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Review Article

Prospect of Animal Models for Acute-on-chronic Liver Failure: A Mini-review

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Abstract

Acute-on-chronic liver failure (ACLF) is a clinical syndrome that develops in patients with chronic liver diseases following a precipitating event and associated with a high mortality rate due to systemic multiorgan failure. Establishing a suitable and stable animal model to precisely elucidate the molecular basis of ACLF pathogenesis is essential for the development of effective early diagnostic and treatment strategies. In this context, this article provides a concise and inclusive review of breakthroughs in ACLF animal model development.

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Introduction

The liver is a unique, irreplaceable, and exceptional multifunctional organ in the vertebrate kingdom,[1] as its vital functions vary with age, ranging from the performance, maintenance, and regulation of hematopoiesis in the fetal liver to the metabolism, detoxification and endo/exocrine secretion of hormones and enzymes in the fully developed liver.[2,3] The mature liver is mainly composed of hepatocytes and cholangiocytes, which are generated from hepatoblast differentiation,[4] as well as five distinct types of cellular components, including sinusoidal endothelial cells, macrophages, different types of lymphocytes, dendritic cells and stellate cells.[5–7] Liver failure, among liver disease burdens, is the major health issue encountered worldwide and spectacularly contributes to increased mortality and morbidity, which has significant implications for universal health.[8–10] Chronic liver disease (CLD) remains a global health challenge, with up to 2.1 million deaths, which constituted 2.3–2.6% of the global deaths rate.[11]

Acute-on-chronic liver failure (ACLF): the clinical dilemma

Standing as a distinct disease entity, ACLF is a catastrophic syndrome characterized by an acute deterioration of pre-existing CLD, usually related to a precipitating event and associated with an increased mortality rate due to multiple organ failure.[12–15] Although ACLF lacks a universal standard definition and the detailed pathogenesis mechanism is still unclear, Moreau *et al*. first identified the ACLF diagnostic features and development criteria over the course of acute decompensation of cirrhosis among Western populations.[16] However, the definition of ACLF based on cirrhosis, irrespective of etiology, remains controversial. Wu *et al*. developed a new ACLF definition based on the fact that hepatitis B virus (HBV)-related ACLF exhibits unique clinical characteristics, and their new definition bridges the gap in the criteria for HBV-related ACLF diagnosis.[13] Recently, researchers highlighted immune-metabolism disorder as a key factor in deciphering ACLF pathophysiology, irrespective of the ACLF disease etiology and/or precipitating event.[17–19] Currently, ACLF-specific treatments are deficient, and organ support and complication prevention are the only substitutes. If medical treatment fails, transplantation is the only option in eligible subjects,[20] which is hindered by the shortage of organ donors, the scarcity of deceased organs and the inherent risk of living donor hepatectomy.[21]

Need of ACLF animal models

The use of animal models is vital in medical research and is mandatory to capture the whole picture of disease pathology to gain beneficial outcomes for both humans and animals, although social debates about the moral aspects of their applications, as well as animal welfare rules, might frequently upsurge.[22] As science has evolved, researchers

Keywords: Liver failure; Acute-on-chronic liver failure; Animal model; Hepatotoxicants; Inflammation.

Abbreviations: ACLF, acute-on-chronic liver failure; CLD, chronic liver disease; COSSH, Chinese Group on the Study of Severe Hepatitis B; D-gal, D-galactosamine; HSA, human serum albumin; HBV, hepatitis B virus; HBV-ACLF, HBV-induced acute-on-chronic liver failure; LPS, lipopolysaccharide; NASH, nonalcoholic-steatohepatitis; PS, porcine serum.

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have taken advantage of genetic factors and engineering tools such as mutations, transgenesis, chromosomal rearrangements and conditional gene knock-in/out modifications to help pave the way for model genome manipulation, to generate animal models that are vulnerable or resilient to specific diseases in situations where natural models are not achievable. The utilization of animal models in liver failure is indispensable for pathogenesis clarification, the recognition of prospective targets and the development of innovative therapeutic strategies for liver failure;[23] therefore, the availability of appropriate animal models is crucial in studying ACLF to improve our understanding of the dynamic nature of disease occurrence, development and severity progression and to develop novel diagnostic, prognostic, and therapeutic key tools that are dependent on the availability of robust and reproducible experimental animal models. Establishing such a suitable model is difficult due to the complex nature of ACLF prognosis, lack of a clear understanding of ACLF pathogenesis, and shortage of mechanistic studies related to sample unavailability, which escalates the difficulty of ACLF prognostic prediction. In this review, we summarize the current state of the development of ACLF models that potentially replicate clinical ACLF features, with credible prospective trends, a full list of the current ACLF animal models are highlighted in Supplementary Table 1.

Developing ACLF animal models

Distinct strategies have been adopted *in vivo* to induce ACLF in animals. The key elements in establishing such models are the initiation of CLD, mostly liver fibrosis and/or its advanced form cirrhosis, representing the mutual conclusive pathway of most types of chronic liver failure,[24] followed by the administration of a second trigger that acts as precipitating acute insult boosting ACLF development. Agents frequently selected for the acute phase challenge are D-galactosamine (D-gal),[25] bacterial lipopolysaccharide (LPS),[26] ethyl alcohol,[27] the combination of CCl_4 and a bacterial load,[28] acetaminophen and LPS,[29] or D-gal and LPS, which prevail among acute phase triggers.[30–33] Repeated administration of hepatotoxicants is considered the principal technique to generate a chronic state of liver failure, and the frequently applied models are listed below.

CCl_4-based models

Being viewed as harmless chemical and introduced in clinical practice as anthelmintic in humans since 1920, CCl_4 had extended documented history of intoxication in humans, either by ingestion or inhalation, causing serious liver injury.[34] CCl_4 is the principal prototypical hepatotoxicant, and CCl_4 intoxication is the classic way to induce liver injuries in experimental animals. Although CCl_4 can also be used in shorter protocols for the study of acute liver injury,[35] chronic repeated administration of CCl_4 has long been one of the most widely accepted models for inducing CLD; however, a great variety of protocols exist, making it sometimes challenging to compare outcomes from different research groups.[36] Differences in the CCl_4 protocols used include differences in the route of administration, dosage adjustment to match body weight alterations, frequency of dosing, nature of vehicle used, percentage of dilution, and eventual use of phenobarbitone in the drinking water as an enzyme inducer.[37] As shown in Figure 1A, CCl_4 is bioactivated via CYP2E1, expressed mainly by centrilobular hepatocytes, to the noxious trichloromethyl radical (CCl_3^-), which mediates hepatocyte toxic effects through the induction of lipid peroxidation and oxidative stress and ultimately leads to hepatotoxic damage, inflammation, and fibrosis that might progress to hepatic cirrhosis.[38,39]

In general, CCl_4 is administered to mice, rats (BALB/c mice have been described to be the most adequate for modeling, while Wistar rats have higher CCl_4 susceptibility) or rabbits through intragastric administration, intraperitoneal injection, subcutaneous injection or inhalation. The protocol duration may vary depending on the dose and species chosen but is generally required for shorter periods of 6–8 weeks to reach a fibrotic state and longer than 8 weeks (8–12 weeks) to reach a stable cirrhotic state.[40–42] Following CCl_4 administration, the administration of suitable trigger as an acute insult results in the generation of ACLF. Zhu and others[43] were the first to generate CCl_4-based ACLF rabbits transplanted with xenogeneic porcine adipose-derived stem cells. Despite the advantages of CCl_4-based models in the study and characterization of ACLF, multiple drawbacks are associated with CCl_4-based models, as they are considered unstable and suffer from substantial death rates during development and inconsistencies in outcomes, which are attributed to animal tolerability. These serious limitations hinder the widespread use of CCl_4-based animal models. Recently, Xiang *et al*.[28] established an advanced CCl_4-based mouse model consisting of a three-hit protocol (chronic CCl_4 + acute CCl_4 + bacterial load) to replicate multiorgan failure, a key phase in ACLF clinical prognosis, which has been described as substantial, novel breakthrough toward understanding and potentially targeting regeneration in ACLF.[44] In the meantime, a new nonalcoholic-steatohepatitis (NASH)-induced cirrhosis-based ACLF, generated by combination of high-fat diet, CCl_4, and repetitive LPS injections and transnasal stool inoculation, was developed to verify the association between advanced NASH and ACLF development in obese patients. Interestingly, the generated ACLF was accompanied by extra-hepatic multiorgan failure.[45] Representatives of CCl_4-dependent models are summarized in Table 1.[28–30,32,45–56]

Heterologous serum-based models

The utilization of heterologous serum, such as swine or horse serum, egg albumin, human gamma globulin, or pig serum (the most commonly used), to induce immune-mediated CLD has been achievable since 1960, as Paronetto and Popper previously reported.[57] These models are characterized by typical hepatic fibrosis/cirrhosis with minimal hepatocellular damage and animal death, which overcomes most limitations associated with CCl_4-based models. Previous studies recommended the administration of human serum albumin (HSA) followed by D-gal/LPS administration to induce ACLF, but the use of HSA is hampered by substantial animal mortality, reaching up to 23%, even before ACLF model generation.[58–60] Recently, porcine serum (PS) has replaced HSA to provoke the fibrosis/cirrhosis in ACLF preclinical models, as PS administration aggravates the immune response coupled with antibody generation that initiates hepatic fibrosis, which closely resembles human clinical manifestations.[61–63] The contribution of the PS antigen immune-mediated response is considered the principal source and the decisive factor for hepatic fibrosis/cirrhosis development, as previously reported.[64] Representative heterologous serum-based models are highlighted in Table 1.

PS-induced liver-cirrhosis-based ACLF models can be used to precisely clarify ACLF disease pathogenesis, and immune-metabolism disorder, characterized by immune dysregulation and metabolic disruption, has been identified

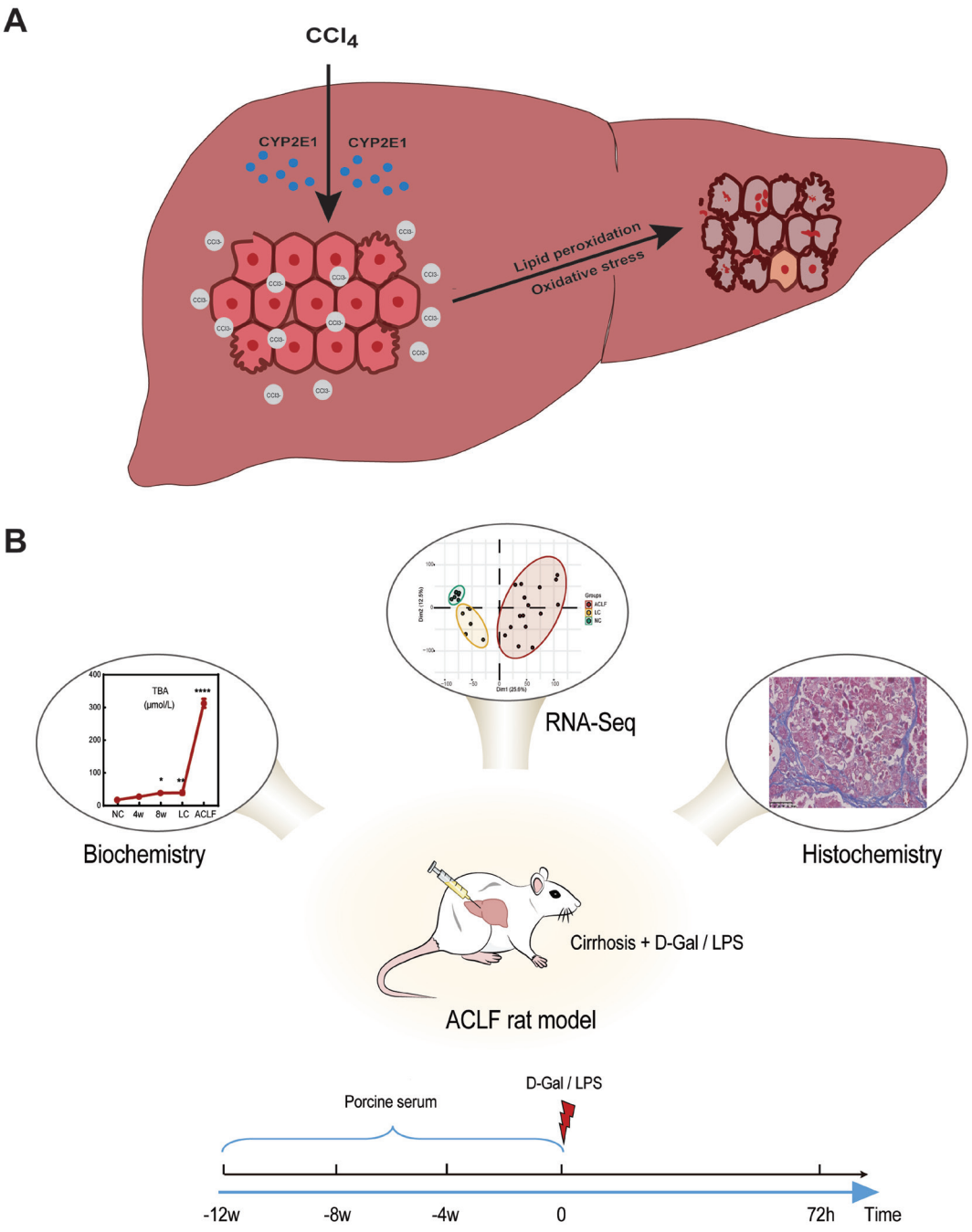

Fig. 1. Hepatotoxicant induction of liver failure. (A) Mechanism of carbon tetrachloride (CCl_4) induction of liver failure. The production of the trichloromethyl radical is the hallmark of oxidative damage. (B) Representative scheme of porcine serum (PS)-induced acute-on-chronic liver failure (ACLF), in which transcriptomic analysis of liver tissues reveals immune-metabolism disorder as the core axis in ACLF pathogenesis.

as the fundamental axis responsible for ACLF development and progression using this model. We recently developed a liver-cirrhosis-based ACLF rat model with a two-hit protocol through the coadministration of PS with D-gal and LPS (Fig. 1B); the model rats show classic ACLF features characterized by cirrhotic nodules surrounded by fibrotic septa, liver dysfunction, cytokine storm, hepatocyte damage, massive necrosis, and cellular apoptosis. Transcriptomic profiling of the significantly differentially expressed genes in the liver tissues showed discernible differences during the process of ACLF rat model building, whereas functional synergy analysis revealed prominent immune dysregulation at the ACLF stage, whereas metabolic disruption was significantly downregulated. Relative proportions of innate-immune-related cells showed significant elevation of monocytes and macrophages, while adaptive-immune-related cells were reduced. Furthermore, validations of the underlying molecular pathogenesis in our generated stable rat model and ACLF patients confirmed that immune-metabolism disorder is indispensable in ACLF pathogenesis.[46]

Table 1. Representative examples of major ACLF animal models

Hepato-toxicant	Animal type	Modeling method		Duration required	Fundamental outcomes	Possibilities of multiorgan failure	Potential represented etiology in humans	Ref.
		Chronic phase	Acute phase					
Carbon tetrachloride (CCl_4)	C57BL6 mice	Intraperitoneal injection of CCl_4	Intraperitoneal injection of APAP followed by LPS	10 weeks for chronic phase followed by acute phase. ACLF state lasts for 11 days	This model shows the clinical and histological features of human ACLF in terms of the presence of jaundice, ascites, acute tubular necrosis, and renal dysfunction	Development of portal hypertension, renal dysfunction, and pulmonary dysfunction	Infection (endotoxemia)-induced ACLF	29
	C57BL6 mice	Intraperitoneal injection of CCl_4	Intraperitoneal injection of double dose CCl_4 followed by *Klebsiella pneumoniae* load	8 weeks for chronic state followed by acute phase. ACLF duration last for up to 7 days	Developing an ACLF mice model with viable bacterial infection for studying liver regeneration and exploring the therapeutic potential of interleukin-22Fc by reprogramming impaired regenerative pathways and attenuating bacterial infection	kidney injury and impairment of blood circulation to the liver and kidney	Sepsis-induced ACLF	28
	SD rats	Intraperitoneal injection of CCl_4	Intraperitoneal injection of D-gal combined with LPS	8–12 weeks for chronic phase followed by acute phase. ACLF duration is 24 h-7 days	These different models were developed to investigates the protection capabilities against ACLF of certain natural products, as well as the influence of the immune system in ACLF pathogenesis	No genuine multiorgan failure has been reported in these models	Inflammation-induced ACLF	30,32, 47–49
	SD rats	High-fat Western diet combined with intraperitoneal CCl_4 injections combined with phenobarbital	Repetitive intraperitoneal injections of LPS combined with transnasal stool inoculation	7 weeks for chronic phase followed by acute phase. ACLF duration is unknown	This model develops ACLF in nonalcoholic-steatohepatitis-induced liver cirrhosis, which might be useful in testing pharmacological treatments	Signs of liver failure, kidney failure, severe respiratory and cerebral failures	nonalcoholic-steatohepatitis-induced ACLF	45
	New Zealand rabbit	Intraperitoneal injection of CCl_4	Intraperitoneal injection of either CCl_4 or D-gal	10 weeks for chronic phase followed by acute phase. ACLF state lasts for 12 h	Establishing a large animal model of ACLF in New Zealand white rabbits to search for suitable targets and biomarkers	No genuine multiorgan failure has been reported	Inflammation-induced ACLF	50

(continued)

Table 1. *(continued)*

Hepato-toxicant	Animal type	Modeling method		Duration required	Fundamental outcomes	Possibilities of multiorgan failure	Potential represented etiology in humans	Ref.
		Chronic phase	Acute phase					
Porcine serum (PS)	SD rats	Intraperitoneal injection of PS	Intraperitoneal injection of D-gal combined with LPS	12 weeks for chronic phase followed by acute phase. ACLF duration is 7 days	This model mimics the clinical pathogenesis and indicates that immune-metabolism disorder is indispensable key core axis in ACLF pathogenesis. The utilization of transcriptomic and multiomic analysis of rat liver is considered a breakthrough in the search for ACLF key molecules and target biomarkers	Signs of renal dysfunction as characterized by elevated levels of serum creatinine and blood urea nitrogen	Immune-mediated/ viral exacerbation-related HBV-ACLF	46
	Wistar rats	Intraperitoneal injection of PS	Intravenous injection of LPS followed by intraperitoneal injection of D-gal	11 weeks for chronic phase followed by acute phase. ACLF duration is 24 h	In this model, the transplantation of human-umbilical-cord-derived mesenchymal stem cells could be used to repair the hepatocellular damage following ACLF onset. This method might pave the way for the future application of hepatocyte-like cells in the management of ACLF	No genuine multiorgan failure has been reported	Immune-related/ infection-induced ACLF	51
Human serum albumin (HSA)	Wistar rats	Intravenous injection of HSA	Injection of D-gal and LPS combination	6 weeks for chronic phase followed by acute phase. ACLF duration is 6–120 h	These different models were developed to analyze the usefulness of certain medicinal plant extracts in alleviating ACLF and the interaction of small molecules with the immune system	Possibilities of accompanying renal dysfunction	Immune-related/ infection-induced ACLF	52–55
Surgery	SD rats	Surgically with BDL operation	Intraperitoneal injection LPS	4 weeks for chronic state followed by acute phase. ACLF duration is 72 h	This model was developed to identify the risk of systemic inflammation in the ACLF prognosis and fatality	No genuine multiorgan failure has been reported	Inflammation-induced ACLF	56

In the HSA-based model, animals were subcutaneously administered repeated injections of Freund's adjuvant containing HSA on days 0, day 14, 24, and 34. Ten days after the last injection, the concentration of serum HSA from these immunized rats was detected to confirm the sensitization status. After that, these sensitized rats were injected with intravenous HSA to develop chronic liver disease status. ACLF, acute-on-chronic liver failure; APAP, acetaminophen; BDL, bile duct ligation; C57BL6, C57 black 6; CCl_4, carbon tetrachloride; D-gal, galactosamine; HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; HSA, human serum albumen; LPS, lipopolysaccharide; PS, porcine serum; SD, Sprague Dawley.

Surrogate animal models

As alternatives to the abovementioned models, several other models have been used to replicate ACLF such as surgical-based models. Hu *et al*.[65] described their two-step rat model established through surgical induction of obstructive jaundice, a method previously reported by Xiping *et al*.[66] Furthermore, Tripathi and his group developed a bile duct ligation model that was irresponsive to LPS secondary insult, despite its merit in generating aggressive cirrhotic status.[26] Nevertheless, preceding findings highlighted the success of sham operation and/or common bile ligation combined with LPS or CCl_4 inhalation in establishing ACLF.[67–69] Recently, Karus *et al*.[70] highlighted the combination of bile duct ligation, ethanol binge drinking, repetitive LPS injections, transnasal stool inoculation and cecal ligation and puncture, a complicated approach to generate a new rat model of cholestatic liver cirrhosis-developing ACLF. The differences in final outcomes might impede the selection and rational application of these models to investigate ACLF pathophysiology. To evaluate target-oriented therapy, Schwarzkopf *et al*. developed a new ACLF model in mice through infection with adenovirus, which precipitates autoimmune hepatitis, resulting in liver fibrosis, followed by paracetamol overdose to trigger ACLF.[71]

The anchor behind the scene: HBV-based models

Infection with HBV and/or viral exacerbation has gained much attention because of the potential development of a series of CLDs, in which HBV-induced ACLF (HBV-ACLF) as the principal clinical entity culminated in a 50–90% death rate, as documented by the Chinese Group on the Study of Severe Hepatitis B (COSSH).[13,17,72] Although HBV-ACLF disease progresses rapidly with limited treatment options, the pathogenesis is unclear, and there is a lack of effective biomarkers for the early diagnosis and prognosis of HBV-ACLF, necessitating the development of a specific and reliable HBV-ACLF animal model. Establishing such a robust model to investigate HBV-ACLF disease development and prognosis seems to be the greatest challenge for researchers, which is attributed to the extremely narrow host range of HBV, which primarily infects humans. While only humans and chimpanzees are sensitive to HBV infection, chimpanzees fail to develop CLD following HBV infection.[73] Therefore, the dual humanized chimeric mouse stands as the most promising ideal HBV model.[74,75] Yuan *et al*. previously developed HBV-related liver cirrhosis in a dual humanized mouse model transplanted with human bone marrow mesenchymal stem cells, which were sensitive to chronic HBV infection and generated liver cirrhosis.[76] This model could better serve as a candidate model for HBV-ACLF following acute insult with appropriate precipitants, although the application of these approaches is questionable because of the very long time required to reach stable cirrhosis.

Transgenic ACLF animal models: beyond the harbor

The analysis of transgenic models provides insight into ACLF animal models in the future. Over the last decades, various strategies have been applied for the integration of exogenous genetic information within the mouse genome, which has become a common tactic in constructing models with variant physiological roles to provide virtual and detailed information about disease pathophysiological aspects.[77,78] Numerous stable transgenic mouse models have been developed to mimic the clinical manifestations of different and intricate diseases, including neurodegenerative diseases,[79] cancers,[80] cardiovascular diseases,[81] and hepatic diseases.[82] Several transgenic mouse models were adopted as resources to study liver failure, which allowed investigators to obtain in-depth clues regarding the progression of CLD.[83] Tsai *et al*.[84] generated a mouse strain to investigate the role of high-fat diet and corticosterone in the pathogenesis of nonalcoholic fatty liver disease, and Fransén-Pettersson *et al*.[85] developed a transgenic mouse that spontaneously developed inflammatory-derived fibrosis of multiple organs, including the liver. Remarkably, a promising approach is to model ethanol-induced acute-on-chronic liver injury in an Abcb4 knockout transgenic mice model with liver preinjury.[86,87] These models could be adopted to clarify the complicated nature of ACLF and provide translational approaches for remarkable achievements in revealing substantial pathophysiology-guided therapeutic targets.

Challenges in selecting an ideal and clinically-relevant ACLF animal model

In fact, we fell short for an appropriate and universally accepted definition for ACLF so far because of the complexity and heterogenic nature of ACLF.[88] Therefore, to assume the existence of an ideal, single ACLF model for interpreting disease pathogenesis, bridging the gap between molecular mechanisms and therapeutic strategies, is not logically possible. The models should distinctively reflect the clinical mechanism and prognosis of human ACLF pathogenesis. Despite those limitations, the above-mentioned models share most of the typical pathophysiological manifestations of ACLF such as severe deterioration of liver function and histology accompanied by single and/or multiorgan failure with concomitant high short-term mortality. The methods and models succeed in mimicking the reactivation of hepatitis viral infection, acute alcoholic hepatitis or acute bacterial infection in Asian populations, as well as alcohol abuse and bacterial infection that aggravate CLD conditions in the Western population. In this context, most ACLF animal models employ chemical induction (drugs/alcoholic/infection) or immune induction (heterologous serum), of CLD followed by an acute trigger to initiate ACLF. Selecting any method or model to imitate certain aspects in human ACLF should be supported by the purpose, strengths, flaws, and rationale of the study in mimicking explicit clinical scenario. Adoption of sophisticated techniques with advanced humanized mice models may represent major breakthroughs in ACLF animal model development. Furthermore, measurable histological and/or pathological endpoint markers should be adopted to ensure the successful recapitulation of the ACLF common disease features clinically seen in humans, such as presence of both chronic and acute liver injury indicators, ascites, encephalopathy, and secondary organ dysfunction.

Future insights in ACLF animal models

Although different models emulate and are complementary to ACLF development and prognosis in humans, the actual clinical manifestations of ACLF are intricate, and precise, stable, and novel ACLF animal models are required to achieve breakthroughs in the study of ACLF pathogenesis. Despite the existence of various models that aided in revealing ACLF pathogenesis and prognosis, a key challenge stands in identifying the utmost ACLF model that precisely replicates all aspects in human ACLF. Most models only can reflect certain features of disease pathophysiology as inflammatory, hepatic and/or extrahepatic organ failure that

ultimately lead to high short-term mortality. In the meantime, establishing a rationale guidance for selecting distinct acute insult triggers as precipitating events in ACLF development, is of great importance. Regardless of the model chosen, adoption of standardized scoring systems for acute insult selection should be strongly encouraged. However, recent studies that focused on the potencies of secondary acute insults in ACLF are lacking. We hope that issue will be addressed in the near future by appropriate studies. The application of integrated investigational approaches with a suitable ACLF animal models using multiomic function correlation analysis and bioenergetic data should be performed in the near future to fully decipher ACLF pathogenesis and identify key molecular target biomarkers for early diagnosis and prediction of the occurrence, development, and prognosis of ACLF.

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Conflict of interest

JL has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2019. HMH has no conflict of interests related to this publication.

Author contributions

Contributed equally to the main review conception and manuscript writing, organizing the presented models, performing the literature search and analysis, preparing figures and tables, and discussing and systematizing the presented literature data, and have approved the final manuscript (HMH, JL).

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