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REVIEW ARTICLE

Prospects of CD44 in hepatocellular carcinoma: An emerging biomarker and therapeutic target

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Abstract

CD44, a single-transmembrane glycoprotein with diverse functional roles, has emerged as a critical regulator of tumor behavior, particularly in hepatocellular carcinoma (HCC). Elevated CD44 expression in HCC correlates with aggressive disease progression, positioning it as a promising diagnostic and prognostic biomarker. At the molecular level, CD44 orchestrates key oncogenic processes, including enhanced cellular proliferation, accelerated cell cycle progression, and increased migratory capacity, thereby driving HCC pathogenesis. As therapeutic strategies for HCC become more aggressive, invasive interventions are associated with adverse clinical outcomes, highlighting the need for targeted approaches. This review comprehensively analyzes current literature on CD44, addressing its structural diversity, isoform-specific functions, and signaling mechanisms in HCC. Furthermore, we discuss its prognostic significance, role in therapeutic resistance, and potential as a molecular target. By synthesizing these findings, this work aims to provide novel insights into early detection, accurate diagnosis, and the development of precision therapies for HCC, ultimately improving clinical outcomes.

Keywords: CD44; Biomarker; Therapeutic target; Hepatocellular carcinoma

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1. Introduction

Liver cancer is an extremely deadly malignancy. It ranks as the second leading cause of cancer-related deaths worldwide, making up 8.2% of all such deaths.[1] Hepatocellular carcinoma (HCC) constitutes the most common type of liver cancer, and more than 80% of patients with this condition have cirrhosis caused by hepatitis B or C virus infections. Excessive alcohol consumption, a well-known risk factor for the development of non-alcoholic fatty liver disease, has been shown to significantly increase the likelihood of HCC.[2,3] Despite significant advancements in diagnosis and treatment, substantial challenges persist. For instance, only 40% of HCC cases can be identified at early stages, and treatment outcomes remain suboptimal. Surgical intervention is still the preferred treatment, but only a small proportion (5–10%) of HCC tumors are considered suitable for this approach.[4] Therefore, there is an urgent need to develop new diagnostic tests

and treatment methods for HCC, given its unfavorable prognosis.

Multiple studies have corroborated a strong association between the recurrence and metastasis of various malignancies and cancer stem cells (CSCs), which play a pivotal role within the tumor microenvironment (TME).[5,6] This is attributable to the intrinsic properties of CSCs, namely their capacity for extensive self-renewal and multipotent differentiation, enabling them to continuously generate novel neoplastic cell populations. Consequently, they are instrumental in the tumor initiation, phenotypic maintenance, and the establishment of cellular heterogeneity. The concept of CSCs was initially proposed in experimental studies of acute myeloid leukemia (AML), where their tumorigenic potential was successfully validated through isolation and identification using specific cell surface markers.[7] Subsequently, with the widespread application of CSC-specific markers, the presence of these cells has been confirmed in a spectrum of solid tumors, including glioblastoma, breast, lung, colon, and liver cancers.[8-11] In the context of HCC research, evidence indicates that liver CSCs are characterized by the heightened expression of key markers such as epithelial cell adhesion molecule (EpCAM), CD13, CD44, and/or CD133. Notably, the expression levels of these molecules are significantly correlated with adverse clinical outcomes in HCC patients, manifesting as higher recurrence rates and shorter overall survival (OS), thereby underscoring the role of CSCs as critical drivers of disease progression.[11-13] Furthermore, CSCs exhibit not only intrinsic tumorigenicity but also pronounced resistance to conventional chemotherapy and radiotherapy. This resistance is mediated by mechanisms, including activation of anti-apoptotic signaling pathways, overexpression of drug efflux pumps, and remarkable adaptability to the surrounding microenvironment. Therefore, although conventional therapies can effectively eliminate the bulk of non-CSC tumor cells, the residual CSCs possess the capacity to repopulate the tumor, ultimately leading to local recurrence and metastasis.[5,6] Thus, the elimination of CSCs is paramount for achieving a definitive cure for cancer, which has propelled the investigation of novel therapeutic strategies targeting CSCs.

The transmembrane glycoprotein CD44 ranks among the most frequently utilized CSC markers.[14] Its gene is composed of 20 exons, 10 of which are variant exons that can undergo alternative splicing to generate numerous isoforms.[15] Notably, the CD44 variant isoform (CD44v), which specifically contains variant exons 8 and 10, is a significant CSC marker that is frequently upregulated in CSCs across various malignancies.[16] This isoform enhances the antioxidant capacity of CSCs by promoting the glutathione (GSH) synthesis through its interaction with xCT, a glutamate–cystine transporter.[17] In contrast, the standard CD44 isoform (CD44s), which lacks these variant exons, is broadly expressed across numerous cell types, including mesenchymal stromal and hematopoietic cells.[18] However, research indicates that liver CSCs predominantly express CD44s, and this isoform is implicated in the process of epithelial–mesenchymal transition (EMT).[19,20]

As a member of the non-kinase, single-pass transmembrane glycoprotein family, CD44 is expressed in embryonic stem cells, various connective tissues, bone marrow, and numerous other cell types.[21,22] Its primary function is mediated through binding to its principal ligand, hyaluronic acid (HA). HA, a major component of the extracellular matrix (ECM), is expressed by both stromal and cancer cells.[23] HA binds to the CD44 ligand-binding domain, inducing conformational changes that facilitate the binding of adaptor proteins or cytoskeletal components to intracellular domains. This interaction plays an important role in many biological and functional activities, including angiogenesis, leukocyte activation, myelopoiesis, lymphogenesis, and cytokine release. Similarly, it is also implicated in pathological processes such as proliferation, EMT, migration, cell growth, metastasis, and invasion.[14,18] The clinicopathological functions of CD44 and its variants in promoting tumorigenesis imply its potential as a promising molecular target in cancer therapy. In addition, CD44 has been identified as a regulator of tumor stemness and functionality following CSC therapy, highlighting its value as a prognostic marker. Currently, clinical development efforts are focusing on targeted therapies for CD44 or strategies to lower CD44 expression.[24-26] The expression of CD44 in HCC and its clinicopathological influence on tumorigenesis has attracted considerable attention. This study aims to explore the signaling pathway and role of CD44 in tumor progression, dissect the structure and isoforms of CD44, assess its prognostic importance in liver cancer, and examine the mechanisms of its involvement in liver cancer development, with the ultimate goal of providing new insights into early detection, diagnosis, and therapeutic strategies.

2. CD44-mediated signaling and cellular function

CD44, a multifunctional protein, plays an essential role in tumor cell behavior. First, by interacting with HA and various components of the ECM, it regulates cell adhesion.[27] This process facilitates the spatial arrangement of cells and enables their movement, thereby influencing tumor cell behavior, particularly aggressiveness and metastatic potential.[18]

Second, various subtypes of CD44 incorporate amino acid sequences encoded by variant exons v3 or v6, which modulate the activation of diverse receptor tyrosine kinases (RTKs) and their downstream signaling pathways.[18,28,29] Specifically, CD44v6 has been demonstrated to be crucial for activating the MET RTK.[30] CD44 functions as a coreceptor in two ways. The extracellular portion of CD44v6 binds hepatocyte growth factor, facilitating MET activation, while he cytoplasmic domain of CD44 initiates downstream signaling pathways. Together, these mechanisms amplify growth and survival signals, which are crucial for tumor cell proliferation.[29,30]

Finally, CD44 undergoes continuous proteolytic cleavage in physiological processes. Its intracellular domains are cleaved by γ-secretase, a process that contributes significantly to transcriptional regulation. Notably, this mechanism affects gene expression in tumor cells, thereby influencing their growth, differentiation, and apoptosis.[31]

3. CD44 structure and isoforms

CD44, a non-kinase transmembrane proteoglycan, is encoded by a gene located on mouse chromosome 2 and human chromosome 11.[32] In humans, this gene consists of 20 exons. Exons 16–20 encode the C-terminal domain, and exons 1–5 encode the N-terminal domain. These two domains form the homologous region common to all members of the CD44 family.[20] The shortest form of CD44, known as CD44s, has a molecular weight ranging from 85 to 95 kDa.[33] In contrast, another isoform, CD44v, is characterized by the presence or absence of alternatively spliced exons located between the C-terminal and N-terminal domains, as depicted in Figure 1.[34] Various subtypes of human CD44 molecule have been implicated in cancer progression and stem cell properties, including those associated with breast cancer,[35] glioma,[36,37] colorectal cancer,[38] prostate cancer,[39] head-and-neck squamous cell carcinoma,[40] and pancreatic cancer.[41,42]

The CD44 protein is structurally characterized by four distinct domains: The extracellular region, the stem region (comprising standard and/or variable stem regions), the transmembrane region, and the short C-terminal intracellular/cytoplasmic region,[43] as shown in Figure 2. Within the extracellular region, there are seven extracellular domains (1–5, 6, and 7 of the constant exon), including the N-terminal domain responsible for ligand binding. The transmembrane region is encoded by exon 8, while the cytoplasmic region is encoded by either exon 9 or exon 10. The stem region, which undergoes alternative splicing, may include one or more variant exons located between exon 5 and exon 6.

CD44 proteins become more complex due to post-translational modifications, specifically aberrant glycosylation involving N-glycans, O-glycans, and glycosaminoglycans such as heparin sulfate and chondroitin sulfate.[43-45] This altered glycosylation significantly impacts the functionality and activity of the protein. In general, CD44, serving as a crucial cell surface receptor, plays a pivotal role in organismal growth and development, as well as the pathogenesis of various diseases. Notably, investigating the role CD44 plays in tumorigenesis, tumors development, and treatment may generate new insights and therapeutic targets. These findings could be useful for tumor diagnosis, prognosis assessment, and development of treatment strategies.

4. CD44 potential as a biomarker for HCC prognosis

4.1. CD44 expression in tumors

As a pivotal tumor marker, the expression pattern of CD44 has been extensively investigated in a variety of malignancies. A substantial body of bioinformatics analyses based on public databases (such as the Cancer Genome Atlas, tumor immune estimation resource, Oncomine, and Gene Expression Profiling Interactive Analysis) consistently demonstrates that CD44 is significantly overexpressed in numerous cancer tissues compared to adjacent normal tissues. This phenomenon has been validated across multiple tumor types, including breast, colorectal, renal, HCC, gallbladder, ovarian cancers, and lymphoma.[46-49] Notably, various isoforms of CD44 (variants) are also aberrantly expressed in different cancers. In liver-related tissues, CD44 positivity is not only observed in HCC tumor tissues but also in adjacent non-tumor tissues, hepatoblastoma, viral hepatitis, and even some normal liver tissues, suggesting its potential involvement in the pathological processes of liver diseases.[50] From a functional perspective, CD44-positive ($CD44^+$) cancer cells have been confirmed to possess key characteristics of CSCs, representing the root cause of tumorigenesis, recurrence, and drug resistance.[18] In HCC, $CD44^+$ CSCs frequently co-express other CSC markers such as CD133 and CD90, further highlighting their central role in the malignant phenotype of liver cancer.[13,51]

4.2. The expression of CD44 and its correlation with clinical significance and prognosis

Clinically, CD44 serves as a crucial biomarker for the diagnosis and prognosis of HCC, with expression levels closely associated with clinicopathological features and patient survival outcomes. Multiple meta-analyses have confirmed that high CD44 expression is positively correlated with the TNM stage of HCC, positioning it as

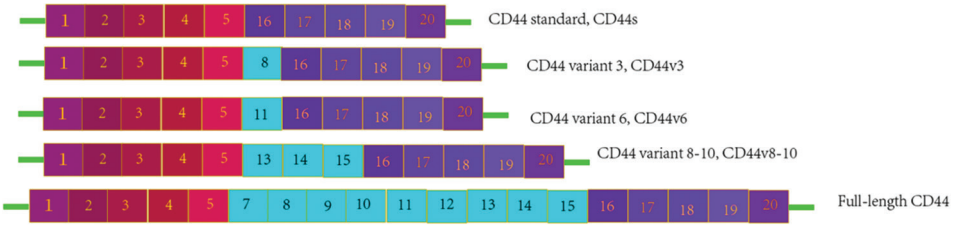


Figure 1. *CD44* gene structure. CD44 is encoded by 19 exons in humans and 20 exons in mice. Humans lack exon 6 encoding CD44 variant 1 (CD44v1). Non-blue exons are always expressed as the standard form of CD44 (CD44s), and up to nine exon variants can be inserted through selective splicing. Figure created by authors.

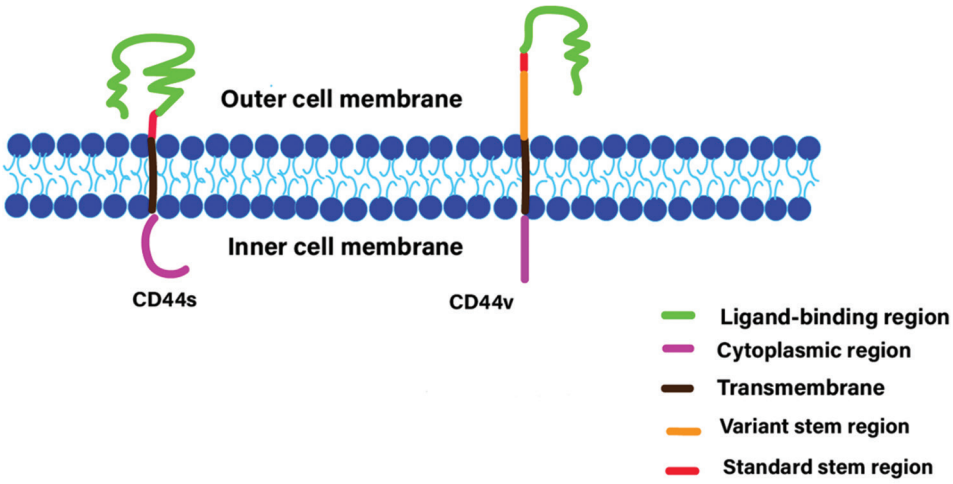


Figure 2. CD44 protein structure. The structural domains of CD44 are color-coded as follows: green denotes the ligand-binding domain, purple indicates the cytoplasmic domain, black represents the transmembrane domain, yellow signifies the variant stem domain, and red designates the standard stem domain. Figure created by authors.
Abbreviations: CD44s: Standard CD44 isoform; CD44v: CD44 variant isoform.

a potential indicator for predicting tumor progression.[52,53] More importantly, high CD44 expression is an independent risk factor for poor prognosis. Studies have shown that patients with CD44 positivity exhibit significantly shorter OS and disease-free survival (DFS) compared to $CD44^-$ patients, accompanied by a markedly reduced 5-year survival rate.[52-54] For instance, a study on patients undergoing surgical resection for HCC revealed that the mean survival time was 73.20 months for those with low CD44 expression but reduced to 44.84 months for those with high expression.[54] Furthermore, the expression of specific CD44 isoforms holds independent prognostic value. Aberrant expression of CD44s and CD44v, including CD44v5, CD44v6, CD44v7-8, and CD44v10, together with the presence of satellite nodules, has been identified as strong predictors of unfavorable prognosis in HCC patients.[55] In patients with hepatitis C virus-positive HCC (HCV^+ HCC), the expression of CD44v9 is significantly associated with poorer OS and DFS, as well as specific clinicopathological characteristics such as younger age, poorly differentiated and invasive phenotype, and elevated levels of alkaline phosphatase.[56] In summary, the expression of CD44 and its isoforms is closely linked to the clinicopathological features and prognosis of HCC, indicating their significant potential for clinical translation (Table 1).

4.3. The role of CD44 in tumor metastasis

Beyond its role in the primary tumor, CD44 plays a critical part in the process of tumor metastasis. Elevated CD44 levels are closely correlated with the metastatic potential of various malignancies.[47-49,57,58] Research by Yang *et al.* elucidated the specific mechanism of CD44 in HCC metastasis, showing that circulating HCC cells exhibit higher levels of CD44 compared to cells in the primary tumor. Furthermore, in mouse models, $CD44^+$ cells demonstrated significantly faster rates of tumorigenesis and metastasis *in vivo* than $CD44^-$ cells, indicating that acquisition of the $CD44^+$ phenotype is a critical step for HCC to develop metastatic capabilities.[51,59] This finding has broader implications. For example, the aberrant expression

Table 1. Overview of CD44 expression in various cancers and its prognostic significance

Cancer type	CD44 expression pattern	Prognostic significance	References
Breast cancer	Elevated	High CD44 expression correlates with poor prognosis	46-49
Colorectal cancer	Elevated	High CD44 expression correlates with poor prognosis	46-49
Renal cancer	Elevated	High CD44 expression correlates with poor prognosis	46-49
HCC	Elevated	High CD44 expression is associated with: • Advanced TNM stage • Shorter OS and DFS • Reduced 5-year survival rate • Specific isoforms (CD44s, CD44v5, v6, v7-8, v10) and satellite nodules predict unfavorable prognosis	46-49,50,13,18,51,52-55
Gallbladder cancer	Elevated	High CD44 expression correlates with poor prognosis	46-49
Ovarian cancer	Elevated	High CD44 expression correlates with poor prognosis	46-49
Lymphoma	Elevated	High CD44 expression correlates with poor prognosis	46-49
HCV^{+}HCC	Elevated	CD44v9 expression correlates with: • Poorer OS and DFS • Poorly differentiated/invasive phenotype	56

Abbreviations: DFS: Disease-free survival; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; OS: Overall survival.

of CD44v6 is closely related to the metastatic potential of pancreatic cancer cells,[60] whereas in lung adenocarcinoma, high expression of CD44v is associated with enhanced CSC properties, accelerated proliferation, and chemoresistance.[61] Therefore, targeting the CD44 pathway may offer novel therapeutic strategies for inhibiting tumor metastasis.

5. CD44 in HCC progression

CD44 is overexpressed in various human cancers and plays a promotive role in tumor growth. In HCC, suppression of CD44 can trigger apoptosis, thereby decreasing tumor development and invasion.[62] Nonetheless, the intricate molecular mechanism underlying this phenomenon is multifaceted and likely involves the activation of numerous signaling pathways.

5.1. CD44-upstream signaling pathways

5.1.1. Regulation of CD44 by miRNAs in activating signaling pathway

Numerous profiling studies have shown that different miRNAs are overexpressed in HCC and activate various signal pathways, such as miR-21, miR-18, and miR-221.[63] In HCC cells, extracellular high mobility group box 1 (HMGB1) can induce the overexpression of miR-21 by activating the RAGE/JNK signaling pathway. The upregulation of miR-21 subsequently augments CD44 expression by activating the OCT4/TGF-β1 signaling pathway, thereby promoting HCC invasion, spheroid formation, and EMT.[64] These findings indicate that HMGB1 plays a crucial role in HCC progression by regulating the miR-21/CD44 axis. Moreover, inhibition of miR-221 leads to a reduction in the downstream effector p-4EBP1 within the PI3K/AKT/mTOR signaling pathway. Likewise, suppression of the PI3K/AKT/mTOR pathway results in a decrease in CD44 protein levels, although it does not alter CD44 mRNA expression. This indicates that miR-221 may act as a novel regulator of CD44 in HCC by activating the PI3K/AKT/mTOR pathway to promote tumorigenesis.[63]

5.1.2. Regulation of CD44 by high cholesterol levels

Elevated cholesterol levels greatly influence postoperative survival and the likelihood of disease recurrence.[65,66] Research found that high levels of cholesterol can significantly inhibit the migration and invasion of liver cancer cells in mice, thereby suppressing the metastasis of liver cancer.[67-69] The main reason is that higher levels of cholesterol can promote the transport of CD44 to lipid rafts and reduce the interaction between CD44 and ezrin, which is crucial for cell migration and cancer metastasis. Furthermore, the investigation revealed that the absence of three N-glycosylation sites on CD44s (N57/N81600/N110) not only disrupted its intracellular distribution but also hindered its capacity to enhance the movement of liver cancer cells.[70]

5.1.3. Regulation of CD44 by TGF-β receptor 1 (TGF-β1/ALK5) activated ATP

Galunisertib (LY2157299), a TGF-β receptor 1 (TGF-β1/ALK5) inhibitor that mimics ATP, is being studied in HCC patients. It selectively affects stem cell-related gene expression in aggressive HCC cells by reducing CD44 expression levels and inhibiting stem cell-related functions of aggressive HCC cells (colony formation, liver spheroid

formation, and aggressive growth).[71] These suggest that CD44 can be regulated by TGF-β1 signaling, contributing to the increased aggressiveness of HCC.

5.2. CD44-downstream signaling pathways

The Hippo signaling pathway, with yes-associated protein (YAP) as a key downstream component,[72] is well recognized for its function in transporting cytoplasmic materials to the nucleus and activating oncogenic genes in a range of cancers, including HCC.[73,74] It has been demonstrated that the upregulation of CD44 can enhance the proliferation and migration of HCC cells. The mechanism lies in CD44, supporting the oncogenic roles of YAP.[72] Research findings indicate that CD44s modulates the expression of YAP1 and its associated target genes via the PI3K/Akt pathway, while also being influenced by the YAP1/TEAD axis, thereby establishing a novel positive feedback regulatory mechanism. The mutual interaction between CD44s and YAP1 may represent a broadly conserved mechanism that promotes the proliferation and invasion of HCC cells.[75]

Moreover, CD44s plays a significant role in regulating autophagy in tumor cells, maintaining the characteristics of CSCs, and regulating oxidative stress. Research has demonstrated that the inhibition of CD44s can impede the activation of caspase-1/IL1B by inducing AMPK-mediated autophagy. Conversely, recombinant human IL-1B can reverse the effects of CD44s deficiency on proliferation, invasion, and EMT phenotypic alterations in HCC cells.[76] Knockout of the *CD44* gene in HuH7 HCC cells expressing only CD44s reduces spheroid formation and increases drug sensitivity. In addition, CD44 deficiency reduces antioxidant capacity, accompanied by low levels of GSH peroxidase 1, and thioredoxin. Meanwhile, the expression of NOTCH3 and its target genes is downregulated in spheres lacking CD44.[77] These findings suggested that CD44s may play a role in sustaining CSCs in HCC cell lines through the NOTCH3 signaling pathway. Overall, this study demonstrates that CD44 plays a significant role in the development and progression of HCC. It elucidates the mechanisms by which CD44 influences the biological functions and cellular signaling pathways, as well as the dedifferentiation of liver cancer cells. These findings deepen our understanding of liver cancer pathophysiology and point to new research directions and potential therapeutic targets for liver cancer prevention and management. Future research could further explore the role of CD44 and its interactions with other signaling pathways in HCC, offering stronger theoretical support and guidance for clinical application.

6. Therapy

Targeted therapy aims to selectively inhibit or block aberrantly activated signal transduction pathways within tumor cells. Given the broad pro-tumorigenic role of CD44 in tumor initiation and progression, inhibiting CD44 may effectively suppress tumor proliferation and enhance the sensitivity of tumor cells to therapeutic interventions. CD44-targeting strategies encompass a spectrum of therapeutic modalities, including antibody therapy, peptide antagonists, small interfering *RNA (siRNA)-mediated* gene silencing, chimeric antigen receptor (CAR) T-cell therapy, HA-modified nanocarriers, pharmacological inhibitors, and natural compound inhibitors. This section provides a focused review of therapeutic strategies targeting CD44 across various types of malignant tumors.

6.1. Targeted antibodies therapy

In the context of CD44-targeted antibody therapy, Arabi *et al.*[78] systematically evaluated the antitumor activity of CD44-modified Doxil (a liposomal formulation of doxorubicin). Their research demonstrated that, compared with unmodified Doxil, the liposomal conjugate decorated with a CD44 monoclonal antibody (mAb) significantly enhanced the cellular uptake efficiency in $CD44^+$ murine colon cancer cells. Subsequent *in vivo* experiments revealed that the intratumoral concentration of doxorubicin was markedly higher in mice treated with the CD44-targeted formulation than in those receiving the unmodified Doxil control. Notably, $CD44^-$ murine embryonic fibroblasts exhibited comparable drug uptake and cytotoxicity under both treatment conditions, highlighting the tumor-selective nature of this strategy.

Another study investigated the humanized mAb RG7356, which demonstrated significant cytotoxicity against chronic lymphocytic leukemia (CLL) cells, particularly CD44-high-expressing leukemic B cells, while exerting minimal effects on normal B cells. Mechanistic investigations elucidated that RG7356 induces rapid internalization of CD44 in $ZAP\text{-}70^+$ CLL cells, which in turn suppresses ZAP-70 activity and ultimately activates a caspase-dependent apoptotic pathway.[79] Transcriptomic analysis further revealed that RG7356 binding to $CD44^+$ tumor cells triggers an immunostimulatory response, characterized by enhanced chemokine secretion, recruitment of macrophages into the TME, and subsequent induction of antibody-dependent cellular phagocytosis.[80]

In prostate cancer research, the mAb F77 specifically targets an epitope encoded within exon 14 of CD44 in PC3 cells. Experimental evidence confirmed that F77 induces apoptosis in PC3 cells through a CD44-dependent mechanism, an effect that was almost completely abrogated by *CD44* gene knockdown.[81] Similarly, the anti-CD44 mAb A3D8 promotes apoptosis in AML cells by binding to the CD44s protein and activating the caspase-8 signaling

cascade.[82] Furthermore, in human ovarian cancer cells with high CD44 expression, anti-CD44 antibody-modified glycosylated paclitaxel liposomes showed enhanced cytotoxicity and superior tumor growth inhibition both *in vitro* and *in vivo*.[83]

6.2. Peptides therapy

Peptide molecules exhibit significant advantages in tumor theranostics due to their unique physicochemical properties. Peptide ligands can bind to cell surface targets with high affinity and rapid kinetics.[84-86] Their low molecular weight facilitates extravasation and diffusion through the enhanced permeability and retention effect, enabling tumor uptake within a few hours *in vivo*.[87] This pharmacokinetic profile aligns well with clinical requirements for early diagnosis and image-guided surgery. Furthermore, peptides are rapidly cleared from the bloodstream, which not only reduces potential hepatotoxicity but also minimizes off-target distribution in non-target tissues.[88-90] These properties make peptides particularly suitable for tumor delivery systems, especially in liver cirrhosis. Notably, peptides also carry a low risk of immunogenicity,[91,92] providing a favorable safety margin for clinical translation.

In CD44-targeted strategies, synthetic peptides have emerged as promising alternatives to antibodies. Park *et al.*[93] employed phage display technology to screen seven CD44-binding peptides (P1-P7), among which P7 (FNLPLPSRPLLR) exhibited the highest binding specificity and affinity. Based on this finding, the researchers developed a polyvalent directional peptide polymer by conjugating P6 and P7 peptides onto a poly-L-lysine backbone. This system demonstrated superior targeting efficacy in breast CSCs compared to traditional antibodies.[94] In another study, HA-modified chitosan nanoparticles loaded with the cationic antimicrobial peptide CM11 significantly enhanced cytotoxicity against lung adenocarcinoma, neuroblastoma, and pancreatic cancer cell lines through CD44-mediated endocytosis.[95]

In diagnostic applications, CD44-targeted peptides labeled with[68] Ga have achieved breakthrough progress. Preclinical studies have shown that[68] Ga-DOTA-A6 exhibits excellent target retention and metabolic stability in $CD44^+$ tumor models, highlighting its potential as a tool for early diagnosis and therapeutic monitoring of HCC.[96] More recently, a newly identified CD44-specific peptide (WKGWSYLWTQQA), which has been validated through both *in vitro* and *in vivo* experiments, enables clear discrimination between HCC and other liver lesions. Its clinical translation potential for image-guided surgery and early diagnosis has also been preliminarily confirmed.[97]

6.3. RNA interference (RNAi) therapy

RNAi is an evolutionarily conserved endogenous biological defense mechanism that silences genes by mediating the sequence-specific degradation of target mRNA, demonstrating immense potential in disease therapeutics.[98-102] As the primary effector molecules of the RNAi pathway, siRNAs facilitate highly specific and potent gene silencing through base-pairing complementarity, theoretically enabling the targeted modulation of any disease-causing gene.[103,104] Leveraging this mechanism, the U.S. Food and Drug Administration has consecutively approved four siRNA-based drugs between 2018 and 2021—patisiran, givosiran, lumasiran, and inclisiran—heralding a new era for the clinical application of oligonucleotide-based therapeutics.[105-107] These drugs capitalize on the multifunctionality of RNA molecules in regulating gene expression. Notably, givosiran (approved in 2019) is indicated for acute hepatic porphyria, while inclisiran (approved in 2021) is the first siRNA drug for heterozygous familial hypercholesterolemia and atherosclerotic cardiovascular disease, requiring co-administration with statins.[107]

In targeted cancer therapy, siRNA-mediated *CD44* gene silencing has shown a significant progress. Studies have demonstrated that transfection of synthetic siRNA into non-small cell lung cancer (NSCLC) cell lines leads to a significant downregulation of CD44 expression, which in turn suppresses cellular proliferation and reduces colony-forming efficiency.[108] In epidermal growth factor receptor (EGFR) wild-type NSCLC, CD44 siRNA not only induces G0/G1 cell cycle arrest and apoptosis but also enhances cisplatin chemosensitivity, promoting EGFR degradation.[109] To address multidrug resistance (MDR), researchers have utilized HA-modified polyethyleneimine and polyethylene glycol nanocarriers to deliver MDR1 siRNA into CD44-overexpressing ovarian cancer cells. This approach achieved specific silencing of the *MDR1* gene, ultimately reversing drug resistance and inhibiting tumor growth.[110] In colon cancer therapy, co-delivery of anti-KRAS siRNA using a polyhexamethylene biguanide/chitosan complex, or the direct use of CD44-specific siRNA and shRNA constructs (e.g., pSUPER-Retro-shMUC5AC), has been shown to inhibit CD44-mediated downstream signaling pathways, including p-Src, p-AKT, and integrin β4, thereby significantly suppressing tumor cell migration and invasion.[111,112]

6.4. CAR-T cell therapy

As a marker of CSCs and a key regulator of the TME, CD44 has emerged as an attractive target for CAR-T therapy in solid tumors. In recent years, numerous preclinical studies

have validated the antitumor activity of CD44-targeted CAR-T cells. Porcellini *et al.*[113] demonstrated that CD44v6-CAR-T cells exhibited significant antitumor effects in various solid tumor models with high CD44v6 expression, including lung and ovarian cancer. These cells not only effectively suppressed tumor growth but also significantly prolonged the survival of tumor-bearing mice. Similarly, in an HCC model, CD44-CAR-T cells demonstrated superior tumor suppression and survival benefits compared with both normal T cells and mock T cells.[114]

To further enhance the antitumor efficacy of CAR-T cells, researchers have developed combination therapeutic strategies. Alhabbab[115] reported that the CD44-CAdTrio system, which combines a CD44v6-specific bispecific T-cell engager with an oncolytic adenovirus (CAdDuo) encoding a PD-L1 antibody (an immune checkpoint inhibitor) and IL-12 (an immunostimulatory cytokine), significantly enhanced the cytolytic activity of HER2-CAR-T cells against CD44v6$^+$ head-and-neck squamous carcinoma cells, leading to improved tumor control and prolonged survival.[116]

Despite these encouraging preclinical data, the clinical translation of CD44-CAR-T therapy faces significant challenges. To date, no CD44-targeted CAR-T cells have entered clinical trials for solid tumors.[115] The primary obstacles are as follows: (1) The constitutive expression of CD44 in various normal tissues, including T cells, fibroblasts, and macrophages, may lead to the risk of on-target, off-tumor toxicity; (2) Existing xenograft models fail to fully recapitulate the complexity of the human tumor immune microenvironment; and (3) The immunosuppressive TME typical of solid tumors, which limits CAR-T cell infiltration and effector function.

6.5. Nanocarrier-based therapy

Liposomal nanoparticles, as a well-established drug delivery system, provide a versatile platform for tumor-targeted therapy. This technology offers significant advantages. On one hand, it can efficiently encapsulate plasmid DNA or therapeutic agents into stable nanocarrier systems, demonstrating excellent biocompatibility and low toxicity.[88,117] On the other hand, when conjugated with tumor-specific targeting ligands, such as CD44-targeting peptides, the active targeting efficiency toward tumor tissues can be significantly enhanced, enabling the precise delivery of therapeutic molecules.[117-119]

In the field of molecular imaging, non-invasive imaging techniques have enabled dynamic monitoring of molecular events within tumors, including alterations in gene expression profiles, tumor progression, and assessment of therapeutic response.[120,121] These imaging modalities play an increasingly crucial role in the precise diagnosis of tumors, prediction of treatment response, and monitoring of therapeutic efficacy, thereby providing a critical basis for the formulation of personalized treatment strategies.[122]

Leveraging the high expression of CD44 in HCC, researchers have developed HA-modified chitosan-encapsulated magnetic nanoparticles (HA-IM-CBs). Studies have confirmed that this targeted delivery system significantly enhances the cytotoxic, anti-proliferative, and pro-apoptotic effects of imatinib (IM) in HepG2 cells, offering a novel strategy for the targeted therapy of HCC.[123] Notably, HA not only functions as a targeting ligand but also promotes the proliferation of HCC by upregulating CD44 expression and activating glucose metabolic pathways. This further substantiates the pivotal regulatory role of CD44 in HCC progression and highlights the therapeutic potential of CD44-targeted therapy.[96]

7. Future perspectives

The extensive body of research detailed in this review establishes CD44 as a central and multifaceted oncogenic driver and a highly promising therapeutic target in HCC. While diverse targeting modalities—from mAbs to CAR-T cells and nanocarriers—have demonstrated promising preclinical efficacy, their successful clinical translation hinges on addressing several key challenges unique to the liver TME.

A promising future direction lies in the strategic integration of CD44-targeted therapies with existing treatment modalities. For instance, combining CD44-targeted agents with immune checkpoint inhibitors presents a promising opportunity to overcome immunosuppression and elicit synergistic antitumor effects. Similarly, such combination strategies could enhance the efficacy of conventional chemotherapy or radiotherapy by sensitizing therapy-resistant CD44$^+$ CSCs.

To realize this potential, future research must prioritize elucidating the isoform-specific roles of CD44 in HCC pathogenesis, metastasis, and therapeutic resistance. Concurrently, the development of advanced delivery systems and multimodal imaging probes will be critical for precise tumor targeting and real-time treatment monitoring. By navigating these challenges, the field can establish a robust paradigm for the precise modulation of the HCC TME and CD44$^+$ CSCs, ultimately improving prognostic stratification, survival, and quality of life.

8. Conclusion

In summary, CD44 holds significant clinical relevance as both a potential diagnostic marker and therapeutic target for liver cancer. Continued research into the mechanisms underlying CD44's involvement in the initiation, progression, and metastasis of liver cancer, as well as the

development of diagnostic techniques and treatment approaches targeting CD44, offer promise in enhancing the prognosis and quality of life for individuals affected by this disease.

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Conflict of interest

The authors declare no conflicts of interest.

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