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Review Article

Therapeutic Implications of Mesenchymal Stem Cells in Liver Injury

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Mesenchymal stem cells (MSCs), represent an attractive tool for the establishment of a successful stem-cell-based therapy of liver diseases. A number of different mechanisms contribute to the therapeutic effects exerted by MSCs, since these cells can differentiate into functional hepatic cells and can also produce a series of growth factors and cytokines able to suppress inflammatory responses, reduce hepatocyte apoptosis, regress liver fibrosis, and enhance hepatocyte functionality. To date, the infusion of MSCs or MSC-conditioned medium has shown encouraging results in the treatment of fulminant hepatic failure and in end-stage liver disease in experimental settings. However, some issues under debate hamper the use of MSCs in clinical trials. This paper summarizes the biological relevance of MSCs and the potential benefits and risks that can result from translating the MSC research to the treatment of liver diseases.

1. Introduction

The liver has a remarkable regenerative capacity in response to acute injury. Mature hepatocytes can reenter the cell cycle and undergo several cell divisions to restore the hepatic mass. However, following chronic liver damage, the regenerative ability of hepatocytes is lost. In such conditions, the liver is unable to maintain its functional mass; this is clinically mirrored by the so-called "liver failure." Currently, orthotopic liver transplantation (OLT) represents the most suitable therapeutic option for patients with advanced liver diseases and hepatic failure. Nevertheless, only a minority of candidates undergo OLT, given the organ shortage. Hence, alternative strategies for the treatment of decompensated liver diseases are needed to be developed [1].

Cell-based therapy has been proposed as a potential alternative to OLT. Indeed, it has been known for more than 30 years that hepatocytes isolated from a donor liver and infused intraportally in animal models of liver damage can be engrafted into the recipient hepatic parenchyma and express metabolic activity. These results have encouraged clinical trials using hepatocytes transplantation to treat a variety of liver diseases [2]. The best outcome of allogeneic hepatocytes transplantation was reported for the treatment of acute liver failure, in which hepatocytes infusion provides the rapid metabolism of liver toxins and the stabilization of hemodynamic parameters. However, transplantation of liver cells provides serious practical problems: donor scarcity, risk of rejection, low hepatocyte viability (only 30% of hepatocytes survive transplantation) and inability maintain and amplify cell cultures [3, 4].

Given this background, a growing enthusiasm has greeted the development of stem-cell-based therapies for liver diseases. In particular, transplantation of hematopoietic bone marrow (BM) stem cells and mesenchymal stem cells (MSCs) has been extensively investigated as potential sources for liver regeneration.

In 1999, Petersen et al. first showed that liver stem cells might be derived from BM, in a rat model of liver injury [5], and it was suggested that BM could contribute to the mature

hepatocyte population. Subsequent studies have shown that BM-derived hepatocytes might arise from cell fusion and not only by direct differentiation [6] and that BM cells give a limited contribution to the hepatocyte population, under physiological conditions or in response to mild injury [7].

MSCs represent another promising candidate for liver stem cell therapy. Several studies have demonstrated that MSCs can differentiate *in vitro* along the hepatogenic lineage [8, 9]. To date, studies on animal models reported the beneficial effect of MSCs in promoting hepatic tissue regeneration. Kuo et al. have shown that both MSC-derived hepatocytes and MSCs, transplanted by either intrasplenic or intravenous route, can be engrafted into the recipient liver and differentiate into functional hepatocytes. Intravenous transplantation was more effective in rescuing liver failure than intrasplenic transplantation. Moreover, MSCs were more resistant to reactive oxygen species *in vitro*, reduced oxidative stress in recipient mice, and accelerated repopulation of hepatocytes after liver damage, suggesting a possible role for paracrine effects [10]. These results have been confirmed also by Banas et al., who evaluated the therapeutic potential of MSCs for the treatment of liver failure and postulated that the beneficial effects of human MSC transplantation were due at least in part to the cells' ability to produce a large number and volume of bioactive factors [11]. To date, only a few clinical trials have been performed in patients with end-stage liver disease caused by hepatitis B, hepatitis C, and alcoholic fibrosis. The results of these studies have shown that MSC injection can be used for the treatment of end-stage liver diseases, with satisfactory tolerability and clinically relevant effects [12]. Nonetheless, these studies have not provided definitive evidence that MSCs have a capability to differentiate into functional hepatocytes *in vivo* [13], because the observed improvements could be attributed to the secretion of soluble growth factors by MSCs, rather than to their transdifferentiation into hepatocytes [7]. MSC cells have also emerged as promising candidate cells for immunomodulation therapy, especially in the setting of liver transplantation, given their ability to interact at various levels with the immune system [14, 15].

Overall, a number of different mechanisms contribute to the therapeutic effects exerted by MSCs, which can differentiate into functional hepatic cells and also produce a series of growth factors and cytokines that can suppress inflammatory responses, reduce hepatocytes apoptosis, regress liver fibrosis, and enhance hepatocytes functionality [16].

2. MSC Properties

MSCs were first described by Friedenstein in the early 1990s, as an adherent, fibroblastoid cell population that showed inherent osteogenic properties [17]. Numerous studies have demonstrated that MSCs have a high degree of plasticity, as they differentiate into cells of the mesenchymal lineage, but they can also transdifferentiate into neurons, splenocytes, and various epithelial cells, including lung, liver, intestine, and kidney cells. BM was originally considered the reference source for MSC isolation, although they have been isolated from a multitude of adult tissues, including muscle, adipose tissue, connective tissue, trabecular bone, synovial fluid, along with perinatal tissues, such as umbilical cord, amniotic fluid, and placenta [18]. In particular, adipose tissue (AT) has several advantages compared to other adult tissues as a source of MSCs. Indeed, AT is abundant and can be easily removed by simple lipoaspirate. Moreover, adipose-tissue-derived MSCs (AT-MSCs) can be maintained longer in culture and possess a higher proliferation capacity than BM-derived MSCs. Thus, AT may be an ideal source of large numbers of autologous stem cells [19].

MSCs do not express the hematopoietic surface markers CD34 and CD45, but stain positive for CD44, CD29, CD105, CD73, and CD166 [20]. Moreover, MSCs express human leukocyte antigen (HLA) class I, but not HLA class II, and secrete several extracellular matrix (ECM) molecules, such as collagen, fibronectin, laminin, and proteoglycans. For this reason it has been postulated that MSCs might play a central role in ECM organization. We performed a high-throughput molecular analysis of BM- and AT-MSCs. The gene expression profile analysis has revealed that they share 190 coherently modulated transcripts, which might represent the molecular "MSC stemness signature." Among them, we found several genes involved in basic biologic mechanisms, such as embryogenesis, organogenesis, signal transduction, cell adhesion, stress response, and transcription regulation. In particular, a key role in determining the outcome of MSC fate determination is played by KLF4, highlighting the specific binding of KLF4 to regulatory sequences of genes involved in adult stem cell maintenance [19].

BM-derived MSCs are known to naturally support hematopoiesis by secreting a number of trophic molecules, including soluble extracellular matrix glycoproteins, cytokines, and growth factors [21, 22]. Recent studies have demonstrated that MSCs can produce some antiapoptotic cytokines such as stromal-cell-derived factor-1 and vascular endothelial growth factor, which efficiently reduce the apoptosis of recipient cells via the stromal cell-derived factor-1/CX chemokine receptor-4 axis. The antiapoptotic effects of MSCs have been observed in liver injury models [23–26]. Furthermore, MSCs can secrete several cytokines such as hepatocyte growth factor (HGF), epidermal growth factor, IL-6, and TNF-α; in turn, these cytokines stimulate hepatocyte proliferation and maintain hepatocyte function, as indicated by the high levels of albumin and urea secretion granted upon MSC transplantation [27]. Finally, MSCs can produce a series of cytokines and signal molecules that can potentially suppress inflammatory responses such as IL-1 receptor antagonists and can upregulate anti-inflammatory cytokines such as IL-10 [25].

3. MSC Plasticity

Given their wide differentiation potential and their self-renewal capacity, MSCs have been considered a promising candidate for cell-based therapy and tissue engineering. Moreover, these cells have the ability to proliferate to an extensive but finite degree, an important characteristic that

should reduce concerns about potential tumorigenicity upon *in vivo* transplantation.

The high degree of plasticity of MSCs has been widely demonstrated during the last decade [28–31]. In particular, *in vitro* models, using culture medium supplemented with a cocktail of growth factors, were used to successfully induce the transdifferentiation of MSCs into hepatic cells with functional properties, such as the production of albumin and urea, along with glycogen storage [32]. Moreover, the *in vivo* transdifferentiation of MSCs into hepatic cells has been described in rats [33], mice [34], and humans [35].

Seo et al. first reported that human AT-MSCs injected into SCID mice, following toxic liver damage, were able to differentiate into hepatocyte-like cells [36]. Several reports have confirmed the possibility of generating hepatocyte-like cells from AT-MSCs [37, 38]. In particular, in a xenogeneic transplantation model of liver regeneration, the engraftment of AT-MSCs predifferentiated *in vitro* to hepatocyte-like cells was significantly more efficient *versus* undifferentiated AT-MSCs, and AT-MSCs were better candidates than BM-MSCs for cell therapies [39].

We confirmed that AT-MSCs can transdifferentiate *in vitro* into hepatocyte-like cells, using a two-step protocol with sequential addition of growth factors. Under this regimen, spindle-shaped fibroblastoid cells differentiated to a layer of compact polygonal epithelial cells. These cells acquired specific liver functions, as shown by their ability to store glycogen and to express hepatic-associated genes and proteins. Moreover, the comparative high-throughput molecular analysis of AT-MSCs, before and after hepatogenic conversion, allowed the identification of a complex interplay between cell receptors, signaling pathways, and transcription factors, responsible for tissue cross-lineage conversion through the mesenchymal-epithelial transition (MET). Our study showed that the AT-MSC plasticity is dependent on MET and suggested that subtle regulations of the canonical pathways of BMP, WNT, and TGF-β may be important to allow MSCs to transdifferentiate into other lineages [40].

The pivotal role that MET plays in determining AT-MSCs transdifferentiation in hepatocytes was also confirmed in an interesting article by Yamamoto and colleagues [41]. The authors compared the transcriptomes of three cell populations, undifferentiated AT-MSCs, AT-MSC-derived hepatocytes (AT-MSC-Hepa) and human primary hepatocytes, and human liver tissue, using microarray analysis. The results indicated that AT-MSC-Hepa and hepatocytes displayed a similar gene expression profile, while undifferentiated AT-MSCs showed a different pattern. The list of genes upregulated in AT-MSC-Hepa, liver cells, and tissue comprised, in particular, genes encoding hepatocyte-specific metabolic enzymes and markers [41]. Interestingly, the microarray data indicated the downregulation of two regulators of the epithelial-mesenchymal transition (EMT), Twist and Snail, along with the upregulation of epithelial markers, such as E-cadherin and a-catenin, in AT-MSC-Hepa. In contrast, the expression of mesenchymal markers, such as N-cadherin and vimentin, was downregulated. These findings support the notion that MET is activated during the hepatic differentiation of AT-MSCs, representing a pivotal step for stem cell transdifferentiation [41].

4. MSCs and Immune System

MSCs express few HLA class I and no HLA class II molecules, allowing them to evade allogeneic immune response. This is the so-called "immunoprivilege," an interesting feature in MSC biology, which makes these cells extremely suitable for both autologous and allogeneic transplantation [42]. Moreover, several studies have established that MSCs exert a generally suppressive effect on a wide variety of cells belonging to both adaptive and innate immunity, including T and B lymphocytes and natural killer cells (NKs). This immunomodulatory effect provides a rational basis for the application of MSCs in the treatment of immune-mediated diseases, such as graft-versus-host disease (GVHD). To date, the mechanisms underlying this immunoregulation remain unclear: some investigators suggested a cell-to-cell contact-mediated suppression, while others hypothesized a soluble-factor-mediated mechanism [43].

MSCs can suppress the activity of CD8+ cytotoxic T lymphocytes both directly by inhibiting their proliferation following antigen stimulation and indirectly by increasing the relative proportion of CD4+ T helper-2 (TH2) lymphocytes and CD4+ regulatory T lymphocytes [44]. Since B-lymphocyte activation is largely T cell dependent, the influence of MSCs on T lymphocytes may also indirectly suppress B-cell functions [45]. Additionally, MSCs exert a direct influence on B-lymphocytes via cell-cell contact and through secretion of paracrine molecules [46].

MSCs exert significant effects on the innate immune system cells, including monocytes, dendritic cells (DCs), macrophages, NKs, and neutrophils. The mechanisms by which MSCs exert their inhibitory effect on DC maturation is still poorly defined. Spaggiari et al. have shown *in vitro* that MSCs inhibit the early stages of the progression from monocytes to immature DCs, induced by interleukin-4 (IL-4) and granulocyte-macrophage colony-stimulating factor (GM-CSF). The authors have shown that different soluble factors mediate the inhibitory effect exerted by MSCs, and they provided a convincing evidence of the pivotal role of prostaglandin E2 (PGE2) [47]. MSCs have a profound inhibitory effect on NK function, suppressing the IL-2-induced cell proliferation, their cytolytic activity, and the production of cytokines. MSCs can inhibit NK-cell function *via* the production of soluble factors, including indoleamine 2,3-dioxygenase (IDO) and PGE2 [48]. Lastly, an *in vitro* study demonstrated that MSCs inhibit apoptosis, expression of adhesion molecules, and migration capability of neutrophils. These results are consistent with the hypothesis that, within the BM niche, MSCs protect neutrophils of the storage pool from apoptosis, preserving their effector functions. Moreover, MSCs reduce intensity of the respiratory burst preventing the excessive or inappropriate activation of the oxidative metabolism. This may be a critical mechanism through which MSCs can limit the severity of tissue damage following ischemic and ischemia/reperfusion (I/R) injury [49].

5. Therapeutic Implications of MSC-Based Treatments of Liver Diseases

The therapeutic potentialities of MSCs are also based on their inherent ability to home in sites of inflammation following tissue injury when injected intravenously. This involves their capability of migrating across endothelial cell layers and being attracted to and retained in the ischemic tissue but not in the remote or intact tissue. Although the mechanisms driving this property are not fully understood, it is likely that injured tissues express specific receptors or ligands that facilitate trafficking, adhesion, and infiltration of MSCs to the damaged site, similarly to leukocytes [50, 51]. It is well known that chemokines are released after tissue damage and that migratory direction follows the chemokine density gradient. In this regard, it has been recently demonstrated that MSCs express chemokine receptors and ligands that are involved in leukocyte migration during inflammation, including the stromal-derived factor-1 (SDF-1) chemokine receptor (chemokine (C-X-C motif) receptor 4, CXCR4) that stimulates the recruitment of progenitor cells to the site of tissue injury [52–55]. MSCs also express several adhesion molecules that respond to SDF-1, as well as chemokines, such as CX3CL1, CXCL16, CCL3, CCL19, and CCL21 [56–58]. Hence, the increase of inflammatory chemokine concentration at the site of inflammation is a key mediator of MSC trafficking to the site of injury [52]. In addition, many integrins, selectins, and chemokine receptors involved in the tethering, rolling, adhesion, and transmigration of leukocytes have also been reported to be expressed on MSCs. In particular, E- and P-selectin, CD44, and VCAM-1, which function in leukocyte adhesion, have been shown to be functionally important in the adhesion of MSCs to the endothelium [59–61].

The therapeutic role of MSCs has been investigated using either autologous or allogeneic transplantation of cells, which were previously expanded in culture and then introduced intravenously or directly into the tissue of interest. To date, infusion of MSCs has shown encouraging results in the treatment of several immune- and inflammatory-mediated conditions including GVHD, diabetes, and ulcerative colitis and in the protection of solid organ grafts from rejection [62]. Recent experimental studies have shown the successful application of MSC transplantation in the treatment of fulminant hepatic failure (FHF), end-stage liver disease (ESLD), and inherited metabolic disorders (IMDs). These studies have shown that MSC transplantation can partially restore the liver function, ameliorate the symptoms, and enhance the survival rates [8, 62].

Different studies have shown that administration of MSC-conditioned medium (MSC-CM), or MSC-derived molecules, might function as alternative or adjuvant tool *versus* MSC direct transplantation alone, for the treatment of FHF [43, 62]. Indeed, Parekkadan et al. showed that the administration of MSC-derived molecules, either by a bolus of MSC-CM or by extracorporeal support using a bioreactor, significantly improved short-term survival in a D-galactosamine-induced rat model of FHF [62]. In another study, van Poll et al. confirmed the effectiveness of MSC-CM in a rat model of FHF. These authors demonstrated that systemic infusion of MSC-CM provides significant survival benefit and prevents the release of liver injury biomarkers [62]. Furthermore, MSC-CM therapy had profound inhibitory effects on hepatocellular death, resulting in a 90% reduction of hepatocyte apoptosis, and enhanced the liver regeneration programs, incrementing the number of proliferating hepatocytes. Taken together, these data support the theory that MSC-CM induces an integrated beneficial response to liver damage [62]. Compared to MSC-CM, transplanted MSCs have the capability to home in the site of injury and ensure continued delivery of trophic signal molecules. However, long-term engraftment rates are low, and invasive methods for the local delivery of MSCs are necessary [11, 63].

A study by Kanazawa and colleagues showed an interesting application for MSCs in the treatment of the hepatic I/R injury that occurs after liver transplantation [64]. These authors reported that transplanted BM-MSCs were able to ameliorate hepatic I/R injury and improve liver regeneration, in a rat model of Hepatectomy plus I/R; the cellular treatment constrained the increase of serum transaminase levels, the most sensitive marker for hepatic I/R injury evaluation. In addition, a significantly lower percentage of apoptotic hepatocytes were observed in the MSCs group compared with the controls. These findings suggested that MSCs might have the potential to protect the liver against I/R injury-induced hepatocyte apoptosis and to enhance liver regeneration [64].

MSCs have been proposed for the treatment of liver cirrhosis, characterized by distortion of the hepatic architecture and formation of regenerative nodules. Liver cirrhosis is generally considered an irreversible process and represents a frequent cause of death worldwide [65]. The autologous MSC injection could be a valid alternative to OLT in the treatment of liver cirrhosis. Indeed, several animal studies and clinical trials have demonstrated that MSCs have the potential to reverse the fibrotic process by inhibiting collagen deposition and transforming growth factor-β1 production [11, 66, 67]. The molecular mechanism underlying the antifibrotic properties of MSCs can mainly reside in the high expression levels of matrix metalloproteinase (MMPs), especially MMP-9, which may directly degrade the extracellular matrix and lead to hepatic stellate cell apoptosis [68, 69].

Recently, Pan et al. have shown that BM-MSCs were able to attenuate liver fibrosis by a direct suppression of hepatic stellate cell activation through the inhibition of delta-like 1 (Dlk1) protein, a member of the EGF-like family of homeotic proteins, in a carbon-tetrachloride- (CCl4-) induced liver fibrosis animal model [70]. In addition, Mohamadnejad and colleagues have conducted a phase 1 clinical trial to determine the safety and feasibility of MSC peripheral vein infusion in patients with decompensated liver cirrhosis: liver function and MELD scores were improved in half of the patients after six months [71].

Despite these encouraging results, the use of MSCs in the hepatologic clinical practice is hampered by the inability to monitor the transplanted cells within the patients and by the lack of standardized clinical protocols. Moreover, the

antifibrotic effect of MSCs is still debated, as MSCs could also potentially differentiate into fibrogenic cells [13, 72].

6. MSCs in Liver Transplantation: Risks and Benefits

Transplantation tolerance is an important goal in the effort to reduce long-term morbidity and mortality in organ-transplant recipients. MSCs can be induced toward hepatic differentiation *ex vivo* and used as a potential valid alternative or a bridging to OLT [10–12], as they could prevent allograft rejection. Such potentiality is based on MSC immunomodulatory properties along with their healing and trophic functions, which could help to minimize ischemia, I/R, and inflammation [15, 73]. The immunomodulatory effect exerted by MSCs on T-lymphocyte response appears to be of primary importance in their ability to prevent allograft rejection. As previously discussed, MSCs suppress the proliferation and function of cytotoxic T lymphocytes while promoting the activities of helper and regulatory T lymphocytes. The precise mechanisms responsible for this effect and whether or not it persists long-term remain to be determined, and further studies are needed to address this issue.

An additional benefit to the use of MSCs for the prevention of solid organ allograft immunorejection is that infusion of these cells at the time of organ transplantation may have the potential to promote a state of immunologic chimerism and long-term tolerance of the transplanted organ by the host immune system [74]. This was achieved in distinct animal models and, in a few notable cases, was associated with long-term graft survival in the absence of immunosuppression [74–76].

Despite the important benefits arising from the use of MSC-based therapy, there are still safety issues to debate about, in particular regarding the long-term effects on immune function and the tumorigenic risk.

Several evidences suggest that MSCs might promote tumor growth *via* transformation, suppression of the antitumor immune response, and direct trophic action on tumor cells [77–86]. The transplantation into nude mice of colon cancer cells mixed with MSCs resulted in larger tumors than did transplantation of cancer cells alone [85]. This effect was associated with a higher degree of neoangiogenesis and lower apoptotic indexes in the tumor mass. MSCs were recruited by colon cancer cells, and in turn they stimulated the migration and invasion of tumor cells through the release of soluble factors [85]. The proangiogenic properties of MSCs can be due to their potential to differentiate into pericytes [86] and, perhaps, endothelial cells, along with the secretion of angiogenic growth factors, including vascular endothelial growth factor, fibroblast-derived growth factor, platelet-derived growth factor, and stromal-derived factor-1 [87]. Moreover, MSCs can provide a stromal scaffold for growing tumors, being a source of carcinoma-associated fibroblasts (CAFs), implicated in important aspects of epithelial solid tumor biology such as neoplastic progression, tumor growth, angiogenesis, and metastasis [88].

However, MSCs immunomodulatory properties may play a potent antitumor effect [89–98]. The exact mechanisms behind the tumor suppressive effects of MSCs are not yet entirely clear, but appear to be related to the modulation of the inflammatory environment that characterizes many tumors [97]. Moreover, MSCs may exert non-immune-related effects, since they are able to interact with cancer cells and inhibit intracellular signaling pathways associated with cell growth and division [97, 98]. In a study by Abdel Aziz and colleagues, the infusion of MSCs, in a rat model of hepatocellular carcinoma, resulted in tumor suppressive effects by downregulation of Wnt signaling target genes related to antiapoptosis, mitogenesis, cell proliferation, and cell cycle regulation. This resulted in the amelioration of both liver histopathological features and function [99].

7. Concluding Remarks

MSCs are considered a potentially relevant therapeutic tool for the treatment of liver diseases, given their high degree of plasticity and immunomodulatory properties. MSCs could represent an alternative to OLT and/or an adjuvant therapy in the prevention of allograft liver rejection. However further studies *in vitro* as well *in vivo* are needed to achieve a better understanding of the potential benefits and risks of MSCs therapeutic use in clinical settings.

Authors Contributions

M. A. Puglisi and V. Tesori contributed equally to this work.

Conflict of Interests

The authors declare no conflict of interests.

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