NF-κB signaling. Front Immunol. 2019;10:176.
80. Godwin P, et al. Targeting nuclear factor-kappa B to overcome resistance to chemotherapy. Front Oncol. 2013;3:120.
81. Bertrand MJ, et al. cIAP1/2 are direct E3 ligases conjugating diverse types of ubiquitin chains to receptor interacting proteins kinases 1 to 4 (RIP1-4). PLoS ONE. 2011;6:e22356.
82. Ding J, Lu Y. [Research progress on receptor interacting proteins in inflammation]. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2018;47:89–96.
83. Ge QY, et al. GRAMD4 inhibits tumour metastasis by recruiting the E3 ligase ITCH to target TAK1 for degradation in hepatocellular carcinoma. Clin Transl Med. 2021;11:e635.
84. Minor MM, Slagle BL. Hepatitis B virus HBx protein interactions with the ubiquitin proteasome system. Viruses. 2014;6:4683–702.
85. Wan T, et al. NEDD4 induces K48-Linked degradative ubiquitination of hepatitis B virus X protein and inhibits HBV-Associated HCC progression. Front Oncol. 2021;11:625169.
86. Shi F, et al. High expression of DHX9 promotes the growth and metastasis of hepatocellular carcinoma. J Clin Lab Anal. 2021;35:e24052.
87. Kiss L, Clift D, Renner N, Neuhaus D, James LC. RING domains act as both substrate and enzyme in a catalytic arrangement to drive self-anchored ubiquitination. Nat Commun. 2021;12:1220.
88. Wu K, et al. Phosphorylation of UHRF2 affects malignant phenotypes of HCC and HBV replication by blocking DHX9 ubiquitylation. Cell Death Discov. 2023;9:27.
89. Levrero M, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. J Hepatol. 2016;64:S84–101.
90. Su IJ, Wang HC, Wu HC, Huang WY. Ground glass hepatocytes contain pre-S mutants and represent preneoplastic lesions in chronic hepatitis B virus infection. J Gastroenterol Hepatol. 2008;23:1169–74.
91. Tilghman J, et al. HMMR maintains the stemness and tumorigenicity of glioblastoma stem-like cells. Cancer Res. 2014;74:3168–79.
92. Mateo F, et al. Modification of BRCA1-associated breast cancer risk by HMMR overexpression. Nat Commun. 2022;13:1895.
93. He L, et al. HMMR alleviates Endoplasmic reticulum stress by promoting autophagolysosomal activity during Endoplasmic reticulum stress-driven hepatocellular carcinoma progression. Cancer Commun (Lond). 2023;43:981–1002.
94. Kar SP, et al. Network-Based integration of GWAS and gene expression identifies a HOX-Centric network associated with serous ovarian Cancer risk. Cancer Epidemiol Biomarkers Prev. 2015;24:1574–84.
95. Sarkar D, Leung EY, Baguley BC, Finlay GJ. Askarian-Amiri, epigenetic regulation in human melanoma: past and future. Epigenetics. 2015;10:103–21.
96. Fischle W, Wang Y, Allis CD. Histone and chromatin cross-talk. Curr Opin Cell Biol. 2003;15:172–83.
97. Barbour H, Daou S, Hendzel M, Affar EB. Polycomb group-mediated histone H2A monoubiquitination in epigenome regulation and nuclear processes. Nat Commun. 2020;11:5947.
98. Kasai H et al. Induction of HOX genes by hepatitis C virus infection via impairment of histone H2A monoubiquitination. J Virol 95, (2021).
99. Belachew B, Gao J, Byrd AK, Raney KD. Hepatitis C virus nonstructural protein NS3 unfolds viral G-quadruplex RNA structures. J Biol Chem. 2022;298:102486.
100. Tokunaga F, et al. Involvement of linear polyubiquitylation of NEMO in NF-kappaB activation. Nat Cell Biol. 2009;11:123–32.
101. Tokunaga F, Iwai K. LUBAC, a novel ubiquitin ligase for linear ubiquitination, is crucial for inflammation and immune responses. Microbes Infect. 2012;14:563–72.
102. Chen Y, et al. The hepatitis C virus protein NS3 suppresses TNF-α-stimulated activation of NF-κB by targeting LUBAC. Sci Signal. 2015;8:ra118.
103. Khan MN, et al. Tumor-associated macrophages and CD8 + T cells: dual players in the pathogenesis of HBV-related HCC. Front Immunol. 2024;15:1472430.
104. Lee HW et al. T-Cell dynamics predicts prognosis of patients with hepatocellular carcinoma receiving Atezolizumab plus bevacizumab. Int J Mol Sci 2024;25.
105. Fan G, et al. DKK1 + tumor cells inhibited the infiltration of CCL19 + fibroblasts and plasma cells contributing to worse immunotherapy response in hepatocellular carcinoma. Cell Death Dis. 2024;15:797.
106. Sun C, Mezzadra R, Schumacher TN. Regulation and function of the PD-L1 checkpoint. Immunity. 2018;48:434–52.
107. Luo XY, Wu KM, He XX. Advances in drug development for hepatocellular carcinoma: clinical trials and potential therapeutic targets. J Exp Clin Cancer Res. 2021;40:172.
108. Zhang J, et al. Cyclin D-CDK4 kinase destabilizes PD-L1 via Cullin 3-SPOP to control cancer immune surveillance. Nature. 2018;553:91–5.
109. Yu Z, et al. BCLAF1 binds SPOP to stabilize PD-L1 and promotes the development and immune escape of hepatocellular carcinoma. Cell Mol Life Sci. 2024;81:82.
110. Lin H, et al. The membrane-associated E3 ubiquitin ligase MARCH3 downregulates the IL-6 receptor and suppresses colitis-associated carcinogenesis. Cell Mol Immunol. 2021;18:2648–59.
111. Cao J et al. Degradation of PARP1 by MARCHF3 in tumor cells triggers cCAS-STING activation in dendritic cells to regulate antitumor immunity in hepatocellular carcinoma. J Immunother Cancer 2024;12.
112. He H, et al. Downregulation of TAB182 promotes cancer stem-like cell properties and therapeutic resistance in triple-negative breast cancer cells. BMC Cancer. 2023;23:1101.
113. Wang Y, et al. TNKS1BP1 facilitates ubiquitination of CNOT4 by TRIM21 to promote hepatocellular carcinoma progression and immune evasion. Cell Death Dis. 2024;15:511.
114. Kim J, et al. Autophagy-dependent splicing control directs translation toward inflammation during senescence. Dev Cell 2024.
115. Nishimura S, et al. Opposing regulation of the STING pathway in hepatic stellate cells by NBR1 and p62 determines the progression of hepatocellular carcinoma. Mol Cell. 2024;84:4660–e46764610.
116. Chen C, et al. T cell-related ubiquitination genes as prognostic indicators in hepatocellular carcinoma. Front Immunol. 2024;15:1424752.
117. Laumont CM, Banville AC, Gilardi M, Hollern DP, Nelson BH. Tumour-infiltrating B cells: immunological mechanisms, clinical impact and therapeutic opportunities. Nat Rev Cancer. 2022;22:414–30.
118. Idrissou M, Maréchal A. The PRP19 ubiquitin ligase, standing at the Cross-Roads of mRNA processing and genome stability. Cancers (Basel). 2022;14(4):878.
119. Liu Z et al. Increased PRP19 in hepatocyte impedes B cell function to promote hepatocarcinogenesis. Adv Sci (Weinh). 2024;11(46):e2407517.
120. Burslem GM, Crews CM. Proteolysis-Targeting chimeras as therapeutics and tools for biological discovery. Cell. 2020;181:102–14.
121. Dale B, et al. Advancing targeted protein degradation for cancer therapy. Nat Rev Cancer. 2021;21:638–54.
122. Wu X, et al. Targeting Deltex E3 ubiquitin ligase 2 inhibits Tumor-associated neutrophils and sensitizes hepatocellular carcinoma cells to immunotherapy. Adv Sci (Weinh). 2025;12:e2408233.

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