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REVIEW

Transplantation of mesenchymal stem cells for the treatment of liver diseases, is there enough evidence?☆

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Abstract Mesenchymal stem cells or multipotent mesenchymal stromal cells (MSCs) have been extensively investigated in small animal models to treat both acute and chronic liver injuries. Mechanisms of action are not clearly elucidated but may include their ability to differentiate into hepatocyte-like cells, to reduce inflammation, and to enhance tissue repair at the site of injury. This approach is controversial and evidence in large animals is missing. Side effects of MSC infusion such as the contribution to a fibrotic process have been reported in experimental settings. Nevertheless, MSCs moved quickly from bench to bedside and over 280 clinical trials are registered, of which 28 focus on the treatment of liver diseases. If no severe side-effects were observed so far, long-term benefits remain uncertain. More preclinical data regarding mechanisms of action, long term safety and efficacy are warranted before initiating large scale clinical application. The proposal of this review is to visit the current state of knowledge regarding mechanisms behind the therapeutic effects of MSCs in the treatment of experimental liver diseases, to address questions about efficacy and risk, and to discuss recent clinical advances involving MSC-based therapies.

Contents

Abbreviations: CCl-4, carbon tetrachloride; GVHD, graft versus host disease; HGF, hepatocyte growth factor; ISCT, International Society of Cellular Therapy; INR, international normalized ratio; IFN-γ, interferon-γ; MSC, mesenchymal stem cell; MELD, Model for End-Stage Liver Disease; TGF-β, transforming growth factor-beta 1; TNF-α, tumor necrosis factor-alpha.

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Introduction

Mesenchymal stem cells (MSCs), also called multipotent mesenchymal stromal cells, are adult progenitor cells originating from neural crest and mesoderm (Slukvin and Vodyanik, 2011; Vodyanik et al., 2010; Takashima et al., 2007). Originally, MSCs were found to reside in the stromal fraction of the bone marrow, wherein they contribute to nonhematopoietic stromal cell renewal including osteoblasts, adipocytes and chondrocytes (Pittenger et al., 1999; Friedenstein et al., 1976; Prockop, 1997). In addition to their mesenchymal differentiation capacities, MSCs may have a multidirectional differentiation potential and differentiate into cell types normally derived from endoderm or ectoderm such as hepatocytes (Hong et al., 2005; K.D. Lee et al., 2004; Snykers et al., 2009). Further, it has been shown that MSCs can be immunosuppressive (Bartholomew et al., 2002; Di Nicola et al., 2002; Glennie et al., 2005; Krampera et al., 2003; Le Blanc et al., 2003; Tse et al., 2003; Le Blanc and Ringden, 2005). Given these remarkable properties, their easy accessibility and strong in vitro expansion ability, MSCs were considered as an ideal cell source for autologous stem-cell-based replacement therapies. Horwitz et al. demonstrated their utility in the treatment of osteogenesis imperfecta in children by taking advantage of the bone microenvironment regeneration capacities of MSCs (Horwitz et al., 1999). Children had increased growth velocity and total body mineral content, and fewer fractures. MSC capacity to regulate the immune system has been investigated in diverse diseases; Le Blanc et al. showed that systemically injected MSCs were effective for the treatment of steroid resistant graft versus host disease (GVHD) in bone marrow transplanted patients (Le Blanc et al., 2004, 2008); of note, 55% of them had a complete response with MSC-based treatment. Other beneficial effects were observed in various clinical situations, such as renal transplantation (as an induction therapy) (Tan et al., 2012), multiple sclerosis (Karussis et al., 2010) or systemic lupus erythematosus (as an adjuvant treatment) (Sun et al., 2009).

Currently, MSCs are investigated with the perspective to treat both acute and chronic liver diseases. Some studies provided experimental and clinical evidences suggesting that transplantation of MSCs can sustain liver function in the situation of an acute or chronic liver injury (Peng et al., 2011; Li et al., 2012). However, the mechanisms of action underlying the anti-fibrotic effects are currently not well understood and long term safety and efficacy of such treatment remain to be determined. MSCs may carry a risk of fibrotic reaction (Baertschiger et al., 2009; Forbes et al., 2004; Li et al., 2009), malignant transformation (Casiraghi et al., 2013) and virus transmission (Sundin et al., 2006, 2008) that may not be outweighed by the clinical benefit. In this context, large animal studies are needed to provide enough valid data to allow large clinical trials to start.

The proposal of this review is to visit the current state of knowledge regarding mechanisms responsible for the therapeutic effects of MSCs in the treatment of experimental liver diseases, to address questions regarding efficacy and safety, and to discuss recent clinical advances involving clinical MSC-based therapies.

MSCs and their physiological function

In the late 1960s Friedenstein and colleagues described bone marrow stromal cells and referred to them as nonhematopoietic colony-forming-unit fibroblasts (Friedenstein et al., 1968, 1970). Later, these cells were found to renew themselves and differentiate in vitro in osteoblasts, chondrocytes and adipocytes (Pittenger et al., 1999; Friedenstein et al., 1974, 1976). Multipotency and self-renewal being the hallmarks of "stemness", MSCs were recognized as osteogenic (i.e. nonhematopoietic) "stem" cells of the bone marrow (Friedenstein et al., 1987), wherein they constitute a small subset accounting for 0.001 to 0.01% of the cells. However, their contribution to nonhematopoietic stromal cell renewal in vivo was demonstrated much later (Morikawa et al., 2009). The term "mesenchymal stem cells" was used first by Caplan (1991). Later on, these cells were found to reside in adipose tissue (Hauner et al., 1989; Zuk et al., 2002; R.H. Lee et al., 2004), peripheral blood (Zvaifler et al., 2000; Fernandez et al., 1997), umbilical cord blood (Erices et al., 2000), various fetal tissues (in't Anker et al., 2003; da Silva Meirelles et al., 2006), placenta (Fukuchi et al., 2004), pancreas (Baertschiger et al., 2008) and liver (Najimi et al., 2007). Thus, the term "mesenchymal stem cell" was used to qualify stromal cells isolated following different protocols and arising from diverse tissues. Facing the heterogeneity of what was called "MSC", the International Society of Cellular Therapy (ISCT) proposed a new terminology, calling