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# USE OF STEM CELLS IN ACUTE PANCREATITIS

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Acute pancreatitis carries a significant disease burden with no definite treatment. They are associated with local and systemic inflammation and lead to numerous complications. Stem cell therapy has been explored for treating other diseases and has gained momentum due to its implications for acute and chronic pancreatitis. Stem cell therapy not only has the potential to aid regeneration but can also prevent pancreatic injury to other organs along with the resultant complications. Stem cells appear to have immunomodulatory properties and clinical potential, as evidenced by numerous studies conducted on animal models. A literature search on the treatment of acute pancreatitis with stem cells was performed in various sections of the Internet. A search was conducted on the Web of Science, Elsevier Science Inc., Scopus, Cochrane Central Register of Controlled Trials, Medline, Pubmed, Google Scholar, etc. by keywords: acute pancreatitis, MSCs, stromal cells, pathogenesis, endogenous intoxication, hemostasis, lipoperoxidation. A theoretical analysis of the data from the reviewed articles was carried out. This review discusses commonly used stem cells and their respective properties that show promise for treating pancreatitis. The use of stem cells in medicine is at a preclinical level. Many experiments are carried out on animals, mainly rats. However, stem cells can not only accelerate the restoration of the organ but also degenerate into tumor neoplasms. Therefore, further study of their behavior is necessary, including in treating pancreatitis, a common disease that leads to a significant deterioration or blocking of the breakdown of nutrients in the small intestine and the endocrine function of the pancreas. The article provides a detailed analysis of the results of using stem cells to treat pancreatitis. The analysis of the main trends in the treatment of pancreatitis with stem cells is carried out and the immediate prospects for the introduction of new technologies in the field of clinical research are identified.

**Key words:** acute pancreatitis, stromal cells, pathogenesis, endogenous intoxication, hemostasis, lipoperoxidation.

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## ЗАСТОСУВАННЯ СТОВБУРОВИХ КЛІТИН ПРИ ГОСТРОМУ ПАНКРЕАТИТІ

Гострі панкреатити є значним тягарем захворювань, які не мають однозначного лікування. Вони супроводжуються місцевим та системним запаленням і призводять до численних ускладнень. Терапія стовбуровими клітинами була досліджена для лікування інших захворювань і набула поширення завдяки своїм можливостям для лікування гострого та хронічного панкреатиту. Терапія стовбуровими клітинами може не тільки сприяти регенерації, але й запобігти пошкодженню підшлункової залози, інших органів та пов'язаних з цим ускладнень. Стовбурові клітини мають імуномодулюючі властивості та клінічний потенціал, про що свідчать численні дослідження, проведені на тваринних моделях. Було проведено пошук літератури з лікування гострого панкреатиту стовбуровими клітинами у різних розділах Інтернету. Проведено пошук за базами Web of Science, Elsevier Science Inc., Scopus, Cochrane Central Register of Controlled Trials, Medline, Pubmed, Google Shcolar, etc. за ключовими словами: гострий панкреатит, МСК, стромальні клітини, патогенез, ендогенна інтоксикація, гемостаз, ліпоперіокислення. Проведено теоретичний аналіз даних статей, що рецензуються. У даному огляді розглядаються широко використовувані стовбурові клітини та їх властивості, перспективні для лікування панкреатиту. Використання стовбурових клітин у медицині знаходиться на доклінічному рівні. Багато експериментів проводяться на тваринах, переважно на щурах. Однак стовбурові клітини можуть не тільки прискорювати відновлення органу, а й перероджуватись у пухлинні новоутворення. Тому необхідно подальше вивчення їхньої поведінки, у тому числі при лікуванні панкреатиту – поширеного захворювання, яке призводить до значного погіршення або блокування розщеплення поживних речовин у тонкому кишечнику та ендокринній функції підшлункової залози. У статті подано докладний аналіз результатів використання стовбурових клітин у лікуванні панкреатиту. Проведено аналіз основних тенденцій у лікуванні панкреатиту стовбуровими клітинами та визначено найближчі перспективи впровадження нових технологій у галузь клінічних досліджень.

**Ключові слова:** гострий панкреатит, стромальні клітини, патогенез, ендогенна інтоксикація, гемостаз, ліпоперіокиснення.

Stem cell therapy has been considered for the treatment of many intractable diseases. MSCs are adult stem cells primarily isolated from bone marrow [12]. MSCs can self-renew and undergo multilineage differentiation [12]. According to the definition provided by the International Society for Cell Therapy, MSCs are characterized as plastic-adherent in standard culture conditions and can be differentiated in vitro into osteoblasts, chondroblasts, and adipocytes [13–15]. MSCs express specific surface markers, such as CD105, CD90, and CD73, but do not express CD45, CD34, CD14, CD11b, CD79 alpha, CD19, or HLA-DR. MSC-like cells have been isolated from other tissues, including the human placenta [16], peripheral blood [17], umbilical cord [18], adipose tissue [19], endometrium [20], and pancreas [12, 21, 22]. MSCs have been used to treat wound injury and acute inflammation because they engraft into wounds and contribute to the remodelling of injured tissues [12, 15]. MSCs reduce the acute inflammatory response via their immunomodulatory effect by secreting anti-inflammatory cytokines, suppressing proinflammatory cytokines, and regulating immune cell activation [23–25]. MSCs suppress T cell proliferation and B cell maturation and activate regulatory T cells to suppress the immune response in vitro further [26, 27]. MSCs

decrease chronic inflammation and subsequent fibrosis via multiple mechanisms, including the downregulation of the expression of TGF-β1, a major regulator of chronic inflammation and fibrosis [28, 29]. MSCs also attenuate local hypoxia and oxidative stress [30, 31]. MSCs decrease the secretion of collagen, which is the main constituent of the extracellular matrix (ECM), to ameliorate the excessive secretion of the ECM and its degradation during fibrosis [32, 33]. MSCs exert their immunosuppressive effect by decreasing the levels of anti-inflammatory cytokines and inhibiting the production of immunoglobulins and active immune cells [24, 25]. Furthermore, MSCs have been shown to specifically translocate to injured tissues and induce angiogenesis in ischemic tissues [26–30]. Given these advantages, MSCs are promising candidates for cell replacement therapy for tissue inflammation. in vitro into osteoblasts, chondroblasts, and adipocytes [13–15]. MSCs express specific stem cells primarily isolated from bone marrow [12]. MSCs can self-renew and undergo multilineage.

The incidence of acute pancreatitis (AP) is marked by increased annual morbidity, the polyetiological nature of the disease, the complexity of the pathogenetic mechanism, and the high mortality rate. Despite improvements in medicine, there has been no visible progress towards solving the problem [1, 2]. However, a detailed study of the pathogenetic processes of AP is needed. It is important to note that the leading cause of fatal outcomes of patients with AP is toxic lesions of vital organs and systems as a result of the formation of a systemic inflammatory response and endotoxemia, on the one hand, and inhibition of the functional potential of the detoxification system, on the other hand. This often occurs during the use of standard treatment and clinical reduction of the inflammatory process [3, 4]. Scientific interest in effective methods of therapy for patients with AP does not wane. The problem of improving the results of treatment of patients with destructive forms of pathology, the lethality that exceeds 30–80 %, is especially urgent [5]. Compared to conservative therapy, treating pathologies of internal organs using stem cells has been insufficiently studied [6]. Introducing stem cell transplantation methods into clinical practice has opened up a fundamentally new approach to managing many diseases. Regenerative medicine methods have not yet been widely used in toxicology. Therefore, experimental and clinical trials are needed to evaluate stem cell transplantation safety and efficacy in diseases caused by exposure to various toxicants in the body [14], leading (except for mild forms) to a violation of exo- and endocrine functions of the pancreas and, consequently, to a lack of formation of products of the breakdown of proteins, fats, and carbohydrates in the small intestine. It results in a gradual loss of working capacity, the development of disability, and a high risk of mortality. The latter is symptomatic and supportive therapy, including analgesic and anti-inflammatory drugs, enzymatic drugs, and diet. Full normalization of the work of the organ will require the restoration of the cellular tissue structure [21].

**Materials and methods.** A literature search on treating acute pancreatitis with stem cells was performed in various Internet sections. The search was conducted through the databases Web of Science, Elsevier Science Inc., Scopus, Cochrane Central Register of Controlled Trials, Medline, Pubmed, Google Scholar, etc. Theoretical analysis of the data of the reviewed articles was carried out. This review discusses commonly used stem cells and their respective properties that show promise for treating pancreatitis. The use of stem cells in medicine is at a preclinical level. The review summarizes the challenges stem cell therapy must overcome to be accepted worldwide. A wide variety of possibilities makes this cutting-edge therapy a turning point in modern medicine. Theoretical analysis of the data was carried out from 2019 to 2024.

The mechanisms of stem cell influence in the regeneration of tissues exposed to acute or chronic damage are not fully understood, but they definitely include regulating immune function to reduce inflammatory changes in the organ. Negative results of human stem cell treatment are known due to the risk of uncontrolled stem cell division and their degeneration into tumor cells. Therefore, at the level of preclinical and clinical research, it is essential to develop ways to transplant stem cells to achieve controlled differentiation of cells and study the mechanisms of acceleration of tissue regeneration after the introduction of source material and the interaction of unspecialized cells with their microenvironment [6].

Over the past 20 years, research into the development of pancreatic inflammation has made significant advances. It has been established that the causes of acute and chronic pancreatitis include lysis of pancreatic tissues from premature activation of proenzymes in acinar cells and long-standing inflammation of the organ, leading to the development of fibrosis, which can affect entire regions of the pancreas. This pathology destroys secretory parenchyma due to necrosis, apoptosis, inflammatory processes, and duct obstruction [8]. Some studies have shown that autoimmune mechanisms are actively involved in developing pancreatitis. In particular, an imbalance exists between pro- and anti-inflammatory cytokines [11].

Two main research directions can be distinguished when analyzing the possibilities of using stem cells in the treatment of AP: deepening the understanding of the pathogenesis of the disease and studying the mechanisms of regeneration in various therapy methods at the level of preclinical studies. Treating severe AP completely using conservative methods is impossible, which requires developing a differentiation method for progenitor cells. Therefore, there is an increased interest in applying stem cells in the therapeutic management of AP [4].

Stem Cell Types and the Potential for Pancreatic Self-Regeneration. Stem cell therapy research has focused on the multipotent type. Totipotent (zygotic cells) and pluripotent (embryonic cells) are characterized by a very high capacity for division and differentiation. Therefore, their development is difficult to control, and the spectrum of sources for obtaining starting material is limited. Multipotent mesenchymal stem cells (MMSCs), permanent in the adult body, are found in bone marrow and various tissues, functioning in tissue maintenance and regeneration. The advantages of their use are the identity of the genetic material with the organ to be repaired and, as a consequence, the absence of immune reactions [14]. The pancreas is known for its capacity for self-regeneration, the presence of which is presumably achieved through the presence of its MMSCs, but in relatively small numbers (1/5000 cells) [10], stem cells from the bone marrow [11] and/or using the biliary tree as a reservoir of undifferentiated cells [12]. Various cell types (ductal epithelium-associated, mesenchyme-like, nestin-expressing, pre-existing acinar cells) are considered possible organ tissue precursors [6]. However, the insufficiency of native components makes it necessary to investigate the effect of exogenous MMSC injections on the injured pancreas [13].

Preclinical Studies on the Use of MMSCs in AP.

Methods of administration of MMSCs and dosages from different literature sources differ during the preclinical research phase: Application of acetic acid (100 %) to the organ wall, L-arginine, Cerulein, or taurocholate to induce mild or severe AP, respectively, 4 % sodium taurocholate [ 9, 13, 15]. Rats were mainly used as experimental animals [9, 13, 16], and mice were used in some studies [17]. The routes of administering MMSCs are: Intraperitoneal/Optimal $2 \times 10^6$ cells twice daily, Tail vein administration /$1 \times 10^6$, Tail vein administration /100 and 1000 μg for mild and severe AP, respectively, Intradorsal penile vein of male rats/$2 \times 10^6$ per 100g [9, 13, 15].

Table 1

**Effect of MMSCs on rats with induced AP**

| Source and dose of MMSC | | Route of administration | Effects | Reference |
|---|---|---|---|---|
| Rat bone marrow | $1 \times 10^7$/ kg | Intraperitoneally | ↓ amylase, angiopoietin, TNFα, IL1, IL6; ↑ IL4, IL10. ↓ edema, PG necrosis due to ↑ expression of miR-181α-5p and suppression of TGF-β1. | [19] |
| | $1 \times 10^6$ | Femoral vein | ↓ amylase, TNFα, ↑ IL10. | [20] |
| | $5 \times 10^6$/ kg | Tail vein | ↓ amylase and lipase, edema, PG necrosis, TNFα, IL1, IL6; ↑ IL4, IL10, anti-apoptotic effect. | [21] |
| Human umbilical cord | $1 \times 10^7$ | | ↓ PG necrosis, ↑angiogenesis in PG. | [22] |
| Rat bone marrow | $1 \times 10^6$ | Tail vein and intraperitoneally | ↓ pancreatic swelling and inflammation, combined administration has a more pronounced effect. | [23] |
| | $1 \times 10^7$/ kg | Tail vein | Anti-apoptotic effect of PG due to stimulation of the secretion of endothelial growth factor A and angiogenesis. | [24] |
| | $1 \times 10^6$ | Jugular vein | Combination of MMSC and antioxidants improves pancreas regeneration and immune-boosting effect. | [25] |
| | $1 \times 10^7$/ kg | Tail vein | ↓ amylase and lipase, edema, infiltration and necrosis of PG, NF-κB, ↑ Nrf2 expression. | [26] |
| Human umbilical cord | $1 \times 10^7$ | Retrograde injection into the biliopancreatic duct | ↓ amylase and levels of the pro-inflammatory cytokines, TNFα treatment has increased the efficacy of vesicles from MMSCs, ↓ necroptosis of acinar cells along the *RIPK3/MLKL* axis. | [27] |

Note: PG – pancreatic gland, TNF – tumor necrosis factor, IL – interleukin, TGF-β1 – transforming growth factor, NF-κB – factor in the expression of genes of the immune response, apoptosis, and cell cycle, Nrf2 – erythroid-2 factor 2 (antioxidant regulator).

At the stage of preclinical studies, various positive effects of MMSC administration in artificially induced different forms of pancreatitis were observed: attenuation of acute pancreatic damage (edema, necrosis, infiltration), improved survival of acinar cells and reduced degeneration; reduction (timing and severity) of the inflammatory process, its inhibition, blocking the systemic inflammatory response; suppression of cytotoxic T-lymphocyte proliferation, in particular $CD3^+$ T-cells, natural killer cells and dendritic cells; reduction of pro-inflammatory cytokines and secretion of growth-stimulating factors, a

decrease of serum amylase, lipase, and myeloperoxidase; decreased translocation of NF-κB p65 (one of the transcription factors of immune response and apoptosis genes), decreased concentration/expression of inflammatory factors (IL-1α, 1β, 6 and TNF-α), increased levels of Foxp3 (a marker of regulatory T-cells) [9, 17, 21]. Using labeled MMSCs, a high level of cell concentration in the pancreas after their injection is exposed [16, 17]. In the MSCs intervention group, transwell plates were inserted into the poles, and the third-generation MSCs were seeded at a density of 1 × 106 cells/mL. The culture medium in the insert and the six-pole plate were fused, establishing the co-culture system of MSCs and acinar cells.

The results of studies by various authors on the effects of MMSCs on modeled AP for 2019–2023 are presented in Table 1.

MMSC cells come from a wide range of sources: autologous – from bone marrow, allogeneic – from umbilical cord blood, placenta, etc. Due to different sources of cells and different methods of collection and preparation, it is impossible to establish a single standard method of efficiency evaluation. MSCs in a rat model of AP have shown that MSCs reduce serum amylase, urea nitrogen, and creatinine [23].

The effect of human stress-resistant human MMSCs (Muse) and SSEA-3 (+) collected from mesenchymal stem cells (MSCs) containing embryonic antigen 3 was investigated. Muse cells and normal human MMSCs ($1.0\times10^5$ cells) were injected into a C57BL/6 mouse model through the jugular vein 6 h after AP induction with taurocholate. It has been revealed that intravenous injection of human Muse cells effectively attenuates edema, inflammation, and apoptosis in the acute phase of AP [31].

MSCs were long spindle-shaped and had potent proliferation activity. Flow cytometry showed umbilical cord-derived MSCs had no expressions of CD45, CD34, CD11b, CD19, and HLA-DR (0.61 %) but high expressions of CD44 (99.99 %), CD73 (99.98 %), CD90 (99.99 %) and CD105 (99.97 %). The induction differentiation experiment by Hong-Bo Meng, Jian Gong et al. showed that MSCs had osteogenesis, adipogenesis, and chondrogenesis capabilities. These findings suggest these cells are MSCs. Pathological examination of the pancreas after MSC transplantation At different time points, there was no edema, infiltration of inflammatory cells, bleeding, or necrosis in the pancreatic lobules in the control group. In the SAP group, pancreatic edema was observed immediately after surgery. One day after surgery, evident expansion of the alveolar septum, parenchymal bleeding, and infiltration of inflammatory cells were noted. The pancreatic parenchymal necrosis (focal patchy necrosis) deteriorated three days after surgery. Five days after surgery, the necrotic area merged, and tubular complexes were observed. In the SAP+MSCs group, pancreatic edema, bleeding, necrosis, and infiltration were also noted, but these pathological changes were milder than in the SAP group. Moreover, the pathological changes in the SAP+MSCs group improved over time, and a few fibrous tissues were observed. Pathological scoring was performed based on pancreatic parenchymal necrosis. Results showed the pathological scores of pancreatic edema, pancreatic parenchymal bleeding and necrosis, and infiltration of inflammatory cells in the SAP group were markedly higher than those in the control group, which was stable and reliable. After MSC transplantation, the serum amylase level reduced to 1080±172 mU/ml, 1020±283.5 mU/ml, and 1180±278.6 mU/ml on days 1, 3, and 5, respectively, which were significantly lower than those in the SAP group (P0.05), but reduced markedly since day 3 (day 3: 1880±204 mU/ml; day 5: 2160±387.8 mU/ml) when compared with SAP group.

Clinical trials. Despite the established efficacy and safety of different types of MMSCs at the preclinical stage against AP, their clinical application has several restrictions: the mechanisms of potential therapeutic action of MMSCs have not been elucidated, adverse side effects and long-term consequences, as well as the risk of oncogenicity of MMSCs have not been sufficiently studied [29]. The study of the therapeutic effect of using MMSCs in correcting homeostatic disorders of severe AP in patients aged 21–55 years has been carried out. It is found that the combination of standard therapy with the use of endo-video surgical intervention and mesenchymal stem cell management in the early period shows a relatively rapid correction of homeostatic disorders of AP, but it is necessary to conduct further research to optimize the dose of cells, the period of application and the number of injections [30, 31]. In clinical studies, it is shown that intravenous administration of cord blood with stem cells, including MMSCs, reduces the degree of intoxication and anemia in patients with necrotizing pancreatitis, normalizes blood glucose and protein profile, reduces the symptoms of cytolytic syndrome by the level of decrease in the activity of aspartate aminotransferase, alanine aminotransferase and gamma-glutamyltranspeptidase, lactate dehydrogenase [32]. When cord tissue is transplanted, the effect is achieved through local action due to the possible migration of endothelial stem cells and MMSCs. Stem cells probably stimulate the obliteration of pancreatic ducts to prevent the formation of postnecrotic pancreatic fistulas and cysts [23, 29]. It has been determined that the concentration of bone marrow MSCs in peripheral blood in patients with AP is lower than in healthy people,

indirectly indicating their mobilization in the inflammation zone [21, 27]. In addition, it has been detected that MSCs obtained from human bone marrow in patients with moderate and severe AP decrease the initial level of C-reactive protein, which is a quantitative and sensitive indicator of inflammation [21, 31].

Table 2

**Studies using stem cell therapy in acute pancreatitis**

| Study conducted by | Source of stem cells | Triggering agent | Animal | Mode of delivery | Stem cell quantity | Outcomes |
|---|---|---|---|---|---|---|
| Tu et al. | Bone marrow (rat) | Sodium deoxy-cholate | Rat | Caudal vein injection | $1\times10^6$ cells/mL | Decreased levels of malonaldehyde, amylase, Lactate dehydrogenase, IL-6, TNF-α Increased superoxide dismutase, survival rate of pancreatic acinar cells, IL-10 Decreased injury of small intestinal epithelium and stimulation of proliferation of enteric epithelium. |
| Wang et al. | Bone marrow (rat) | 5 % sodium taurocholate | Rat | Caudal vein injection | $1\times10^6$ cells/mL | Decreased levels of myeloperoxidase, amylase Decreased expression of mRNA of TNF-α and substance P Decreased pulmonary edema, injury and inflammation. |
| Sun et al. | Bone marrow (rat) | L-arginine | Rat | Intraperitoneal injection | $5\times10^6$ cells | Decreased expression of TNF-α mRNA and IL-1β mRNA Decreased pancreatic and small intestinal injury Effects are indirect and not by differentiation into various cell lines. |
| Yang et al. | Umbilical cord (human) | 5 % sodium taurocholate | Rat | Tail vein injection | Variable ($5\times10^6$ cells/kg at 0 h, 1 h, 6 h and 12 h in one group and $5\times10^4$ cells/kg $5\times10^5$ cells/kg $1\times10^7$ cells/kg at 1 h after induction in other groups) | Decreased mortality rates, wet-dry pancreatic weight, ascites, amylase levels. Decreased levels of TNF-α and INF-γ. Decreased evidence of injury of pancreas and lungs on pathology examination. Time and dose-dependent reduction in pancreatic injury seen. |
| Chen et al. | Bone marrow (rat) | 5 % sodium taurocholate | Rat | Tail vein injection | $1\times10^6$ cells/mL | Decreased blood urea nitrogen, creatinine, amylase levels<br>Decreased damage of pancreatic tissue and renal interstitial capillary barrier<br>Increased expression of aquaporin 1 in the kidney (helps promote renal reabsorption of water and hence circulating blood volume). |
| Cui et al. | Bone marrow (mice) | L-arginine | Mice | Tail vein injection | $2\times10^7$ cells | Decreased amylase levels, mortality rates. Decreased gross and microscopic evidence of pathological pancreatic damage |
| Meng et al. | Umbilical cord (human) | 3 % sodium taurocholate | Rat | Tail vein injection | $1\times10^7$ cells | Decreased serum lipase and amylase levels. Decreased features of pancreatic injury (edema, hemorrhage, necrosis, inflammatory cell infiltrate). |
| Hua et al. | Umbilical cord (human) | 3 % sodium taurocholate | Rat | Tail vein injection | $2\times10^6$ cells | Decreased serum lipase and amylase levels Decreased pancreatic injury (lower pancreatitis severity scores). Decreased pro-inflammatory cytokines (TNF-α, IFN-γ, IL-1β, and IL-6). Angiopoietin-1 (ANGPT1)-transfected MSCs stimulate pancreatic angiogenesis. Synergistic role of MSCs and ANGPT1. |
| Jung et al. | Bone marrow (human) | Cerulein and lipopoly saccharide | Rat | Intra-peritoneal injection | $1\times10^6$ cells | Decreased pancreatic edema, necrosis, inflammatory infiltration, malondialdehyde. Increased levels of glutathione peroxidase, superoxide dismutase. Decreased expression of proinflammatory mediators and cytokines Increased expression of SOX9. |
| Kim et al. | Adipose tissue (canine) | 3 % sodium taurocholate | Rat | Injection into common biliopancreatic duct | $1\times10^7$ cells/kg | Decreased acinar cell necrosis, edema, inflammation. Decreased expression of the pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12, IL-17, and IL-23 IFN-γ). Increased expression of the anti-inflammatory cytokines (IL-4, IL-10). Decreased numbers of CD 3(+) T cells and increased numbers of forkhead box P3-positive T cells. |
| Zhao et al. | Bone marrow (rat) | 3 % sodium taurocholate | Rat | Injection into the biliopan-creatic duct | $5–7\times10^7$ cells | Increased rates of survival. Decreased expression of TNF-α and IL-1β mRNA. |
| Kawakubo et al. | Amniotic membranes (human) | Dibutyltin dichloride | Rat | Intravenous | $1\times10^6$ cells | Inhibition of pancreatic stellate cell activation Inhibition of pancreatic stellate cell activation Decreased histological score, reduced infiltration of CD68-positive macrophages. Reduced expression of MCP-1 and amylase. |

All studies were performed in rodents and showed pronounced heterogeneity in the outcome assessment; hence, conducting a meta-analysis was not feasible. Heterogeneity was observed in the technique used to induce pancreatitis, the type of MSCs used, the time of therapy after the disease onset, the source of the MSCs (human or murine), and the dose of the MSCs. AP is a common acute abdominal disease characterized by self-digestion, edema, bleeding, and necrosis (features of inflammation) due to the activation of trypsin in the pancreas. The incidence of AP increases with the elevation of living standards [19]. Less than 20 % of patients with AP may develop SAP, which has a lot of complications and high mortality. Thus, SAP has been a dangerous and refractory acute abdominal disease [1]. Currently, SAP is managed with traditional supportive therapy or surgical interventions, and no effective strategy has been developed for treating SAP to date. Cell therapy with MSCs has been found to promote the repair of acute and chronic injuries, regulate immune function, and attenuate inflammatory response [8]. It has been confirmed that MSCs can improve the inflammatory response in the liver, kidney, and lung and have favorable promise in clinical application in myocardial infarction, Crohn's disease, and organ transplantation. Studies have shown that multiple inflammatory cytokines are involved in the pathogenesis of SAP, including pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and antiinflammatory cytokines (IL-4, IL-10) [20, 21]. Thus, MSCs have the potential for the treatment of pancreatitis due to the anti-inflammatory effect of MSCs. In addition, MSCs can be induced to differentiate into different cell types, including insulin-secreting and endothelial cells [22, 23]. Thus, it is feasible to promote pancreatic regeneration and repair the microvascular endothelium of the pancreas with MSCs. Retrograde cholangiopancreatic injection of sodium taurocholate was employed to induce acute obstructive pancreatitis, similar to the pathogenesis of clinical pancreatitis. This animal model is easy to establish and feasible. The pathological examination and pancreatic enzyme detection showed this animal model was stable. The main pathological findings were pancreatic edema, infiltration of massive inflammatory cells, pancreatic parenchymal bleeding, and acinar cell necrosis. The umbilical cord-derived MSCs were injected into SAP rats via the tail vein, and results showed the serum levels of amylase and lipase reduced, pancreatic pathology and acinar cell apoptosis improved, serum levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) reduced, and those of anti-inflammatory cytokines increased (IL-4, IL-10). These findings suggest that MSCs have favorable therapeutic effects on SAP. When compared with the SAP group, MSCs transplantation significantly reduced serum levels of amylase and lipase (amylase: 48 % on day 1; 55 % on day 3, 60 % on day 5; lipase: 20 % on day 1, 50 % on day 3, 53 % on day 5), suggesting that MSCs transplantation may protect the structural integrity of acinar cells. MSCs transplantation facilitates the recovery of pancreatic pathology, characterized by improved pancreatic edema, reduction of inflammatory cells, and attenuation of pancreatic parenchymal bleeding and necrosis. However, the specific mechanisms are still poorly understood. Previous studies have shown that bone marrow-derived MSCs can migrate into the injured pancreas and differentiate into pancreatic cells to repair the injured pancreas. In the SAP, more MSCs migrate into the pancreas. This suggests that the homing ability of MSCs is related to the severity of injury [24]. However, in recent years, MSCs have been found to secret some cytokines (IL10, TGF-β, IL-1Reg, and HGF) in a paracrine-dependent manner to exert the anti-inflammatory effect [25]. More recent studies reveal that the TNF-α and IL-1 may activate MSCs, which then secret the anti-inflammatory protein TSG-6, which is found to be involved in the anti-inflammatory effect of MSCs [26-28]. Our results showed that MSCs transplantation reduced the serum levels of pro-inflammatory cytokines and increased those of anti-inflammatory cytokines, consistent with the anti-inflammatory effect of TSG-6. Thus, the therapeutic effect of MSCs transplantation might be associated with the TSG-6 secreted by MSCs. UC-MSCs for treatment of severe acute pancreatitis 2711 Int J Clin Exp Pathol 2013;6(12):2703-2712 Pancreatic acinar cell apoptosis plays an important role in the pathogenesis of SAP. Enacting pancreatic acinar cell apoptosis is regarded as a protective response to inflammation-related stimulation in cells [29]. The apoptosis and necrosis of pancreatic acinar cells have reciprocal transformation. Thus, reducing the apoptotic acinar cells may also attenuate the necrosis of acinar cells to a certain extent [30]. In the present study, many apoptotic acinar cells were observed in the pancreas of SAP rats, and the number of apoptotic acinar cells increased over time. However, in the SAP+MSCs group, the apoptotic acinar cells were reduced significantly compared with SAP. This suggests that MSCs transplantation attenuates pancreatitis and inhibits apoptotic initiation, which prevents further attack on acinar cells and improves acinar cell necrosis. The present study transplants umbilical cord-derived MSCs into rats with SAP. Results demonstrate that MSCs transplantation may protect the structural integration of acinar cells, improve pancreatic pathology, regulate inflammatory response, and attenuate acinar cell apoptosis. The specific mechanism underlying the therapeutic effect of MSCs transplantation may be attributed to the homing and transdifferentiation of MSCs or the paracrine effect of MSCs.

However, more studies are required to investigate the exact mechanism underlying the therapeutic efficacy of stem cells, which may provide evidence for a novel strategy for the treatment of SAP. Due to the lack of consistency, determining the most effective form of MSC therapy for pancreatitis is challenging. Similarly, none of the studies investigating chronic pancreatitis evaluated the efficacy of MSC therapy in a dose-dependent manner or followed up on the disease progression. The included studies failed to address selection and detection biases using techniques such as randomization, blinding, and sample size calculations. These limitations in the study methodologies may have led to an exaggeration of the reported therapeutic effect. Thus, these factors should be evaluated in future preclinical studies to ensure their validity because the currently available data do not sufficiently warrant the use of MSCs in clinical trials. In addition to morbidity, mortality is an important parameter in evaluating new therapies, particularly in a debilitating diagnosis, such as severe acute pancreatitis. Mortality is a frequent sequela (may reach up to 30–47 %) of acute pancreatitis due to the complications of organ failure and tissue necrosis. Most of the evaluated studies did not assess mortality after the MSC infusion. Because the first 24 hours after the onset of acute pancreatitis are critical for prognosis, the therapeutic effect of the injected MSCs should be evaluated within this time frame. Studies investigating MSC therapy have shown that the time frame for the maximum therapeutic effect is an important determining factor, and early intervention is almost always necessary. Indeed, only a few studies evaluated the outcome of MSC administration within 24 hours of the induction of severe acute pancreatitis.

Thus, multipotent mesenchymal stem cells can reduce the expression of various inflammatory factors, suppress autoimmune responses, and promote regeneration of various tissues/organs. The potential of stem cells for acute pancreatitis has been preclinically investigated to a greater extent. The introduction of stem cells into clinical practice in the treatment of acute pancreatitis requires further studies to determine the etiology of the disease, the influence of stem cells on the preclinical and clinical levels, as well as to improve minimally invasive methods of intervention, selection of methods of cell material delivery and dosage.

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