Role of ubiquitin regulatory X domain-containing protein 3B in the development of hepatocellular carcinoma (Review)

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Abstract. The majority of new cases and fatalities from hepatocellular carcinoma (HCC) occur in China; however, the overall morbidity and mortality rates are decreasing. A major risk factor due to the evolving epidemiology is improper lipid metabolism. Although investigations on aberrant lipid metabolism are numerous, there are only a limited number of studies available on proteasomal degradation processes. The degradation process is mainly involved in endoplasmic reticulum stabilization, the balance of lipid metabolism, and physiological functions of Golgi apparatus, endoplasmic reticulum, lysosomes and other organelles, however, this process has been little studied in the development of tumorigenesis. In order to provide some theoretical support for future research on ubiquitin regulatory X domain-containing protein 3B (UBXN3B), the present review focuses on the role of UBXN3B, which is involved in the stabilization of the endoplasmic reticulum and the maintenance of lipid homeostasis, as well as in the promotion and development of non-alcoholic fatty liver disease and HCC.

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Abbreviations: HCC, hepatocellular carcinoma; UBXN3B, ubiquitin regulatory X domain-containing proteins 3B; ER, endoplasmic reticulum; NAFLD, non-alcoholic fatty liver disease; ERAD, endoplasmic reticulum-associated degradation; NASH, non-alcoholic steatohepatitis; LDs, lipid droplets; FAS, fatty acid synthase; RIG-I, retinoic acid-inducible; NF-κB, nuclear factor-κB; ATP, adenosine triphosphate; VCP, valosin-containing protein; LXRα, liver X receptor α; SREBP-1, sterol regulatory element-binding protein 1; INSIG-1, insulin-inducible gene 1; HMGCR, 3-hydroxy-3-methylglutaryl coenzyme A reductase; mRNA, messenger ribonucleic acid; STING, stimulator of interferon genes; IFN-I, type I interferon; ISRE, interferon-stimulated response element; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FFAs, free fatty acids; TNF, tumor necrosis factor; IL, interleukin; DCs, dendritic cells; NKT cells, natural killer T-cells; UPR, unfolded protein response; mRNPs, mRNA-protein complexes; AREs, AU-rich elements; α-TCR, α-T-cell antigen receptor; PERK, protein kinase RNA like ER kinase; ATF-6α, activated transcription factor-6α

Key words: hepatocellular carcinoma, lipid metabolism, ubiquitin regulatory X domain-containing protein 3B, endoplasmic reticulum, endoplasmic reticulum-associated degradation

Contents

1. Introduction

Hepatocellular carcinoma (HCC) is the fourth most prevalent type of cancer worldwide and the sixth most frequent malignancy (1). In 2020, 45% of the year's new cases (910,000) and 47% of the year's fatalities (830,000) occurred in China (2). The data for GCC in China are still not encouraging, despite the recent worldwide reduction in the incidence of this type of cancer. The explanation for this may be related to a shift in the etiology; an increasing number of HCC cases are being linked to faulty lipid metabolism, which also causes non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis and even HCC. As a result, a new risk factor is replacing the classic theory of the evolution of viral hepatitis, namely abnormal lipid metabolism.

The dysregulation of lipid droplets (LDs) may interact with the endoplasmic reticulum (ER), mitochondria, peroxisomes, vesicles and lysosomes under normal oxygen conditions (3). In addition, the tumor microenvironment may lead to dysregulation via factors, such hyperinsulinemia caused by insulin resistance and increased pro-inflammatory cytokine levels (4). Previous research has emphasized the role of modifications in signaling pathways and enzyme metabolism during the production of fatty acid synthesis (FAS) (5). However, available data on the association between the ubiquitin regulatory X domain-containing protein (UBX) family and endoplasmic reticulum-associated degradation (ERAD) are limited. The UBX family, in contrast to earlier research (6), increases

cellular stability, primarily through ERAD or increased intranuclear translocation mechanisms, a process that even inhibits FAS. Despite this apparent contradiction with the main line of inquiry, there is still evidence to support the increased expression of UBX family genes or proteins in HCC and their roles as poor prognostic factors (7).

The UBX family, which consists of the 13 members UBXN1, UBXN2A-2C, UBXN3A-3B, UBXN4 and UBXN6-11, has a structural domain that is comparable to the N terminus of ubiquitin. The N terminus of the receptor protein is identified and transported to the proteasome, where it undergoes the standard protein degradation process and finally degrades into smaller polypeptides and amino acids (8). An essential organelle for the synthesis, folding, secretion and recycling of proteins across organelles is the ER. When elements such as Ca^{2+} levels, energy and nutrition are aberrant, abnormal protein folding occurs in the ER, a process known as ER stress, which is required to maintain ER homeostasis (9). As a result, ERAD is a crucial process that eliminates unfolded or misfolded proteins when ER stress arises in order to return the ER to its normal state and function (10).

Of the UBX family, nine members, namely UBXN1, UBXN2A-2C, UBXN3B, UBXN4, UBXN6, UBXN8 and UBXN10, are involved in ERAD during lipid metabolism (Fig. 1). UBXN1 interacts with apoptosis protein inhibitors, blocks and interferes with retinoic acid-inducible gene (RIG-I)-like receptors and the nuclear factor (NF)-κB pathway, and is a key player in cell signaling, endocytosis and DNA damage repair (11). UBXN1 is a component of the reverse translocation degradation complex (11) and is involved in ER stress-mediated de-glycosylation (11). Trimers of UBXN2A, 2B and 2C bind to cytoplasmic p97 and are involved in the stability of the ER, the Golgi apparatus and the rearrangement of the mitotic terminal (12). Based on remodeling mechanisms, p97, an enzyme belonging to the adenosine triphosphate (ATP) enzyme family, is connected to a number of cellular processes and activities (13). p97 may alternatively be considered as an 'enzymatic dissociative activity' protein (13). p97 has two different mechanisms for protein degradation: One involves the p97-Ufd1-Npl4 complex, which binds to various ubiquitinated ERAD substrates on the cytoplasmic side of the ER membrane before being reverse transcribed and transported to the proteasome for degradation (14); the other involves a protein degradation pathway that connects the ER to p97 through a number of cofactors, primarily members of the UBX family. In addition to regulating the ERAD pathway to preserve ER function under conditions of ER stress (15), UBXN3B plays a crucial role in ERAD by limiting the activity of phospholipases in LDs and preventing the degradation of LDs (15). In order to attract valosin-containing protein (VCP) to the ER and encourage ERAD, UBXN4, an essential membrane protein of the ER, serves as a platform (16). UBXN6 participates in lysosomal degradation, may play a role in misfolded proteins in ERAD, and may adversely affect ATP-driven VCP (17). One of the cofactors of p97, VCP, is a component of the ATPase complex known as UBXN8, which binds to p97 and promotes ERAD. VCP/p97 factor UBXN10, a VCP/p97 binding protein necessary for cilia promotion, has a VCP/p97 substrate specificity (18).

In the UBX family, UBXN3B has a specific and crucial function in cancer cells when LD production and enhanced ERAD occur simultaneously. Other members, on the other hand, perform unique tasks relating to cellular activity, apoptosis, innate immunity, Golgi apparatus and lysosomes. As a result, the main aim of the present review was to describe the mechanisms through which UBXN3B contributes to the development of HCC.

2. Transcriptional regulation of UBXN3B

UBXN3B maintains ER stability. UBXN3B is a hairpin-like structural protein that resembles a hairpin and is comprised of hydrophobic amino acid residues that are introduced into the ER cytoplasm. UBXD8 migrates from the ER to the surface of fatty acid-rich LDs in fatty acid-deficient cells (19), and it has a UBX structural domain that interacts with p97 (13), which is necessary for ERAD (8). By repressing the transcriptional activity and target of NAFLD, UBXD8 inhibits the transcriptional activity of the liver X receptor (LXR), a key regulator of the enterohepatic cycle. It also inhibits the transcriptional activity of the sterol regulatory element-binding protein 1 (SREBP-1), and it stimulates the transcription of genes encoding proteins necessary for FAS (20). FAS, acetyl coenzyme A carboxylase, and stearoyl coenzyme A desaturase-1 are all directly activated by the LXR (20). The first and rate-limiting steps of FAS, which are carried out by these three enzymes, control how rapidly monounsaturated fatty acids are produced. The transcription factor termed SREBP-1, which is found in the ER, stimulates the expression of all the genes necessary for fatty acid metabolism (21). Its cytoplasmic N-terminal structural domain is connected to the insulin-inducible gene 1 (INSIG-1) and is located there (22). Without fatty acids, UBXD8 binds to INSIG-1 and induces the rapid proteasomal degradation of the receptor protein by attracting p97 to the protein (23). SREBP-1 is moved from the ER to the Golgi without INSIG-1, where it is broken by two Golgi-localized proteases (24). This cleavage allows SREBP-1 to enter the nucleus and activate all FAS-required genes, as it frees the protein's N-terminal structural domain from the membrane (21).

By identifying and destroying the ubiquitin-like structural domains of lipid-binding proteins in the ER, ERAD guarantees the structural normalcy of the ER. Hepatocytes release apolipoprotein (Apo) B-100, a glycoprotein with a molecular weight >500 kDa. Several phases in the lipoprotein transport mechanism control the production of this protein. When there are more lipids in the ER lumen, Apo B-100 may develop. Lipid-carrying Apo B-100 is ubiquitinated by ERAD, which causes the proteasome to degrade lipid-poor Apo B-100. On the other hand, ubiquitinated Apo B-100 builds up in the LDs when the proteasome is blocked, and it has been proposed that this may act as a platform for Apo B-100 breakdown (25). It should be noted that this is only conjecture. According to another study, Apo B-100 predominantly lipidates and builds up in LDs (25). As lipidation only occurs in the ER lumen, lipidated Apo B-100 is moved to the cytoplasmic side near the LDs. Thus, the buildup of lipidated Apo B-100 aids in the development of specific Apo B-100 structures linked to ER-LD. It should be noted that UBX family members are

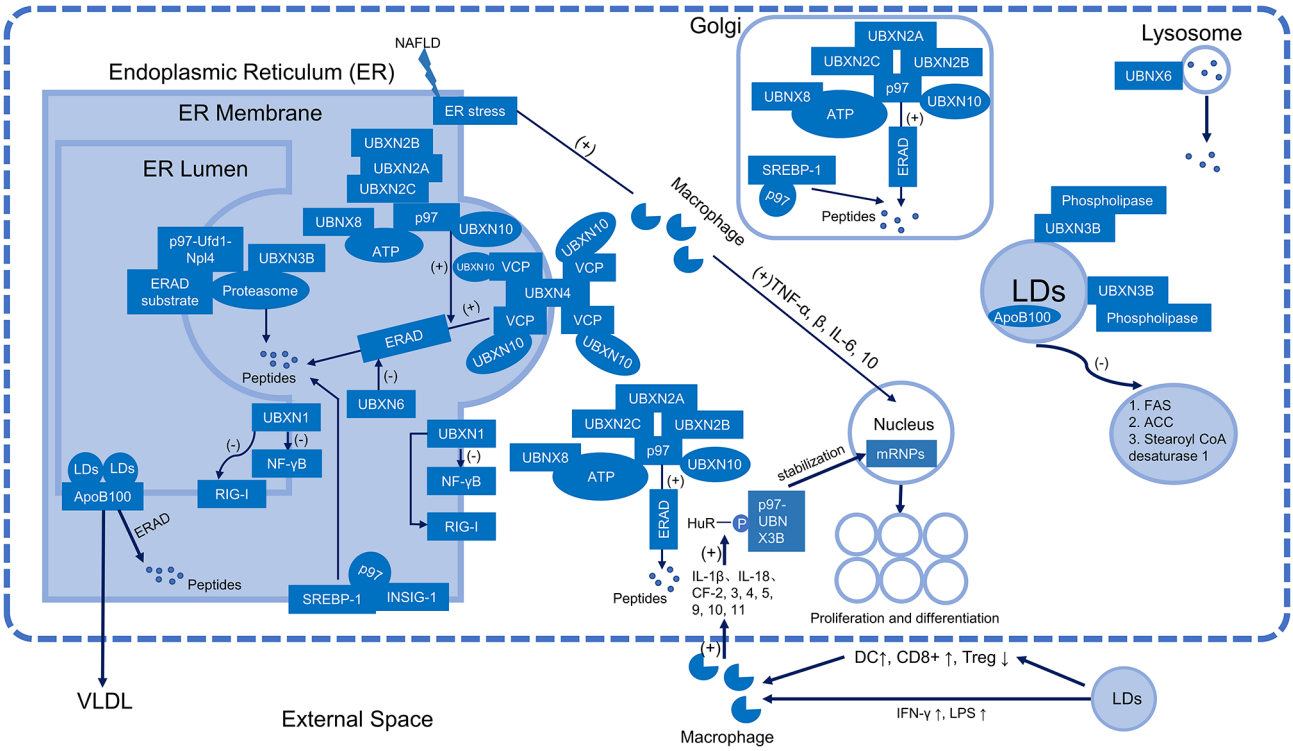

Figure 1. Schematic representation of the ER and LD model with the UBXN family and the lipolysis of LDs. ER, endoplasmic reticulum; LDs, lipid droplets; VLDL, very low-density lipoprotein; Apo, apolipoprotein; ERAD, endoplasmic reticulum-associated degradation; UBXN, ubiquitin regulatory X domain-containing protein; NF-κB, nuclear factor-κB; SREBP-1, sterol regulatory element-binding protein 1; INSIG-1, insulin-inducible gene 1; RIG-1, retinoic acid-inducible; ATP, adenosine triphosphate; NAFLD, non-alcoholic fatty liver disease; mRNPs, mRNA-protein complexes; FAS, fatty acid synthase; ACC, acetyl CoA carboxylase; LPS, lipopolysaccharide; DC, dendritic cell; IFN, interferon; IL, interleukin; CF, chemokine factor; VCP, valosin-containing protein.

ubiquitinated proteins that the ubiquitination-proteasome system degrades under 'non-essential' conditions (26). In other words, ubiquitinated proteins may be deubiquitinated and retrieved in a hypothesized non-degradation mechanism rather than necessarily being subject to destruction (26). According to this hypothesis, damaged proteins either accumulate or continue to degrade in response to environmental changes and ERAD only functions under specified circumstances. An essential protein involved in ER stability is the p97-UBXN3B complex.

UBXN3B maintains fatty acid and triglyceride homeostasis. The p97-UBXN3B complex regulates the production of triglycerides and breaks down ubiquitinated proteins in the ER. p97-UBXN3B controls triglyceride metabolism, in addition to serving as a sensor of long-chain unsaturated fatty acids (15,23,24). Unsaturated fatty acids enhance the purification and polymerization of UBXN3B (15) when it is cultivated *in vitro*; in cells without lipids, UBXN3B prevents triglyceride production, since this process requires the attachment and the conversion of fatty acids (27). Fatty acids in cells are linked to phospholipids and do not participate in triglyceride production when triglyceride synthesis is terminated (15). Excess long-chain unsaturated fatty acids have the ability to polymerize UBXN3B and interfere with its ability to perform its functions, resulting in unaltered triglyceride production (15). By blocking the rate-limiting enzyme of triglyceride production, the recruitment of p97 from the ER to the LD surface by UBXN3B increases the size of LDs and prevents triglyceride hydrolysis to fatty acids (15). While saturated fatty acids are unable to interact with UBXN3B, they promote the conversion of extra unsaturated fatty acids into triglycerides for storage in the LDs and prevent breakdown by attaching to phospholipases and blocking their activity (15). Since UBXN3B promotes triglyceride accumulation in the LDs, while inhibiting triglyceride production and binding to phospholipids in the ER, this protein constantly cycles between the two tissues to carry out its various roles (19).

Other mechanisms. Coenzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) is a necessary protein for the ER membrane, and p97 and ERAD are required for its destruction (26). The degradation of HMGCR induced by sterols is prevented by the silencing of UBXN3B (28). In hepatocytes, UBXN3B is a poor predictor of HMGCR degradation. It can thus be hypothesized that UBXN3B knockdown promotes the production of cholesterol. However, in hepatocytes with higher HMGCR levels induced by sterol depletion, there were no changes in messenger ribonucleic acid (mRNA) or protein expression levels, indicating that sterol-dependent UBXN3B expression did not promote HMGCR breakdown (28). Type I interferon and immunological inflammatory reactions are promoted by the stimulatory interferon genes (STING) (29). The UBX protein family activates and controls the biological activities of the interferon-stimulated response element (ISRE) (30). High amounts of UBXN3B do not, however,

substantially promote ISRE, indicating that UBXN3B and STING-dependent signaling pathways only have a positive connection. Additionally, STING is ubiquitinated, dimerized and is maintained in a phosphorylated state by UBXN3B, which causes SRING to be destroyed by binding to p97 and the other E3 ubiquitin ligases (8). Although the aforementioned HMGCR degradation, ISRE activation and STING stimulation do not appear to directly interact with UBXN3B, numerous specific mechanisms of these pathways still need to be addressed by more extensive research.

3. Mechanisms of progression from NAFLD to HCC

LD metabolic disorders are associated with a number of metabolic illnesses, including obesity, fatty liver, diabetes and cardiovascular disease (31). In clinical practice, blood concentrations of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides and free fatty acids (FFA) are used to determine the lipid status of a patient. Diseases with high levels of LDs enhance the risk of tumorigenesis in viral infections (32).

The liver serves as the hub for lipid metabolism (33). Issues regarding systemic glucose and NAFLD are tightly related (34). Although excess hepatic lipid levels have been established to be an independent risk factor and are strongly associated with the development of HCC, the mechanisms through which this contributes to fatty acid metabolism remain unclear (35).

By interfering with signaling pathways and cytokines via a variety of methods, lipid dysregulation may either directly or indirectly contribute to the development of cancers (e.g., lipid regulation, spontaneous synthesis of lipids, ER stress, increased inflammatory cytokines and immune cells).

Abnormal lipid regulation. Enzymes expressed by a variety of key transcriptional proteins control normal lipid metabolism (36). Triglycerides do not specifically harm or destroy cells (8). When the accumulation of triglycerides sensitizes cells to damage, it disrupts signaling pathways and gene function, leading to the dysfunction of lipid-related factors (37).

De novo biosynthesis. The proliferation, invasion and metastasis of cancer cells, including those in hepatocellular, breast, renal, colorectal and prostate malignancies, are mediated by high levels of LDs (38). The unique function of the liver is to both use and resynthesize FFAs, which are released by other organs. External lipid absorption is the primary mechanism through which the enhanced metabolism required for lipolysis as a means of cell survival is accomplished. Instead, during the process of cellular energy acquisition, the citric acid cycle, ATP citrate lyase, and acetyl coenzyme A carboxylase may transform the pyruvate generated by glycolysis into oxaloacetate and acetyl coenzyme in the mitochondria (39). Saturated fatty acids may be created from acetyl coenzyme A via binding and conversion mechanisms (40). Stearoyl coenzyme A desaturase converts them to monounsaturated fatty acids (39,40). In this particular *de novo* biosynthesis procedure, the key building blocks of prostaglandin and membrane production are unsaturated fatty acids. By triggering autophagy, promoting cell membrane renewal, affecting intracellular signaling and gene transcription, and boosting energy generation, the unsaturated fatty acids are crucial for cell survival. Energy is produced in this process by lipid 'starvation', which combines extracellular resources with lipid *de novo* production (41). ATP citrate lyase and acetyl coenzyme A carboxylase are abundantly expressed in NAFLD after FAS has developed, increasing FAS, an early sign of NAFLD and fibrosis (42).

ER stress. ER stress may be observed in patients with NAFLD (43). The reduction of ER stress improves NAFLD (43). Even in the absence of carcinogenic therapy, spontaneous fatty liver disease may result in HCC, indicating that ER stress is sufficient to convert NAFLD to HCC. Mechanistically, increased levels of ER stress cause macrophages to produce increased levels of tumor necrosis factor (TNF), which promotes cell growth, anti-apoptotic activity and eventually, tumor development (13). These findings suggest that when NAFLD progresses to HCC, ER stress may initiate malignant transformation. The section that follows provides a more in-depth discussion of what is connected to ER stress.

Inflammatory factors associated with NAFLD. TNF-α and interleukin (IL)-6 are two inflammatory factors that are linked to NAFLD (44). Additionally, NAFLD induces the production of anti-inflammatory cytokines, such as IL-10 or IL-1 receptor antagonists, which prevent NF-κB from being activated and prevent the release of chemokines, TNF-α and IL-6 (44,45). TNF-α expression is elevated in individuals with NAFLD, cirrhosis and HCC, which results in the release of additional cytokines and chemokines (45,46). TNF-α gene polymorphisms also have a greater propensity to cirrhosis and NAFLD (45,46).

IL-6 is a significant inducer of C-reactive protein and hepatocyte production (47) and may play a role in NAFLD. The direct pathogenic factors are IL-6 and TNF-α. In addition to IL-6 and TNF-α, hepatocyte injury, the disruption of signaling cascades and functional protein loss are also induced by IL-10, IL-1 inhibitors and growth factors, which in turn result in aberrant lipid metabolism. In response to stress-induced intracellular changes, a surge in inflammatory substances alters LD proteins and signaling pathways, which in turn causes cancer cell conversion.

Macrophage function. Numerous immune cells are found in the liver, where they are affected by portal blood and endure a special tolerant environment where they may react to foreign pathogens, but avoid innocuous antigens caused by dietary antigens and microbial products (48,49). An increased inflammatory activity is associated with the lipid burden in macrophages (50). M1- and M2-macrophages may arise as a result of macrophage involvement, depending on the changed microenvironment. While the latter has an anti-inflammatory and immunomodulatory function, the former causes the generation of inflammatory cytokines (51).

M1-macrophages are known to play a role in NAFLD, with the bacterial endotoxin, lipopolysaccharide, and interferon-γ helping to activate M1-macrophages and increase the production of pro-inflammatory cytokines and chemokines, reactive oxygen species and nitric oxide. According to research, individuals with NAFLD have higher hepatic

levels of certain M1-specific cytokines and chemokines, such as IL-1β, IL-18, and chemokines 2-5 and 9-11 (52). The increased activation of cytokines and chemokines, in addition to lipids, oxidation products, or chemicals produced following hepatocyte damage that may directly contribute to liver injury, can aggravate M1-transformation (53). Changes in the M1/M2 phenotype of macrophages may be influenced by the environment. Lipid-rich dendritic cells (DCs) struggle to digest antigens in the presence of tumors (54). Similar to this, under conditions of steatosis, DCs are recruited into hepatocytes and are maintained at high levels, despite the fact that their function is activated. Conversely, the depletion of DCs leads to an increase in liver inflammation, a decrease in the numbers of Treg, an increase in $CD8^+$ T-cell function, an increase in immune effector cell activity and the production of pro-inflammatory cytokines, an increase in hepatocyte apoptosis, and ultimately, in the acceleration of liver fibrosis (55). However, another study found higher levels of natural killer (NK)$p46^+$ cells in NAFLD, which trigger local and invading macrophages to differentiate into M1 and stop fibrosis from inducing M2-cells (56). M2-macrophages, however, have been linked to HCC brought on by NAFLD (57). The influence of the macroenvironment on macrophage activity and its involvement in the development of NAFLD-promoted HCC warrant further investigation.

4. Role of UBXN3B in HCC

ER stress. Increasing attention has been paid to the role that ER stress plays in the growth, metastasis, angiogenesis and even treatment resistance of HCC cells (58). Proteotoxic ER stress refers to disruptions in protein folding in the ER, which triggers unfolded protein responses (UPRs). UPR activation by ER stress is often observed as an adaptive mechanism to preserve *in vivo* protein homeostasis. In terms of stability to mRNA and ERAD substrates and modified signaling pathways, the present review also discusses the mechanisms through which the UBXN3B protein reacts to ER stress.

Stability of mRNA. The biogenesis and metabolic functions of mRNAs are connected to a number of different proteins. Pre-mRNA processing, nuclear export, translation, localization and mRNA decay processes are the key factors influencing the remodeling events that the resultant mRNA-protein complexes (mRNPs) go through (59). The most extensively studied effect on mRNPs is the influence of ATP-dependent RNA helicases, through which mRNAs are modified to facilitate the 'metabolism' of mRNPs (58). The UBX family plays a significant role in preserving their stability, since they rely on ubiquitination signals; HuR, a dominant binding protein that binds multiple AU-rich regions, is one of these mRNA stabilizers and performs a crucial stabilizing function as a cytokine and transcription factor under conditions of cellular stress (58). HuR is often overexpressed and serves as a representation of the very dynamic alterations that occur during the recombination and dissociation of mRNPs (60). Researchers have investigated how phosphorylated HuR regulates protein abundance by influencing the location and stability of organelles (61). That is, phosphorylated HuR maintains mRNA stability, while transporting proteins to the nucleus or degrading proteins in the ER to regulate protein abundance in the cytoplasm. Through a non-degradative ubiquitination signaling mechanism that disrupts the metabolism of mRNPs, the p97-UBXD8 complex affects HuR. In fact, HuR only interacts with the p97-UBXD8 complex and not p97 or UBXD8 alone (7). The primary characteristic of the p97-UBXD8 complex, among the ubiquitination signals of the non-degradation route, is that the ubiquitinated HuR is not degraded by the ubiquitin-proteasome system (62). The protein may instead be deubiquitinated and regenerated via a process known as a non-degradation route. According to a previous study (63), the p97-UBXD8 complex is involved in HuR-mRNA modification during the stress response. When cancer develops, the stabilizing factors, the p97-UBXD8 complex and the phosphorylated HuR transition, are activated to serve their stabilizing roles after organelle function and structure have been compromised, mostly by transitory proliferation and metabolic abnormalities. The UBX family, particularly the p97-UBXD8 complex, is one of these modifications that not only improves cellular stability, but also controls it through autoregulation.

Stabilization of ERAD substrates. Based on the heterogeneity of the N-terminal structural domains of the UBX family, wherein only five of the 13 proteins in this family possess N-terminal AAA-enriched structures in mammals (UBXN1, UBXN2C, UBXN3A, UBXN3B and UBXN7), the UBX proteins have been split into two groups (8,11,64,). Park *et al* (64) reported that these five proteins fold abnormally to the ER, as ERAD substrates. The expression of all five proteins was shown to be upregulated in cells treated with cyclooxygenase, according to RT-PCR data (64). Among these proteins, UBXN2C, UBXN1 and UBXN3B are 'immediate' responders to endogenous stress, whereas UBXN3A and UBXN7 are 'late' responders. This indicates that whereas UBXN3A and UBXN7 are affected by other variables and do not reflect the ER stress in a timely and efficient manner, UBXN2C, UBXN1 and UBXN3B directly reflect increased ER stress.

Of note, UBXN2C and UBXN3B have higher expression levels than UBXN1 across all ERAD substrates, but UBXN1 has lower expression levels (11). Additional research revealed that UBXN1 has no affinity for certain ERAD substrates. Stable α-T-cell antigen receptor (α-TCR)-expressing cells under conditions of stress exhibit higher levels of UBXN2C and UBXN3B and lower levels of UBXN1. When UBXN2C or UBXN3B are overexpressed, the degradation of α-TCR occurs more rapidly; UBXN1 has the reverse effect. The degradation of α-TCR is caused by the overexpression of UBXN1. ERAD is one of the key elements in overcoming ER stress by activating the UPR (11). These findings imply that the expression levels of these five genes are altered by both ER stress and the overexpression of ERAD substrates (64). Although these five proteins function as the primary proteins for proteasomal degradation, the expression of several genes affects the outcomes when a certain role is played. This paradox can be explained by the fact that, on the one hand, UPRs build up in the ER and that, under conditions of ER stress, the overexpression of ERAD substrates can partially reduce this buildup; on the other hand, an increase in misfolded proteins in the cell and an increase in their demand can decrease the rate of proteasomal degradation of ERAD substrates. When UBXN2C and UBXN3B levels are

high in a significant number of misfolded proteins, particularly in cells expressing α-TCR, and when UBXN1 is downregulated to further promote degradation, this may explain the enhanced participation of UBXN2C and UBXN3B in the feedback loop during ER stress.

Altered signaling pathways. Under typical circumstances, the three primary transmembrane sensors inositolase-1α, protein kinase RNA-like ER kinase (PERK) and activated transcription factor-6α (ATF-6α) are all active in the lumen. Apoptosis may be caused if ER homeostasis is not recovered.

The inositolase-1α pathway is a transmembrane protein that is present in the UPRs and has kinase and ribonucleic acid endonuclease as its cytoplasmic structural domains (65). In a healthy state, inositolase-1 binds to immunoglobulins and is inactive. In response to stress, inositolase-1 is released, dimerized and activated, resulting in conformational alterations. As an alternative, unfolded proteins may bind directly to the structural domain of inositolase-1, causing conformational alterations and activation (66). The transcription factor known as the X-box binding protein, which is produced as a result of activated inositolase-1α, improves the capacity of the protein to fold and the function of ERAD in the ER. When ER stress is unrecoverable, the function of inositolase-1 is interrupted, which causes mRNA that is linked to it to degrade or to be recruited by TNF, which then stimulates cellular and mitochondrial death via apoptotic signaling (67). As a result, the inositolase-1 pathway reacts to ER stress by either boosting apoptotic pathways or upregulating ERAD, both of which include the UBX protein family. By inhibiting and interfering with the RIG-I-like receptors and the NF-κB pathway, UBXN1 is a member of the complex necessary to engage in the de-glycosylation and proteasome-mediated destruction of misfolded proteins under ER stress via reverse translocation (11). Similar to inositolase-1, PERK is a transmembrane protein that is inactive in a physiological setting (68). Dimerization and tetrameric pattern-mediated autophosphorylation are required for its activation (69). When PERK is activated, it may also phosphorylate translation initiation factors (70), which causes ERAD to reduce the amount of protein (71). This pathway also causes cell death by upregulating apoptosis-related genes (71). ATF-6α is translocated to the Golgi apparatus when the ER is stressed, despite the fact that it is primarily engaged in the control of ER plasmalogens (72).

Abnormal lipid metabolism. As a type of proteotoxic ER stress, the changed protein folding burden in the ER (73) interferes with aberrant protein folding, misfolded, unfolded or altered folding density. UPRs are also known as lipotoxic ER stress, as they may be directly triggered by toxic lipids in addition to being reliant on the buildup of misfolded proteins. Both forms of stress are induced by the involvement of the ER in the folding and transport of proteins, which is connected to lipid production and transport and activates UPRs to bring about homeostasis.

Genes associated with FAS, such as ATP acetyl coenzyme A carboxylase, which causes the conversion of citric acid into acetyl coenzyme A, malonyl coenzyme A, and fatty acids, are often overexpressed or upregulated in HCC (74). Through the examination of gene expression, a number of studies have investigated the causes and purposes of HCC development (6-8,11,14-18). As has already been established, as UBXN3B levels increase, so do the amounts of lipidated Apo B-100 in LDs and ubiquitinated Apo B-100 in ER. Both ubiquitinated and lipidated Apo B-100 have the ability to speed up proteasomal breakdown, while promoting lipid transport. The associated metabolism between LD and ER is regulated by UBXN3B.

Changes in the microenvironment. NK T-cells (NKT cells) are innate and adaptive immune cells with a variety of immunomodulatory functions (75). Changes in the metabolic profile of tumor lipids may also modify the type of lipid antigens, which may affect the immunomodulatory activity of NKT cells, as they predominantly detect lipid antigens (76). In a mouse model of NAFLD, increased lipids were shown to cause NKT cell death, which reduced the amount of hepatic NKT cells (77). Type I NKT cells are activated by a lipid surplus, and this leads to a more potent pro-inflammatory cytokine environment. However, despite the higher hepatic lipid content in HCC, another study found no significant difference in the number of NKT cells (78). These contradictory results suggest that further more in-depth experiments are required to examine the effects of lipid changes on NKT cells in NAFLD and HCC.

Additionally, processes including aberrant lipid metabolism and Golgi expansion control the proliferation of cells, such as myeloid-derived suppressor cells, $CD8^+$ T-cells, DCs and tumor-associated macrophages, which are all implicated in the growth of tumors (79). The expression of the UBX protein and the development of HCC may be affected by mitochondrial defects, changes in lipid signaling molecules and pathways, fatty acid biosynthetic pathways, lipidomics, other genetic mutations, chronic viral infections, cholesterol efflux factors, ER autophagy, and post-translational modifications of proteins. The mechanisms through which the UBX protein family affects ER stress, lipid metabolism and microenvironmental changes remain unknown.

5. Conclusions and future perspectives

As a member of the UBX family, UBXN3B is primarily involved in the ER stress mechanism known as ERAD. It performs a variety of roles in LDs and ERs under various clinical conditions and develops into a new HCC biomarker. In order to maintain fatty acid and triglyceride homeostasis, maintain intracellular signaling pathways, and normalize cytokines, UBXN3B participates in ER stability, maintains fatty acid and triglyceride homeostasis, and has an impact on cholesterol production. UBXN3B is also involved in the progression of ER stress, the dysregulation of lipid metabolism, the driving of inflammatory factors and the immune microenvironment. However, a number of physiological processes of UBXN3B remain unknown and require support and clarification by further fundamental experimental and clinical studies.

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ZG and JL drafted, read and approved the final manuscript, and conceived and designed the study. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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