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Research Status of LCN2 in the Regulation of Hepatocellular Carcinoma

Wenyao Wang, Shujun Zhou, Shuai Wang*

Department of Hepatobiliary Surgery, Jingzhou Hospital Affiliated to Yangtze University, Jingzhou, China
Email: *15348404014@163.com

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Abstract

Lipocalin-2 (LCN2), also known as neutrophil gelatinase-associated lipocalin (NGAL), is a multifunctional secreted iron-binding glycoprotein widely involved in physiological processes including systemic iron homeostasis, innate immune defense, and inflammatory responses. Accumulating recent evidence has demonstrated that LCN2 plays pivotal regulatory roles in the initiation, progression, drug resistance, and metastasis of hepatocellular carcinoma (HCC). Notably, LCN2 exhibits prominent context-dependent dual functions in HCC, exerting both oncogenic and tumor-suppressive effects, which renders it a research hotspot in HCC tumor biology and targeted therapy. On one hand, LCN2 promotes migration and invasion of HCC cells, remodels the tumor microenvironment, inhibits ferroptosis, and thereby induces sorafenib resistance and bone metastasis via activating signaling cascades such as Met/FAK and JAK1/STAT3. On the other hand, LCN2 exerts tumor-suppressive effects by inhibiting epithelial-mesenchymal transition (EMT) through the EGF/TGF-β1/Twist1 axis and triggering mitochondrial-dependent apoptosis. The LIFR-NF-κB-LCN2 axis, which mediates ferroptosis-related drug resistance, represents one of the most well-characterized pathways with high translational potential in this field. Combination regimens targeting LCN2 together with targeted drugs and immunotherapy have been reported. This review systematically summarizes the core physiological functions of LCN2, dissects the molecular mechanisms underlying its dual roles in HCC, evaluates its value as a clinical biomarker, and discusses existing controversies, cutting-edge advances, and remaining research gaps. It provides theoretical references for mechanistic investigations, biomarker development, and optimization of therapeutic strategies for HCC.

Keywords

Lipocalin-2, Hepatocellular Carcinoma, Iron Homeostasis, Ferroptosis, Tumor

*Corresponding author.

Drug Resistance, Dual Function, Biomarker

1. Biological Characteristics of LCN2 and Its Fundamental Roles in Hepatocellular Carcinoma

1.1. Structure and Physiological Functions of LCN2

Lipocalin-2 (LCN2), also referred to as neutrophil gelatinase-associated lipocalin (NGAL), siderocalin, α_2-microglobulin-related protein, or 24p3 protein, is a small secreted glycoprotein belonging to the lipocalin superfamily. It transports circulating lipophilic molecules including steroids, lipopolysaccharides, iron, and fatty acids, and fulfills critical functions in innate immunity and pathological processes [1]. Large quantities of NGAL are stored in neutrophils; additionally, its synthesis and secretion can be induced upon stimulation in epithelial cells, macrophages, renal tubular cells, and tumor cells [2]. The human LCN2 gene is located on chromosome 9 and encodes a 197-amino-acid polypeptide. Its tertiary structure adopts an eight-stranded antiparallel β-barrel fold [2]-[4]. This three-dimensional scaffold accommodates diverse ligands, including bacterial siderophores, mammalian catechol-based endogenous siderophores, retinol, and fatty acids [5]. LCN2 exists mainly in three molecular forms: a 25 kDa monomer, a homodimer, and a heteromultimer covalently formed with matrix metalloproteinase-9 (MMP-9) via intermolecular disulfide bonds [3] [6] [7]. The heterodimeric complex of LCN2-MMP-9 constitutes one physiological form of human gelatinase. Free MMP-9 is biochemically unstable, whereas binding to LCN2 markedly enhances its protein stability and enzymatic activity, an effect of great physiological and pathological significance [7].

Since its discovery, LCN2 has been recognized as a central multifunctional molecule linking iron metabolism, immune responses, and inflammation. Its physiological activities largely rely on iron-binding properties, and it is indispensable for organism homeostasis. Current evidence indicates that the core physiological functions of LCN2 fall into four categories: iron-homeostasis regulation, innate immune defense, inflammatory modulation, and hepatic injury repair.

In terms of iron homeostasis, LCN2 binds the bacterial siderophore-ferric iron complex with high affinity and precisely regulates cellular iron metabolism via switching its iron-binding status: iron-bound LCN2 mediates intracellular iron delivery to support normal iron-dependent cellular metabolism, while apo-LCN2 (iron-free LCN2 without siderophore ligands) chelates excess intracellular iron and promotes iron efflux, thereby alleviating oxidative stress damage triggered by iron overload. Through the above mechanisms, LCN2 participates in the regulation of iron-dependent metabolism, oxidative stress, and cell death programs. Notably, LCN2 does not directly bind free ferric ions; instead, it binds iron in the form of siderophore complexes. Its biological functions are ligand-dependent, and the final biological effect is jointly determined by its ligand-binding status and the

uptake machinery of target cells, which enables the maintenance of iron homeostasis at both the cellular and organismal levels [8]-[10].

Antimicrobial innate immunity represents a classical function of LCN2. As an effector molecule of nutritional immunity, LCN2 competitively sequesters bacterial siderophores to deprive bacteria of essential iron and thereby exerts broad-spectrum bacteriostatic activity. Meanwhile, LCN2 acts as a neutrophil chemoattractant to recruit immune-cell infiltration and participates in the formation of neutrophil extracellular traps (NETs), contributing substantially to host anti-infective immunity [11].

LCN2 is a typical acute-phase reactant deeply involved in inflammatory cascades. Inflammatory stimuli robustly upregulate LCN2 expression through the IL-6/STAT3 pathway, and LCN2 further amplifies inflammatory responses by engaging receptors such as CXCR2. Notably, LCN2 exerts bidirectional inflammatory effects: it plays a protective anti-inflammatory role in acute hepatic injury by alleviating oxidative stress and restraining excessive inflammation; conversely, it exhibits pro-inflammatory properties in chronic liver disease and sustains the chronic inflammatory microenvironment [11] [12].

Within hepatic tissue, LCN2 serves as a crucial homeostatic mediator during liver damage repair. Upon acute liver injury, damaged hepatocytes rapidly secrete abundant LCN2, which attenuates oxidative stress and limits hepatocyte apoptosis. In multiple experimental acute-liver-injury models induced by CCl_4, LPS, or ConA, Lcn2-knockout mice display exacerbated hepatic damage, elevated pro-inflammatory cytokine levels, and increased hepatocyte apoptosis compared with wild-type counterparts, demonstrating the protective role of LCN2 in preserving liver homeostasis [12].

1.2. Dual Mechanisms of LCN2 in Hepatocellular Carcinoma

1.2.1. Oncogenic Mechanisms of LCN2 in HCC

Accumulating high-quality original studies have shown that LCN2 predominantly exerts oncogenic functions in advanced-stage HCC, highly invasive HCC cells, and stroma-driven tumor microenvironments. It drives HCC malignant progression by facilitating tumor migration-invasion, remodeling the tumor microenvironment, mediating therapeutic resistance, and promoting distant metastasis.

Promotion of tumor migration and invasion constitutes a fundamental oncogenic activity of LCN2. Thyroid hormone T_3, via thyroid hormone receptors (TR), binds to thyroid-hormone-response elements (TRE) within the LCN2 promoter and transcriptionally up-regulates LCN2. Elevated LCN2 activates the Met/FAK signaling cascade, augments the enzymatic activities of MMP-2 and MMP-9, degrades the extracellular matrix, and potentiates migratory and invasive phenotypes of HCC cells *in vitro*. *In-vivo* xenograft experiments and clinical-sample validation reveal that LCN2 overexpression accelerates tumor growth and invasiveness in nude mice. In human HCC specimens, LCN2 expression positively correlates with TRα; high co-expression of both markers associates with higher

tumor grade, advanced tumor stage, and vascular invasion, serving as biomarkers for malignant HCC progression [13].

LCN2 accelerates HCC progression by reshaping the tumor microenvironment. Activated hepatic stellate cells (HSCs), key stromal constituents of the hepatic tumor microenvironment, secrete large amounts of LCN2. Microfluidic tri-cell co-culture models demonstrate that HSC-derived LCN2 enhances endothelial-cell invasiveness and tumor angiogenesis to sustain tumor proliferation and metastasis. Furthermore, LCN2 induces NK-cell exhaustion within the tumor niche, impairs NK-cell-mediated anti-tumor cytotoxicity, and establishes an immunosuppressive microenvironment. Therapeutic interference against LCN2 suppresses angiogenesis, restores NK-cell immune competence, and robustly restrains HCC progression [14].

Mediating sorafenib resistance represents a research hotspot regarding LCN2-driven therapeutic resistance in HCC. Ferroptosis is a major mechanism underlying sorafenib-induced HCC-cell killing. Furthermore, LCN2 binding to siderophores can inhibit ferroptosis of tumor cells and consequently lead to the development of drug resistance. Two well-defined regulatory axes have been characterized. First, the LIFR-NF-κB-LCN2 axis: LIFR is frequently down-regulated in HCC. Loss of LIFR triggers SHP1-dependent NF-κB activation and enhances LCN2 secretion. Highly expressed LCN2 sequesters abundant intracellular free iron via siderophores, reduces cellular iron levels, inhibits lipid peroxidation and ferroptosis, and ultimately leads to sorafenib resistance. Second, the ESR1-LCN2 axis: estrogen receptor ESR1 functions as a transcriptional repressor binding to the LCN2 promoter. ESR1 silencing in HCC relieves transcriptional repression of LCN2. Subsequent LCN2 overexpression inhibits autophagy-dependent ferroptosis and renders HCC cells refractory to sorafenib. Pre-clinical patient-derived xenograft (PDX) models confirm that combined treatment with anti-LCN2 neutralizing antibody and sorafenib restores ferroptosis sensitivity and substantially improves anti-tumor efficacy, highlighting promising translational prospects [15] [16].

Recent advances expand the oncogenic repertoire of LCN2 by establishing its role in HCC bone metastasis. HMGB1 promotes osteoclast activation and subsequent LCN2 release from osteoclasts. Exogenous osteoclast-derived LCN2 activates the JAK1/STAT3 pathway in HCC cells and forms a positive-feedback "osteoclast-LCN2-tumor-cell" loop, exacerbating osteolytic bone resorption and facilitating HCC bone dissemination [17].

1.2.2. Tumor-Suppressive Mechanisms of LCN2 in HCC

Contrasting with its oncogenic effects, classic studies report tumor-suppressive activities for LCN2 in well-differentiated early-stage HCC. LCN2 counteracts HCC proliferation and metastasis by repressing EMT and triggering tumor-cell apoptosis.

LCN2 inhibits EMT in HCC through the EGF/TGF-β1/LCN2/Twist1 pathway. Growth factors EGF and TGF-β1 down-regulate LCN2 while inducing the transcription factor Twist1, thereby driving EMT and conferring invasive properties

upon HCC cells. LCN2 acts upstream of Twist1 and reverses growth-factor-provoked EMT. Adenovirus-mediated LCN2 overexpression reduces mesenchymal markers such as N-cadherin and vimentin, elevates epithelial markers including CK8/CK18, and reverts the EMT phenotype. Stable LCN2 overexpression inhibits HCC-cell proliferation and invasion in vitro and restrains xenograft tumor growth and metastasis in vivo. Clinical-sample analyses demonstrate preferential LCN2 expression in well-differentiated early-stage HCC, supporting its tumor-suppressive role at early tumor phases [18].

Activation of the mitochondrial-apoptosis cascade constitutes another tumor-suppressive mechanism of LCN2. Clinical specimens show that both LCN2 and its receptor LCN2R are markedly down-regulated in HCC, and reduced expression correlates with more aggressive disease. *In-vitro* assays demonstrate that ectopic LCN2 expression impairs viability of Huh-7 and SK-Hep-1 HCC cells, induces sub-G1-phase-cycle arrest, and triggers DNA fragmentation and chromatin condensation. Mechanistically, LCN2 collapses mitochondrial membrane potential, down-regulates anti-apoptotic Bcl-2, up-regulates pro-apoptotic Bax, and activates caspase-9, caspase-8, caspase-3, and PARP cleavage to initiate mitochondrial-dependent apoptosis. Both caspase inhibitors and LCN2-neutralizing antibodies abolish this pro-apoptotic effect, verifying LCN2-mediated tumor suppression [19]. Asimakopoulou *et al.* [20]. further investigated whether LCN2 governs hepatic lipid metabolism and lipid-droplet biogenesis. *In-vivo* experiments revealed exacerbated hepatic lipid accumulation in Lcn2-deficient livers. Re-introduction of an LCN2 overexpression plasmid into Lcn2-knockout primary hepatocytes restored PLIN5 protein abundance, establishing LCN2 as a positive upstream regulator of PLIN5.

Based on available studies, we propose a hypothesis that LCN2 exerts a concentration-dependent, bidirectional regulatory effect on mitochondria in hepatocytes: physiological or low concentrations of LCN2 confer protective effects on normal hepatocytes, whereas overexpressed LCN2 in the hepatocellular carcinoma microenvironment induces apoptosis in HCC cells. These findings allow reconstruction of an integrated LCN2-centered tumor-protective regulatory network spanning metabolic disturbance, tumor-cell survival, and tumor invasion-metastasis during hepatic disease progression. First, at the level of metabolic regulation, LCN2 up-regulates hepatic PLIN5 expression, thereby inhibiting aberrant lipid accumulation and alleviating lipotoxic injury in hepatocytes. Second, at the cell-survival level, high LCN2 triggers mitochondrial-dependent apoptosis and restrains uncontrolled HCC-cell proliferation. Third, at the invasion-metastasis level, LCN2 negatively modulates the TGF-β/Twist1 axis, represses HCC EMT, and thereby impedes tumor invasion and distant dissemination.

1.3. Diagnostic and Prognostic Value of LCN2 in Hepatocellular Carcinoma

Both mRNA and protein levels of LCN2 and LCN2R are significantly elevated in

HCC patients and HCC tissues. Survival analyses reveal that higher LCN2 expression correlates with poorer clinical outcomes and shorter overall survival relative to cases with low LCN2 abundance. Increased LCN2 also positively associates with adverse clinicopathological features, including vascular invasion, advanced TNM stage, and tumor recurrence. These observations suggest that LCN2 represents a promising prognostic biomarker and potential therapeutic target for HCC [14] [21] [22].

For serum-based diagnosis, aptamer-based sandwich assays achieve highly sensitive quantification of circulating LCN2, with a detection range of 2.5 - 500 ng/mL and a limit of detection as low as 0.6 ng/mL, outperforming conventional ELISA. This methodological advance enables non-invasive serum measurement in HCC patients, compensates for insufficient sensitivity of alpha-fetoprotein (AFP), and supports combined-diagnosis applications [23]. A single-center prospective clinical study performed at Zagazig University in Egypt proposed serum LCN2 cut-off value >225 ng/mL as a promising non-invasive diagnostic biomarker for HCC. Compared with AFP, serum LCN2 achieves superior sensitivity, specificity, and overall diagnostic accuracy for discriminating HCC superimposed on cirrhosis and reduces false-positive rates during screening of cirrhotic populations [24].

Additional clinical work indicates diagnostic as well as prognostic relevance for circulating LCN2: serum LCN2 concentrations above 217.5 μg/L correlate with increased mortality among HCC patients [25]. A clinical cohort of 138 HCC patients receiving curative resection demonstrated marked up-regulation of tumor-tissue NGAL (LCN2) and NGALR with strong positive correlation between the two molecules ($r = 0.89$, $P < 0.001$). High LCN2 expression correlates with vascular invasion, advanced TNM stage, and post-operative tumor recurrence. Patients with high LCN2 exhibit shortened overall survival, and multivariate regression identifies LCN2 as an independent adverse prognostic factor suitable for post-resection risk stratification [21].

For disease-progression monitoring, LCN2 facilitates surveillance of NAFLD/NASH-associated HCC. LCN2 expression progressively rises throughout NASH, hepatic fibrosis, and NASH-driven HCC and reflects chronic hepatic inflammation and malignant transformation. Nevertheless, inconsistencies exist among available datasets. The discriminatory power of LCN2 for distinguishing benign liver disorders from early malignant lesions still requires validation in large-scale clinical cohorts, and its monitoring value in metabolic-liver-disease-related carcinogenesis remains to be further defined [22].

2. Research Controversies, Hotspots and Existing Gaps

2.1. The Dual-Function Paradox of LCN2

Context-dependent dual activities constitute the major ongoing controversy surrounding LCN2 in HCC. A landmark 2013 Hepatology report first described tumor-suppressive LCN2 functions manifested as EMT inhibition and metastasis restraint. Two independent studies published in 2015 reported contradictory ob-

servations: LCN2 promoted tumor invasion through the Met/FAK pathway while simultaneously inducing HCC-cell apoptosis via mitochondrial cascades. Subsequent studies from 2023 to 2025 further validated oncogenic, pro-metastatic, and drug-resistance-promoting roles for LCN2, creating apparent discrepancies with earlier tumor-suppressive conclusions.

A 2024 systematic review proposed that LCN2 duality arises predominantly from biological context. Four key determinants shape its functional output: 1) cellular origin: LCN2 derived from tumor cells, immune cells, or stromal cells exerts distinct biological activities; 2) tumor-progression stage: LCN2 primarily suppresses malignancy in well-differentiated early-stage HCC but switches toward oncogenic phenotypes in advanced disease; 3) protein-iron-loading status: iron-bound versus apo-LCN2 exert opposing effects on cellular iron metabolism and downstream biological outcomes; 4) tumor-microenvironment composition: stromal compartments including hepatic stellate cells, NK cells, and macrophages reprogram LCN2-driven signaling responses. This conceptual framework reconciles conflicting experimental findings in this research domain.

2.2. LCN2-Mediated Ferroptosis and Therapeutic-Drug Resistance

Regulation of ferroptosis and targeted-therapy resistance represents one of the most active research frontiers for LCN2-related HCC investigations. Of high translational relevance, multiple pre-clinical studies demonstrate that LCN2-targeting interventions reverse therapeutic resistance. Combination regimens using anti-LCN2 neutralizing antibody plus sorafenib achieve prominent anti-tumor efficacy in PDX models featuring low LIFR and high LCN2 expression, providing novel intervention strategies for sorafenib-resistant HCC and warranting further translational investigation.

3. Summary and Future Perspectives

LCN2 is a multifunctional iron-binding glycoprotein balancing physiological homeostasis and malignant tumor progression. In healthy liver tissue, LCN2 participates in iron homeostasis, anti-infective immunity, and acute-injury repair and serves as a hepatoprotective molecule. During HCC pathogenesis, LCN2 displays prominent context-dependent duality and modulates tumor proliferation, invasion-metastasis, ferroptosis, and targeted-drug resistance through multiple signaling circuits, functioning as a central hub connecting hepatic inflammation, metabolic perturbation, and malignant transformation. The molecular cascade whereby LCN2 confers sorafenib resistance has been largely deciphered; LCN2-targeted combinatorial therapies exhibit encouraging translational prospects, and preliminary clinical evidence supports LCN2 as a non-invasive diagnostic and prognostic biomarker for HCC.

Nevertheless, several challenges persist: incomplete mechanistic networks governing LCN2 function, insufficient clinical-translational evidence, and limited targeting modalities. Future investigations should prioritize unresolved questions

regarding context-specific regulatory circuits, cell-type-specific LCN2 activities, and immunotherapy-combination potential. Further research should characterize functional distinctions among LCN2 variants secreted by different cell populations, refine its signaling networks, validate biomarker performance in large-scale prospective cohorts, and accelerate clinical translation of LCN2-targeted therapeutics. These efforts may deliver innovative strategies supporting precise diagnosis, resistance reversal, and personalized management for HCC patients.

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Author Contributions

The author conceived and designed the study, performed the experiments, analyzed the data, drafted and revised the manuscript, and approved the final version.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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