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A General Overview of Mesenchymal Stem Cell Therapies in Drug- and Chemical-Induced Liver Injury Models

İlaç ve Kimyasal Kaynaklı Karaciğer Hasarı Modellerinde Mezenkimal Kök Hücre Tedavi Uygulamalarına Genel Bir Bakış

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ABSTRACT

Liver injury is commonly seen in the population depending on the drug and chemical usage. Different groups of drugs and chemicals lead to different pathogeneses in the liver, such as necrosis, fibrosis, or inflammation. Although the liver has a high regenerative capability, drug- and chemical-induced liver injury may result in organ failure. Because of the limitations of liver transplantation, therapy methods alternative to organ transplantation still need to be studied. Owing to their differentiation and regeneration abilities, mesenchymal stem cells (MSCs) have recently drawn attention as potential therapeutic agents. In this review, we focused on the effects of human MSCs derived from adipose tissue, bone marrow, umbilical cord, placenta, and amniotic membrane on drug- and chemical-induced liver injury models. Recent studies have reported recovery by the application of human MSCs from different sources. Although MSC therapy leads to amelioration in liver function, researchers still try to improve therapeutic efficacy. To this end, different modifications and application modalities of MSCs were investigated in drug-induced liver injury models. To understand the molecular mechanisms of MSCs' effects on liver injury, animal studies are required to drive research perspectives for future progress.

Keywords: Drugs and chemicals, liver injury, liver regeneration, mesenchymal stem cells

ÖZ

İlaç ve kimyasal kullanımına bağlı olarak toplumda karaciğer hasarı yaygın olarak görülmektedir. Farklı ilaç ve kimyasal grupları karaciğerde nekroz, fibrozis veya enflamasyon gibi farklı patogenezlere yol açmaktadır. Karaciğer yüksek bir yenilenme kapasitesine sahip olmasına rağmen ilaç ve kimyasalların neden olduğu karaciğer hasarı organ yetmezliği ile sonuçlanabilmektedir. Karaciğer naklinde karşılaşılan zorluklar nedeniyle organ nakline alternatif tedavi yöntemlerinin daha fazla araştırılması gerekmektedir. Farklılaşma ve rejenerasyon kapasiteleri nedeniyle mezenkimal kök hücreler (MKH) son zamanlarda potansiyel terapötik ajanlar olarak dikkat çekmektedir. Bu derlemede, yağ dokusu, kemik iliği, göbek kordonu, plasenta ve amniyotik membrandan elde edilen insan MKH'lerin ilaç ve kimyasal kaynaklı karaciğer hasarı modelleri üzerindeki etkilerine odaklanılmıştır. Güncel çalışmalar, farklı dokulardan elde edilen insan MKH'lerinin uygulanmasıyla iyileşmenin görüldüğünü bildirmektedir. MKH tedavisi, karaciğer fonksiyonlarında iyileşme sağlasa da, araştırmacılar hala MKH'lerin terapötik etkinliklerini artırmaya yönelik çalışmalarını sürdürmektedir. Bu amaçla ilaca bağlı karaciğer hasarı modellerinde MKH'lerin farklı modifikasyonları ve uygulama yöntemleri araştırılmıştır. MKH'lerin karaciğer hasarı üzerindeki etkilerinin moleküler mekanizmalarını anlamak ve gelecekteki çalışmalara yönelik araştırma perspektifine yön vermek amacıyla hayvan çalışmaları gerekmektedir.

Anahtar Sözcükler: İlaçlar ve kimyasallar, karaciğer hasarı, karaciğer rejenerasyonu, mezenkimal kök hücreler

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INTRODUCTION

The liver is an organ prone to drug- and chemical-induced damage because it metabolizes many xenobiotics. Drug-induced liver injury may be categorized as either idiosyncratic or intrinsic depending on individual factors or the dose of drug, respectively (1). Mitochondrial damage, protein adducts formed by reactive metabolites, endoplasmic reticulum stress, and apoptosis contribute to the pathological molecular basis of drug-induced liver injury (2). Different types of drugs may cause acute hepatotoxicity. Use of drugs such as rifampicin, sulfonamide, isoniazid, and disulfiram may lead to acute hepatic damage characterized by hepatocyte degeneration, apoptotic bodies, and small necrotic foci in all zones. Drugs such as diphenylhydantoin and diaminodiphenyl-sulfone induce lymphocyte and eosinophil infiltration, and cause necrosis in the portal area of the liver. Although drugs such as halothane, acetaminophen (APAP), and ketoconazole cause hepatocyte necrosis and also disruption of microcirculation specifically in the centrilobular area (zone 3), hepatocyte necrosis may become more severe in some cases and may be seen also in periportal area (zone 1). Fibrosis may be mild or absent in the histopathology of hepatotoxicity induced by such drugs. In addition, these drugs can cause hepatocyte loss, resulting in liver damage characterized by extensive necrosis (3). Although the liver is an organ with a high regeneration capacity, there are many conditions leading to liver failure due to necrosis and fibrosis in acute or chronic processes. These conditions include infections such as viral hepatitis and chemical or biological factors such as drugs and toxic substances. Liver transplantation, the most effective treatment for liver failure, is a challenging approach because of transplant rejection, limited number of donors (4), and side effects resulting from immunosuppression (5). Therefore, experimental and clinical studies reviewing regenerative therapeutic approaches provide new insights into treatment strategies alternative to transplantation. In this paper, we reviewed experimental studies investigating the effects of human MSCs obtained from different sources, including adipose tissue, bone marrow, umbilical cord, placenta, and amniotic membrane, on drug- and chemical-induced liver injury (Figure 1, Table 1). We limited our literature review to the key words "drug-induced liver injury" and the name of the mesenchymal stem cell (MSC) types and looked into the Web of Science and PubMed databases.

Table 1. Effects of hMSCs and their derivatives on drug- and chemical-induced liver injury

MSCs/source		Drug/chemical agent	Action principle	Outputs
Human adipose tissue-derived mesenchymal stem cells	Human adipose-derived MSCs (6)	CCl4	Paracrine signaling	- Decreased ALT levels - Increased PCNA expression - Improvement in histopathological alterations
	Fox2-overexpressing hAD-MSCs (7)	TAA	Paracrine signaling	- No change in ALT and AST levels - Improvement in necrosis - Recovery in ALB and BIL levels
	Lipid-conjugated heparin-coated hAD-MSCs (8)	APAP	Greater engraftment with coating	- Reduction in ALT and AST levels - Decreased CYP2E1 expression - Increased HGF expression
	HLC with 3D-AHAM scaffold (9)	CCl4	Long-term and improved incorporation	- Reduction in the ALT level - Improvement in histopathological alterations
	Secretome (10)	AMI	Paracrine signaling	- Reduced necrosis - Improved inflammation - Decreased αSMA expression and apoptosis - Enhanced proliferation
Human placenta-derived mesenchymal stem cells	Human placenta-derived MSCs (11)	CCl4	Anti-fibrotic effect	- Improvement in the biochemical parameters - Decreased Col I and αSMA expressions
	Human placenta-derived MSCs (12)	TAA	Anti-inflammatory and antioxidant effects	- Decreased TNFα and IL6 levels - Increased HO1 expression and SOD1 and CAT activities
	Human placenta-derived MSCs (13)	CCl4	Autophagy-related signaling pathways	- Increased Beclin1, LC3 II, ATG7, Cyc A, and Cyc E expressions
Human Amniotic-derived Mesenchymal Stem Cells	Hepatocyte progenitor-like cells (14)	CCl4	Paracrine effect and hepatogenic differentiation	- Decreased ALT and AST levels - Reduced TNFα and IL2 levels - Increased IL-10 level
	$CD34^+$ and $CD34^-$ hAM-MSCs (15)	TAA	Anti-fibrotic effect	- Decreased ALT and AST levels - Reduced col I, αSMA and TGFβ expressions

Table 1. Continued

MSCs/source		Drug/chemical agent	Action principle	Outputs
Human umbilical cord-derived mesenchymal stem cells	Human umbilical cord-derived MSCs (16)	CCl4	Hepatogenic differentiation	- Decreased ALT and AST levels - Reduced apoptosis - Increased proliferation
	Exosomes (17)	CCl4	Antioxidant and anti-inflammatory effects of GPX1	- Decreased 8-OHdgG expression - Reduced apoptosis and oxidative stress
	MSC-derived miR-455-3p-enriched exosomes (18)	CCl4	Anti-inflammatory effect	- Decreased ALT and AST levels - Reduced G-CSF, IL6, IL17, MCP-1, and IP-10 levels - Improvement in histopathological alterations
	Preconditioning of MSCs (19)	CCl4	Anti-inflammatory effect	- Decreased MCP-1, TNF-α, IL-6, and CXCL1 levels
Human bone marrow-derived mesenchymal stem cells	Human bone marrow-derived MSCs (20)	CCl4	Paracrine effect	- Reduced necrosis and fibrosis
	Human bone marrow-derived MSCs (21)	CCl4	Anti-mutagenic effect	- Decreased chromosomal aberrations and DNA fragmentation

8-OHdgG: 8-hydroxy-2′-deoxyguanosine, αSMA: α smooth muscle actin, ALB: Albumin, ALT: Alanine aminotransferase, AMI: Amiodarone, APAP: Acetaminophen, AST: Aspartate aminotransferase, BIL: Bilirubin, CCl4: Carbon tetrachloride, Col I: Collagen I, CYP2E1: Cytochrome 2E1, G-CSF: Granulocyte colony stimulating factor, HGF: Hepatocyte growth factor, HO1: Heme oxygenase-1, IL: Interleukin, IP-10: Interferon gamma-induced protein 10, MCP-1: Monocyte chemoattractant protein-1, MSCs: Mesenchymal stem cells, PCNA: Proliferating cell nuclear antigen, TAA: Thioacetamide, TGFβ: Transforming growth factor beta.

2. Possible Therapeutic Use of Human MSCs in Drug- and Chemical-Induced Hepatic Injury

Animals used to establish liver injury models in studies investigating cellular treatments include mice, rats, guinea pigs, and cats (22). APAP, carbon tetrachloride (CCl4), thioacetamide (TAA), acetylsalicylic acid, cocaine, chemotherapy, amoxicillin-clavulanate, cephalosporins, isoniazid, and bromobenzene are the common agents used to form drug- and chemical-induced liver injury models (22-24).

Different perinatal and adult tissue sources such as amniotic fluid, amniotic membrane, umbilical cord blood and stroma, placenta, bone marrow, and adipose tissue serve as MSC sources (25). MSCs, resembling fibroblasts morphologically, express CD105, CD73, and CD90 surface markers, whereas they lack CD14, CD34, CD45, CD11B, CD79α, CD19, and human leukocyte antigen-DR isotype (HLA-DR) (26). In addition to *in vitro* differentiation into adipocytes, osteoblasts, and chondrocytes, studies have revealed that MSCs are able to differentiate into various cell lineages including endothelial cells, smooth muscle cells, cardiomyocyte, hepatocytes, pancreatic β-cells and neuronal cells, and *in vitro* differentiation of MSCs requires different culture conditions in accordance with their tissue of origin (27-28). Furthermore, it was revealed that MSCs, which can differentiate into endoderm-derived hepatocytes *in vitro*, exhibit hepatocyte-specific protein expression as well as hepatocyte functions such as glucose production and storage (29,30).

One of the reasons underlying the use of MSCs in cellular therapy for tissue damage is that when they are administered through blood circulation, these cells tend to migrate to the injured area and contribute to the healing process by different mechanisms (31). Owing to their high proliferative capacity and multipotency, MSCs are frequently used in studies on tissue regeneration because they can directly differentiate into the parenchymal cells of the tissue to be transplanted and transform into stromal components to support the parenchyma (32). For instance, in cases of liver injury, some transplanted MSCs turn into hepatocytes, whereas others contribute to liver regeneration by providing revascularization through vascular endothelial growth factor (VEGF) regulation (33). Studies have shown that the contribution of these cells to the healing process is not limited to the differentiation into tissue components; they also display paracrine effects through the substances they secrete (7,34). MSCs participate in regeneration by secreting soluble proteins, nucleic acids, lipids, and exosomes. Notably, exosomes are of particular importance for research on cell-free treatment approaches (35). MSCs secrete various paracrine substances, including proangiogenic and immunoregulatory factors, factors regulating the extracellular matrix, and factors that induce the migration and proliferation of MSCs (36). Hence, in case of tissue injury, MSCs are able to regulate angiogenesis and support regeneration with paracrine effects with chemokines that they secrete, such as fibroblast growth factor, insulin-like growth factor, hepatocyte growth factor (HGF), and VEGF (31). Regulation of angiogenesis, attenuation of fibrosis with factors they excrete (11,26), prevention of the resident cells from undergoing apoptosis, and regulation of the pro-inflammatory and anti-inflammatory cell balance (37) are some of their regulatory actions contributing to the tissue regeneration process (38).

2.1. Adipose Tissue-Derived MSCs in Drug- and Chemical-Induced Hepatic Injury Models

Besides medical treatments and organ transplantation, there are also MSC therapy approaches in drugs or chemical-induced liver injury in clinical practice (31,39), and experimental studies are needed to bring new insights into clinical research. In one of the experimental studies, Gad et al. (40) revealed a recovery by the administration of an adipose tissue-derived MSC (AD-MSC) acute

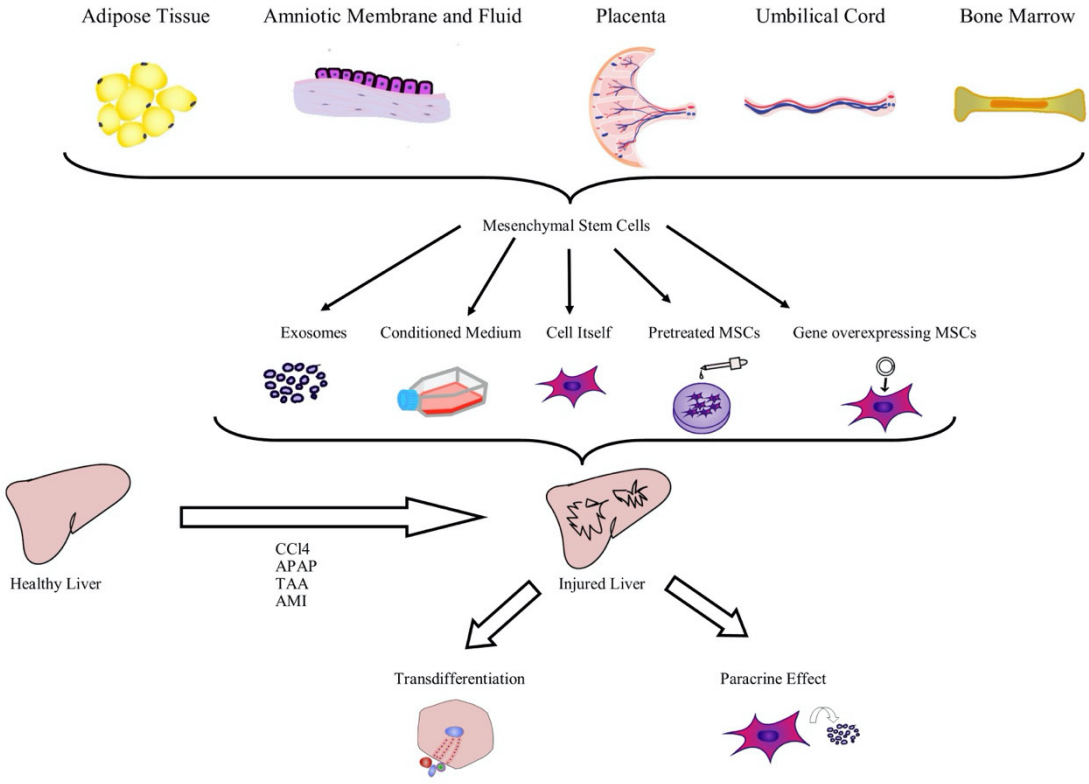

Figure 1. Schematic representation of mesenchymal stem cells and their products or different modification strategies used for treating drug- and chemical-induced liver injury.

AMI: Amiodarone, APAP: Acetaminophen, CCl4: Carbon tetrachloride, TAA: Thioacetamide, MSCs: Mesenchymal stem cells.

hepatotoxicity model. In addition, Saidi et al. (6) compared the effects of different doses of AD-MSC on liver regeneration in which they administered either $1x10^6$ and $2×10^6$ human AD-MSC (hAD-MSC) to mice with CCl4-induced acute liver failure. A significant decrease in alanine aminotransferase (ALT) levels, attenuation in congestion, vacuolization, and necrosis, and enhancement in PCNA expression were reported at both doses. Although it was suggested that hAD-MSC transplantation has a therapeutic effect by supporting regeneration and preventing necrosis, it was also pointed out that the recovery was more prominent in the animals given $2×10^6$ of cells (6).

Further experimental research is also conducted to improve the therapeutic outcomes and to overcome the limitations. Thus, substances obtained from cells and manipulations such as preconditioning were also investigated. In a study, Chae et al. (7) analyzed the differences that may occur as a result of gene overexpression in MSCs. When they examined both the *in vitro* and *in vivo* differentiation of hAD-MSCs into hepatogenic cells, markers indicating hepatic differentiation, such as alpha fetoprotein (AFP), cytokeratin 18 (CK18), dipeptidyl peptidase 4 (CD26), connexin 32 mRNA levels, and cytochrome 450 (CYP450) expression, were shown to be elevated in cells that highly express forkhead box protein a2 (Foxa2), a major transcription factor for liver trans-differentiation. Furthermore, when the hAD-MSCs overexpressing Foxa2 were subcutaneously transplanted into nude mice with liver injury, there was a decrease in hepatic necrosis and an improvement in albumin (ALB) and bilirubin (BIL) levels, whereas there was no change in ALT and aspartate aminotransferase (AST) values. In accordance with the conditioned medium (CM) analysis, researchers suggested that cells overexpressing Foxa2 displayed their therapeutic effects with paracrine signaling (7).

In another study, the effects of culture medium-related conditions on cell transformation were investigated. Yin et al. (41) examined the therapeutic effects and *in vitro* and *in vivo* differentiation of hAD-MSCs into hepatocytes. As a result, they demonstrated that AD-MSCs incubated with serum-medium much notably exhibited hepatocyte-specific features such as polygonal morphology and glycogen accumulation. When evaluated functionally, these cells were revealed to exhibit an appropriate morphological transformation in serum-free medium, also expressed ALB and AFP, and could store glycogen. They observed that the addition of trichostatin A (TSA), a histone deacetylase inhibitor, to the differentiation protocol stimulated hepatocyte maturation of these cells, resulting in an increase in ALB synthesis and a gradual decrease in AFP synthesis. Moreover, while LDL uptake was not carried out by the cells that were not exposed to TSA, the emergence of this function by TSA application manifested the effectiveness of TSA in inducing differentiation. In the continuation of the study, they stated that hAD-MSC application improved liver function by decreasing serum levels of ALT, AST, and direct BIL during the acute phase of

CCl4-induced liver injury; however, it did not produce a difference in histopathological evaluation. Liver sections labeled with a human-specific ALB antibody demonstrated that the transplanted cells were engrafted and functional; however, they did not exhibit hepatocyte morphology (41). Although the contribution of hAD-MSCs to the regeneration of injured liver through paracrine effects or direct transformation into hepatocytes is not yet clear, Yin et al. (41) demonstrated the potential of these cells to differentiate into mature hepatocyte-like cells (HLC) *in vivo* and *in vitro*.

In a study, lipid-conjugated heparin coating for the liver-targeted delivery of MSCs was used to enhance the outcomes. Hwang et al. (8) analyzed the therapeutic efficacy of hAD-MSC coated with lipid-conjugated heparin in a mice model of acute liver failure induced by APAP administration. Hepatoma (HepG2) cells were exposed to APAP and then cultured with either hAD-MSC-CM or CM harvested from lipid-conjugated heparin-coated hAD-MSC culture (Lip-hep/hAD-MSC-CM). They obtained the result demonstrating that both CMs improved the viability and functionality of injured HepG2 cells compared to the regular medium. In the next step of this investigation, Hwang et al. (8) administered hAD-MSC and Lip-hep/hAD-MSC to mice with liver injury induced by APAP. They achieved better outcomes by Lip-hep/hAD-MSC administration compared to hAD-MSC only administration, that a better recovery at ALT and AST levels were accompanied by an increment in HGF expression and a reduction in the level of CYP2E1. Moreover, they observed that cells coated with lipid-conjugated heparin displayed a greater degree of engraftment into the injured liver (8).

MSC transplantation is a therapeutic approach that is advantageous from many aspects; however, insufficient engraftment of transplanted cells remains an important issue that reduces its efficacy. To overcome this point, Yuan et al. (9) constructed a graft that was a combination of acellular human amniotic membrane (AhAM) and HLCs derived from hAD-MSCs (hAD-MSC-HLCs). They attempted to explore the effects of this graft on the fate of transplanted cells. hAD-MSC-HLCs cultured either on two-dimensional-AHAM (2D-AHAM) or on Col I were compared with freshly differentiated hAD-MSC-HLCs with respect to *in vitro* differentiation both morphologically and functionally. Morphology and CYP and ALB expressions were found to be better with the use of hAD-MSC-HLCs cultured on 2D-AHAM, rather than with the use of Col I or freshly differentiated hAD-MSC-HLCs. Furthermore, when three-dimensional AHAM (3D-AHAM) was examined, the best results were achieved among all these modalities. 3D-AHAM yielded higher ALB and urea concentrations and greater CYP activities than 2D-AHAM and freshly differentiated hAD-MSC-HLCs. In the next step, researchers evaluated the *in vivo* fate of 3D-AHAM application with and without hAD-MSC-HLCs in CCl4-induced damage. They observed a decrease in areas of inflammation, congestion, and hemorrhage and an improvement in serum ALT levels in animals transplanted with hAD-MSC-HLC-3D-AHAM compared with animals transplanted with only 3D-AHAM. They revealed that combination with 3D-AHAM may provide complete and long-term integration of transplanted hAD-MSC-HLC to the host liver (9).

Along with approaches involving modifications, preconditioning, or pretreatments of cells to be transplanted, the effects of other cellular components of the host on the engraftment and differentiation of transplanted cells became a considerable point to investigate. In this regard, Hong et al. (42) analyzed the effects of Kupffer cell activity on liver damage. First, they established a liver injury model using 2-acetylaminofluorene, and they treated the injured animals with glycine in order to prevent the resident macrophages, the Kupffer cells, to generate an inflammatory reaction. When they administered glycine alone, they suppressed the secretion of tumor necrosis factor-alpha (TNF-α) without any alteration in the number of Kupffer cells. They significantly reduced both the levels of TNF-α and the number of Kupffer cells with the combined delivery of glycine and hAD-MSCs, without having any toxic side effects. Kupffer cell inhibition by means of glycine application yielded an enhancement in both engraftment of transplanted cells and transdifferentiation of them into hepatocytes (42).

Huang et al. (10) evaluated the effects of the secretome of hAD-MSCs on drug-induced liver injury by two different drugs, tamoxifen and amiodarone (AMI). Two different hepatocyte cell lines (HEPG2 and HepaRG) with different expression levels of CYP enzymes were examined in the *in vitro* part of the study. Treatment with the secretome of hAD-MSCs increased proliferation and a decrease in apoptosis compared with non-secretome-treated cells. While the ROS (reactive oxygen species) production decreased by hAD-MSC secretome treatment in both cell lines, it was shown that TNF-α, interleukin-6 (IL-6), and iNOS expressions increased in only the HepaRG cell line due to its higher levels of CYP enzyme expression compared to HEPG2 cells. *In vivo* protective effects of the secretome of hAD-MSCs were examined in a high-fat diet mouse model with AMI-induced liver injury, since mice with normal diet were not affected by AMI. hAD-MSC secretome administration alleviated injury by decreasing steatosis, necrosis, and infiltration of T-lymphocytes and macrophages. Moreover, secretome treatment reversed the damage by decreasing fibrosis and apoptosis and increasing proliferation, as indicated by PCNA expression in AMI-induced liver injury (10).

2.2. Placenta-Derived MSCs in Drug- and Chemical-Induced Hepatic Injury Models

MSCs of fetal origin display differentiation potency on a scale between embryonic and adult MSCs. They have more advantageous than adult MSCs in terms of their wider range of differentiation potency and lower immunogenicity. Although their differentiation potency remains lower than that of embryonic stem cells, they do not lead to tumors as in embryonic stem cells. As one of the MSCs of fetal origin, placenta-derived MSCs have been examined in many studies, including those on liver injury and regeneration (43). Lee et al. (11) examined the effects of chorionic plate-derived MSC (CP-MSC) obtained from term placenta on CCl4-induced liver injury in rats. Homing of transplanted CP-MSCs and their transdifferentiation into hepatocytes were verified by the expression of human-specific nuclei and CK18 and CK19 hepatocyte markers. In addition, the reduction of CCl4-induced fibrosis in the CP-MSC-transplanted animals was demonstrated by the decrease in Col I and αSMA expressions, in addition to Masson's trichrome staining. In addition to morphological regeneration, improvement in hepatic functions in the transplanted animals was also revealed by biochemical parameters, including blood levels of glutamate-oxaloacetate transaminase, glutamate-pyruvate transaminase, and total BIL. Thus, it has been suggested that CP-MSC transplantation, owing to

its anti-fibrotic effect, is a new treatment alternative in cases of liver injury (11). The anti-inflammatory effect of CP-MSC transplantation in addition to anti-fibrotic effect was also demonstrated in one of the current studies, in which Na et al. (12) generated a liver injury model by the administration of TAA. CP-MSC transplantation resulted in a decrease in pro-inflammatory factors such as IL-6 and TNF-α, whereas an increase in IL-10 levels was found. Antioxidant effects of CP-MSCs were also introduced in this study; CP-MSC transplantation led to an increase in the expression of heme oxygenase-1, superoxide dismutase 1, and catalase. In addition, CP-MSC transplantation resulted in increased regenerative capacity, as revealed by elevated ALB and nicotinamide adenine dinucleotide phosphatase (NADPH) oxidase 4 (NOX4) expression (12).

In a similar study, Jung et al. (13) revealed the pathways involved in the regenerative effects of CP-MSC transplantation in liver injury. The anti-inflammatory effect of CP-MSCs was demonstrated by decreased leukocyte infiltration and elevated IL-10 expression. Additionally, it was underlined that hypoxia-inducible factor 1-α expression, which is involved in survival-related signal transmission, and its transition to the nucleus was higher in the CP-MSC-transplanted animals. B-cell lymphoma 2 (Bcl2) and Bax (Bcl-2-associated X protein) expressions were found to be higher in the CP-MSC-transplanted animals, whereas cleaved PARP [poly (ADP-ribose) polymerase] and caspase 3/7 activities were lower than that of the non-transplanted animals, indicating the regulatory effects of CP-MSCs on apoptosis. In addition, it has been shown that autophagy-related factors (such as PI3K class III, Beclin1, ATG7, ATG5-12 and LC3 II) and proteins involved in proliferation (such as PI3Kp110α, Smad2/3, cyclin A, cyclin E, and PTTG1) were overexpressed because of CP-MSC administration in cases of CCl4-induced liver damage. Furthermore, Ki67 (+) cell number and protein levels related to liver regeneration (such as IL-6, gp130, SCF, ABCG1, ABCG2) were elevated in the animals transplanted with CP-MSC. As a result, CP-MSC transplantation appears to contribute to liver regeneration through autophagy- related pathways (13).

2.3. Amniotic Membrane- and Fluid-Derived MSCs in Drug- and Chemical-Induced Hepatic Injury Models

Similar to other MSCs of fetal origin, MSCs derived from the amniotic fluid or amniotic membrane display superiority to adult MSCs in terms of potency and do not stimulate a rejection response owing to their low immunogenicity, that they do not express HLA-DR (44-46).

Zagoura et al. (14) examined the therapeutic efficacy of human amniotic fluid-derived MSCs (hAF-MSCs) and their derivatives at different differentiation states on CCL4-induced hepatic injury. Although *in vitro* studies showed that HLCs differentiated from hAF-MSCs tended to resemble liver cells with respect to their morphology, functions, and cell markers, they failed to engraft injured liver and improve its function. Therefore, only hAF-MSCs and hepatocyte progenitor-like cells differentiated from hAF-MSCs (HPLC) were preferred to be compared in terms of their therapeutic effects. HPLC significantly decreased AST and ALT levels compared with undifferentiated hAF-MSCs, whereas their effects on the improvement of ALB secretion and the survival of the injured animals were comparable. As for the modulatory effects on inflammation, HPLC was revealed to display more prominent effects on the modulation of the inflammatory response, that HPLC apparently elevated IL-10 levels while decreasing the TNF-α and IL-2. Results of CM analysis, and moreover the improvement provided by the intrahepatic administration of these CMs suggest that the therapeutic effects of cell transplantation are due to not only *in situ* differentiation but also to the paracrine effects of these cells and the substances they secrete (14).

A previous study by Lee et al. (15) presented the effects of CD34(+) and CD34(-) human amniotic membrane-derived MSCs (hAM-MSCs) on TAA-induced liver injury. *In vitro* experiments indicated that CD34(+) hAM-MSCs exhibited much more potential in terms of differentiation into neurogenic, cardiomyogenic, and hepatic lineages in comparison to CD34(-) hAM-MSCs. In the TAA-induced injury model, both CD34(+) and CD34(-) hAM-MSCs led to a better reduction in fibrosis than AD-MSCs, as demonstrated by collagen deposition and the amount of hydroxyproline. In addition, the expression of genes related to fibrosis [e.g. col I, αSMA, transforming growth factor beta (TGF-β)] reduced in hAM-MSC- transplanted animals in contrast to the AD-MSC-administered group. Both CD34(+) and CD34(-) hAM-MSCs decreased the ALT and AST levels significantly; however, only CD34(+) hAM-MSC transplantation resulted in a drastic increase in ALB amount. After 3 weeks of transplantation, they observed the PKH26-labelled cells, indicating the engraftment of hAM-MSCs, near the portal tract and fibrotic regions in the injured liver. Because of the study, they suggested that CD34(+) hAM-MSCs provided recovery in TAA-induced liver injury in comparison to CD34(-) hAM-MSCs. In addition, they disclosed that the reason for the insufficient recovery effects of AD-MSC could be related to its administration route (15).

2.4. Umbilical Cord-Derived MSCs in Drug- and Chemical-Induced Hepatic Injury Models

Similar to other fetal MSCs, human umbilical cord MSCs (hUC-MSCs) are harvested from a type of tissue that is routinely discarded during delivery; thus, they do not require an invasive procedure to be harvested. Therefore, UC-MSCs serve as a reasonable and safe MSC source for autogenic and allogenic transplantation because of their differentiation potency and low immunogenicity. Yan et al. (16) transplanted hUC-MSCs to rats injured by CCI4 and revealed an improvement in histopathology and biochemical parameters (ALT and AST) in a time-dependent manner. Moreover, transplantation of hUC-MSCs induced proliferation and decreased apoptosis in CCI4-induced liver injury compared with non-transplanted animals. They demonstrated that transplanted cells were sequestrated in both kidney and lung but also successfully engrafted into the liver, revealed using human 17α gene expression. In addition, the cells engrafted into the liver started to express AFP and CK18, indicating hepatogenic differentiation (16). To reveal the effects of the microenvironment on cell differentiation and functionality, Xue et al. (47) investigated the changes in hUC-MSC culture exposed to liver homogenate supernatant. They reported that cultured cells started to express the hepatocyte markers AFP, CK18, and tryptophan 2,3-dioxygenase (TPH2). Furthermore, it was revealed that these cells released ALB and urea and CYP3A activity. The number of PKH26-labeled hUC-MSCs was increased in CCl4-induced liver injury compared with the control, which may indicate homing and the potential of pathotropic migratory properties of hUC-MSCs.

Results indicated a time-dependent increase in the expression of AFP, CK18, TPH2, and ALB in the liver of rats administered hUC-MSCs following CCl4-induced injury. In addition, they showed the improving effects of directly administered hUC-MSCs on biochemical and histopathological alterations (47).

Yan et al. (17) compared the different administration routes and dose-dependent efficiency of exosomes derived from hUC-MSC (hUC-MSC-Ex). They administered hUC-MSC-Ex through either the tail vein or oral gavage at determined doses of 8, 16, 32 mg/kg. Although there was not a significant difference between the efficiency with respect to routes, there was a significant difference between the survival rate in terms of different doses, with the best one achieved at 32 mg/kg. They revealed that all tried doses led to improvement in biochemical analysis; however, recovery in terms of histology was achieved at both 16 and 32 mg/kg doses, indicating the poor effect of 8 mg/kg application. To demonstrate the effects of hUC-MSC-Ex on antioxidant and apoptotic processes, they performed 2'-7'-dichlorofluorescein diacetate (DCF-DA), 8-hydroxy-2'-deoxyguanosine (8-OHdgG), malondialdehyde, and terminal deoxynucleotidyl transferase (TdT) dUTP Nick-End Labeling (TUNEL) assays. The results showed that oxidative stress and proinflammatory cytokines were decreased by hUC-MSC-Ex therapy. In addition, TUNEL assay results revealed a decreased apoptotic rate of hepatocytes in hUC-MSC-Ex-administered animals. Because of further *in vitro* studies of the research in question, they showed that hUC-MSC-Ex reduced apoptosis by increasing Bcl2 expression and decreasing cleaved Caspase3 expression, as well as Annexin V and Hoechst 33342 staining. To determine the molecular basis of the effects of hUC-MSC-Ex, they investigated the glutathione peroxidase 1 (GPX1) activity in CCl4-injured L02 cells treated with hUC-MSC-Ex. They found that the activity levels of GPX1 in injured cells treated with hUC-MSC-Ex increased compared with injured cells treated with human lung fibroblast (HFL-1)-derived exosomes (HFL-Ex). Knockdown of GPX1 resulted in the reversal of all the *in vitro* and *in vivo* therapeutic effects of hUC-MSC-Ex, proving that the therapeutic mechanisms were under the control of the GPX1 enzyme (17).

In one of their previous studies in which they induced liver injury by toxins (LPS and α-amatoxin), Guo et al. (48) suggested that MSCs reduce injury by suppressing cytokine storm through IL-6 reduction. Based on this conclusion, Shao et al. (18) hypothesized that exosomes derived from IL-6-preconditioned hUC-MSCs may attenuate liver injury. Exposure to IL-6 resulted in both an increase in concentration and a change in the composition of exosomes. According to sequencing results, Mir-455-3p, which is related to IL-6 signaling pathways, was upregulated within the exosomes after IL-6 preconditioning. TargetScan and miRanda analyses revealed that a possible target of Mir-455-3p was the PIK3r1 gene. Transfection of macrophages with Mir-455-3p decreased PIK3r1 expression; therefore, they suggested that Mir-455-3p interrupted macrophage activation in a PIK3r1-dependent manner. When they injected Mir-455-3p into animals with either endotoxin or chemically induced liver injury, they found that Mir-455-3p delivery decreased the levels of inflammatory cytokines and improved liver function in both models (18).

De Witte et al. (19) proposed that preconditioning of hUC-MSCs with cytokines, growth factors, and cell culture conditions enhanced their immunosuppressive potential and decreased their immunogenicity. For this purpose, hUC-MSCs were treated with inflammatory factors [interferon gamma (IFN-γ), IFN-ß, TGF-ß, TNF-α], vitamins (vitamin D3, vitamin B6, retinoic acid), and serum starvation. The *in vitro* results of experiments revealed that pretreatment of hUC-MSCs with IFN-γ and multiple cytokine cocktail (MC) led to hUC-MSCs decreasing T-cell proliferation. In addition, IFN-γ, MC, and TGF-ß treatment inhibited natural killer cell lysis. When pretreated hUC-MSCs were intravenously administered to mice with CCl4-induced liver injury, no differences were observed between the experimental groups with respect to the immunomodulatory effects of hUC-MSCs or ALT levels. They suggested that the reason for failure was the distribution of hUC-MSCs because most of the hUC-MSCs were entrapped in the lung. Therefore, in the following step, the effect of pretreated hUC-MSCs on inflammation was analyzed in an *ex vivo* liver tissue model established by LPS exposure. *Ex vivo* experiment results showed that MC pretreatment decreased the expression of inflammatory genes, including monocyte chemoattractant protein-1, TNF-α and interferon gamma-induced protein 10. Based on these findings, they suggested that intrahepatic delivery of hUC-MSCs pretreated with multiple cytokine combinations would be advantageous in ameliorating liver injury (19).

2.5. Bone Marrow-Derived MSCs in Drug- and Chemical-Induced Hepatic Injury Models

Miryounesi et al. (20) compared the therapeutic effects of single-dose and repeated administration of human bone marrow-derived MSCs (hBM-MSCs). The same total number of cells ($3x10^6$ cells) was transplanted to mice with CCl4-induced liver injury, either as a single dose or as dividing in three equal doses at intervals of one week. Repeated delivery of the cells yielded more effective engraftment of the cells. Animals with repeated administration displayed significantly less liver fibrosis than those with single dose administration. When transdifferentiation of the implanted cells was investigated with the demonstration of human-specific ALB expression, no positivity was observed. Therefore, recovery in the injured liver is attributed to the paracrine effects of engrafted cells rather than their direct transdifferentiation into liver cells (20).

In another study, Aithal et al. (21) combined hBM-MSC transplantation with silymarin, which is known to display hepatoprotective effects, and compared the efficacy with their individual effects on liver injury induced by CCI4. Better results were achieved with either single high-dose hBM-MSCs or combined therapy in terms of plasma HGF levels. High-dose hBM-MSC application showed a significant antimutagenic effect, which was further amplified with the addition of silymarin, as revealed by chromosomal aberration assay. The pathways related to the antimutagenic effects of hBM-MSCs were not still fully understood but might be related to their antioxidant abilities (21).

CONCLUSION

Over the years, MSCs have been the subject of hundreds of investigations. In preclinical research, MSCs have been investigated to treat different pathological conditions such as cancer, cardiovascular, and neurodegenerative diseases (25,49-51). In the earlier periods of these investigations, basic issues such as the type of MSCs, optimal cell doses and delivery routes, engraftment, and

use of cell-itself or its *in vitro* transdifferentiate derivatives were assessed. Later, researchers focused on the microenvironment that actually predominated the *in vivo* behavioral pattern of the cells. Therefore, many preconditioning methods have been attempted to enhance the *in vivo* transdifferentiation of transplanted cells. Among the research on drug- and chemical-induced liver injury, many preconditioning methods and modalities for targeted delivery or graft construction have been investigated to overcome inadequate engraftment and enhance the *in vivo* transdifferentiation of transplanted cells. Further studies may be conducted to compare the efficiency of these methods in combination with different MSC types.

Many studies have revealed that MSCs reduce fibrosis, regulate inflammation, and decrease the apoptosis of host cells, rather than contributing to the healing process by direct transdifferentiation. Thus, the paracrine effects of MSCs in addition to their differentiation potency became the center of research interest. In this regard, cell products such as exosomes or secretes harvested from MSCs were investigated in terms of their effects on injury. There are also studies demonstrating the paracrine effects of MSCs on drug-induced liver injury models (52,53). Among the MSC types, hCP-MSCs were directly applied to animals without any modifications. Different studies have emphasized the anti-inflammatory and antioxidant effects of hCP-MSCs; however, little is known about the secretory or exosome derived from these cells to show the paracrine effects. In contrast to hCP-MSCs, hUC-MSCs and their exosomes and preconditioned hUC-MSCs with cytokines or vitamins were analyzed in a study. The results revealed that these modifications of hUC-MSCs increased potential therapeutic effects compared with cell-only administration. In addition, umbilical cord-derived MSCs have a higher proliferation rate and a greater diversity of paracrine secretions than other MSCs of fetal origin (54). This may explain why researchers are interested in hUC-MSCs.

There are limited number of experimental studies using hBM-MSCs. This approach may depend on many factors such as the invasiveness of MSC isolation and rejection response in allogeneic transplantation. Thus, most experimental studies utilize animal BM-MSCs. Because we focused on the use of only human-derived MSCs, critical inference was made throughout the limited studies reviewed in this paper.

Animal models play a crucial role in pre-clinical studies. Prior to clinical application, it is essential to have information about the physiopathological mechanisms underlying liver injury. We observed that mostly CCl4, TAA, APAP, and AMI were used to mimic drug- and chemical-induced liver injury. However, different drugs may induce liver injury through different molecular mechanisms, such as inducing immune system activation (55). Considering this, there are still few studies exploring the effects of MSCs in damage induced by different drugs such as chemotherapeutics. Because adverse effects of chemotherapy are crucial in clinical practice, studies on the effects of MSCs in chemotherapy-induced liver injury may reveal whether MSCs, which are known for their immunomodulatory effects, can be used as a supportive treatment to the chemotherapeutic agent (25). Therefore, the effects of MSC cells on chemotherapeutic-induced liver injury must be investigated *in vivo,* as well.

In conclusion, to increase the efficacy of stem cell-based therapies and to find new modalities alternative to liver transplantation in clinical practice, treatment strategies based on detailed analyses of products derived from MSCs are required.

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Ethics

Authorship Contributions

Concept: M.Ş.C., S.Ö., Z.Y., Design: M.Ş.C., S.Ö., Z.Y., Analysis or Interpretation: M.Ş.C., S.Ö., Z.Y., Literature Search: M.Ş.C., Writing: M.Ş.C., S.Ö., Z.Y.

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