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Review Article



Mesenchymal stem cells have a crucial role in liver fibrosis treatment: An overview

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Abstract

Liver fibrosis is a wound-healing process where ECM accumulation occurs in the liver. It mainly occurs by inducing a variety of hepatotoxic agents, lipid decomposition, drugs, alcohol consumption, viruses, and autoimmune reactions. Among various processes, liver transplantation is the best way of treatment for patients in critical conditions. This transplantation process has various limitations. So, another mechanism is discovered, the name is cell-based therapy. Cell therapy using stem cells (from various sources) is an alternative approach for treating liver fibrosis. Transplanted mesenchymal stem cells could be a replacement for damaged hepatocytes. And it has the capacity to induce apoptosis of activated hepatocyte cells. This present review will go to balance the latest discoveries about mesenchymal stem cell-based therapies to treat liver fibrosis. All discoveries are in vivo experimentally proved and all studies with pre-clinical and clinical trials. Several studies suggest, in the world, that liver disease accounts for about 3-4% of death mesenchymal stem cells have the ability to reduce liver fibrosis and recover liver function.

Keywords: Cargos, Cell-Based Therapy, Extracellular Vesicles, Exosomes, Immunomodulatory Effects, Hepatic Stellate Cells, Liver Fibrosis, Stem Cells.

Introduction

Liver disease accounts for nearly 3-4% of all death worldwide today. liver diseases are various types, liver fibrosis is the most common type of liver injury among all of them. When the liver is induced by viruses (such as hepatitis B and hepatitis C virus), autoimmune hepatitis, alcoholic steatohepatitis, non-alcoholic steatohepatitis, and other metabolic defects leading to its injury (like liver cirrhosis, liver fibrosis, and liver cancer liver injuries lead to liver cirrhosis. In the case of direct liver transplantation therapies, there have many limitations. These limitations are the short collection of liver donors and the high costs of functional livers. Also, the ethical issue of liver transplantation is restricted by donor scarcity (Cao et al., 2020). For many limitations of the direct liver transplantation method, recently mesenchymal stem cells (MSCs) have gained a lot of importance in various areas of health and medical sciences research. Based on this information they assume that it has some potential to treat in the field of liver diseases. Many

basic and clinical experiments suggest that stem cell-based have a beneficial role in liver fibrosis (Lee et al., 2004). Mesenchymal stem cells are the multipotent type of stem cell (which easily made many types of cells and factors). It is also shown that MSCs not only present some of specific tissue in our body, but it's also present in several tissue (fat tissue, amniotic fluid, myeloid tissue, soft gelatinous tissue, birth cord, menstrual blood, and placenta). MSCs show low immunogenicity, inherently. It doesn't express any type of major histocompatibility complex (MHC) antigens of class II and has low levels of MHC class I. Also, MSCs have an advantage point it lacks the co-stimulatory factor which is important for immune detection, including the cluster of differentiation (CD) 80, CD 86, and CD 40 (Cao et al., 2020).

For all those reasons MSCs have generally low immunogenicity and easily avoid immune rejection by the recipient. On that basis occurs the foundation of the allogenic application. MSCs have some unique properties that made them important for use in therapeutic purposes. The properties

are self-renewal capacity, homing of the site of injury, immunomodulatory, and secretion of some trophic factors that promote the regeneration and rejuvenation of damaged tissue (Driscoll et al., 2019).

In 1976, there were first MSCs isolated from mouse bone marrow (BM) called bone marrow stromal cells. In those times various fundamental and clinical research trials have revealed that MSCs have the potency to induce liver function and also suggest it is a way to treat liver cirrhosis safely and effectively. Not only BM-MSCs are used to treat cases of fibrosis, but simultaneously umbilical cord mesenchymal stem cells (UC-MSCs) are used for studies in the field of liver fibrosis. Scientists studied the route of MSCs in human beings, and they also showed that intravenously injected UC-MSCs improve liver function and decrease the damaged area in the liver (Viñas et al., 2003).

In this review, we are going to say about the essential signaling pathways for liver fibrosis and what are the actual reasons for liver damage. And also recently discovered the clinical applications using via MSCs. Also, we summarized the trophic factors (which are secreted by MSCs) and their contribution to the improvement of fibrosis.

Histology of liver fibrosis

Liver fibrosis is successfully caused by many complex pathways. Hepatocytes (liver cells) are the basic structural component of the liver, 80% of the total liver volume hepatocytes are arranged radially within the lobule from cellular plates. Hepatotoxic agents (chemicals that are responsible for liver injury) are one of the most dominant reasons for liver fibrosis. More than 900 drugs have been implicated in causing liver injury and it is the most common reason for a drug to be withdrawn from the market. Some are very dangerous for the liver, they might be totally lost liver functions. For those reasons many of drugs have been completely withdrawn from the market (Al-Dhamin et al., 2020).

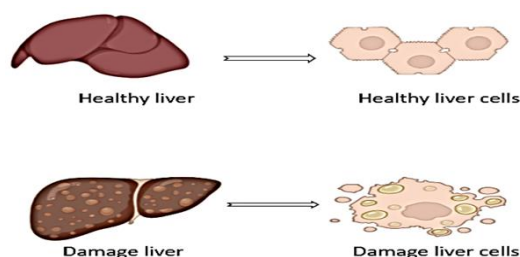


Fig. 1 Histology of liver fibrosis

Firstly, hepatotoxic agents target the liver cells for triggering apoptosis. Reactive oxygen species (ROS) have come from damaged hepatocytes and apoptotic bodies, they can induce surrounding hepatic stellate cells (HSCs). Then anaplectic the inflammation process of inflammatory cells. After

inflammation, demagogic cells produce a huge number of inflammatory substances. Inflammatory substances control a high level of inflammation in the liver and stimulate HSC to fabricate collagen and another extracellular matrix (Viñas et al., 2003). In the liver one type of macrophage is present, the named kuffer cell (KCs). KCs are classified into two types. One type is pro-inflammatory macrophages (M1) and another one is immunomodulatory macrophages (M2). They can participate to cause liver-related diseases and control the triggered state of HSCs. Liver fibrosis is identified by the property of high levels of ECM, and most other components are secreted by activated HSCs. In normal conditions, HSCs are produced collagen and also other ECM proteins but in the case of liver fibrosis HSCs are transformed into a myofibroblast-like phenotype. When HSCs are transformed to the activated stage, they become more harmful to compare normal stage. In this activated stage they lose their many functional properties like the ability to reserve vitamin A-droplets, acquire styptic, proinflammatory, fibrogenic properties, and wring out alpha-smooth muscle actin (alpha-SMA). During liver injury, ECM changes its composition and folds six times compared to normal. It highly consists of collagens, fibronectin, vimentin, elastin, and laminin (Campbell et al., 2005).

Various signaling pathways of liver fibrosis

Behind the successful causing of liver fibrosis, there are hidden several signaling pathways and specifically hepatic satellite cell (HSC) activation. Tumor growth factor-beta (TGF-beta)/SMAD pathways are one of the main pathways. TGF-beta is a type of tumor suppressor because it inhibits normal cell growth and division, and induces cells to the way of the dead. When TGF-beta is more produced, then it is stored in an extracellular matrix (ECM). It is a latent type of precursor, produced by many types of macrophages, hepatocytes, and activated hepatic satellite cells (HSCs). TGF-beta has autocatalytic activity, so it is split by a protease and capriole to a target surface receptor. The cleaved bounded molecules lead to the start the signaling pathway that occurs through the phosphorylation of SMAD molecules. The result is formed a complex molecule that contains phosphorylated SMAD2 and SMAD3. The whole complex shifted in the nucleus and maintain various fibrotic marker expressions (Tzavlaki et al., 2020).

Another important signaling pathway is Wnt/beta-catenin signaling pathway. This pathway consists of wnt protein and beta-catenin. Wnt protein is one type of surface protein that controls the activity of beta-catenin. Beta-catenin is a transcription factor and has adhesion properties (Nishikawa et al., 2018). This pathway has been completed in two ways. One Wnt on state another Wnt off state. When Wnt is on then it inhibits beta-catenin phosphorylation. The result is the unphosphorylated beta-catenin number increasing in the cytosol. That will persuade beta-catenin complex translocation in the nucleus and maintain transcription of different genes in the nucleus such as Myc, Axin-2, and c-Jun (Bedford et al., 2010).

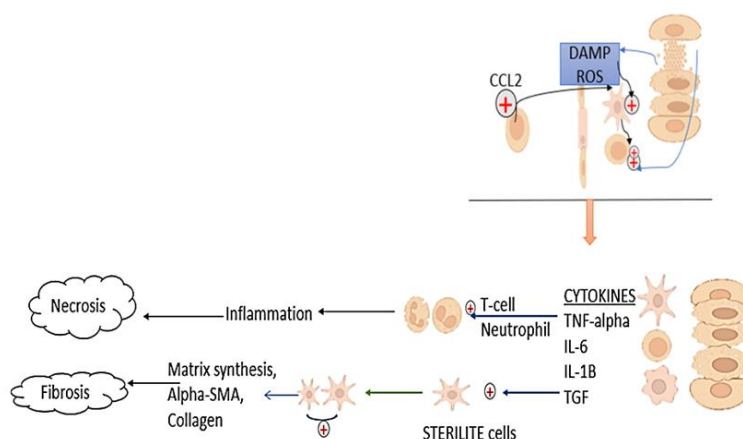


Fig. 2 Pathogenesis of Liver fibrosis. It is the basic pathway of liver fibrosis. Damage-associated molecular patterns (DAMP) and Reactive oxidative species (ROS) initiate the signaling pathways. Later TNF-alpha, IL-6, TGF many others also lead to liver damage

Th2 polarization and CD4+ T cells also induce the fibrogenesis process. These cells participate in type 2 immune responses and exterminate parasites. They secrete interleukin (IL) -5, IL-4, IL-13, and IL-10. Secretary interleukins are responsible for the distinction of fibro-genic myeloid cells and macrophages. Chemokines are a class of chemotactic molecules with cytokine-like functions. They are well known for inflammatory responses within different organs in our body. The exodus of HSCs to the site of injury is encouraged by several chemokines such as (CCL5, CCL3, CCL4, CXCL1, CSXL9, CSXL8, and CSXL10). These chemokines are secreted by activated HSCs which express the respective receptors (Lee et al., 2011).

Platelet-derived growth factor (PDGF) is one of the strongest mitogens. It leads to the HSCs activation process. PDGF is generally present in dimeric form. PDGF-beta subunit binds to the surface receptor and many signaling pathways are activated like Ras-MAP Kinase, P13K-AKT/PKB, and phosphate kinase pathway. Also, other factors present like – the epidermal growth factor and vascular endothelial growth factor (VEGF) can stimulate HSCs activation.

In times of liver injury, the body’s endocrine system is up-regulated. Many cannabinoid signaling pathways are induced and also secrete many cannabinoids (CB). The activation of the CB-1 receptor is pro-fibrotic but CB-2 is anti-fibrotic. Serotonin, opioid, and dopamine pathways as well as thyroid hormones have a pro-fibrotic contribution (Lee et al., 2011).

Source and dominance of MSCs

In the field of MSCs-based experimental studies, bone marrow stromal stem cells are mainly used for their high working efficiency. But BM-MSCs abundance is very low. So, we go with another available source of mesenchymal stem cells. Other available sources are adipose tissue, dental pulp,

muscle, umbilical cord, amniotic tissue, fetal origin, and placenta (Malgieri et al., 2006). It was reported that MSCs which are found in adipose tissue, have a high abundance compared to other sources MSCs. Also reported that MSCs isolated from the birth cord have the maximum boost power compared to other MSCs. Another report suggests AD-MSCs are most capable of liver regeneration. UC-MSCs have a higher capability for hepatic differentiation potential. Due to its high potency, it also uses more than BM-MSCs (Jin et al., 2013).

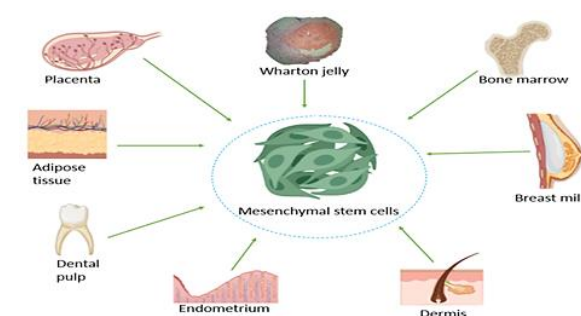


Fig. 3 Sources of Mesenchymal stem cells. MSCs present in several tissues (fat tissue, amniotic fluid, myeloid tissue, soft gelatinous tissue, birth cord, menstrual blood, and placenta).

MSCs-based therapeutic mechanisms aggregate via the paracrine soluble factors. These are Prostaglandin E2, indoleamine 2,3-dioxygenase, hepatocyte growth factor, and vascular endothelial growth factor. These factors change the microenvironment rather than differentiation alone. MSC-conditioned media (MSC-CM) may help as another opportunistic comparison to direct transplantation of the liver. MSC-CM helps inhibit the apoptosis process and assists in the proliferation of hepatocytes (Xagorari, et al., 2013). MSCs

show low immunogenicity, inherently. It doesn't express any type of major histocompatibility complex (MHC) antigens of class II and has low levels of MHC class I. MSCs have the advantage point it lacks the co-stimulatory factors which are important for immune detection, including the cluster of differentiation (CD) 40, CD 86, and CD 80. For all those reasons MSCs have generally low immunogenicity and can easily avoid rejection by the recipient (Cao et al., 2020).

MSC-CM is involved in recovering liver fibrosis, it secretes more amount of anti-inflammatory IL-10 (Lotfinia et al., 2016). Reported that MSC-CM also enhanced the histological and biochemical components of the liver. The exosome is another important component that is secreted by MSC-CM. Exosomes play a major therapeutic role in liver injuries. MSC-derived exosomes (MSC-Exo) are similar to general exosomes. MSC-Exo also carried many vesicles containing nucleic acids, lipids, and proteins. And the result is the alternation of different signaling pathways. MSC-Exo has the capability of movement. It migrates to sites of injury. (Jiang et al., 2018) Reported that umbilical-derived MSCs (UM-MSCs) secrete one type of exosome, presenting more antioxidant and hepatoprotective effects than other treatments. Although, AD-MS-C-Exo correctly increased liver failure and suppress the inflammatory activities of macrophages (Liu et al., 2018).

Innate immune regulation of MSCs

Macrophages, Mostly, in the liver, there are two types of macrophages present. One is activated M1 and another is alternative-activated M2. M1 is activated by degraded matrix, pathogen components, and Th1 lymphokines, and it leads to secretions of inflammatory cytokines. Those inflammatory cytokines induced liver damage and lead to liver fibrosis. Oppositely, M2 activates leads to wound repair of the liver and slowly recovering from the liver injury. M2 is a type of anti-inflammatory macrophage, it is activated by Th2 lymphokines, apoptotic cells, and secretes IL-10. The imbalance ratio of M1/M2 causes the activation of HSC and it leads the liver fibrosis (Bility et al., 2016).

In dendritic cells, one of the effective components is Prostaglandin E2 used for the treatment of liver injury. PGE2 is a potent physiological suppressor molecule of liver fibrosis. It is secreted by Dendritic cells. It increases the immune tolerance of the liver. Particularly, it decreases the secretion of pro-inflammatory cytokines and increases the secretion of anti-inflammatory cytokines like- IL-10 in DCs (Eom et al., 2015).

NK cells, Natural killer cells have anti-fibrotic properties. Hence it helps in the treatment of the liver injury. NK cells selectively killed activated hepatic stellate cells via the production of interferon-gamma. Interferon-gamma also kills activated HSCs via another mechanism. The mechanism is cell cycle arrest and induced apoptosis. And subsequently decreases liver injury (Gao et al., 2013).

Innate lymphoid cells, Innate lymphoid cells released cytokines such as IL-3, IL-13, and IL-5. These cytokines can respond to IL-33 and IL-25. ILCs release cytokines in response to liver infection and liver tissue damage. In vitro, it was approved that ILC3s and MSCs can interact. And the result is MSCs can secrete IL-22. IL-22 acts on epithelial homeostasis and damage tissue repair (Van Hoeven et al., 2018).

Adaptive immune regulation of MSCs

B Cells, In vitro mouse model experiment, suggests that B cells have a major role in liver pathogenesis. Firstly, the level of B cells is increased. The result is the activation of IgG and TNF-alpha production. BM-MS-C transplantation can also increase the infiltration of liver cells protective against IL-10 (Gazdic et al., 2018).

T Cells, It Recently, discovered that T cells including Tc and Th cells both are common in liver fibrosis. Th2 cells can promote the injury process via secreting IL-4 and IL-3 but Th1 have anti-fibrotic property. So, the regulation of T-cells is important in liver fibrosis. The result found from an in vitro experiment, MSCs can inhibit T cell proliferation via the process of direct interaction or secreting of some factors (e.g., PGE2, IDO, and TGF-beta1). MSCs inhibit the migration of T cells toward the target tissues by the process of decreasing the production of chemokines, including CCL1, CCL3, CCL8, CCL17, and CCL22 (Lim et al., 2017).

Role of MSCs -derived molecules in liver regeneration

MSCs have the capability to secrete various molecules and they have many important roles to treat liver diseases. MSCs release molecules are free nucleic acids, soluble proteins, lipids and extracellular vesicles. Also, many anti-inflammatory substances, cytokines, and growth factors came out from MSCs. It also demonstrates that these derived factors help the recovered damaged liver in many ways. These are immunomodulatory pathway response, anti-apoptotic activity, control of angiogenesis, restorative of wound healing and tissue rebuilding, and various anti-microbial effects (Vizoso et al., 2017). Many, different factors contain in MSCs derived secretomes, like Tumor necrosis factors (TNF-beta1), and ciliary neurotrophic factors. It basically told that MSCs release more amount of growth factors such as HGF1, KGF, LIF, etc (Dubey et al., 2018).

Recently, many reports suggested that MSCs not only release many types of growth factors, antifibrotic factors. It also secretes different types of extracellular vehicles and nanovesicles. These all vesicles and particles are originated from the plasma membrane. They are very small in size. Many vesicles are made up of lipid bilayers. They have a very crucial role in the therapeutic treatment of liver diseases (Abels & Breakfield, 2016).

Effects of extra-cellular vesicles

Many signaling pathways are responsible for the successful spread of liver fibrosis. Pathways are tumor growth factor-beta1, Wnt/beta-catenin pathway, etc. Extracellular vesicles basically originated from the plasma membrane and are made up of lipid bilayers. They inhibit many signaling pathways, which are responsible to cause liver fibrosis. Nano vesicles which are derived from MSCs have various properties. These properties are they can restore autophagy, hamper hepatocyte apoptosis, bring down collagen decomposition, and stop

further activation of hepatic cells. MSCs sourced Extracellular vesicles lessen the demonstration of different types of fibrotic significance markers. Fibrotic markers mainly accumulate in the liver at the time of fibrosis. Fibrotic markers are alpha-SMA, collagens, TGF-beta1, etc. Artificially a liver fibrotic mice model was established by treating TAA (thioacetamide), and hence it was proved that human birth cord MSCs-EVs can stop all signaling pathways and demonstrate the accumulation of fibrotic markers (Zhang et al., 2021).

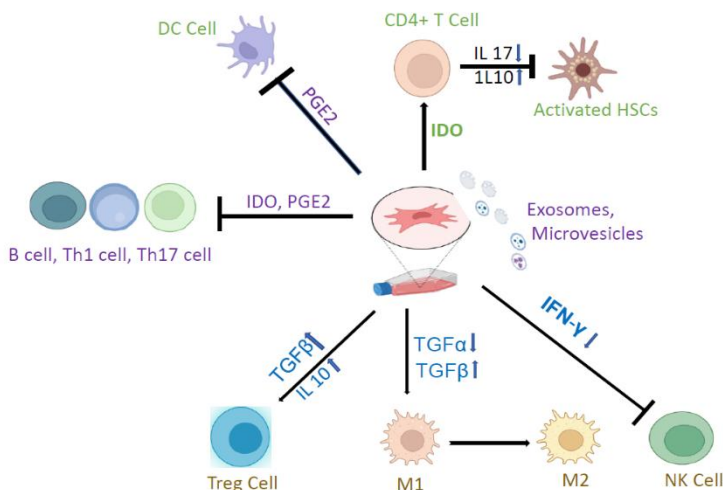


Fig. 4 Potential mechanism of MSCs and EVs. EVs act upon some signaling pathways. MSCs-derived extracellular vesicles also do bracing autophagy, hinder liver cell apoptosis, deduced collagen decomposition, and stop the activation of HSCs.

Another major contribution of nanovesicles is they can stop or try to impede liver cell apoptosis. An artificial rat model study told that hUC-MSCs-derived vesicles have the competence to impede apoptosis, via the secretion of anti-apoptotic family chemicals such as Bcl-2. With that, they can decrease the expression of caspases 3, and the pro-apoptotic family molecules such as Bax, etc. They also can be reduced inflammation by the way of suppressing inflammatory cells. That's all studies say about the anti-apoptotic property of MSCs-derived vesicles (Jiang et al., 2018).

Recent studies suggest that in kupffer cells, EVs isolated from AMSCs can downregulate the expression of TNF-alpha, IL-1beta, and Mcp-1. hUC-MSC-EXs added in mice which are CCL4-induced liver fibrosis results show that bring down of the aggression of inflammatory cells. Jin et al. artificially isolated extracellular vesicles from fatty tissues. After that these isolated fatty tissue vesicles are added into the medium where already D-amino-galactose-induced acute liver diseases are present. And then it was proved that AD-MSCs-nanovesicles can downregulate the expression of chemotactic

factors such as CCL20, 2alpha/beta, CINC-1, CINC -3, CNTF, CXCL7 (Jin et al., 2018).

Mscs-derived exosomes with overexpressed cargo such as microRNA

Many exosomes are derived from MSCs but they have different properties. These exosomes contain microRNA. When these exosomes are added to the liver damages tissue, then they try to secrete some of the overexpressed proteins and microRNA. By secreting those microRNA and proteins MSCs interfere with those signaling pathways which are responsible for successfully spreading liver damage.

In vitro experiment said that miR122 came out, particularly one of the sources of mesenchymal stem cells. That one is fatty tissues. AD-MSCs secreted miR122 main function to downregulate the LX2 HSC cell line. Many genes are particularly responsible for causing liver-related diseases by activation of HSCs. These genes are CCNG1, P4HG1, and IGF1R. miR122 target also these genes. miR122 suppressed

the mRNA transcript from those genes. Experimentally, it also shows in a mice model which is induced with CCL4. So, the mice came up with a model of liver fibrosis. Then miR122 inject into the model and observed the changes were. From the observations, we see that the factors that help in liver damage such as TGF-beta1, alpha-SMA, etc quantity slowly decreased and the anti-damaging factors quantity slowly increased (Lou et al., 2017).

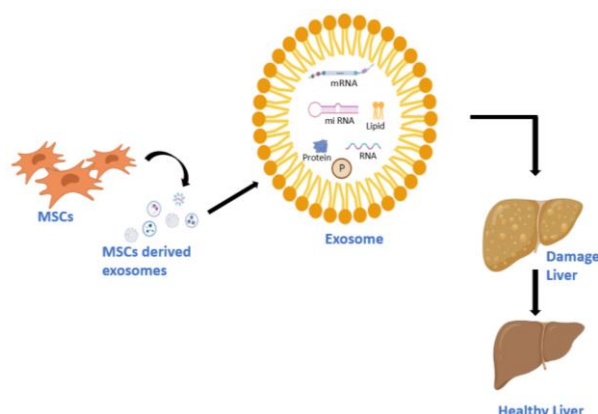


Fig. 5 MSC-Exosomes effects in liver fibrosis. miR-122 has an important role in liver fibrosis, by decreasing pro-apoptotic factors. Also, miR-181-5p, miR17, and miR145-5p also have several roles in liver fibrosis treatment.

Another in vitro study said about miR-181-5p. miR-181-5p can control the corresponding state of hepatic progenitor cells. In vitro experiment done in a mouse, where investigates that AD-MSCs derived exosomes containing miR-181-5p have the capability to repress HSCs cell line. This miR-181-5p containing exosomes can target the Bcl2 family of genes. Not only do that, but it also induces the autophagy process by enhancing the expression of Beclin1 (Qu et al., 2017).

Also, many other studies or in vitro experiments said that miR-17 and miR-145-5p have other roles in liver fibrosis treatment. Many of them can control the inflammation process. Others can control directly apoptosis process. Not only microRNA contained in exosomes, but many noncoding RNAs also have important roles to control liver fibrosis mechanisms. Noncoding RNAs can enhance proliferation and suppress liver cell apoptosis (Jin et al., 2018).

Future prospects

As direct liver transplantation is not easy for patients to survive and also has limitations for donors. Concerns have been raised over the past few years regarding the long-term efficiency of MSC-based therapies and the potential for side effects such as tumorigenic risk. Previously we discussed the evidence about MSCs can promote tumor growth in vivo. Conversely, MSCs have immunomodulatory effects, so they

can modulate many inflammatory environments. It also described that MSCs can inhibit cancer cells, block many different signaling pathways, and inhibit cell division. However, there is a lack of many things that are not standardized yet. It has been reported that chromosomal abnormalities occur in cultured cells, although research has shown the transplantation of MSCs to be safe in clinical and preclinical. A Standard protocol is lacking for MSCs transplantation. The best root for mesenchymal stem cell transfer, optimum doses for maximum efficiency, timing, and frequency of injection differ considerably among different studies.

We may think about that in future studies, on how to control randomized trials, and the long-term efficiency, of MSC-based therapies. May the patient's competence or not for mesenchymal stem cells, is tested before the injection.

Conclusion

The liver is a very essential organ in our body. It also plays a very important role in bile production, excretion of molecules, metabolites many macromolecules, acts as a storage organ, stores many vitamins, glycogen, and minerals, synthesizes many plasma proteins and clotting factors, and detoxified many poisonous molecules. It has many immunomodulatory functions. All in all, it is very important to have a healthy liver. To keep the liver healthy, be careful about alcohol consumption, wash produce and steer clear of toxins, prevent hepatitis A, B, and C, exercise, and eat right. If liver function is dis balanced it dedicates to liver injuries. As the direct liver transplantation process is not easy, we go to cell-based therapy. And MSCs have many potentials for the treatment of liver injuries. Therapy based on MSCs is a potential approach to the several medical procedures now in use for the treatment of liver illness and the best match therapy to prevent liver injuries. Together to optimize the therapeutic doses and route of MSCs, mechanisms, and clinical investigations should create closer cooperation between academic and industrial researchers.

Conflict of Interest

The author hereby declares no conflict of interest.

Consent for publication

The author declares that the work has consent for publication.

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