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Contents

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OPINION REVIEW

1224 Collagen matrix scaffolds: Future perspectives for the management of chronic liver diseases

Martinez-Castillo M, Altamirano-Mendoza I, Zielinski R, Priebe W, Piña-Barba C, Gutierrez-Reyes G

MINIREVIEWS

1236 Sex dimorphism and metabolic profiles in management of metabolic-associated fatty liver disease

Martin-Grau M, Monleon D

1245 Epidemiology and etiology of chemical ocular injury: A brief review

Akgun Z, Selver OB

1252 Review of the prevalence, diagnostics, and containment measures of the current mpox outbreak

Sanyaolu A, Marinkovic A, Okorie C, Prakash S, Haider N, Dixon Y, Izurieta R, Badaru O, Smith S

1261 Clinical and pathophysiological understanding of the hepatorenal syndrome: Still wrong or still not exactly right?

Wilde B, Canbay A, Katsounas A

1267 Flare of the silent pandemic in the era of the COVID-19 pandemic: Obstacles and opportunities

Rayan RA

1275 Implications of metabolic dysfunction associated fatty liver disease in COVID-19

Chakraborty R, Sharma D, Kapoor DU, Dwivedi A, Khabiya R, Sen S

ORIGINAL ARTICLE

Retrospective Study

1287 Hyperglycemia in COVID-19 infection without diabetes mellitus: Association with inflammatory markers

Geetha HS, Singh G, Sekar A, Gogtay M, Singh Y, Abraham GM, Trivedi N

Clinical Trials Study

1299 Efficacy of invisible advancement correction for mandibular retraction in adolescents based on Pancherz analysis

Kong L, Liu XQ

Observational Study

1310 Survey study of the etiology of non-traumatic altered consciousness in the Emergency Department at Suez Canal University Hospital in Egypt

Moussa BS, Abd Elatiff ZM, Kamal Eldin Elhadary GM

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 6 February 26, 2023

Contents

1318 Metformin effect on internal carotid artery blood flow assessed by area under the curve of carotid artery Doppler in women with polycystic ovarian syndrome

Akram W, Nori W, Abdul Ghani Zghair M

1330 Effect of continuous nursing combined with respiratory exercise nursing on pulmonary function of postoperative patients with lung cancer

Qiu QX, Li WJ, Ma XM, Feng XH

CASE REPORT

1341 Functioning gonadotroph adenoma with hyperestrogenemia and ovarian hyperstimulation in a reproductive-aged woman: A case report and review of literature

He Y, Gao YT, Sun L

1349 Clinical manifestations of adult hereditary spherocytosis with novel *SPTB* gene mutations and hyperjaundice: A case report

Jiang N, Mao WY, Peng BX, Yang TY, Mao XR

1356 Post-traumatic cauda equina nerve calcification: A case report

Liu YD, Deng Q, Li JJ, Yang HY, Han XF, Zhang KD, Peng RD, Xiang QQ

1365 Endometriosis-associated endometrioid adenocarcinoma of the fallopian tube synchronized with endometrial adenocarcinoma: A case report

Feng JY, Jiang QP, He H

1372 Gemcitabine-induced peripheral vascular disease and prolonged response in a patient with metastatic pancreatic adenocarcinoma: A case report

Fabien MB, Elodie P, Anna S, Addeo P, Meher B

1379 Epidemic Japanese B encephalitis combined with contactin-associated protein-like 2 antibody-positive autoimmune encephalitis: A case report

Huang P

1385 Acute pancreatitis as initial presentation of acute myeloid leukemia-M2 subtype: A case report

Yang WX, An K, Liu GF, Zhou HY, Gao JC

1393 Postoperative jaundice related to *UGT1A1* and *ABCB11* gene mutations: A case report and literature review

Jiang JL, Liu X, Pan ZQ, Jiang XL, Shi JH, Chen Y, Yi Y, Zhong WW, Liu KY, He YH

1403 Hidrotic ectodermal dysplasia in a Chinese pedigree: A case report

Liao MY, Peng H, Li LN, Yang T, Xiong SY, Ye XY

1410 Hepatitis A virus-associated acute acalculous cholecystitis in an adult-onset Still's disease patient: A case report and review of the literature

Chang CH, Wang YY, Jiao Y

1419 Transverse myelitis caused by herpes zoster following COVID-19 vaccination: A case report

Cho SY, Jang BH, Seo JW, Kim SW, Lim KJ, Lee HY, Kim DJ

1426 Primary malignant melanoma of the esophagus: A case report

Wang QQ, Li YM, Qin G, Liu F, Xu YY

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 6 February 26, 2023

Contents

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OPINION REVIEW

Collagen matrix scaffolds: Future perspectives for the management of chronic liver diseases

Moises Martinez-Castillo, Itzel Altamirano-Mendoza, Rafal Zielinski, Waldemar Priebe, Cristina Piña-Barba, Gabriela Gutierrez-Reyes

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Abstract

Approximately 1.5 billion chronic liver disease (CLD) cases have been estimated worldwide, encompassing a wide range of liver damage severities. Moreover, liver disease causes approximately 1.75 million deaths per year. CLD is typically characterized by the silent and progressive deterioration of liver parenchyma due to an incessant inflammatory process, cell death, over deposition of extracellular matrix proteins, and dysregulated regeneration. Overall, these processes impair the correct function of this vital organ. Cirrhosis and liver cancer are the main complications of CLD, which accounts for 3.5% of all deaths worldwide. Liver transplantation is the optimal therapeutic option for advanced liver damage. The liver is one of the most common organs transplanted; however, only 10% of liver transplants are successful. In this context, regenerative medicine has made significant progress in the design of biomaterials, such as collagen matrix scaffolds, to address the limitations of organ transplantation (*e.g.*, low donation rates and biocompatibility). Thus, it remains crucial to continue with experimental and clinical studies to validate the use of collagen matrix scaffolds in liver disease.

Key Words: Liver; Chronic liver disease; Collagen matrix scaffold; Transplant; Management

Core Tip: The relevance of this review-opinion focuses on new strategies of regenerative medicine and the use of collagen matrix scaffolds as an option in the field of chronic liver disease (fibrosis/cirrhosis and hepatocellular carcinoma). Collagen matrix scaffold can be used as a niche for native or stem cells and as a carrier for antineoplastic drugs; these strategies exhibit the potential to restore liver function and address problems associated with the scarcity of organ donors.

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INTRODUCTION

Chronic liver disease (CLD) constitutes a complex health problem, as it can be induced by various factors, including hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol abuse and nonalcoholic fatty liver disease (NAFLD), among other genetic and autoimmune conditions[1,2]. In the last 50 years, several advances have been made in the field of CLD, including the development of vaccines and antiviral regimens against viral hepatitis (HBV and HCV, respectively)[3]. Vaccination and antiviral treatment programs have reduced HBV incidence and its complications[4]. Moreover, patients with chronic HCV can be treated with direct-acting antiviral agents (DAAs)[5]. The World Health Organization (WHO) estimates that HCV will be eradicated by 2030; however, less than 10% of HCV-infected individuals have successfully completed treatment since the introduction of DAAs in 2014[6,7]. Furthermore, reactivation of HBV after treatment with DAAs has been reported, and some patients who initially showed complete elimination of HCV by DAA exhibited progressive liver damage and developed cirrhosis or liver cancer[8,9]. On the other hand, for patients with alcoholic liver cirrhosis, liver transplantation (LT) remains the only therapeutic option[10]. Stringent clinical and social criteria must be fulfilled to qualify for the transplant, which significantly impacts the life expectation[10]. NAFLD and nonalcoholic steatohepatitis (NASH) are also considered growing health problems[11]. In fact, complex NAFLD/NASH is among the top causes of hepatocellular carcinoma (HCC) in the United States, whereas NASH is the second most common indication for LT in the United States[12].

Regenerative medicine represents a promising approach in the field of tissue damage restoration and organ transplantation. Typically, tissue-engineered grafts consist mainly of three elements: scaffolds (or templates), stem cells, and growth-stimulating factors[13]. The scaffolds play a fundamental role as structural support for cell attachment, survival, and proliferation. Thus, its structure and biological and physiochemical properties must be compatible with the organ or tissue without the risk of chronic inflammation and rejection. Additionally, the ideal scaffold needs to be biodegradable and mimic the shape and function of the specific organ[14,15]. At present, several biomaterials have been reported as suitable scaffolds, including natural and synthetic polymers (*e.g.*, polylactic acid, polyglycolic acid, and polycaprolactone)[16]. Natural biomaterial that have been modeled include collagen, fibrin, laminin, and fibronectin, which are components of the extracellular matrix (ECM). Collagen is the protein of choice during the construction of synthetic and natural scaffolds, showing great biocompatibility and minimal immunogenicity. Furthermore, this protein can be degraded by the host[15,17]. It is important to mention that the generation of extracellular matrix scaffolds (EMSs) involves lyophilization and/or electrospinning methods; thus, the associated physical or chemical treatments may affect the native properties of collagen[14]. The decellularization process is another strategy for obtaining an intact EMS. This process has gained great traction; however, it needs an organ source, which requires an allogenic or xenogeneic donor[16,18,19]. After retrieval, the organ is processed by physical (*e.g.*, sonication, pressure gradient), chemical (*e.g.*, detergents, acidic or basic solutions) or biological treatments (*e.g.*, enzymes, such as trypsin and dispase) that may interfere with the compatibility and stability of the biomaterial [16]. Recently, the production of a collagen matrix scaffold (CMS) from the bone matrix after a demineralization process was described in the literature, which does not imply aggressive treatments[15,20,21]. A few studies have been conducted using ECM as a strategy to restore normal organ function in cirrhosis and HCC[18,19,22,23]. It is important to mention that the regenerative capacity of the liver can be inhibited by the excessive accumulation of ECM because it can reduce the area for liver parenchymal cell proliferation[15]. Additionally, studies in animal models have shown that stem cell transplantation promotes hepatocyte proliferation and improves liver function[24,25]. In preclinical studies, the infusion of mesenchymal stem cells (MSCs) is typically achieved by intravenous, intraarterial, intraperitoneal,

intraportal, or intrasplenic routes; consequently, the number of cells and doses required are uncertain [25]. It is possible that CMS could be used as a vehicle for the direct administration of MSCs[25,26]. Moreover, the implantation of CMS after the surgical extraction of partial tissue can function as an anchor for hepatocyte proliferation, thus improving organ function[15].

Overview of the management and LT for CLDs

Although therapeutic options largely depend on the underlying cause of liver disease, there are few proven effective treatments for advanced stages[27]. In recent years, DAAs have transformed the treatment of HCV in patients with advanced fibrosis or compensated cirrhosis. For instance, it has been shown that a long-term sustained viral response (SVR) is associated with a significant decrease in liver tissue collagen content and even regression of fibrosis in greater than 60% of patients[28]. However, the impact of such treatment in patients with decompensated cirrhosis is limited, achieving only marginal improvements[29]. The incidence of HCV-related decompensated cirrhosis and HCC are expected to decrease due to the advent of DAAs[30]. Despite these promising results, a large group of patients will still be at risk of developing HCC even after SVR has been achieved. These patients will continue to represent potential candidates for LT. Untreated HCV prior to LT results in universal recurrence of allograft infection, accelerated liver fibrosis, and subsequent graft failure[31]. The recurrence of HCV infection is universal in patients with detectable HCV RNA at the time of LT. Of the total number of recipients with post-transplantation HCV recurrence, one-third will develop cirrhosis within 5 years of LT in the absence of antiviral treatment[32]. Graft survival is lower in HCV patients compared with noninfected recipients due to various factors, such as HCV recurrences, extrahepatic manifestations of HCV infection, management issues, and complications of immunosuppression[33,34]. Complete abstinence from alcohol consumption is the cornerstone in the management of every spectrum of alcoholic liver disease (ALD)[35]. However, there are several factors that make abstinence difficult to achieve, such as lack of social support, psychiatric comorbidities, polysubstance abuse, environmental influences, and family history of alcoholism[36]. On the other hand, dietary and physical approaches are the mainstay of the management of NAFLD[37]. The amount of weight loss considered to be an effective therapeutic option is achievable in trial settings but is challenging in the clinical environment[38]. To date, several new therapeutic targets have been proposed, leading to new pharmacological therapies being tested for ALD and NAFLD; however, the majority have not been approved or evaluated in advanced liver disease[39,40].

LT is the most effective therapeutic option for patients with end-stage liver disease[41]. The procedure is typically justified in liver failure, decompensated cirrhosis (MELD ≥ 15), and/or HCC[31,35,37,41,42]. In cirrhosis, survival after LT is restricted to patients with advanced decompensation, whereas LT does not improve survival of patients with intermediate disease severity[37,43,44]. Recently, an unequivocal survival increment was demonstrated in patients with alcoholic hepatitis not responding to medical therapy compared with patients who received early transplantation[35,41,45]. However, LT is not a formal indication in all transplant centers, especially in the United States[46]. Typically, a 6-mo period of abstinence is required to identify ALD patients who will be able to refrain from alcohol consumption and not relapse after LT. However, this criterion is not mandatory in some organizations, such as the United Network for Organ Sharing, International LT Society, European Association for the Study of the Liver, and American College of Gastroenterology[35,41]. Although the requirements are changing worldwide, the number of donors is not enough to meet the demand for patients waiting for transplant. LT during end-stage liver disease related to NAFLD represents a challenge due to the high incidence of associated comorbid diseases, such as obesity, type 2 diabetes, and hypertension, with 50% of patients with BMI > 35 kg/m^2 dying within the 1st year of transplantation [47,48]. However, an upper limit of BMI that contraindicates the procedure has not been identified[49]. The post-transplant survival in NAFLD is significantly higher than that in HCV (5-year survival: NAFLD 77.81% *vs* HCV 72.15%)[50]. Although quality of life and liver function improve in patients after LT, both decrease with time[51]. For instance, in a meta-analysis, the mean 1-, 3-, and 5-year incidence rates of recurrent and de novo NAFLD after LT were 59%, 57%, and 82% as well as 67%, 40%, and 78%, respectively[52]. Nonetheless, it has been demonstrated that the prevalence of advanced fibrosis is low after LT with values of 2%–5% at 5 years, 5%–10% at 10 years, and up to 24% reported in one of the studies that followed the patients up to 15 years[53-56]. In contrast, the recurrence of alcoholic cirrhosis was responsible for approximately 90% of deaths in recipients who resumed abusive alcohol drinking [41]. Transplant recipients have a higher incidence of cardiovascular events and neoplastic diseases. The risk of de novo malignancies increases from 6% before LT to 55% by 15 years post-LT[57]. The incidence of de novo tumors as a cause of death was at least twofold higher in patients transplanted for ALD compared to other indications[58]. Additionally, tobacco use has been particularly associated with this increased risk[58]. In addition to host factors, immunosuppression is an important contributing factor for developing malignancies. NAFLD carries an increased risk of death from cardiovascular complications and sepsis[59,60]. Screening for neoplastic and cardiovascular diseases during the transplant evaluation process is crucial[35,37,41,49]. Although the number of patients waiting for LT is expected to increase, donor availability is predicted to decrease, highlighting the demand for new therapeutic options for CLD[20,60].

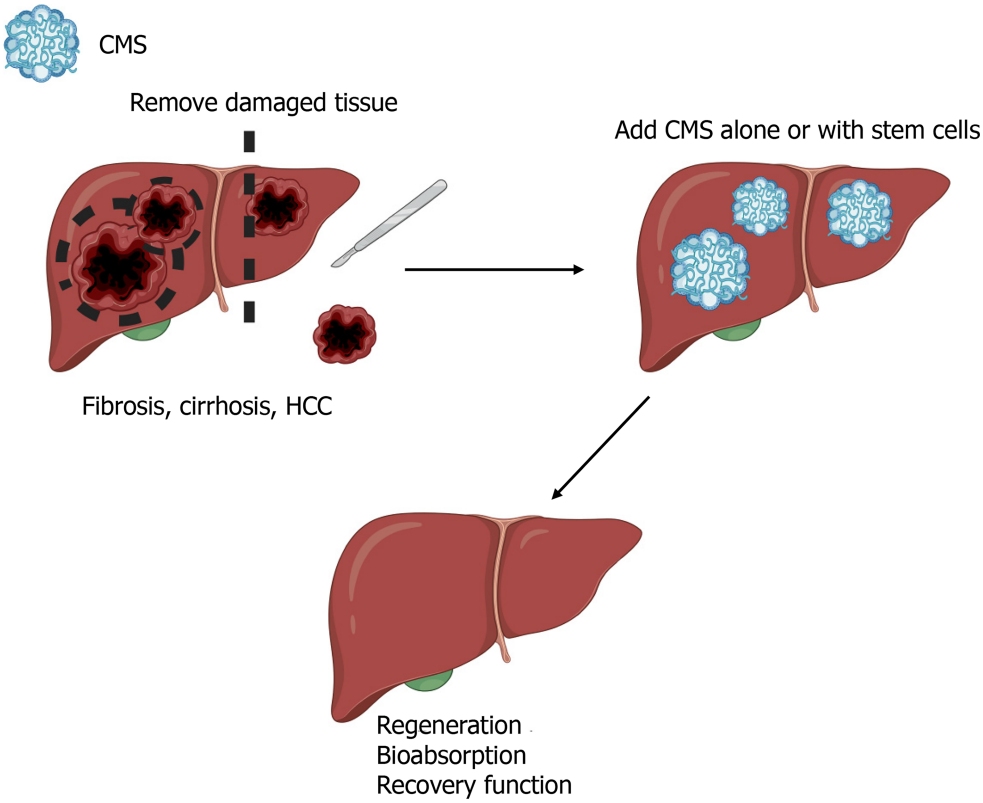

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Figure 1 Collagen matrix scaffold implantation in chronic liver disease. A: Identification and extirpation of zones with excessive damaged tissue at early or advanced stages of chronic liver disease; B: Implantation of a collagen matrix scaffold (CMS) that mimics normal liver tissue alone or in combination with mesenchymal stem cells; C: Restoration and normal function and subsequent natural elimination of CMS by the host.

CMSs and the liver

It is well understood that the main sources of fibrillar collagens in the liver are hepatic stellate cells[61]. The use of exogenous collagen during liver disease is an unconventional idea because the liver has the capability to produce and degrade its own ECM compounds[61,62]. However, it is important to highlight that dysregulation of collagen synthesis occurs in patients with liver disease and is especially marked in later stages[61-63]. For this reason, the use of CMS made with the same collagens that are present in the healthy liver could delay the progression of liver disease[15,20]. The use of CMS as a niche for liver cells was recently investigated, and positive results were revealed[15]. The authors demonstrated that CMS from bovine condyles does not cause rejection or exacerbate the inflammatory response; moreover, they demonstrated that cells like-hepatocytes, grew in the CMS. After 21 d, this biomaterial showed natural biodegradation. Nevertheless, the cellular and biological processes were not examined[15,20]. Liver regeneration has been associated with the presence of hepatic progenitor cells and a plethora of other signaling mechanisms[64,65]; however, control over regeneration is lost in CLD [65]. The allosteric effect of excessive production of ECM has been suggested as a possible mechanism that inhibits proliferation; moreover, the ratio of proliferation and apoptosis is dysregulated in advanced CLD[15,66]. The use of stem cells for tissue regeneration has been explored in several organs and tissues, but it remains an important challenge in the liver[25]. However, recent in vitro studies of human stem cells seeded in CMS have been published, showing that CMS is a good niche for this type of cells[25]. Furthermore, the use of CMS alone or in combination with MSCs can be used to restart or improve regeneration and organ function (Figure 1).

Use of CMSs to study cirrhosis

Liver cirrhosis is among the top 20 causes of disability-adjusted life years and years of life lost worldwide[67]. The incidence of liver cirrhosis is rapidly increasing worldwide, and the currently available treatment is suboptimal[68]. At present, the most effective therapeutic option is LT[41]. However, the lifelong consequences of transplantation and the scarcity of donors limits patient eligibility[69]. This leads to poor quality of life and eventually to death. Patients with cirrhosis have disease-related barriers preventing liver regeneration, but novel strategies, such as scaffolds, have driven progress toward the development of successful therapies for this condition[70,71]. In a CCl4-induced cirrhosis rat model, a comparative evaluation indicated that the group that underwent implantation of scaffolds with cultured hepatocytes displayed a better long-term recovery of liver

function than the group with direct infusion of liver cells[72]. Moreover, in the same study, the authors reported better outcomes regarding liver function in the group that underwent implantation of the scaffold cultured *in vitro* with hepatocytes compared to the cell-free scaffold group[72]. The ECM is an important regulator of liver fibrogenesis[73]. It is well known that ECM proteins have an immunomodulatory role in the liver disease microenvironment, leading to the chemotaxis of leukocytes; modulation of growth factor and cytokine functions, such as TGF-β1 and TNF-α, fibroblast migration; and some anti-inflammatory responses[62,73,74]. Recently, ECM proteins were described as prognostic biomarkers of early-stage cirrhosis[75]. Given the role of the ECM in disease progression, the incorporation of scaffolds as models *in vitro* is essential in creating the appropriate microenvironment that allows investigation of underlying pathological mechanisms and/or testing new therapies. In this context, cirrhotic human 3D liver scaffolds have been obtained through a decellularization process[76]. The cirrhotic 3D scaffold was used as a novel model to evaluate the inherent features of cirrhotic human liver and the ECM microenvironment, including the efficient homing and targeting of cells to their correct localization[19,76].

CMSs in liver cancer

HCC is among the principal causes of cancer deaths worldwide[23]. The liver parenchyma in HCC typically exhibits necrosis, inflammation, oxidative stress, and a dysregulated ECM. These events are related to genetic alterations and deregulation of multiple signaling pathways[66,77-79]. LT, resection, novel thermal and nonthermal techniques for tumor ablation and embolization are the preferred strategies to treat HCC[23]. Moreover, only a few pharmacological options (*e.g.*, bevacizumab, cabozantinib, lenvatinib, ramucirumab, regorafenib, and sorafenib), immunotherapy (*e.g.*, atezolizumab, nivolumab, and pembrolizumab), and radiation therapy (*e.g.*, conformal, stereotactic and proton beam radiation) have been used in the treatment of HCC, and these treatments are typically reserved for the advanced phase of HCC with limited success[23]. The study of HCC includes cell lines (*e.g.*, HEP-G2, HEPA 1-6, HuH7, SK-HEP-1, Hep3B)[80,81] and animal models (*e.g.*, orthotopic and xenotransplantation)[82,83]. Moreover, decellularized tumors have been proposed as a strategy of study[22]. Recently, decellularization of liver explants from human cirrhotic liver tissue (explant primary sclerosing cholangitis; cirrhotic 3D scaffolds) were used for the first time as a model for the evaluation of HCC[76]. Immunohistochemical staining showed that collagen types I, III and IV; fibronectin; and laminin were present after the decellularization process. The authors also compared the expression of different proteins after seeding Hep-G2 cells in cirrhotic 3D scaffolds[76]. Interestingly, their results showed that cell repopulation of cirrhotic scaffolds highlighted a unique upregulation in genes related to epithelial to mesenchymal transition and TGFβ signaling. Moreover, higher concentrations of TGFβ1 and fibronectin were produced by seed cells in cirrhotic scaffolds than in healthy scaffolds. This methodology allowed the authors to evaluate the microenvironment in HCC and healthy ECM from the liver with the possibility of identifying new potential therapeutic targets for drug development[76].

The ECM plays a pivotal role from the beginning of tumorigenesis to metastasis. Collagen, fibronectin and laminin can induce intracellular signaling that participates in apoptosis evasion, metastasis, angiogenesis, and proliferation[62]. Nevertheless, opposing results regarding the role of the ECM in tumor progression have been reported. Specifically, in pancreatic tumors, ECM composition inhibits tumor progression, whereas an increase in the deposition of ECM stimulates tumor progression in breast cancer. Thus, the role of ECM may depend on the cancer type[62]. Collagen synthesis increases in severe liver fibrosis (F3 and F4) compared with a healthy liver (fibrillar collagen types I, III and V)[84,85]. In fact, collagen and other ECM proteins are used as biomarkers to determine the stage of fibrosis and as predictors of cancer development[73,86,87]. It is possible that the use of CMS containing similar collagen to healthy livers from human or other mammal sources (such as ®Nukbone) improves the regeneration process. The use of CMS as support alone or in combination with HCC cell lines represents an excellent strategy for: (1) The evaluation of therapeutic drugs, including assessments of the IC_{50}, stability and the diffusion ratio[26,88,89]; (2) Implantation of CMS plus HCC cells in animals to evaluate the progression of HCC in situ and/or as a metastasis model; and (3) Tumor ablation and implantation of CMS impregnated with antineoplastic drugs to ensure elimination of all malignant cells to reduce recurrence (Figure 2)[88].

Challenges and limitations of CMSs in CLD

In a general context, the collagen used during CMS design is commonly derived from bovine, porcine, rodent, human, and marine sources, which are commercially available[90,91]. Collagen obtained from these sources exhibits differences in primary amino acid sequence, and it has been estimated that approximately 3% of the population is allergic to bovine collagen I[91-93]. Human collagen is the ideal source of collagen to eliminate certain concerns associated with xenogeneic sources, but the mass production of recombinant collagen is unsustainably expensive. Furthermore, the synthesis of hybrid collagen matrices has been proposed as a method to extract and purify collagen and modify its mechanical properties. Another important consideration is that during the creation of CMSs, the fiber arrangement/alignment is not equal to native disposition (anisotropic)[17]. However, this last concern seems to be eliminated with the incorporation of new strategies, such as CMS from Nukbone®[15,20,94]. Despite the disadvantages mentioned, collagen from bovine and porcine sources is widely and

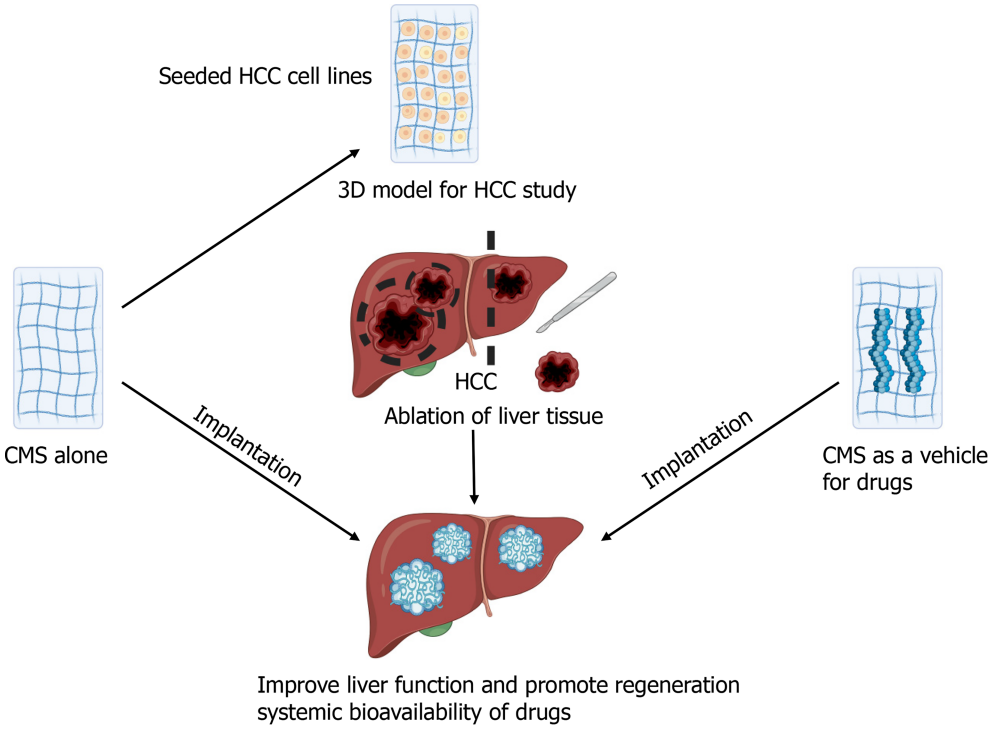

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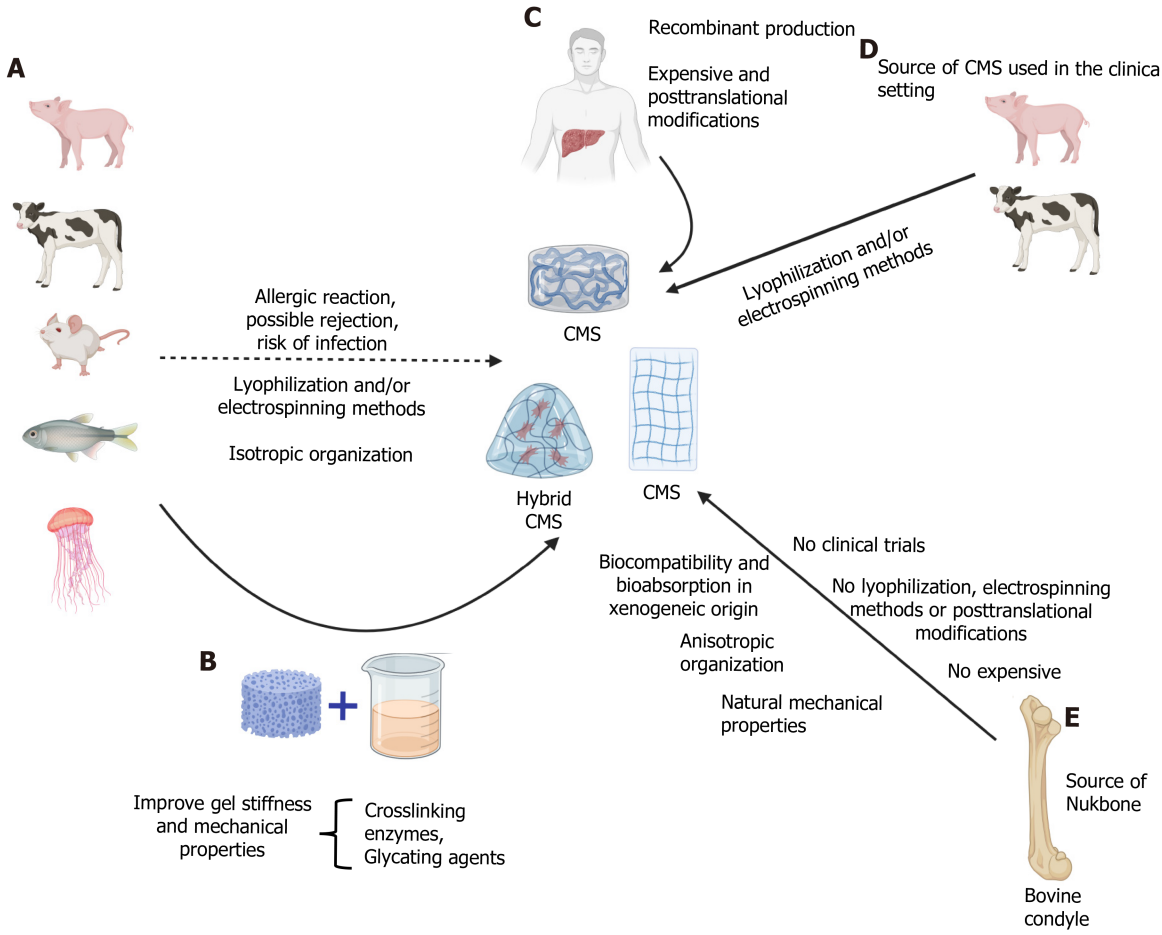
Figure 2 Collagen matrix scaffold implantation in hepatocellular carcinoma. Collagen matrix scaffold (CMS) can be used alone or in combination with hepatocellular carcinoma cell lines (*e.g.*, HEP-G2 and/or HuH7) as a 3D model. Resection of tumor- or liver-damaged tissue and subsequent implantation of CMS alone or impregnated with antineoplastic drugs can be used to evaluate drug bioavailability and improve liver function.

successfully used in clinical settings[95,96] (Figure 3).

It is important to mention that the predominant type of collagen in healthy liver is collagen I, III and V, whereas the dysregulation of several collagens has been reported during liver disease progression induced by different factors[86]. In this sense, it was reported that patients with ALD displayed higher levels of type III collagen in the cirrhosis stage than healthy controls[97]. Moreover, collagen III formation progressively supersedes the degradation of this type of collagen. However, increased collagen VI degradation compared with synthesis (PRO-C3) was noted in the same stages[97]. In a similar manner, PRO-C3 (marker of synthesis) allowed discrimination of F3 and F4 in NAFLD, and the results revealed superior ROCs at this stage compared with the aspartate aminotransferase to platelet ratio index, FIB-4, and NAFLD fibrosis score[98]. In addition, collagens III, IV, V, and VI showed significant increases from early to late fibrosis (F4 or cirrhosis) in hepatitis C. Collagen IV was the most useful discriminator between early and late stages, whereas collagen V and VI showed the strongest expression in early fibrosis stages[99]. Taken together, these studies provide evidence that the synthesis and degradation of collagens is not a static process. The extirpation of liver zones with excessive deposition of atypical collagens followed by the implantation of CMS that mimics normal liver tissue collagen, such as CMS from Nukbone®, could improve and restore normal liver function[15]. However, it is important to research the implications of the use of different types of collagen in the context of CLD and CMS during fibrosis, cirrhosis, and HCC induced by the different etiologies.

CONCLUSION

The use of CMS in CLD is a promising tissue engineering strategy to recover liver function. It avoids the use of organs from donors and, thus, also sidesteps the transplant waiting list, compatibility issues, pre- and postoperative care (immunosuppression), and other ethical considerations. The use of CMS also represents an exciting and important, novel tool for the development and evaluation of pharmacological options for cirrhosis and HCC. Furthermore, CMS could even be developed in the future as a treatment targeting the early stages of liver disease, including fibrosis.



DOI: 10.12998/wjcc.v11.i6.1224

Figure 3 Challenges and limitations of collagen matrix scaffolds. A: Xenogeneic sources of collagen promote allergic reactions, rejection or risk of infections (*e.g.*, bovine spongiform encephalopathy). Lyophilization and/or electrospinning methods are used to obtain collagen matrix scaffold (CMS), which alter their natural properties, including isotropic organization; B: Hybrid collagen matrices using crosslinking enzymes (*e.g.*, lysyl oxidase and transglutaminase) and glycating agents (high concentrations of ribose) to improve mechanical properties and stiffness; C: The production of human recombinant collagen is expensive, and current recombinant systems lack native prolyl 4-hydroxylase activity; D: The available sources of CMS are obtained from bovines and pigs using lyophilization and/or electrospinning methods; E: Nukbone obtained from bovine condyles as a CMS source showed great advantages; however, it is important to validate its use in clinical trials. The next step of CMS is explored in the context of the different stages of chronic liver disease induced by distinct liver insults.

FOOTNOTES

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