**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 72324

**Manuscript Type:** MINIREVIEWS

**Adipose-derived stem cells in the treatment of hepatobiliary diseases and sepsis**

Satilmis B *et al*. Adipose-derived mesenchymal stem cells and liver

Basri Satilmis, Gizem Selen Cicek, Egemen Cicek, Sami Akbulut, Tevfik Tolga Sahin, Sezai Yilmaz

**Basri Satilmis, Tevfik Tolga Sahin, Sezai Yilmaz,** Hepatology Research Laboratory, Liver Transplant Institute, Inonu University, Malatya 44000, Battalgazi, Turkey

**Basri Satilmis,** Department of Biochemistry, Faculty of Pharmacy, Inonu University, Malatya 44000, Battalgazi, Turkey

**Gizem Selen Cicek,** Department of Anesthesiology and Reanimation, Malatya Training and Research Hospital, Malatya 44000, Yesilyurt, Turkey

**Egemen Cicek, Sami Akbulut, Tevfik Tolga Sahin, Sezai Yilmaz,** Liver Transplant Institute, Inonu University, Malatya 44000, Battalgazi, Turkey

**Author contributions:** Satilmis B and Sahin TT designed and wrote the paper; Cicek E and Cicek GS performed the literature analysis; Akbulut AS and Yılmaz S reviewed the paper.

**Corresponding author: Tevfik Tolga Sahin, FACS, MD, PhD, Professor,** Hepatology Research Laboratory, Liver Transplant Institute, Inonu University, Battalgazi Malatya, Malatya 44000, Battalgazi, Turkey. tevfiktolgaa@gmail.com

**Received:** October 11, 2021

**Revised:** January 13, 2022

**Accepted:** March 25, 2022

**Published online:** May 16, 2022

**Abstract**

Determination of the mesenchymal stem cells is one of the greatest and most exciting achievements that tissue engineering and regenerative medicine have achieved. Adipose-derived mesenchymal stem cells (AD-MSC) are easily isolated and cultured for a long time before losing their stem cell characteristics, which are self-renewal and pluripotency. AD-MSC are mesenchymal stem cells that have pluripotent lineage characteristics. They are easily accessible, and the fraction of stem cells in the adipose tissue lysates is highest among all other sources of mesenchymal stem cells. It is also HLA-DR negative and can be transplanted allogenically without the need for immunosuppression. These advantages have popularized its use in many fields including plastic reconstructive surgery. However, in the field of hepatology and liver transplantation, the progress is slower. AD-MSC have the potential to modulate inflammation, ameliorate ischemia-reperfusion injury, and support liver and biliary tract regeneration. These are very important for the treatment of various hepatobiliary diseases. Furthermore, the anti-inflammatory potential of these cells has paramount importance in the treatment of sepsis. We need alternative therapeutic approaches to treat end-stage liver failure. AD-MSC can provide a means of therapy to bridge to definitive therapeutic alternatives such as liver transplantation. Here we propose to review theoretic applications of AD-MSC in the treatment of hepatobiliary diseases and sepsis.

**Key Words:** Adipose-derived stem cells; Hepatobiliary diseases; Sepsis; Mesenchymal stem cells; Theoretic application

**©The** **Author(s) 2022.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Satilmis B, Cicek GS, Cicek E, Akbulut S, Sahin TT, Yilmaz S. Adipose-derived stem cells in the treatment of hepatobiliary diseases and sepsis. *World J Clin Cases* 2022; 10(14): 4348-4356

**URL:** https://www.wjgnet.com/2307-8960/full/v10/i14/4348.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i14.4348

**Core Tip:** Adipose-derived mesenchymal stem cells (AD-MSC) are mesenchymal stem cells that have pluripotent lineage characteristics. They are easily accessible, and the fraction of stem cells in the adipose tissue lysates is the highest among all other sources of mesenchymal stem cells. It is also HLA-DR negative and can be transplanted allogenically without the need for immunosuppression. We clearly need alternative therapeutic approaches to treat end-stage liver failure. AD-MSC can provide a means of bridge therapy to definitive therapeutic alternatives such as liver transplantation. We review the theoretic applications of AD-MSC in the treatment of hepatobiliary diseases.

**INTRODUCTION**

Stem cell therapy provides limitless therapeutic options in the field of medicine, which is the direct result of the achievements obtained by the field of regenerative medicine. The therapeutic applications are early in its stages, and the clinical trials are ongoing[1]. Ideal stem cells should have the ability of self-renewal, multilineage capacity, and easily isolated, and cultivation conditions should be simple[2,3]. Mesenchymal stem cells (MSC) have been used abundantly for this purpose[3,4]. MSC have an intricate cell biology and are amenable to being utilized in tissue engineering. They secrete various potent growth factors and cytokines, they have pluripotent differentiation capabilities, and they are abundant in the body including the bone marrow, oral cavity, and adipose tissue[5].

In 2001, Zuk *et al*[6] isolated and defined the stromal vascular fraction of adipose tissue. The stromal vascular fraction contains a mixture of erythrocytes, fibromyoblasts, endothelial cells, smooth muscle cells, pericytes of vascular origin, and fat cells. The stromal vascular fraction can be cultured, forming fibroblast-like cells that are adherent to the culture flask. These cells were originally named pre-adipocytes[7,8]. However, it has been shown that these cells have mesodermal multipotent differentiation ability, and they are currently called adipose-derived MSC (AD-MSC)[7]. Currently, advancements in tissue engineering and regenerative medicine have shown that these cells can differentiate into cells and tissues of endodermal, mesodermal, and ectodermal origin[1,2]. There are some advantages to using AD-MSC in regenerative medicine. The most important one is the abundance of stem cells in the adipose tissue[9,10]. Adipose tissue contains at least 100 times higher amounts of stem cells when compared to other sources such as the bone marrow[1,11]. Furthermore, the isolation procedure is very simple and efficient[1,2,6,7,12]. Obtaining the fat tissue from individuals is very easy. The proliferative capacity and durability of AD-MSC exceed MSC obtained from other sources[2,13-15].

The isolation procedure is very simple and has been done for a long time[16]. It includes mechanical disruption of the tissue followed by enzymatic digestion and ultracentrifugation (Figure 1). It is cultured in standard cell culture media without the need of a special culture media. During the standard culture of eukaryotic cells 10% (v/v), fetal bovine serum is used. This can lead to certain problems such as immune reactivity and transmission of zoonotic infections[17]. For this reason, platelet-rich plasma can be used as an alternative to fetal bovine serum. Platelet-rich plasma has also been shown to enhance AD-MSC growth *in vitro*[18].

There is a uniform pattern of surface marker expression for AD-MSC, which is the presence of CD90, CD73, CD105, and CD44[19,20]. Expression of CD34 and CD49d is highly reserved for AD-MSC and is absent in other MSC types[21]. The secretion profile of AD-MSC includes a wide range of cytokines, chemokines, and growth factors. The effects of the secreted factors are paracrine in their activity. There are factors that promote angiogenesis such as fibroblast growth factor 2, vascular endothelial growth factor, hepatocyte growth factor, and insulin-like growth factor 1[22]. Also, matrix metalloproteinase-3 and matrix metalloproteinase-9 contribute to their proangiogenic activity[23]. Their effect on the system is usually induction of immunoregulatory type changes promoting tissue injury and angiogenesis. The factors that are responsible for the immune effects of AD-MSC are macrophage-colony stimulating factor, granulocyte-colony stimulating factor, interleukin (IL) 6, tumor necrosis factor, and prostaglandin E2[23]. Therefore, there is T helper type 2 polarization of CD4-positive T cells and M2 polarization of the macrophages. All these changes reduce inflammation and increase the wound healing capacity of the tissues[24,25].

In acute and chronic liver failure, the regenerative capacity of the liver is overwhelmed by the noxious stimuli[26,27]. Therefore, regeneration or repair of the liver is very complicated due to the presence of a variety of parenchymal cells[28]. These cells include the hepatocytes, cholangiocytes, hepatic stellate cells, and immune cells including the Kupffer cells, natural killer cells, natural killer T cells, and eosinophils[28,29].

In summary, through the paracrine effects of the AD-MSC-derived cytokines, chemokines, and growth factors, AD-MSC stimulate angiogenesis, exert antiapoptotic effects, and recruit other MSC and progenitor cells to the site of injury[27,30,31]. In addition, they stimulate the proliferation and differentiation of the wide range of cells present in the site of injury. They also reduce the reactive oxygen species in the microenvironment and reduce reactive oxygen species-mediated injury to the tissues[27,30,31]. One unique feature of MSC is their ability to fuse with parenchymal cells in the injury site to promote intercellular interactions and exchange cellular macromolecules through the intercellular nanochannels that are formed[27,30-32].

The aim of the present study was to summarize the current literature in terms of AD-MSC in the cellular therapy for hepatic and biliary regeneration. Also, we briefly summarize the role of AD-MSC in the treatment of septic conditions. We hope this will help the readers to grasp the potential of AD-MSC in the treatment of hepatobiliary diseases.

**AD-MSC IN HEPATIC DISEASE AND REGENERATION**

The immune regulatory and antiapoptotic effects of AD-MSC aid regeneration of the liver and help healing of liver injury caused by viral infections, toxins, and genetic diseases[33,34]. Studies have shown that AD-MSC express liver specific markers even if they are not targeted *in vitro*[35]. There are many sources for AD-MSC, and each have different biological behavior. Liver falciform ligament-derived AD-MSC show higher proliferative capacity and higher embryonic stem cell capabilities[36]. Falciform ligament is readily available during liver surgery and can be used to enhance healing of the tissue following liver surgery. Surgeons have been using falciform ligament flaps to support anastomosis or to fill a gap in the liver following resection for a long time[37]. This may be attributed to the enhanced healing capacity of the stem cells present in the falciform ligament.

Experimental studies are abundant showing reduced inflammation, support of hepatic regeneration, and normalization of metabolic derangements in liver failure experimental models. We briefly summarize some of the cornerstone experiments that are present in the literature. Experimental studies have shown that the condition of the host determined the type of differentiation of the AD-MSC. In an experimental model of acute liver failure, it has been shown that AD-MSC showed increased expression of specific markers for hepatocytes[38]. AD-MSC have been shown to be amenable to *in vitro* targeting to hepatocytes, which can later be used to treat an experimental model of acute liver failure[39]. Transplantation of AD-MSC 24 h before 70% hepatectomy model in rats ameliorated hepatic dysfunction and improved liver regeneration by normalizing the metabolic processes in the liver[40]. Banas *et al*[41] have also reported their results in a carbon tetrachloride treated acute liver failure model. They have shown that treatment with AD-MSC that were preconditioned *in* *vitro* ameliorated the liver failure and normalized liver function tests in animals in the treatment arm[41]. AD-MSC given as treatment after the development of acute liver failure have also been shown to be effective in improving liver regeneration and functions[42]. Preconditioning of AD-MSC has resulted in development of functional liver tissue (liver bud) in experimental models[43]. AD-MSC were shown to significantly inhibit the proliferation and activation of hematopoietic stem cells and promote the programmed cell death of hematopoietic stem cells thereby reducing hepatic fibrosis in experimental models[44,45].

AD-MSC can also be used together with nanoparticle technology to increase the engraftment rates and enhance the efficacy of the AD-MSC in reversal of liver injury and liver fibrosis[43]. Furthermore, the use of liver bioscaffolds has been shown to support the growth of neonatal multilineage progenitor cells into fully functional liver tissue[46]. If stem cells are used during the recellularization process, the results seem to be better when comparted to primary parenchymal cells such as the hepatocytes[43]. Apart from supporting the regenerative process, AD-MSC reduce the ischemia and reperfusion injury during liver surgery and diseases. It has been shown that AD-MSC reduce ischemia reperfusion injury in liver by reduction of various inflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor[47]. Furthermore, AD-MSC secrete counter regulatory cytokines such as IL-10 and secrete factors such as hepatocyte growth factor and cyclin D1, which are effective in hepatic regeneration[47]. The effects of AD-MSC include immune regulation, reduction of oxidative and inflammatory tissue destruction, and regeneration of the parenchymal cells. The proposed mechanisms of action of AD-MSC are summarized in Figure 2. The clinical trials so far have been successful and have shown a good safety profile of AD-MSC in humans. It prevented acute-on-chronic liver failure and improved liver functions in patients with cirrhosis with various etiologies[48–50]. The summary of the preclinical studies and clinical trials are summarized in Supplementary Table 1 and 2.

**THE ROLE OF AD-MSC IN BILIARY REGENERATION**

Liver resection and transplantation are among the definitive treatments of life-threatening chronic liver disease and primary/secondary liver tumors. The most frequent complication following liver disease is the biliary complications[51,52]. Some of these complications may even cause mortality in the patients. Stenosis is one of the biliary complications that are observed following hepatobiliary surgery. In major surgeries like living donor liver transplantation, it has been reported to affect 10%-30% of the patients[53]. Treatment of this complication requires repeated procedures, restorative operations, and frequent prolonged hospitalizations.

The majority of the complications are due to ischemia and reperfusion injury. Ischemia reperfusion injury has adverse effects on both hepatic and biliary regeneration[54,55]. Zhu *et al*[55] reported that warm ischemia times exceeding 20 min were associated with biliary complication and biliary epithelial damage in an experimental model. The cholangiocytes have pluripotent differentiation potential, but it is overwhelmed during ischemia and reperfusion injury[54,55]. MSC therapy may be an alternative or adjunct to conventional therapies for biliary complications. AD-MSC are preferred alternatives for they are easily accessible, and they promote anti-inflammatory mechanisms and regeneration in the tissue, which may be beneficial for biliary regeneration[55,56]. There are limited studies regarding the versatility of AD-MSC in biliary regeneration[47,57]. Abraham *et al*[57] showed that AD-MSC sheets were effective in preventing biliary strictures in duct-to-duct anastomoses. However, the studies were limited regarding the role of AD-MSC in biliary regeneration. Further studies will provide innovative therapeutic options for biliary complications.

**THE ROLE OF AD-MSC IN THE TREATMENT OF SEPSIS**

Sepsis is an overwhelming inflammatory response to invading microorganisms. The severity of the disease depends on the virulence of the microbial pathogen, amount of toxins secreted by the pathogen, and the physiologic status of the host. The recovery from sepsis depends on the balance between the proinflammatory cytokines and anti-inflammatory mechanisms that counterbalance inflammation[58]. Tumor necrosis factor-α3 and IL-6 are the potent proinflammatory cytokines that have a major role during the pathogenesis of sepsis[59,60]. As our understanding of the physiopathology increases, alternative immunomodulatory therapies are being developed and investigated for clinical use[61].

Currently, MSC are being used for the treatment of sepsis. The majority of these are isolated from the bone marrow, which is not an easy process[62]. AD-MSC have been shown to be effective in endotoxemia-induced sepsis models in rats by reducing apoptosis and the rate of multi-organ failure[63]. The anti-inflammatory action of MSC can be a direct effect through cell-to-cell interaction or may be through paracrine effects of the secreted mediators or secretion of exosomes/microvesicles to the inflammatory microenvironment[62]. MSC have been shown to reduce proinflammatory cytokines and increase cytokines such as IL-10 and induce a regulatory phenotype in the immune cells[64]. Through this mechanism, MSC reduce the amount of macrophage and neutrophil infiltration in target organs such as the lungs, kidneys, and the liver, thus reducing the risk of multiple organ failure[62,65–67]. MSC also increase the phagocytic activity of monocytes in circulation and reduce the effective microbial concentrations[68].

In sepsis or viral pneumonia such as the one seen in coronavirus disease 2019, traditional therapeutic options were insufficient[69]. Bone marrow-derived MSC played an important role for both reduction of inflammatory damage in end-organs and in clearance of microbial agents from the circulation of the patients. The studies regarding the role of AD-MSC in sepsis are not enough, and further studies are needed. The proposed mechanism of action of AD-MSC in hepatobiliary diseases and sepsis are summarized in Figure 2.

**CONCLUSION**

There are many unknown points regarding the role of AD-MSC in the treatment of hepatobiliary diseases. However, the results of preclinical studies and limited clinical trials are promising. It seems to be a good alternative treatment to bridge acute or acute-on-chronic liver failure until a definitive liver transplantation can be performed. Furthermore, it may promote the wound-healing process preventing many complications in the biliary tract following major liver surgeries.

The utility of AD-MSC in the treatment of hepatobiliary disease and sepsis is relatively new. Brief reports are showing the efficacy of AD-MSC in controlling inflammation and regenerating parenchymal tissue. However, there is not a firmly established protocol. The dose and dosing intervals of the allogenic AD-MSC transplantation requires further research for establishing universal protocols. Furthermore, the role of targeted or genetically modified AD-MSC are unknown. Bioscaffolds may also provide modeling of the tissue and providing precursors for the liver and biliary tract. Combination of AD-MSC with nanoparticles for potentiating the anti-inflammatory response will be an important area of research in the future. Therefore, further research is needed to guide physicians for future innovative clinical applications.

**REFERENCES**

1 **Chu DT**, Nguyen Thi Phuong T, Tien NLB, Tran DK, Minh LB, Thanh VV, Gia Anh P, Pham VH, Thi Nga V. Adipose Tissue Stem Cells for Therapy: An Update on the Progress of Isolation, Culture, Storage, and Clinical Application. *J Clin Med* 2019; **8** [PMID: 31247996 DOI: 10.3390/jcm8070917]

2 **Zhang J**, Liu Y, Chen Y, Yuan L, Liu H, Wang J, Liu Q, Zhang Y. Adipose-Derived Stem Cells: Current Applications and Future Directions in the Regeneration of Multiple Tissues. *Stem Cells Int* 2020; **2020**: 8810813 [PMID: 33488736 DOI: 10.1155/2020/8810813]

3 **Dominici M**, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop Dj, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 2006; **8**: 315-317 [PMID: 16923606 DOI: 10.1080/14653240600855905]

4 **Zakrzewski W**, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. *Stem Cell Res Ther* 2019; **10**: 68 [PMID: 30808416 DOI: 10.1186/s13287-019-1165-5]

5 **Pittenger MF**, Discher DE, Péault BM, Phinney DG, Hare JM, Caplan AI. Mesenchymal stem cell perspective: cell biology to clinical progress. *NPJ Regen Med* 2019; **4**: 22 [PMID: 31815001 DOI: 10.1038/s41536-019-0083-6]

6 **Zuk PA**, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, Benhaim P, Lorenz HP, Hedrick MH. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng* 2001; **7**: 211-228 [PMID: 11304456 DOI: 10.1089/107632701300062859]

7 **Zhu M**, Heydarkhan-Hagvall S, Hedrick M, Benhaim P, Zuk P. Manual isolation of adipose-derived stem cells from human lipoaspirates. *J Vis Exp* 2013: e50585 [PMID: 24121366 DOI: 10.3791/50585]

8 **Bunnell BA**, Flaat M, Gagliardi C, Patel B, Ripoll C. Adipose-derived stem cells: isolation, expansion and differentiation. *Methods* 2008; **45**: 115-120 [PMID: 18593609 DOI: 10.1016/j.ymeth.2008.03.006]

9 **Semon JA**, Maness C, Zhang X, Sharkey SA, Beuttler MM, Shah FS, Pandey AC, Gimble JM, Zhang S, Scruggs BA, Strong AL, Strong TA, Bunnell BA. Comparison of human adult stem cells from adipose tissue and bone marrow in the treatment of experimental autoimmune encephalomyelitis. *Stem Cell Res Ther* 2014; **5**: 2 [PMID: 24405805 DOI: 10.1186/scrt391]

10 **Mazini L**, Rochette L, Amine M, Malka G. Regenerative Capacity of Adipose Derived Stem Cells (ADSCs), Comparison with Mesenchymal Stem Cells (MSCs). *Int J Mol Sci* 2019; **20** [PMID: 31121953 DOI: 10.3390/ijms20102523]

11 **Chu DT**, Tao Y, Son LH, Le DH. Cell source, differentiation, functional stimulation, and potential application of human thermogenic adipocytes in vitro. *J Physiol Biochem* 2016; **73**: 315-321 [PMID: 28612196 DOI: 10.1007/s13105-017-0567-z]

12 **Djouad F**, Bouffi C, Ghannam S, Noël D, Jorgensen C. Mesenchymal stem cells: innovative therapeutic tools for rheumatic diseases. *Nat Rev Rheumatol* 2009; **5**: 392-399 [PMID: 19568253 DOI: 10.1038/nrrheum.2009.104]

13 **Chen YJ**, Liu HY, Chang YT, Cheng YH, Mersmann HJ, Kuo WH, Ding ST. Isolation and Differentiation of Adipose-Derived Stem Cells from Porcine Subcutaneous Adipose Tissues. *J Vis Exp* 2016: e53886 [PMID: 27077225 DOI: 10.3791/53886]

14 **Dai R**, Wang Z, Samanipour R, Koo KI, Kim K. Adipose-Derived Stem Cells for Tissue Engineering and Regenerative Medicine Applications. *Stem Cells Int* 2016; **2016**: 6737345 [PMID: 27057174 DOI: 10.1155/2016/6737345]

15 **Gu X**, Li C, Yin F, Yang G. Adipose-derived stem cells in articular cartilage regeneration: current concepts and optimization strategies. *Histol Histopathol* 2018; **33**: 639-653 [PMID: 29243770 DOI: 10.14670/HH-11-955]

16 **Rodbell M.** Metabolism of isolated fat cells. i. effects of hormones on glucose metabolism and lipolysis . *J Biol Chem* 1964; **239**: 375-380 [PMID: 14169133]

17 **Laitinen A**, Oja S, Kilpinen L, Kaartinen T, Möller J, Laitinen S, Korhonen M, Nystedt J. A robust and reproducible animal serum-free culture method for clinical-grade bone marrow-derived mesenchymal stromal cells. *Cytotechnology* 2016; **68**: 891-906 [PMID: 25777046 DOI: 10.1007/s10616-014-9841-x]

18 **Atashi F**, Jaconi ME, Pittet-Cuénod B, Modarressi A. Autologous platelet-rich plasma: a biological supplement to enhance adipose-derived mesenchymal stem cell expansion. *Tissue Eng Part C Methods* 2015; **21**: 253-262 [PMID: 25025830 DOI: 10.1089/ten.TEC.2014.0206]

19 **Mildmay-White A**, Khan W. Cell Surface Markers on Adipose-Derived Stem Cells: A Systematic Review. *Curr Stem Cell Res Ther* 2017; **12**: 484-492 [PMID: 27133085 DOI: 10.2174/1574888X11666160429122133]

20 **Samadi P**, Saki S, Manoochehri H, Sheykhhasan M. Therapeutic Applications of Mesenchymal Stem Cells: A Comprehensive Review. *Curr Stem Cell Res Ther* 2021; **16**: 323-353 [PMID: 32928093 DOI: 10.2174/1574888X15666200914142709]

21 **Kocan B**, Maziarz A, Tabarkiewicz J, Ochiya T, Banaś-Ząbczyk A. Trophic Activity and Phenotype of Adipose Tissue-Derived Mesenchymal Stem Cells as a Background of Their Regenerative Potential. *Stem Cells Int* 2017; **2017**: 1653254 [PMID: 28757877 DOI: 10.1155/2017/1653254]

22 **Combellack EJ**, Jessop ZM, Naderi N, Griffin M, Dobbs T, Ibrahim A, Evans S, Burnell S, Doak SH, Whitaker IS. Adipose regeneration and implications for breast reconstruction: update and the future. *Gland Surg* 2016; **5**: 227-241 [PMID: 27047789 DOI: 10.3978/j.issn.2227-684X.2016.01.01]

23 **Gokce A**, Abd Elmageed ZY, Lasker GF, Bouljihad M, Kim H, Trost LW, Kadowitz PJ, Abdel-Mageed AB, Sikka SC, Hellstrom WJ. Adipose tissue-derived stem cell therapy for prevention and treatment of erectile dysfunction in a rat model of Peyronie's disease. *Andrology* 2014; **2**: 244-251 [PMID: 24574095 DOI: 10.1111/j.2047-2927.2013.00181.x]

24 **Schon HT**, Weiskirchen R. Immunomodulatory effects of transforming growth factor-β in the liver. *Hepatobiliary Surg Nutr* 2014; **3**: 386-406 [PMID: 25568862 DOI: 10.3978/j.issn.2304-3881.2014.11.06]

25 **Kokai LE**, Marra K, Rubin JP. Adipose stem cells: biology and clinical applications for tissue repair and regeneration. *Transl Res* 2014; **163**: 399-408 [PMID: 24361334 DOI: 10.1016/j.trsl.2013.11.009]

26 **Yang X**, He C, Zhu L, Zhao W, Li S, Xia C, Xu C. Comparative Analysis of Regulatory Role of Notch Signaling Pathway in 8 Types Liver Cell During Liver Regeneration. *Biochem Genet* 2019; **57**: 1-19 [PMID: 29961162 DOI: 10.1007/s10528-018-9869-2]

27 **Mok PL**, Leong CF, Cheong SK. Cellular mechanisms of emerging applications of mesenchymal stem cells. *Malays J Pathol* 2013; **35**: 17-32 [PMID: 23817392]

28 **D'Ambrosio DN**, Walewski JL, Clugston RD, Berk PD, Rippe RA, Blaner WS. Distinct populations of hepatic stellate cells in the mouse liver have different capacities for retinoid and lipid storage. *PLoS One* 2011; **6**: e24993 [PMID: 21949825 DOI: 10.1371/journal.pone.0024993]

29 **Ding BS**, Nolan DJ, Butler JM, James D, Babazadeh AO, Rosenwaks Z, Mittal V, Kobayashi H, Shido K, Lyden D, Sato TN, Rabbany SY, Rafii S. Inductive angiocrine signals from sinusoidal endothelium are required for liver regeneration. *Nature* 2010; **468**: 310-315 [PMID: 21068842 DOI: 10.1038/nature09493]

30 **Nowak WN**, Taha H, Kachamakova-Trojanowska N, Stępniewski J, Markiewicz JA, Kusienicka A, Szade K, Szade A, Bukowska-Strakova K, Hajduk K, Klóska D, Kopacz A, Grochot-Przęczek A, Barthenheier K, Cauvin C, Dulak J, Józkowicz A. Murine Bone Marrow Mesenchymal Stromal Cells Respond Efficiently to Oxidative Stress Despite the Low Level of Heme Oxygenases 1 and 2. *Antioxid Redox Signal* 2018; **29**: 111-127 [PMID: 29065700 DOI: 10.1089/ars.2017.7097]

31 **Polymeri A**, Giannobile WV, Kaigler D. Bone Marrow Stromal Stem Cells in Tissue Engineering and Regenerative Medicine. *Horm Metab Res* 2016; **48**: 700-713 [PMID: 27871114 DOI: 10.1055/s-0042-118458]

32 **Chan YW**, So C, Yau KL, Chiu KC, Wang X, Chan FL, Tsang SY. Adipose-derived stem cells and cancer cells fuse to generate cancer stem cell-like cells with increased tumorigenicity. *J Cell Physiol* 2020; **235**: 6794-6807 [PMID: 31994190 DOI: 10.1002/jcp.29574]

33 **Berardis S**, Lombard C, Evraerts J, El Taghdouini A, Rosseels V, Sancho-Bru P, Lozano JJ, van Grunsven L, Sokal E, Najimi M. Gene expression profiling and secretome analysis differentiate adult-derived human liver stem/progenitor cells and human hepatic stellate cells. *PLoS One* 2014; **9**: e86137 [PMID: 24516514 DOI: 10.1371/journal.pone.0086137]

34 **Liang H**, Ding X, Yu Y, Zhang H, Wang L, Kan Q, Ma S, Guan F, Sun T. Adipose-derived mesenchymal stem cells ameliorate acute liver injury in rat model of CLP induced-sepsis via sTNFR1. *Exp Cell Res* 2019; **383**: 111465 [PMID: 31201811 DOI: 10.1016/j.yexcr.2019.06.010]

35 **Zemel R**, Bachmetov L, Ad-El D, Abraham A, Tur-Kaspa R. Expression of liver-specific markers in naïve adipose-derived mesenchymal stem cells. *Liver Int* 2009; **29**: 1326-1337 [PMID: 19515222 DOI: 10.1111/j.1478-3231.2009.02054.x]

36 **Lee SW**, Chong JU, Min SO, Bak SY, Kim KS. Are Adipose-Derived Stem Cells From Liver Falciform Ligaments Another Possible Source of Mesenchymal Stem Cells? *Cell Transplant* 2017; **26**: 855-866 [PMID: 27938473 DOI: 10.3727/096368916X693833]

37 **Ozmen MM**, Coskun F, Ziraman I. Falciform ligament in the management of the residual cavity for liver hydatidosis: new surgical technique. *World J Surg* 2006; **30**: 1722-1728 [PMID: 16807665 DOI: 10.1007/s00268-005-0726-1]

38 **Hu C**, Zhou N, Li J, Shi D, Cao H, Li J, Li L. Porcine Adipose-Derived Mesenchymal Stem Cells Retain Their Stem Cell Characteristics and Cell Activities While Enhancing the Expression of Liver-Specific Genes after Acute Liver Failure. *Int J Mol Sci* 2016; **17** [PMID: 26742034 DOI: 10.3390/ijms17010062]

39 **Liang L**, Ma T, Chen W, Hu J, Bai X, Li J, Liang T. Therapeutic potential and related signal pathway of adipose-derived stem cell transplantation for rat liver injury. *Hepatol Res* 2009; **39**: 822-832 [PMID: 19473439 DOI: 10.1111/j.1872-034X.2009.00506.x]

40 **Tautenhahn HM**, Brückner S, Baumann S, Winkler S, Otto W, von Bergen M, Bartels M, Christ B. Attenuation of Postoperative Acute Liver Failure by Mesenchymal Stem Cell Treatment Due to Metabolic Implications. *Ann Surg* 2016; **263**: 546-556 [PMID: 25775061 DOI: 10.1097/SLA.0000000000001155]

41 **Banas A**, Teratani T, Yamamoto Y, Tokuhara M, Takeshita F, Osaki M, Kato T, Okochi H, Ochiya T. Rapid hepatic fate specification of adipose-derived stem cells and their therapeutic potential for liver failure. *J Gastroenterol Hepatol* 2009; **24**: 70-77 [PMID: 18624899 DOI: 10.1111/j.1440-1746.2008.05496.x]

42 **Zare H**, Jamshidi S, Dehghan MM, Saheli M, Piryaei A. Bone marrow or adipose tissue mesenchymal stem cells: Comparison of the therapeutic potentials in mice model of acute liver failure. *J Cell Biochem* 2018; **119**: 5834-5842 [PMID: 29575235 DOI: 10.1002/jcb.26772]

43 **Zhang Y**, Chen XM, Sun DL. Effects of coencapsulation of hepatocytes with adipose-derived stem cells in the treatment of rats with acute-on-chronic liver failure. *Int J Artif Organs* 2014; **37**: 133-141 [PMID: 24619896 DOI: 10.5301/ijao.5000284]

44 **Hao T**, Chen J, Zhi S, Zhang Q, Chen G, Yu F. Comparison of bone marrow-vs. adipose tissue-derived mesenchymal stem cells for attenuating liver fibrosis. *Exp Ther Med* 2017; **14**: 5956-5964 [PMID: 29285145 DOI: 10.3892/etm.2017.5333]

45 **Nguyen NH,** Le T Van, Do HQ, Ngo DQ, Le HM, Truong NH. Comparative treatment efficiency of adipose and bone marrow derived allogenic mesenchymal stem cell transplantation in mouse models of liver fibrosis. *Biomed Res Ther* 2017; **4:** 1374 [DOI: 10.15419/bmrat.v4i06.179]

46 **Hassanein W**, Cimeno A, Werdesheim A, Buckingham B, Harrison J, Uluer MC, Khalifeh A, Rivera-Pratt C, Klepfer S, Woodall JD, Dhru U, Bromberg E, Parsell D, Drachenberg C, Barth RN, LaMattina JC. Liver Scaffolds Support Survival and Metabolic Function of Multilineage Neonatal Allogenic Cells. *Tissue Eng Part A* 2018; **24**: 786-793 [PMID: 29017397 DOI: 10.1089/ten.TEA.2017.0279]

47 **Ge Y**, Zhang Q, Jiao Z, Li H, Bai G, Wang H. Adipose-derived stem cells reduce liver oxidative stress and autophagy induced by ischemia-reperfusion and hepatectomy injury in swine. *Life Sci* 2018; **214**: 62-69 [PMID: 30381247 DOI: 10.1016/j.lfs.2018.10.054]

48 **Götze T**, Krueger M, Meutsch J, Dörfel M, Born S, Sowa JP, Canbay A. Three Cases of Alcohol-Induced Acute-On-Chronic Liver Failure With Successful Support by Adipose-Derived Stem Cells. *Clin Transl Gastroenterol* 2019; **10**: e00095 [PMID: 31789934 DOI: 10.14309/ctg.0000000000000095]

49 **Huang KC**, Chuang MH, Lin ZS, Lin YC, Chen CH, Chang CL, Huang PC, Syu WS, Chiou TW, Hong ZH, Tsai YC, Harn HJ, Lin PC, Lin SZ. Transplantation with GXHPC1 for Liver Cirrhosis: Phase 1 Trial. *Cell Transplant* 2019; **28**: 100S-111S [PMID: 31722556 DOI: 10.1177/0963689719884885]

50 **Sakai Y**, Takamura M, Seki A, Sunagozaka H, Terashima T, Komura T, Yamato M, Miyazawa M, Kawaguchi K, Nasti A, Mochida H, Usui S, Otani N, Ochiya T, Wada T, Honda M, Kaneko S. Phase I clinical study of liver regenerative therapy for cirrhosis by intrahepatic arterial infusion of freshly isolated autologous adipose tissue-derived stromal/stem (regenerative) cell. *Regen Ther* 2017; **6**: 52-64 [PMID: 30271839 DOI: 10.1016/j.reth.2016.12.001]

51 **Chang JH**, Lee IS, Choi JY, Yoon SK, Kim DG, You YK, Chun HJ, Lee DK, Choi MG, Chung IS. Biliary Stricture after Adult Right-Lobe Living-Donor Liver Transplantation with Duct-to-Duct Anastomosis: Long-Term Outcome and Its Related Factors after Endoscopic Treatment. *Gut Liver* 2010; **4**: 226-233 [PMID: 20559526 DOI: 10.5009/gnl.2010.4.2.226]

52 **Park JK**, Yang JI, Lee JK, Park JK, Lee KH, Lee KT, Joh JW, Kwon CHD, Kim JM. Long-term Outcome of Endoscopic Retrograde Biliary Drainage of Biliary Stricture Following Living Donor Liver Transplantation. *Gut Liver* 2020; **14**: 125-134 [PMID: 30970446 DOI: 10.5009/gnl18387]

53 **Wojcicki M**, Milkiewicz P, Silva M. Biliary tract complications after liver transplantation: a review. *Dig Surg* 2008; **25**: 245-257 [PMID: 18628624 DOI: 10.1159/000144653]

54 **Saidi RF**, Rajeshkumar B, Shariftabrizi A, Bogdanov AA, Zheng S, Dresser K, Walter O. Human adipose-derived mesenchymal stem cells attenuate liver ischemia-reperfusion injury and promote liver regeneration. *Surgery* 2014; **156**: 1225-1231 [PMID: 25262218 DOI: 10.1016/j.surg.2014.05.008]

55 **Zhu XH**, Pan JP, Wu YF, Ding YT. Establishment of a rat liver transplantation model with prolonged biliary warm ischemia time. *World J Gastroenterol* 2012; **18**: 7194-7200 [PMID: 23326124 DOI: 10.3748/wjg.v18.i48.7194]

56 **Baglio SR**, Pegtel DM, Baldini N. Mesenchymal stem cell secreted vesicles provide novel opportunities in (stem) cell-free therapy. *Front Physiol* 2012; **3**: 359 [PMID: 22973239 DOI: 10.3389/fphys.2012.00359]

57 **Abraham E**, Wunderink R, Silverman H, Perl TM, Nasraway S, Levy H, Bone R, Wenzel RP, Balk R, Allred R. Efficacy and safety of monoclonal antibody to human tumor necrosis factor alpha in patients with sepsis syndrome. A randomized, controlled, double-blind, multicenter clinical trial. TNF-alpha MAb Sepsis Study Group. *JAMA* 1995; **273**: 934-941 [PMID: 7884952 DOI: 10.1016/j.reth.2019.11.001]

58 **Opal SM**, DePalo VA. Anti-inflammatory cytokines. *Chest* 2000; **117**: 1162-1172 [PMID: 10767254 DOI: 10.1378/chest.117.4.1162]

59 **Huang M**, Cai S, Su J. The Pathogenesis of Sepsis and Potential Therapeutic Targets. *Int J Mol Sci* 2019; **20**: 5376 [PMID: 31671729 DOI: 10.3390/ijms20215376]

60 **Mira JP**, Cariou A, Grall F, Delclaux C, Losser MR, Heshmati F, Cheval C, Monchi M, Teboul JL, Riché F, Leleu G, Arbibe L, Mignon A, Delpech M, Dhainaut JF. Association of TNF2, a TNF-alpha promoter polymorphism, with septic shock susceptibility and mortality: a multicenter study. *JAMA* 1999; **282**: 561-568 [PMID: 10450718 DOI: 10.1001/jama.282.6.561]

61 **Cribbs SK**, Matthay MA, Martin GS. Stem cells in sepsis and acute lung injury. *Crit Care Med* 2010; **38**: 2379-2385 [PMID: 20838330 DOI: 10.1097/CCM.0b013e3181f96f5f]

62 **Keane C**, Jerkic M, Laffey JG. Stem Cell-based Therapies for Sepsis. *Anesthesiology* 2017; **127**: 1017-1034 [PMID: 28872482 DOI: 10.1097/ALN.0000000000001882]

63 **Hu Y**, Qin C, Zheng G, Lai D, Tao H, Zhang Y, Qiu G, Ge M, Huang L, Chen L, Cheng B, Shu Q, Xu J. Mesenchymal Stem Cell-Educated Macrophages Ameliorate LPS-Induced Systemic Response. *Mediators Inflamm* 2016; **2016**: 3735452 [PMID: 27546994 DOI: 10.1155/2016/3735452]

64 **Sun J**, Sun X, Chen J, Liao X, He Y, Wang J, Chen R, Hu S, Qiu C. microRNA-27b shuttled by mesenchymal stem cell-derived exosomes prevents sepsis by targeting JMJD3 and downregulating NF-κB signaling pathway. *Stem Cell Res Ther* 2021; **12**: 14 [PMID: 33413595 DOI: 10.1186/s13287-020-02068-w]

65 **Chen J**, Li C, Liang Z, Li C, Li Y, Zhao Z, Qiu T, Hao H, Niu R, Chen L. Human mesenchymal stromal cells small extracellular vesicles attenuate sepsis-induced acute lung injury in a mouse model: the role of oxidative stress and the mitogen-activated protein kinase/nuclear factor kappa B pathway. *Cytotherapy* 2021; **23**: 918-930 [PMID: 34272174 DOI: 10.1016/j.jcyt.2021.05.009]

66 **Sheng M**, Lin Y, Xu D, Tian Y, Zhan Y, Li C, Farmer DG, Kupiec-Weglinski JW, Ke B. CD47-Mediated Hedgehog/SMO/GLI1 Signaling Promotes Mesenchymal Stem Cell Immunomodulation in Mouse Liver Inflammation. *Hepatology* 2021; **74**: 1560-1577 [PMID: 33765345 DOI: 10.1002/hep.31831]

67 **Luo CJ**, Zhang FJ, Zhang L, Geng YQ, Li QG, Hong Q, Fu B, Zhu F, Cui SY, Feng Z, Sun XF, Chen XM. Mesenchymal stem cells ameliorate sepsis-associated acute kidney injury in mice. *Shock* 2014; **41**: 123-129 [PMID: 24169208 DOI: 10.1097/SHK.0000000000000080]

68 **Krasnodembskaya A**, Samarani G, Song Y, Zhuo H, Su X, Lee JW, Gupta N, Petrini M, Matthay MA. Human mesenchymal stem cells reduce mortality and bacteremia in gram-negative sepsis in mice in part by enhancing the phagocytic activity of blood monocytes. *Am J Physiol Lung Cell Mol Physiol* 2012; **302**: L1003-L1013 [PMID: 22427530 DOI: 10.1152/ajplung.00180.2011]

69 **Wang L**, Li Y, Xu M, Deng Z, Zhao Y, Yang M, Liu Y, Yuan R, Sun Y, Zhang H, Wang H, Qian Z, Kang H. Regulation of Inflammatory Cytokine Storms by Mesenchymal Stem Cells. *Front Immunol* 2021; **12**: 726909 [PMID: 34394132 DOI: 10.3389/fimmu.2021.726909]

**Footnotes**

**Conflict-of-interest:** The authors declare that they have no conflicts of interest for the present study.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; externally peer reviewed.

**Peer-review model:** Single blind

**Corresponding Author’s Membership in Various Associations:** American Association of Cancer Research, 233259; American College of Surgeons, 3223715.

**Peer-review started:** October 11, 2021

**First decision:** November 15, 2021

**Article in press:** March 25, 2022

**Specialty type:** Transplantation

**Country/Territory of origin:** Turkey

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Rodrigues AT, Brazil; Sheykhhasan M, Iran **S-Editor:** Liu JH **L-Editor:** Filipodia **P-Editor:** Liu JH

**Figure Legends**



**Figure 1 Summary of the potential sources and isolation process of adipose-derived mesenchymal stem cells.**



**Figure 2 Possible mechanisms of action of adipose-derived mesenchymal stem cells in liver disease and inflammation.** AD-MSC: Adipose-derived mesenchymal stem cells, ECM: Extracellular matrix, MMP: Matrix metalloproteinase, TIMP: Tissue inhibitor of matrix metalloproteinase, TGF-β1: Transforming growth factor-β1.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2022 Baishideng Publishing Group Inc. All rights reserved.**