Mesenchymal stem cell therapy for acute and chronic pancreatitis

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Abstract Mesenchymal stem cells (MSCs) have attracted attention as a cell source for regenerative medicine. In particular, MSCs have an anti-inflammatory effect by secreting several kinds of bioactive molecules. MSC therapy is now being applied to various gastrointestinal diseases, such as graft-versus-host disease, inflammatory bowel disease, and liver cirrhosis. Therefore, MSC therapy has the potential to be a novel treatment for acute and chronic pancreatitis by suppressing inflammation. Several studies have investigated the effect of MSC therapy on acute and chronic pancreatitis, but the underlying mechanisms remain unknown. In this review, we summarize the present status of MSC therapy for acute and chronic pancreatitis.

Keywords Mesenchymal stem cells · Acute pancreatitis · Chronic pancreatitis · Regenerative medicine · Cell therapy

Introduction

Mesenchymal stem cells (MSCs) are multipotent cells that occur in several tissues, such as bone marrow, adipose tissue, and fetal membranes [1]. MSCs have been investigated for regenerative medicine because of their immunomodulatory effects on the secretion of a variety of

anti-inflammatory molecules [2]. Because MSCs do not have the major histocompatibility complex class II antigen, rejection does not occur, even after allogenic transplantation. The effect of MSC transplantation has been investigated in several gastrointestinal diseases in animal models [3–5] and in human trials [6].

Acute pancreatitis (AP) and chronic pancreatitis (CP) are inflammatory disorders of the pancreas [7, 8]. The anti-inflammatory effect of MSCs is considered a promising treatment strategy for AP and CP [9–11]. In this review article, we summarize the current evidence of MSC therapy for AP and CP and their underlying mechanisms.

Mesenchymal stem cells

MSCs were first isolated and characterized in 1976 [12]. They possess a self-renewal ability and can differentiate into cells of multiple lineages, including mesoderm lineages, such as chondrocytes, osteocytes and adipocytes, and ectodermic and endodermic cells [1]. MSCs can be isolated from the bone marrow, adipose tissue, and umbilical cord, and are easily expanded in vitro. In general, MSCs must (a) remain plastic-adherent under standard culture conditions; (b) express CD105, CD73, and CD90, but not CD45, CD34, CD14, CD11b, CD79a CD19, or HLA-DR; and (c) differentiate into osteoblasts, adipocytes, and chondrocytes in vitro [13]. Cell surface markers were confirmed by flow cytometric analysis. Multilineage differentiation was induced by incubation in adipogenic, osteogenic, and chondrogenic media in vitro.

In 2004, Le Blanc et al. reported that a graft-versus-host disease patient was successfully treated by transplantation of MSCs [14]. Since then, several clinical trials of MSCs have been reported. At first, MSC therapy focused on their

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capacity for multilineage differentiation. However, several studies revealed that a large fraction of systemically infused MSCs were trapped within the lungs as emboli owing to their large size [15]. Furthermore, MSC therapy was shown to suppress inflammation, apoptosis, and fibrosis in numerous disease models without MSC differentiation and engraftment in the injured tissue [5, 16]. Therefore, clinical trials have shifted toward utilizing the biological functions of MSCs through trophic mechanisms and from local to systemic administration [17–21]. This is the main advantage of MSC therapy over embryonic stem (ES) cells and inducible pluripotent stem (iPS) cells, which require differentiation into specific cell lineages and engraftment in the target tissue; moreover, ES and iPS cells can form teratomas [22, 23].

MSC therapy for acute pancreatitis

Table 1 summarizes MSC therapy for AP. The sources of MSCs vary and include bone marrow, umbilical cord, adipose tissue, and fetal membranes. Allogenic and autologous MSC transplantation have been performed. MSC therapy for AP was first described in 2009 by Jung et al. [24]. They evaluated the effect of human bone marrow-derived MSC transplantation in rats with mild and severe AP. MSCs attenuate histological scoring in the pancreas and reduce inflammatory cytokine expression in the pancreas as well as serum levels of transforming growth factor (TGF)- β , tumor necrosis factor (TNF)- α , and interferon (IFN)- γ . They also found that the number of Foxp3+

positive regulatory T cells increases in the lymph node and pancreas. Another study reported that MSCs decrease the number of CD3-positive T cells and increase the number of Fox-P3 positive T cells in the pancreas [25]. Several studies have reported that MSCs suppress serum and pancreatic levels of pro-inflammatory cytokines and increase anti-inflammatory cytokines [24, 26]. Yang et al. reported that the anti-inflammatory effect of MSC transplantation is time- and dose-dependent [27]. MSCs transplanted immediately after induction of AP have a better anti-inflammatory effect than those transplanted several hours after initiation. MSCs themselves have anti-inflammatory properties and serve as a vector for gene therapy. Hua et al. reported that angiopoietin-1 transfected MSCs reduce inflammation in rats with AP more than MSCs do alone [28] (Fig. 1).

The small intestine is damaged in AP because microcirculation is altered following fluid loss, hypovolemia, splanchnic vasoconstriction, and ischemia-reperfusion injury. Tu et al. reported that MSCs improve intestinal injury during severe AP by increasing aquaporin (AQP)-1 expression, reducing mucosal permeability of the intestine, promoting the recovery of intestinal epithelial cells, and maintaining integrity of the intestinal mucosal barrier [29]. Infusing MSCs reduces serum levels of malondialdehyde, superoxide dismutase levels, interleukin (IL)-6, IL-10, and TNF- α . Transplanting MSCs attenuates intestinal mucosal injury and promotes mucosal repair in rats with severe AP [30]. Another study also showed that MSCs reduce damage to the small intestinal capillary endothelial barrier by increasing AQP-1 expression in the small intestine [31].

Table 1 MSC for animal models of acute pancreatitis

Authors	MSCs source	Routes	Dose (cells)	Animal	Induction
Jung [24]	Human BM	IV	1×10^6	Rat	Cerulein, 3% TCA
Tu [30]	Rat BM	IV	$2 \times 10^7/\text{kg}$	Rat	Deoxy STC
Meng [26]	Human UC	IV	$1 \times 10^7/\text{kg}$	Rat	3% TCA
Yang [27]	Human UC	IV	$5 \times 10^6/\text{kg}$	Rat	3% TCA
Hua [28]	Human UC	IV	2×10^6	Rat	3% TCA
Jung [32]	Human BM	IV	1×10^6	Rat	Cerulein + LPS
Qian [34]	BM	IV	$1 \times 10^7/\text{kg}$	Rat	3% TCA
Yin [36]	Rat BM	IV	1×10^6	Rat	L-Arg
He [35]	Human BM	IV	2×10^6	Mouse	2% TCA
Kawakubo [33]	Rat FM	IV	1×10^6	Rat	4% TCA
Kim [25]	Canine AT	IV	$1 \times 10^7/\text{kg}$	Rat	3% TCA
Yin [36]	Rat BM	IV	NA	Mouse	Cerulein
				Rat	4% TCA
Zhao [37]	Rat BM	IV	$5\text{--}7 \times 10^7$	Rat	3% TCA
Lu [31]	Rat BM	IV	1×10^6	Rat	5% TCA

MSC mesenchymal stem cell, BM bone marrow, TCA taurocholate, UC umbilical cord, FM fetal membrane, AT adipose tissue, NA not available, IV intravenous

Fig. 1 Presumed mechanisms of mesenchymal stem cell (MSC) therapy for acute and chronic pancreatitis. MSCs secrete several kinds of bioactive molecules that affect several targets. MSCs migrate and home to the pancreas

Another mechanism of MSCs for suppressing inflammation in AP is the anti-apoptosis effect [32, 33]. MSCs promote repair and angiogenesis via the stromal cell derived factor (SDF)-1 α /C-X-C chemokine receptor type 4 (CXCR4) axis [34]. The precise mechanism remains controversial, but several bioactive molecules secreted by MSCs have important roles. He et al. reported that tumor necrosis factor- α stimulated gene/protein 6 (TSG6) is secreted by MSCs [35]. Yin et al. showed that microvesicles from MSCs attenuate injury due to AP [36]. However, several studies have described that MSCs can migrate and implant in several organs including the pancreas [24, 35, 37]. Further studies are necessary to investigate the underlying mechanisms of MSCs in inflammation due to AP.

MSC therapy for chronic pancreatitis

In contrast to AP, only a few studies have investigated the effects of MSCs in a CP model (Table 2). Zhou et al. reported that umbilical cord-derived MSCs reduce pancreatic fibrosis in a dibutyltin dichloride-induced rat model of CP by suppressing inflammatory cytokines in the pancreas [38]. We have demonstrated that human amnion-

derived MSCs decrease monocyte chemotactic protein-1 (MCP-1) expression in the pancreas [33]. Pancreatic stellate cells are responsible for fibrosis in CP. We showed that conditioned medium obtained from human amnion-derived MSCs suppresses MCP-1 and IL-8 expression in pancreatic stellate cells. The precise mechanisms and roles of MSCs in CP remain unknown, and further studies are warranted in the future.

Perspectives

Numerous animal model studies have documented the therapeutic potential of MSCs and their safety and efficacy in vivo. However, their clinical application was hampered by several remaining issues, i.e., the quality of MSCs and their non-uniform effect due to the requirement for living donors and culture. Standardized methods to control the quality of MSC therapy should be established. The factors secreted by MSCs responsible for their effects are unknown and their kinetics should be elucidated. The optimal conditions for homing and cytokine production by MSCs should be elucidated. The optimal timing and dosing of MSC administration should be determined and the most responsive patient groups should be identified.

Table 2 MSC for animal model of chronic pancreatitis

Authors	MSCs source	Routes	Dose (cells)	Animal	Induction
Zhou [38]	Rat UC	IV	$2 \times 10^6/\text{kg}$	Rat	DBTC
Kawakubo [33]	Human amnion	IV	1×10^6	Rat	DBTC

MSC mesenchymal stem cell, BM bone marrow, DBTC dibutyltin dichloride, UC umbilical cord, IV intravenous

Conclusions

No human clinical trials have used MSCs to treat AP or CP. However, animal trials have revealed that MSC transplantation would be a novel therapy for AP and CP.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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