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Immunomodulatory Properties and Associated Mechanisms of Mesenchymal Stem Cell Transplantation for the Treatment of Liver Diseases

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ABSTRACT

The global threat to human health posed by liver disease is a serious issue. Liver transplantation is now thought to be the only viable medication for an end-stage liver disorder, but it is constrained by a lack of organ donors, surgical complications, long-term immunosuppressant, and a hefty price tag for care. Because of this, not all patients can access it. Mesenchymal stem cell (MSC) treatment has recently been touted as a possible alternative strategy for treating end-stage liver disease. MSCs are multipotent adult progenitor cells that develop from the embryonic mesoderm and are present in a variety of mesenchymal tissues, such as the liver, fat tissue, umbilical cord blood, bone marrow, cord blood, and lung. MSCs are able to stop the course of liver damage and enhance liver function, despite the specific processes behind MSC transplantation remaining unknown. By dividing, moving to damaged sites, and differentiating into other cell types, including hepatocytes, MSCs may sustain themselves. Additionally, MSCs secrete paracrine-soluble substances and have immune-modulatory qualities. Animal studies have shown that MSC treatment is both safe and effective for treating liver disorders. The efficacy of MSC treatment for liver illness has been demonstrated in several clinical trials; however, its use has not been supported and licensed. Before using MSC treatment in clinical settings, several problems still need to be resolved. The processing and MSC engraftment need to be standardized, and the forms of liver disease most suited for MSC application must be identified. In this review, we spoke about the crucial therapeutic immuno-modulatory pathways that MSCs use to treat liver disease.

Keywords: Liver diseases, Transplantation, Mesenchymal stem cell, Therapeutic mechanism, Immuno-modulatory

Abbreviations: AF-MSCs: Amniotic Fluid Mesenchymal Stem Cells; aGVHD: Acute Graft-vs-Host Diseases; ALF: Acute Liver Failure: BM-MSCs: Bone Marrow Mesenchymal Stem Cells; EPCs: Endothelial Progenitor Cells; HCC: Hepatocellular Carcinomas; HE: Hepatic Encephalopathy; HGF: Hepatocyte Growth Factor; HLA-G: Human Leucocyte Antigen-G; HLCs: Hepatocyte Like Cells; hP-MSCs: Human Placenta Mesenchymal Stem Cells; IDO: Indole Amine 2,3-Dioxigenase; IGF-1: Insulin-Like Growth Factor; IL: Interleukin; iNOS: Inducible Nitric Oxide Synthase: LC: Liver Cirrhosis; MenSCs: Menstrual Stem Cells; MMPs: Matrix Metalloproteinases; MSCs: Mesenchymal Stem Cells; NLRP: Nod- Like Receptor Protein; PDGF: Platelet-Derived Growth Factor; PGE2: Prostaglandin E2; TGF: Transforming Growth Factor; TNF: Tumor Necrosis Factor; UC-MSCs: Umbilical Cord Mesenchymal Stem Cells; XBP: X-Box Binding Protein; YAP: Yes-Associated Protein

INTRODUCTION

There are several aetiologies for liver disease, which is a serious health issue. The three most prevalent liver illnesses are an acute liver failure (ALF), cirrhosis, and liver cancer. Hepatocyte necrosis which is an extensive and inflammatory infiltrate brought on by hepatotoxic medications, immune-mediated assaults, or viral infections the hallmark of the deadly clinical condition known as ALF [1,2]. ALF advanced quickly in the clinical setting while presenting poorly for medical care [3]. The last stage of liver fibrosis, known as cirrhosis, is capable of a variety of problems, such as infection, bleeding, hepatic encephalopathy (HE), spontaneous peritonitis, etc. The most recent worldwide study places liver cancer sixth in terms of cancer cases and fourth in terms of cancer mortality in 2015 [4]. Most initial

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liver cancers (85-90%) are hepatocellular carcinomas (HCC) [5]. The only suggested treatment option for severe liver disorders is liver transplantation; however, it is expensive and difficult to find donor organs [6]. The therapy of liver illnesses has fresh promise thanks to MSC transplantation. Numerous types of life-threatening liver illnesses can be successfully treated by cell-based therapy, as demonstrated by preclinical and clinical research over three decades, despite their disparate etiologies, physiological processes and symptoms.

MSCs are described as pluripotent cells having the ability to self-renew and give birth to a variety of distinct kinds of differentiated mesenchymal cells [7]. The first stromal cells from bone marrow were extracted and recognized by Friedenstein [8] in 1966. MSCs (Mesenchymal stem cells) were recovered from a variety of tissues, including dental pulp, adipose tissue, amniotic fluid, and the umbilical cord [9-18]. MSCs are the perfect candidates for therapeutic applications in a variety of disorders because of their immunomodulatory capabilities, the constrained ability for self-renewal, and multi-lineage development [19]. MSCs' low intrinsic immunogenicity ensures the safety of transplants [20]. Even MSCs that are HLA-mismatched might be employed in several therapeutic settings, particularly for stem cell-based treatments [19]. Additionally, the main therapeutic effect of MSC transplantation is the capacity of these cells to localize to certain lesions and organs [20].

The major factor in surgical failure and patient postoperative mortality is subsequent rejection, particularly acute graft-vs-host disease (aGVHD), which is the only known therapeutic therapy for end-stage liver disorders [21]. The onset and progression of rejection are mediated by a number of immunological cells including Natural Killer cells, Tregs, T cells, and dendrite cells (DCs) [22]. A growing body of research has shown that transplantation of MSC can greatly lessen the problem of aGVHD because MSCs have immunomodulatory effects [22-24]. The cytological and molecular processes, however, still need to be investigated. This review's objective is to explain the therapeutic immuno-modulatory pathways that MSCs use to treat liver disease.

Role of Mesenchymal Stem Cell in Repair and Regeneration of Liver

Mesenchymal Stem Cells (MSCs) may considerably enhance regeneration of liver cell in a variety of liver disorders, according to clinical and laboratory studies. Amniotic fluid mesenchymal stem cells (AF-MSCs) increased survival and regeneration of liver following mice with 80% hepatectomy, as demonstrated by Despeyroux [25].

However, Chen [26] showed that MSCs from menstrual blood were attracted to damaged liver locations in liver fibrosis brought on by carbon tetrachloride (CCl4) mice models, but that only a small number of transplanted cells transformed into hepatocyte-like cells (HLCs). Shi [27] found that following infusion of BM-MSCs (3x 10^6 cells/kg) through intraportal vein in D-gal (D-galactosamine) induced pigs' model, the proportion of human-derived hepatocytes to all pig hepatocytes was only 4.5% [27]. Even little-expanded BM-MSCs demonstrated no ectopic tissue growth and only little long-term engraftment upon intravascular injection, according to research by von Bahr [28]. Accordingly, MSCs may primarily stimulate liver regeneration by methods other than their differentiation into HLCs. Through the secretion of several immunomodulatory substances, MSC can in vivo develop into hepatocytes and serve a significant therapeutic function in the cure of liver fibrosis. Following MSC treatment, hepatocyte growth factor (HGF) and Insulin-like growth factor (IGF-1) levels increased along with stimulation of angiogenetic and mito-genetic factors [29].

MSCs have been shown in *in vitro* investigations to decrease collagen formation and encourage the death of hepatic stellate cells. The PDGF and Notch signaling pathways were responsible for the improved cell proliferation and angiogenic capability that resulted from endothelial progenitor cells directly cocultured (EPCs) with MSCs *in vitro* [30]. Through the release of inflammatory factors such as growth-related oncogene, IL-8, HGF, interleukin-6 (IL-6), and osteoprotegerin, MSCs prevented the proliferation of LX2 (a hepatic stellate cell line) in an indirect coculture experiment [26]. Through their paracrine activity, MSCs took part in cell communication either directly or indirectly.

Immunomodulatory Mechanisms of Mesenchymal Stem Cell Transplantation for the Treatment of Liver Disease

The majority of earlier investigations have demonstrated that MSCs may enhance or restore damaged tissue by direct cell-to-cell communication or paracrine secretion by influencing tissue immune responses. MSCs could alter immune responses, both innate and adaptive. For MSC-mediated immunomodulation to occur, regulatory T cells (Tregs) must be induced to become CD4+CD25+FoxP3+. Previous research suggested that alcohol-induced liver disease and chronic hepatitis B, and autoimmune hepatitis may all have a link with an imbalance in Treg/T17 cells. According to a random study, the IL-17 (interleukin-17), TNF (tumor necrosis factor)), and IL-6 (interleukin-6) blood levels were lesser in the transplanted group compared to those in the control group. Further evidence that BM-MSCs demonstrate effective anti-inflammatory and immunosuppressive actions via the modulation of the inflammatory cytokines levels in serum was found in the transplanted group, including a large rise in Tregs and a noticeably decreased number of T17 cells [31]. Shi [32] conducted pilot research employing MSCs for curing liver transplant patients, which is consistent with the earlier work. The findings demonstrated that T17 cells were downregulated and Tregs were increased in the liver following MSC infusion. Additionally, they discovered that

after receiving UC-MSC infusions, the number of HLA-DR+ CD4+ T cells significantly reduced, which may help to suppress alloreactive reactions. *Ex-vivo* immunologic investigations have only sometimes been incorporated into clinical regimens up to this point in order to better understand the molecular consequences of MSC treatment in liver disease. The immunoregulatory ability of transplanted MSCs in rodent models of liver problems is being supported by a growing body of research. Prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS), Hepatocyte growth factor (HGF) and transforming growth factor (TGF)- are just a few of the chemicals released by MSCs that have been shown to have an immunomodulatory influence on T-cell activity in nonclinical tests [33,34]. A different investigation found that MSCs can release MMPs (matrix metalloproteinases) (MMPs), including MMP-2 and MMP-9, which inhibit T cell activation by cleaving the T cells surface CD25 molecules [35]. MSCs suppress T cells by preventing CD25 translation via the LKB1-AMPK-mTOR pathway, as demonstrated by Yoo [36]. Furthermore, Zhang et al. discovered the potential for the human placenta (hP)-MSCs to control the interaction between Nrf2 and NF-B signaling pathways to limit PD-1 expression in IL-10 +CD4+T cells and reduce liver injury in a mouse model of graft versus host disease [37]. Additionally, it has been demonstrated that MSCs stimulate the production and expansion of Tregs by possibly producing transforming growth factor-ß (TGF-ß). Notably, the immunosuppressive properties of TGF- ß reduces inflammation of liver [38], but it can also hasten the development of liver fibrosis [39,40]. According to Yan et al. research's MSCs produced IL-10 may have a role in the higher immunosuppression that was generated when Tregs and MSCs were co-cultured [41]. Through the Notch signaling pathway, Toll-like receptors 3 and 4 which are extensively expressed in MSCs can trigger the development of Tregs [42]. Additionally, it has been shown that MSCs have immunomodulatory effects on macrophages, which are essential for both liver fibrosis and fibrotic resolution. B lymphocytes also contribute to the pathophysiology of liver fibrosis. MSCs may prevent B cell proliferation by halting the cell cycle to the G0/G1 phase. Additionally, B cell's ability to differentiate and produce chemotactic cytokines was suppressed [43]. The key players in adaptive immunity are T and B cells. As previously mentioned, MSCs prevent DC maturation, which lowers T cell activation. By inhibiting T cells in the G0/G1 phase of the cell cycle instead of causing T cell death, the MSCs significantly reduce the proliferation of activated T cells as well [44]. A number of soluble molecules, including chemokine ligand 2 (CCL2), heme oxygenase-1, galectin (Gal), HLA-G (human leucocyte antigen-G), IDO, HGF, IL-10, and PGE2 (HO-1), and TGF-1, have been implicated in studies as mediating the inhibitory effect of MSCs on the proliferation and activation of T cells [45-48]. Additionally, MSCs' released PD-L1 and PD-L2 can prevent CD4+ T cell activation and cause permanent T cell hypo-reactivity [49]. Watanabe [50] discovered that MSCs might induce an M2 anti-inflammatory phenotype in macrophages, which involves the release of several anti-inflammatory substances, such as CCL-1 (chemokine ligand 1) and IL-10. It stimulates the phagocytosis of hepatic cell debris (during which macrophages raise the levels of pro-regenerative substances) and the increased synthesis of matrix metalloproteinases to reduce ECM [50]. Similar to the previous work, it was shown that murine adipose-derived MSCs dramatically increased the number of M2-like cells by boosting Arginase 1 activity and IL-10 [51]. We discovered that adoptive transfer of MSCs decreased hepatocellular damage and changed the polarization of macrophages from the M1 to M2 phenotype of ischemia/reperfusion (IR)-induced sterile inflammatory damage occurs in mice's liver of the liver. MSCs often suppress M1 (a pro-inflammatory subtype) and activate M2 (an anti-inflammatory subtype), which promotes tissue regeneration and the resolution of inflammation. Through the actions of prostaglandin E2, indoleamine-2, cyclooxygenase 2, 3-dioxygenase (IDO), TGF-1, and IL-6, activated MSCs help polarize monocytes (M0) into the M2-type [52-54]. By encouraging the Hippo signaling pathway, Li [55] demonstrated that BM-MSCs promote the reprogramming of macrophage polarization to an anti-inflammatory M2 phenotype [55]. The primary elements of the innate immune system, dendritic cells (DCs), process antigens before presenting them to T cells. By secreting soluble factors such as PGE2, IDO, HGF, TGF-, and nitric oxide (NO), the MSCs prevent DCs from differentiating, maturing, and migrating [56-58]. Natural killer (NK) cells are essential for the activation of circulating lymphocytes, controlling hepatic inflammation, and providing the first line of defense against invasive infections. MSCs can suppress NK cells by secreting IDO and PGE2, according to Spaggiari [59]. Further investigation revealed that MSCs boost the activity of the macrophage Hippo pathway, which in turn regulates XBP1-mediated NLRP3 activation and controls NLRP3 activation through direct communication between YAP and catenin [55]. This reprogramming of macrophage polarization toward an anti-inflammatory M2 phenotype occurs **Figure 1**.

T lymphocytes, Monocytes, and B cells are infiltrated along with chronic liver damage brought on by inflammation [60]. According to reports, immunosuppressive medications can help the liver regenerate both after and before liver transplantation [61,62]. In this way, liver disease may benefit from the immunomodulatory abilities of MSCs. First, through producing a variety of soluble substances such as Interleukin (IL)-6, IL-10, prostaglandin E (PGE)-2, nitric oxide, and indoleamine 2, 3-dioxygenase, and human leukocyte antigen G, MSCs can downregulate T cells. These elements have the power to affect Treg cell activity and immune cell proliferation [63]. MSCs can also stop the growth of T cells by interacting with T-lymphocytes directly. Interferon, IL-1, and tumor necrosis factor (TNF)

are cytokines that work together to give MSCs their immunosuppressive properties [64]. These cytokines aid immune cells and certain chemokines in maintaining contact with MSCs and controlling immunological responses.

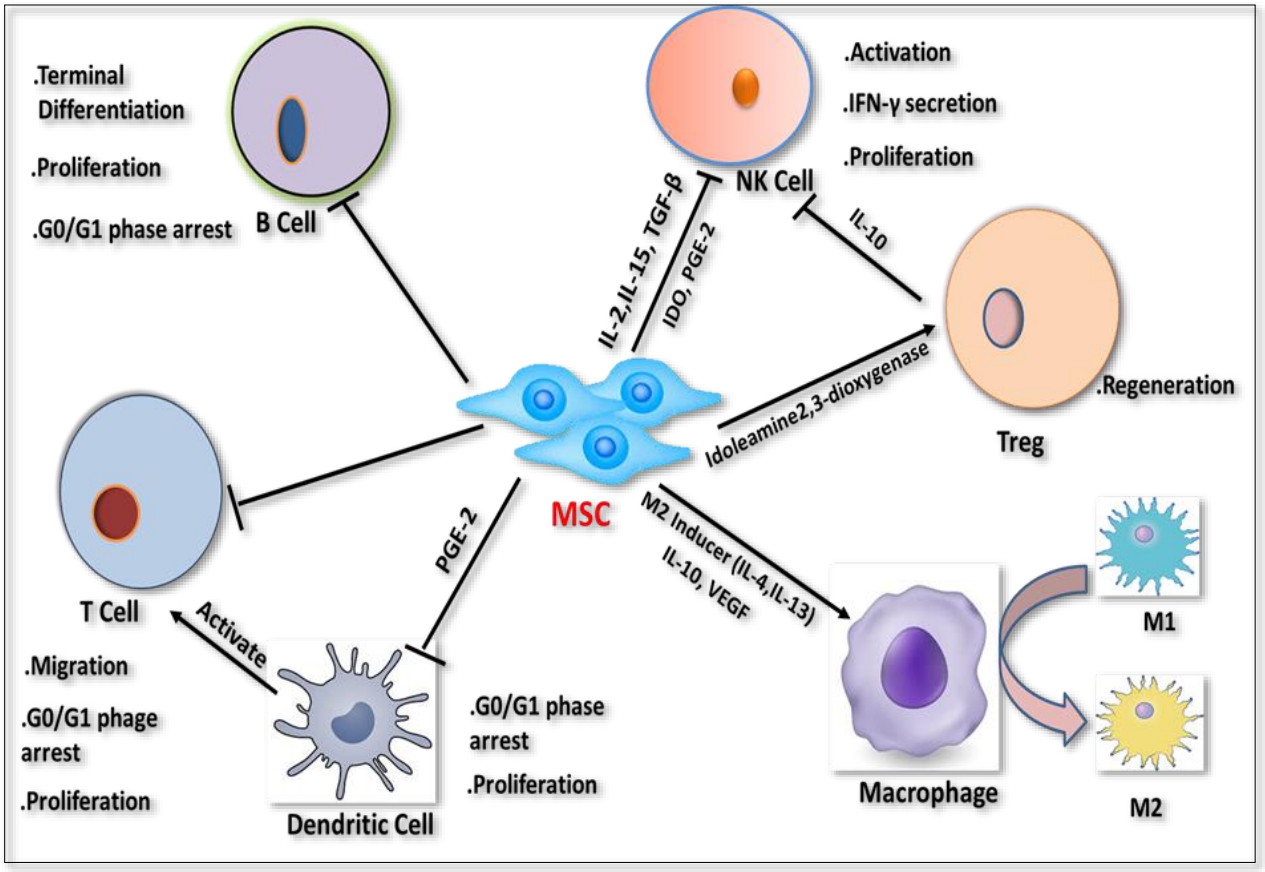

Figure 1. The MSC's immunomodulatory abilities and associated pathways/mechanisms.

Additionally, MSCs have the ability to prevent B cell activation, which lowers immunoglobulin levels. Chemokine receptors (XCR5, XCR4, and XCR7) have been shown to express much less on their surface when co-cultured with MSCs [45]. Additionally, natural killer (NK) cells play a well-established role in immunological responses to cancer and viral infections [65]. By either cell-to-cell contacts or the release of soluble substances like PGE2 and transforming growth factor (TGF)-, MSCs cause the production of IL-2, which reduces the secretion of IL-15 from IL-2-induced NK cells [66]. Finally, it has been demonstrated that MSCs cause inflammatory macrophages to polarize toward alternative macrophages. This change improves liver damage by releasing soluble factors (IL-10 and IL1Ra) [67].

CONCLUSIONS AND FUTURE PROSPECTIVE

In conclusion, it was established that MSCs had a potential therapeutic impact in the treatment of liver disease. Clarification of the underlying principle of stem cell therapeutic benefits will require more research. According to the ideal time interval and appropriate treatment dosage, standard protocols should be devised. The therapeutic use of MSCs needs to better establish cell kind, injection method, and observation time points. Through its immunomodulation capabilities, MSC regenerative therapy has been demonstrated to be useful in the treatment of chronic liver disease. Numerous clinical trials have shown how MSCs may effectively heal damaged hepatocytes by reducing tissue fibrosis and enhancing liver function. There are still a number of issues to be addressed, including limited migration, poor cell viability, the possibility of cancer development, and the spread of viruses. Additionally, MSC-derived EVs appear to offer therapeutic advantages over cell-free cell therapy in MSC-based transplantation by maintaining at least part of the cells and its immunomodulatory characteristics. Standardization of the cell source, growing conditions, method of administration, and results of upcoming large-scale clinical studies will define the future of MSC-based cell treatment for chronic liver disease.

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CONFLICT OF INTEREST

None.

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