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Narrative Review

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Casein kinase 1 epsilon (CK1ε) as a potential therapeutic target in chronic liver disease

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ABSTRACT

Importance: Chronic liver disease (CLD) is a significant global health concern, often progressing to hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma in both humans and animals. Despite substantial research efforts, effective CLD treatments remain scarce. Casein kinase 1 epsilon (CK1ε), a serine/threonine kinase, plays a pivotal role in several critical signaling pathways, including the Wingless/Integrated (Wnt)/β-catenin, HIPPO, and mitogen-activated protein kinase (MAPK) pathways, all of which contribute to liver disease progression.
Observations: CK1ε regulates key pathways that drive liver fibrosis, inflammation, and cancer. Its involvement in lipid metabolism and adipogenesis links CK1ε to metabolic dysfunctional-associated steatotic liver disease. Elevated CK1ε levels are observed in disease models beyond CLD, underscoring its broad role in pathological conditions. Moreover, CK1ε phosphorylates critical proteins such as Wnt/β-catenin, RAS/MAPK, phosphoinositide 3-kinase/protein kinase B, transcription coactivators yes-associated protein 1 and the PDZ-binding motif, and Sprouty homolog 2, suggesting potential influence on liver cell function and fibrosis development. Preclinical models demonstrate that CK1ε inhibitors, including PF-4800567, PF-670462, and IC261, effectively reduce tumor growth and fibrosis of variable etiologies.
Conclusions and Relevance: CK1ε's central role in liver disease progression makes it a compelling target for therapeutic strategies. Targeting CK1ε with small molecules or gene therapies could offer novel treatment avenues for CLD. However, challenges related to target specificity and safety must be addressed. Further research and translational studies could pave the way for precision medicine approaches, enhancing treatment outcomes for both animals and humans with CLD.

Keywords: Casein kinase 1 epsilon; end stage liver disease; signal transduction pathways; therapeutics

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Conflict of Interest
The authors declare no conflicts of interest.

Data Availability Statement
The datasets used or analyzed during the current investigation (**Supplementary Fig. 1**) are available from the corresponding author upon reasonable request.

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INTRODUCTION

Chronic liver disease (CLD) represents a global health burden, characterized by the replacement of healthy tissue with scar tissue [1]. This pathological remodeling leads to fibrosis and a decline in liver function [2]. Patients with CLD may develop cirrhosis, hepatocellular carcinoma (HCC), or hepatic failure [3]. According to a 2023 update on liver disease, cirrhosis and HCC cause approximately two million deaths annually, highlighting a significant public health crisis [4]. In veterinary medicine, liver diseases are commonly diagnosed in dogs [5], often as a consequence of chronic hepatitis, and similar conditions have been reported in camels [6] and felines [7]. Although the exact pathogenesis of liver fibrosis in dogs and cats is still under investigation [5,7] existing evidence suggests that the fibrogenic mechanisms, particularly those leading to hepatic stellate cell activation, are comparable to those observed in humans and other animal species [8].

Despite the widespread impact of liver disease in both animals and humans, with etiologies including metabolic syndrome (e.g., metabolic dysfunctional-associated steatotic liver disease, MASLD), toxins, infections (e.g., viral hepatitis), genetic factors, alcoholism, and autoimmune diseases [9], researchers continue to seek an effective and safe management strategy to mitigate the risk of end-stage liver diseases like HCC, which are associated with high comorbidity and mortality rates [10]. The liver performs critical functions, including plasma protein-albumin production, bilirubin metabolism, detoxification, and the maintenance of homeostasis through clotting factors [11]. Consequently, the loss of liver function has profound effects on overall health, contributing to a spectrum of systemic complications that increase morbidity and mortality rates in affected individuals [12]. Current therapeutic approaches rely heavily on lifestyle modifications, pharmacological interventions, and, in advanced cases, liver transplantation [13]. However, these strategies are often insufficient to halt disease progression, particularly in patients with metabolic or autoimmune etiologies, necessitating the development of novel and precise treatments. Therefore, noninvasive therapeutic approaches should be explored for CLD, particularly when lifestyle interventions are ineffective. Moreover, CLD has significant implications for veterinary medicine, as animals with fibrotic livers, cirrhosis, and/or HCC have declined liver function resulting in systemic complications that may culminate into poor health and well-being of animal.

Gene therapy, emerging as a promising option in modern therapies for inherited metabolic liver disorders, diversifies treatment options [14] and is consequently attracting increased attention from researchers. Recent discoveries in molecular and cellular biology have offered opportunities for treating non-inherited forms of liver disease via gene-directed therapies [15]. By focussing on molecular drivers of fibrosis and carcinogenesis, gene therapy may address important gaps in the present therapeutic landscape, providing noninvasive and perhaps curative options for CLD patients. To verify the preclinical efficacy of innovative gene-targeted therapies that may reverse scar formation, extensive research is necessary to identify the genes involved in the pathogenesis of liver failure. Thus, this review will attempt to validate the consideration of a protein kinase known as casein kinase 1 epsilon (CK1ε) as a potential therapeutic target in CLD, while acknowledging that this hypothesis involves multiple factors and pathways that cannot be extensively explored. Translational research [16] aims to find novel molecular targets like CK1ε, which has great potential to change the therapy paradigm for CLD. Recent advances in precision medicine have shown that targeting individual kinases can have a transformative effect on other diseases, such as cancer and inflammatory disorders, by modifying disease-causing pathways [17].

The CK1ε protein, encoded by the CSNK1E gene, is part of the CK1 family of serine-threonine-specific protein kinases, and includes seven other isoforms: α, β, γ1, γ2, γ3, δ, and ε as well as several splice variants for CK1α, δ, ε, and γ3 (**Fig. 1A**) [18]. The CK1 protein family is essential in numerous cellular functions, including membrane trafficking, cytokinesis, vesicular transport, ribosome synthesis [19], DNA repair, signal transduction pathways, and as regulators of circadian rhythm biological activities in eukaryotic cells [20,21]. CK1 kinases are ubiquitous and have been identified as auxiliary drivers in various biological functions [22], linked to metabolic diseases and cancers [23,24].

Dysregulation of the CK1ε enzyme is associated with various physiological conditions, ranging from tumorigenesis to neurological diseases [25]. CK1ε recognizes N-terminally acidic amino acids, donating phosphate from ATP, with its affinity for ATP dependent on substrate type. CK1ε activity is linked to the Wingless/Integrated (Wnt) signaling cascade and membrane transport because its acceptor amino acids are often primed by phosphorylated serine or threonine [26]. Due to its ubiquitous nature, CK1ε plays critical roles in various

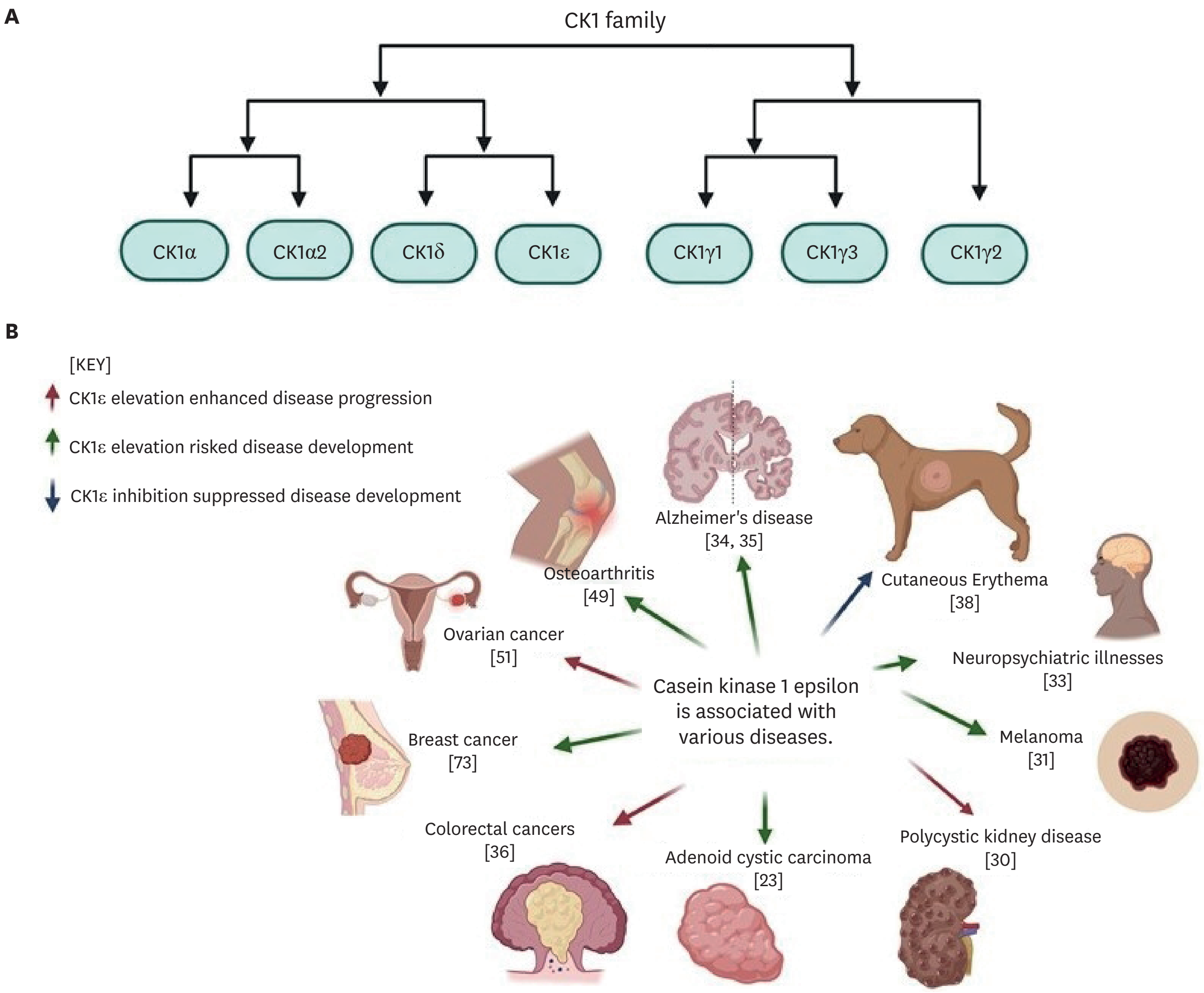

Fig. 1. CK1ε is typically elevated in other disease models. (A) CK1 protein isoforms α, γ1-3, δ, and phylogenetic tree based on [24]. (B) CK1ε is associated with various pathological conditions such as neurodegenerative diseases and tumorigenesis. This graph was created with BioRender.com.
CK1, casein kinase 1.

cellular processes, including cell survival, cell cycle regulation, metabolism, tumorigenesis, vesicular transport, DNA repair, and circadian rhythm regulation [24]. Extensive research has linked CK1ε to circadian rhythms, particularly through the CK1-dependent phosphoswitch controlling period circadian protein homologs 1–3 [27]. Furthermore, dysregulation of circadian rhythms has been linked to the onset of metabolic liver diseases such as MASLD and metabolic dysfunction-associated steatohepatitis (MASH) in mice [28]. Given its involvement in circadian biology, metabolism, and signal transduction, CK1ε represents a nexus of pathways critical to liver health and disease. Moreover, among the other CK family members in the public gene expression repository expression omnibus (GEO) database (www.ncbi.nlm.nih.gov/geo/), the CK1ε gene in liver samples from both healthy individuals and patients with MASLD or MASH shows overexpression (**Supplementary Fig. 1**) [29]. In the context of liver physiology and pathophysiology, our research has demonstrated that CK1ε regulates lipid metabolism via tumor necrosis factor receptor (TNF)-associated factor 3-transforming growth factor (TGF)-β activated kinase 1-dependent signaling. Initial studies using liver-specific CK1ε deficient mice have revealed its regulatory effects on metabolism, notably exhibiting a phenotype that promotes fatty liver by upregulating the mitogen-activated protein kinase (MAPK) pathway [29]. This emerging evidence suggests that CK1ε's regulatory network extends beyond its canonical functions, potentially influencing systemic metabolic homeostasis and liver regeneration. The dysregulation of CK1ε in liver disease models could provide new insights into veterinary clinical practice, especially in terms of improving early diagnosis and treatment strategies for CLD in animals.

Mounting evidence supports targeting CK1ε as a therapeutic approach due to its role in the pathogenesis of CLD. Therefore, this review explores CK1ε's unique position at the crossroads of inflammation, fibrosis, and carcinogenesis making it an attractive candidate for drug development, particularly in the context of personalized medicine approaches. Additionally, the potential to leverage CK1ε in combination therapies may provide novel avenues for addressing the heterogeneity of liver disease progression, tailoring interventions to individual patient profiles/animals based on molecular and genetic markers. The review further discusses the challenges of developing CK1ε-targeted therapies, including issues of specificity and delivery, and outlines future directions for research that could inform the design of innovative treatments for CLD.

METHODS

In this review, we examined CK1ε expression patterns in various disease models and explored the signaling pathways linking CK1ε to liver disease progression. A comprehensive literature search was conducted using peer-reviewed databases, including PubMed, Scopus, and Web of Science. To capture the broader scope of CK1ε research, we included studies investigating its expression and functional roles across diverse disease models, such as cancer, neurodegenerative disorders, and inflammatory diseases, to identify commonalities and unique mechanisms relevant to liver disease progression. Thus, data extraction centered on the role of CK1ε in molecular pathways, its involvement in liver fibrosis and carcinogenesis, and its potential as a therapeutic target. Additionally, the graphical figure (**Fig. 1**) was created using Science Suite Inc. DBA BioRender (Canada), and **Fig. 2** was created using Microsoft PowerPoint (Microsoft, USA).

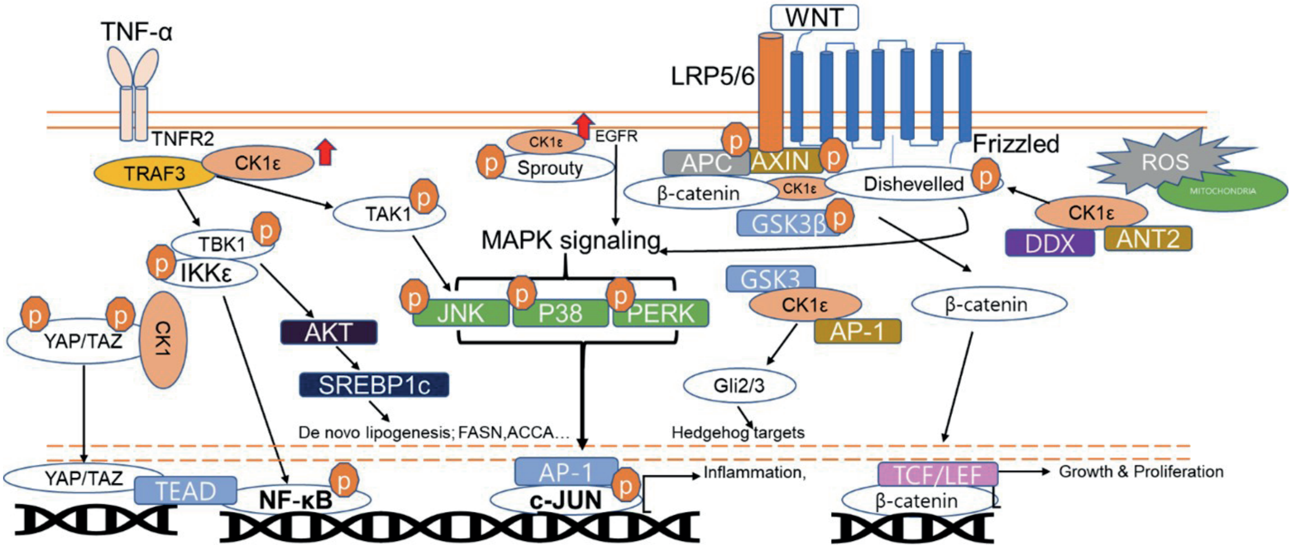

Fig. 2. Activation of signaling pathways associated involving CK1ε protein important for chronic liver disease progression. Key signaling proteins include: Wnt-β-catenin signaling via DVL [48], RAS/MAPK and PI3K/AKT pathways [61-63], the hedgehog pathway [52], HIPPO signaling pathway [82], and SMAD family of proteins [83]. This graph was created using Microsoft PowerPoint.

CK1, casein kinase 1; Wnt, Wingless/Integrated; DVL, disheveled; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3 kinase; AKT, protein kinase B; TNF, tumor necrosis factor receptor; YAP, yes-associated protein 1; TAZ, PDZ-binding motif; GSK, glycogen synthase kinase; ROS, reactive oxygen species; DDX, DEAD-box RNA helicases; ANT2, adenine nucleotide translocase 2; JNK, c-Jun N-terminal kinase; Gli, glioma-associated oncogene homolog; NF-κB, nuclear factor-kappa B.

RESULTS

Changes of CK1ε levels in various diseases including CLD

Protein kinases have broadly been implicated in human and animal diseases; however, the therapeutic potential of CK1ε in liver diseases remains to be established. A previous study revealed that both mRNA and protein levels of CK1ε are associated with the development of polycystic kidney disease in mice and humans (**Fig. 1B**) [30]. Moreover, another study assessed the association between the cytoplasmic expression of the CK1ε protein in melanoma cells and clinical outcomes, finding that melanoma patients who overexpress this protein are at a higher risk for distant metastases [31]. Furthermore, in 687 multiple myeloma patient samples, elevated levels of CK1ε, CSNK1D (CK1δ), and OxPhos genes were linked to disease progression and poor prognosis [32]. Comprehensive genotyping in 384 schizophrenic patients and 502 healthy controls from the Chinese Han population revealed that a genetic variant in the CK1ε gene significantly increases schizophrenia risk [33]. Further research into neurodegenerative conditions such as Alzheimer's disease, characterized by memory loss, speech issues, and mood swings, identified elevated CK1ε in the human brain [34,35]. Additionally, CK1δ/ε regulated the degradation of the amino-terminal enhancer of split and promoted the growth of colorectal tumor organoids in the Apc$^{Min/+}$ colon cancer model (mouse-bearing intestinal cancers) and liver metastases, highlighting the significance of CK1ε in the progression and spread of colorectal cancer [36]. In a study examining the planar cell polarity (PCP) pathway's role in progressing severe lymphocytic leukemia, an upregulation of CK1ε among other proteins was noted in the B lymphocytes of patients, establishing this PCP as a critical regulator of chronic lymphocytic leukemia [37]. Most molecular signaling pathways depend on the extent of CK1ε elevation, suggesting that its prominent role in other diseases may indicate CK1ε as a potential driver of CLD pathogenesis. Additionally, CK1ε could serve as a biomarker for CLD and as a therapeutic target. Elevated

CK1ε levels in the liver tissues and sera of patients with advanced CLD correlate with the severity of the disease, indicating that monitoring CK1ε levels may provide useful insights into illness development and therapy response.

CK1ε levels may provide valuable insights into disease progression and therapeutic responses, making it a significant target in liver fibrosis. Beyond human medicine, CK1ε's role could extend to veterinary applications, particularly in animals with CLD. Its involvement in stellate cell activation in animal models offers crucial perspectives for comparative medicine [8]. Highlighting its veterinary relevance, a study investigating the effects of selective CK1ε/δ inhibition using PF670462 in canine mast cells revealed that PF670462 reduced the mRNA expression of FcεRIα and β, but not γ, and also decreased protein expression of FcεRI in a canine mast cell line [38]. Furthermore, PF670462 suppressed IgE-mediated immediate-type cutaneous erythema in dogs, suggesting that CK1ε/δ regulate FcεRI expression and IgE-mediated cutaneous reactions.

CK1ε involvement in signal transduction pathways involved in liver disease progression

The Wnt/β-catenin signaling pathway is a fundamental process that regulates embryonic development, cellular proliferation, and differentiation [39], and it plays a significant role in the pathogenesis of CLDs, including HCC and cholangiocarcinoma [40]. CK1ε, a protein involved in Wnt/β-catenin signaling pathway, interacts with dishevelled (DVL), a key component of the Wnt signaling pathway. This interaction also targets a protein called dead box RNA helicase (DDX3X), phosphorylating it at its c-terminus. This phosphorylation creates an environment conducive to malignancies, neurological diseases, and viral infections (**Table 1**) [41,42]. DVL proteins help regulate a range of cellular activities [43]. When CK1ε activates DVL through its interaction with DDX3X, it leads to the regulation of Wnt signaling by facilitating the phosphorylation of Axin and DVL 2 proteins [44,45]. Interesting observation is reported that in the activated canine hepatic progenitor cell niche, the Wnt/β-catenin and Notch signaling pathways are enhanced [46]. CK1ε being known for its regulatory role in these pathways, could be a crucial mediator in activation and proliferation of animal's hepatic progenitor cells. Notably, during liver scar formation, Wnt signaling can be β-catenin dependent or independent, with β-catenin-independent signaling referring to the unconventional PCP pathway [47]. As illustrated in **Fig. 2**, CK1ε interaction also influences downstream effects on the stress-activated MAPK family pathway [48]. In other experimental evidence, CK1ε has been implicated in the development of osteoarthritis (OA) in model mice, where CK1ε was overexpressed in knee joint cartilage of OA patients and mice with posttraumatic OA. In this study, chemical inhibition of CK1ε with PF4800567 mitigated the increase in matrix metalloproteinase (MMP) expression 3 and MMP13 mRNA expression induced by interleukin (IL)-1β, depending on c-Jun N-terminal kinase (JNK) but not on β-catenin clear translocation [49]. Consequently, inhibiting CK1ε disrupted the Wnt/β-catenin signaling pathway, affecting cell cycle progression and reducing apoptosis. Another study quantified emerging trends in Wnt signaling in liver diseases, underscoring its correlation with liver fibrosis during 2015–2016, and concluded that Wnt signaling promotes hepatic stellate cell activation and survival [50], a hallmark of CLD. Moreover, in the context of ovarian cancer, the interaction between CK1ε and mitochondrial proteins in human ovarian cancer cells highlights the functional importance of the CK1ε -mitochondrial protein interaction including adenine nucleotide translocase 2 (ANT2), which is associated with poor prognosis. Interestingly, CK1ε participation also resulted in reduced β-catenin activity, which in turn promoted the proliferation and survival of ovarian cancer

Table 1. CK1ε target substrates across various cellular processes

Target protein	Cellular process	Reference
DEAD box RNA helicase 9 (DDX3)	DNA repair	[41]
Beta-catenin Dishevelled, dsh homolog 1–3	Wnt signaling	[48]
Sprouty2 (SPRY2)	FGF-signaling	[65]
Gli family zinc finger 1–3 (Gli1–3)	Hedgehog signaling	[54]
TRAF3	MAPK	[29]
Adenine nucleotide translocase 2 (ANT2)	Mitochondrial function	[51]
Yes-associated protein 1 (YAP)	Hippo signaling pathway	[82]
SMAD family member 3	TGF-beta/Smad signaling	[77]

CK1ε, casein kinase 1 epsilon; Wnt, Wingless/Integrated; FGF, fibroblast growth factor; MAPK, mitogen-activated protein kinase; TGF, transforming growth factor; TRAF3, tumor necrosis factor receptor-associated factor.

cells. Because CK1ε has been identified as a critical player in cancer cell survival through its interaction with mitochondrial proteins, it is suggested that CK1ε could be a viable therapeutic target for developing new anticancer drugs [51]. Therefore, CK1ε interacts with ANT2, coupling mitochondrial function to Wnt/β-catenin signaling, potentially influencing cellular metabolism and energy homeostasis. CK1ε's participation in pathways such as MAPK, MMP3, ANT2, and β-catenin implies its potential impact on CLD pathogenesis. These pathways are critical in mediating inflammatory responses, tissue remodelling, and fibrosis.

Over the years, the hedgehog pathway has emerged as a potential target for liver disease therapy. Known as a 'sister' pathway to Wnt signaling, it plays a role in controlling embryonic development and maintaining adult tissue homeostasis [52]. A dysregulated hedgehog pathway is linked to tumorigenesis. CK1ε modulates the Hedgehog signaling system, affecting the balance between liver regeneration and fibrosis, making it a possible therapeutic target for CLDs. Inhibiting CK1ε may diminish the nucleus accumulation of active Gli proteins, potentially alleviating the pathway's pro-fibrotic and tumorigenic effects in CLDs. Furthermore, CK1 activity influences hedgehog signaling pathways through the proteolysis of cubitus interruptus/glioma-associated oncogene homolog (Gli) [53]. The Gli family zinc finger proteins 1–3, expressed at low levels in differentiated tissues, are transcriptional effectors, suggesting that their inhibition at the pathway's end could be a therapeutic strategy [54]. Nevertheless, CK1ε, governed by protein kinase A and glycogen synthase kinase-3β (GSK-3β), plays a role in the cytoplasmic sequential phosphorylation of the Gli sequestering complex, and inhibiting it could decrease the likelihood of subsequent Gli phosphorylation. CLDs, such as MASLD and MASH, comprehensively show how the hedgehog pathway is linked with the eventual nuclear accumulation of Gli-positive cells [55-57]. Nevertheless, by modulating the Hedgehog signaling pathway, CK1ε can impact the balance between liver repair and fibrosis, making it a potential target for therapeutic strategies in treating CLDs. Inhibiting CK1ε might reduce the nuclear accumulation of active Gli proteins, thereby potentially mitigating the pathway's pro-fibrotic and tumorigenic effects in chronic liver conditions.

The MAPK pathway is implicated in liver injury by regulating events leading to inflammation, apoptosis, and fibrosis, often in association with the RAS protein [58]. RAS, a small GTPase, activates the MAPK pathway in response to extracellular stimuli [59], which in turn triggers various MAPK branches, including extracellular signal-regulated kinase (ERK), p38 MAPK, and JNK. In liver damage, RAS/MAPK signaling promotes inflammation by enhancing the production of pro-inflammatory cytokines like TNF-α and IL-6, activating Kupffer cells, and inducing hepatocyte death through JNK activation [60]. Over time, this process can lead to the progression of liver disease, ultimately resulting in cirrhosis and impaired liver function. Additionally, RAS/MAPK activation stimulates hepatic stellate cells, contributing to fibrosis [61]. The RAS/MAPK pathway is tightly linked with the phosphoinositide 3 kinase/protein kinase B (PI3K/AKT) pathway, both of which contribute significantly to liver injury by regulating cellular growth, survival [62], and metabolism [63]. RAS functions as a molecular switch in response to fibroblast growth factor (FGF), binding to their FGF receptors [64]. Phosphorylation of Sprouty2 (SPRY2) by CK1δ and CK1ε negatively regulates the FGF receptor tyrosine kinase signaling [65], thereby modulating cell signaling pathways. Sprouty proteins, conserved modulators of the MAPK/ERK pathway, play a crucial role in various developmental and physiological processes. In malignant conditions, ERK activation can lead to Sprouty deregulation, impacting cancer development, progression, and metastasis [66]. An inverse association between CK1 transcript abundance and FGF1/FGF7 suggests their potential benefits in treating FGF/SPRY2-related illnesses [65]. Generally, the FGF cellular pathway stimulates the RAS/MAPK and PI3K/AKT pathways [67,68]. This cascade is crucial because our previous study demonstrated that CK1ε plays a significant role in amplifying downstream MAPK signaling. This amplification lead to the recruitment of AKT-GSK-3β proteins, particularly in MASH model mice [29]. The recruitment of these proteins disrupted lipid metabolism thereby increasing inflammation, a hallmark of MASH, by influencing the translation of c-Jun, a component of the AP-1 transcription factor complex involved in inflammatory responses. Therefore, studying CK1ε and its role in CLD could have important implications in both human and veterinary medicine, making it a relevant area of research. Early prevention and treatment of CLDs may be possible by recognizing the factors driving the molecular pathways of these diseases. However, due to the cryptogenic nature of most liver diseases [69], damage-associated molecular pattern-mediated activation of the AKT/mammalian target of rapamycin (mTOR) and RAS/MAPK pathways can lead to rapid liver tumor growth [70]. CLD from different causes may result in HCC through various mechanisms showing clinical and pathological diversity, often characterized by consistent mRNA expression of ERK, PI3K, and BRAF in tumorous tissues regardless of CLD etiology [71]. The PI3K/AKT/mTOR cascade is pivotal in hepatocarcinogenesis [72]. In breast cancer cell lines, CK1ε positively influences AKT signaling by inhibiting protein phosphatase 2A [73]. Furthermore, CK1ε enhances c-myc protein levels by phosphorylating eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) at residues different from those affected by mTOR. Interestingly, most mTORC1 inhibitors do not significantly affect 4E-BP1 phosphorylation or cell proliferation across various cell types [74]. This finding suggests that CK1ε may be a contributing factor in various metabolic diseases, as 4E-BP1 sequesters EIF4E, inducing active dependent adipogenesis of the EIF4A complex [75]. This pathway could elevate the risk of diet-related liver diseases, such as MASH syndrome. Research indicates that 4E-BP1 is regulated via AMP-activated protein kinase (AMPK) [76]. Intriguingly, CK1ε has been found to be activated through the phosphorylation of AMPK at its regulatory tail at S389 [77]. This crucial energy sensor, AMPK, subsequently modulates the transcription factors peroxisome proliferator-activated receptor gamma and CCAAT/enhancer-binding protein, governing adipocyte differentiation [78]. Therefore, CK1ε plays a central role in modulating RAS/MAPK and PI3K/AKT signaling. CK1ε achieves this through the direct phosphorylation of SPRY2 and DDX3X, which regulate critical aspects of liver cell function. CK1ε activation amplifies MAPK signaling and recruits proteins like AKT and GSK-3β that drive liver damage. Therefore, targeting CK1ε and its associated pathways, including RAS/MAPK, PI3K/AKT, and FGF/SPRY2, has the potential to create therapeutic techniques to mitigate liver disorders and their development to HCC.

In another liver biology-associated signaling pathway, the HIPPO signaling pathway has been found to regulate liver metabolism and cell proliferation through the downstream regulation of the transcription coactivators yes-associated protein 1 (YAP) and the PDZ-binding motif (TAZ) [79]. Phosphorylation at Ser 381 is crucial for inducing phosphorylation of a phosphodegron in YAP by CK1δ/ε [80,81]. As a temporal regulator, CK1ε phosphorylates YAP at SER-127 [82]. Consequently, YAP/TAZ can regulate other oncogenic pathways including the Wnt pathway, the AMPK protein family, and Notch, which drive liver fibrosis and cancer development. Therefore, targeting CK1ε to prevent phosphorylation of YAP could effectively influence other transcription factors associated with liver disease.

Another study found that CK1ε plays a key part in regulating TGF-β in the SMAD family of proteins [83]. TGF-β is a critical regulator of liver fibrosis, which is a common characteristic of CLD. CK1ε regulates TGF-β signaling by affecting the stability and activity of critical components. Dysregulation of TGF-β signaling in CLD causes increased extracellular matrix formation and fibrosis [83]. Therefore, targeting CK1ε could offer a novel therapeutic approach for mitigating liver fibrosis and slowing the progression of CLDs.

Potential therapeutic approaches to alleviate CLD

CK1ε inhibitors have garnered significant interest due to CK1ε's role in critical pathways associated with CLD. Numerous small-molecule inhibitors of CK1ε have been synthesized and are currently being evaluated for their therapeutic potential [25,84,85]. Preclinical studies have confirmed the effectiveness of these inhibitors in reducing cancer rates, justifying further investigation in clinical trials [85]. Examples of such inhibitors include PF-4800567 and PF-6704624. PF-4800567 is a pyrazolopyrimidine IUPAC name 3-[(3-Chlorophenoxy)methyl]-1-(Tetrahydro-2h-Pyran-4-Yl)-1h-Pyrazolo[3,4-D]pyrimidin-4-Amine [86], and PF-6704624 is a compound named 3-[(3-chlorophenoxy)methyl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine [87]. These two Pfizer CK1ε inhibitors have proven valuable in the study of CK1ε and CK1δ inhibition [86]. Pharmacological suppression of ovarian cancer cell lines by PF-670462 and PF-4800567 led to significant reductions in growth rates [51]. The study also revealed that overexpression of the CK1ε isoform, abundantly expressed in normal ovarian surface epithelial cells, is crucial for cancer cell proliferation and migration [51]. Furthermore, PF-670462, a dual CK1δ/ε inhibitor, significantly reduces bleomycin-induced lung fibrosis in rats, indicating CK1δ/ε as a potential therapeutic target for inflammatory pulmonary fibrosis [87]. Therefore, exploring PF-4800567 and PF-670462 for liver diseases, based on their inhibitory effects on CK1δ and CK1ε and the involvement of these kinases in various pathophysiological processes, is warranted. If CK1ε is overexpressed in HCC, as in ovarian cancer, CK1 inhibitors such as PF-4800567 and PF-670462 could potentially reduce tumor growth or metastasis [88], offering a novel therapeutic strategy for HCC, especially in CK1ε-driven tumors.

IC261, a CK1δ/ε specific inhibitor with the IUPAC name 3-[(2,4,6-trimethoxyphenyl) methylidenyl]-indolin-2-one, has demonstrated anti-tumor effects against pancreatic tumors and glioblastoma, and has been effective in HCC treatment. IC261 showed significant anti-tumor activity in HCC cell lines and xenograft models [89]. By inhibiting CK1δ/ε, IC261 significantly alters the pathways regulated by these kinases, exhibiting robust anti-tumor efficacy [90], positioning it as a potential candidate for liver cancer therapy.

D4476, with the IUPAC 4-[4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-5-pyridin-2-yl-1H-imidazol-2-yl]benzamide, is a selective inhibitor of CK1δ/ε [91]. It effectively inhibits CK1-mediated signaling pathways crucial to cancer, including the Wnt/β-catenin pathway, thereby limiting cancer cell proliferation [92,93]. Furthermore, SR-3029 is a potent and selective inhibitor of

Table 2. CK1ε inhibitors: targets, and therapeutic potential in liver disease

Inhibitor	IUPAC	Target	Therapeutic potential
PF-4800567	3-[(3-Chlorophenoxy)methyl]-1-(Tetrahydro-2h-Pyran-4-Yl)-1h-Pyrazolo[3,4-D]pyrimidin-4-Amine	CK1ε/δ	Reduces cancer growth and metastasis [88]: potential therapy for HCC
PF-6704624	3-[(3-chlorophenoxy)methyl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine	CK1ε/δ	Reduces lung fibrosis [86]: therapeutic potential for CK1ε-driven fibrosis
IC261	3-[(2,4,6trimethoxyphenyl)methylidenyl]-indolin-2-one)	CK1ε/δ	Robust efficacy in HCC [89]: potential anti-tumour effects in CLD
D4476	4-[4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-5-pyridin-2-yl-1H-imidazol-2-yl]benzamide	CK1ε/δ	Inhibits Wnt/β-catenin [92 93]: potential in limiting cancer progression
SR-3029	6,7-Difluoro-1H-benzoimidazol-2-ylmethyl)-[9-(3-fluoro-phenyl)-2-morpholin-4-yl-9H-purin-6-yl]-amine	CK1ε/δ	Inhibition of CK1δ/CK1ε provokes myeloma cell death [32]: therapeutic potential fibrosis reduction, HCC and MASLD
Pyrvinium pamoate	2-(2-(2,5-Dimethyl-1-phenyl-1H-pyrrol-3-yl)vinyl)-6-(dimethylamino)-1-methylquinolin-1-ium bis-4,4'-methylenebis(3-hydroxy-2-naphthoate)	Wnt/β-catenin	Anti-tumor activity [94]: potential anti-tumor/fibrotic effects in liver disease.
(R)-Isomer of CR8	(2*R*)-2-[[9-propan-2-yl-6-[(4-pyridin-2-ylphenyl) methylamino]purin-2-yl]amino]butan-1-ol	Wnt/β-catenin	Inhibition of Wnt/β-catenin pathway [30]: potential as an anti-fibrotic and anti-tumor agent
TAK 715	N-[4-[2-ethyl-4-(3-methylphenyl)-1,3-thiazol-5-yl] pyridin-2-yl]benzamide	Wnt/β-catenin/CK1ε/δ	Inhibition of the Wnt/β-catenin pathway [95]: potential to prevent the aberrant activation of β-catenin, which plays a role in the activation of HSCs, leading to fibrosis

CK1, casein kinase 1; HCC, hepatocellular carcinoma; CLD, chronic liver disease; MASLD, metabolic dysfunctional-associated steatotic liver disease; Wnt, Wingless/Integrated; HSC, hepatic stellate cell.

CK1δ and CK1ε [32]. It effectively suppresses tumor growth by disrupting the circadian clock and blocking Wnt signaling, both pivotal in cancer progression. It has shown promising preclinical activity against several cancers, including colorectal and breast cancer [90].

Additional CK1 activity-affecting inhibitors also include pyrvinium pamoate [94], CR8, (R)-Isomer [30], and TAK 715 [95] (**Table 2**). These inhibitors are potent antagonists of the Wnt/β-catenin signaling pathway but have been minimally studied in the context of liver fibrosis.

Various genetic methods can target CK1ε and mitigate CLD; however, in the context of liver disease, these are relatively specialized. Gene silencing technologies, such as siRNA [29] and CRISPR/Cas9 [96], provide another strategy for targeting CK1ε in CLD. These modalities could specifically reduce CK1ε expression in liver cells, thus influencing the pathological mechanisms underlying CLD progression. However, the delivery and specificity of these genetic tools present challenges that need resolution.

DISCUSSION

Liver fibrosis is a progressive condition characterized by excessive deposition of extracellular matrix proteins that can result in cirrhosis and HCC, both of which are hallmarks of CLD [97,98]. CK1ε regulates signaling cascades such as; TGF-β and Wnt/β-catenin, which are key drivers of fibrogenesis, making it a potential target for therapeutic intervention [99]. Recent studies suggest that CK1ε may be involved in lipid metabolism and hepatic steatosis, processes central to MASLD progression [29]. Moreover, CK1ε is involved in the Wnt/β-catenin pathway, a crucial pathway in liver fibrosis and regeneration [100,101]. It phosphorylates β-catenin, promoting gene transcription and activating HSCs, a key effector cell in fibrogenesis [102]. Understanding CK1ε interactions with other key metabolic and fibrotic pathways could help tailor therapeutic strategies for a broader range of liver diseases. By modulating CK1ε activity, we could potentially attenuate fibrosis, improve liver function, and reduce tumorigenesis in advanced liver disease.

CK1ε's involvement in liver diseases and metabolic disorders extends beyond human medicine, making it relevant in veterinary care. In animals, liver fibrosis and metabolic diseases like fatty liver disease and MASH are also major concerns, particularly in species such as dogs and cats [103]. Additionally, as research has indicated the role of CK1ε in immune responses, there may be therapeutic opportunities for managing autoimmune conditions or inflammatory diseases that affect the liver in veterinary species. Given that CK1ε plays a significant role in regulating immune responses, studies on CK1ε in veterinary species could offer insights into new treatment options for conditions like hepatic inflammation, fibrotic diseases, and liver tumors in companion animals, such as dogs and cats. Understanding the role of CK1ε in veterinary species could also help tailor more targeted therapies for CLDs in animals, with the potential for improved clinical outcomes.

Exploring the therapeutic potential of CK1ε can steer research towards the development of CK1ε-specific inhibitors, expanding treatment options for CLD. However, targeting CK1ε with drugs faces challenges due to its high homology with CK1δ [104]. Existing inhibitors lack specificity for CK1ε; therefore, off-target effects are a significant concern, underscoring the need for dependable delivery systems for genetic therapies. Hence, the therapeutic targeting of CK1ε presents substantial potential; yet, how to specifically identify CK1ε activation sites within these substrates remains uncertain. Comprehensive clinical studies are necessary to confirm the safety and effectiveness of CK1ε-targeted therapies in CLD patients. Further research into the underlying mechanisms could illuminate aspects of substrate specificity, subcellular localization, and the catalytic action of these proteins. Such therapeutic advances demand rigorous, focused research in metabolic and/or fibrotic liver disease models, as exploring CK1ε-focused gene therapy could lead to more precise treatments. Future studies should aim at developing selective CK1ε inhibitors with fewer side effects and identifying patient subgroups most likely to benefit from CK1ε-targeted treatments. Additionally, the role of CK1ε in the broader context of liver disease, including its interactions with other signaling pathways, merits further exploration.

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SUPPLEMENTARY MATERIAL

Supplementary Fig. 1

Human hepatic gene expressions of the different CK1 family of proteins in liver disease patients. (A) Pooled RNA-sequencing dataset obtained from normal, MASLD, and (B) metabolic dysfunction-associated steatohepatitis human liver samples and CK1ε (CSNK1E) gene expression at various MASLD activity levels (commonly referred to as NAFLD scores) in human liver samples.

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