Stem cell therapy: a potential for the perils of pancreatitis

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ABSTRACT

Acute and chronic pancreatitides carry 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, 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. This review discusses commonly used stem cells and their respective properties that show promise for treating pancreatitis.

Keywords: *Stem cell, pancreas, therapy, treatment*

INTRODUCTION

Pancreatitis is a disease process that carries significant morbidity and mortality. Acute pancreatitis can become recurrent and progress to chronic pancreatitis. It is characterized by acute onset of an inflammatory process that leads to autodigestion of the pancreas. An acute injury to the pancreas lead to cascading events that involve stimulation or production of digestive enzymes that damage the pancreatic tissue, resulting in an inflammatory response (1, 2). Injury to the pancreatic acinar cells allows for the release of pancreatic enzymes such as elastase, trypsin, and chymotrypsin (2). The release of these enzymes into the pancreatic tissue leads to their activation and these activated enzymes digest the pancreatic tissue (2). There is infiltration of inflammatory cells and proinflammatory markers such as interleukin (IL)-6, interferon gamma, and tumor necrosis factor alpha are also produced (1, 2). Acute pancreatitis can be of various types and approximately 85% cases are of acute interstitial edematous pancreatitis and about 15% of necrotizing pancreatitis (3). Acute pancreatitis can progress from a localized inflammatory process within the pancreas to more widespread inflammation leading to a multiorgan failure (4). Approximately 20% cases are severe, in which the mortality rates can reach up to 30% once multiorgan dysfunction occurs (5). The prognosis depends on whether there is a multiorgan failure present along with any infected pancreatic necrosis, and in such cases, the mortality can be as high as 15-30% (6). Oxidative stress is also believed to play a role in cases of acute pancreatitis and this was depicted in a study conducted by Esrefoglu et al. (7, 8) in cerulein-induced pancreatitis along with the potential benefits of antioxidants such as melatonin, N-acetyl cysteine, and ascorbic acid. An important indicator of chronic pancreatitis is fibrosis of the pancreatic tissue that leads to secondary to irreversible damage due to persistent inflammation (9). Due to inflammation and fibrosis, there is damage to both endocrine and exocrine portions of the pancreas. The inflammatory response leads to the activation of the myofibroblast-like cells along with the pancreatic stellate cells, which are located in the exocrine portion of the pancreas (10). They travel to the areas of insult and aid in the process of regeneration and repair; however, due to the presence of oxidative stress, there is necrosis and fibrosis of the acini (10). Damage to the pancreatic ducts leads to blockage due to the accumulation of protein plugs (10). This entire process ultimately leads to scarring and fibrosis and resultant dysfunction of the pancreas. Both acute and chronic pancreatitis can lead to local and systemic complications. Therapeutic options are limited and primarily focus on supportive care and control of the symptomatology and attempt to prevent the complications from developing further.

An emerging novel concept that is being extensively studied is the use of stem cells for numerous gastrointestinal disease processes including acute and chronic pancreatitis. Stem cells can be used to repair as well as replace the damaged tissue, and also carry the ability to influence

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the immunological response as well as inflammatory response (11-13). Mesenchymal stem cells (MSCs) are also known as multipotent stem cells or adult stem cells (9). They can regenerate and differentiate into several cell lineages including mesoderm (osteocytes, chondrocytes, and adipocytes) as well as endoderm and ectoderm (14). As these multipotent stem cells are genetic replicas of their hosts, they do not induce immunological reactions (9). There are several limitations to their use as well as potential consequences such as uncontrolled replication and hence further research and testing need to be performed. Thus far, the trials have primarily been carried out in animal models but do show promising results.

Types of Stem Cells

Pancreatic Stem Cells

It remains unclear as to whether or not there are any stem cells in the postnatal pancreas as various studies have shown conflicting evidence. The studies that do reveal that there may exist stem cells in the pancreatic tissue also attest to their rarity. Scarce populations of stem cells have been detected that carry OCT4 and OX2, which are the pluripotency genes that may potentially allow for differentiation into various cell lineages (15-17). In a study conducted by Smukler et al. (15), stem cells derived from the pancreas were very limited (1 in 5000 pancreatic cells) though they were able to give various cells such as endocrine cells and neurons. On the contrary, the study performed by Gong et al. (18) with nestin (stem cell marker) revealed evidence that suggested the pancreas does not harbor stem cells and any stem cells identified may come from the bone marrow (BM) instead. This implies that stem cells originating from the BM will aid in the repair and regeneration of damaged pancreatic tissues (18). There is also research that reveals that the biliary tree is a source of stem cells for the pancreas as shown by Wang et al. (19). Their study depicted that the pancreatic and biliary systems are closely linked to each other and that there are stem cells always available to give rise to devoted pancreatic cell types such as pancreatic ducts and glands (9, 19). The postnatal pancreas is believed to only have committed precursors that are located in the ducts and glands (20-22). During prenatal development, the stage of the primary transition pancreas, there are multipotent stem cells present that can give rise to all epithelial cell lineages of the parenchyma (23, 24). During the secondary transition process, the epithelium extends into the adjacent mesenchyme with the formation of a structure with a trunk and a tip resembling that of a tree (25, 26). The precursors in the trunk can give rise to the endocrine as well as the duct cells with the tips forming the acini (9, 24, 27, 28). These endocrine cells then migrate to form the mature islet cells, whereas the remaining cells form the pancreatic duct (29-32). The process of pancreatic regeneration consists of proliferation and the subsequent delineation into pancreatic cell precursors (33).

MAIN POINTS

- *Stem cell therapy is being explored for its therapeutic and research potential across the medical field and could have benefit in pancreatitis as well.*
- *In both acute and chronic pancreatitis, stem cells may be used due to their immunomodulatory properties.*
- *Stem cells may help to prevent pancreatic damage, fibrosis, and suppresses inflammation along with a reduction in markers of inflammation and cell injury.*

Clonogenic cells with the ability to differentiate into multiple lineages, as mentioned above, have rarely been in the postnatal pancreas and the ones seen have been best described in the pancreatic ducts (34). The centriacinar cell is specialized (situated at the junction of a terminal duct and an acinus) and can form a "pancreatosphere" in vitro and can proliferate in vivo under the stress of injury (35). These structures also had the potential to differentiate into both the endocrine and exocrine portions of the pancreas when used in an adult mouse study (35).

Mesenchymal stem cells

These can be derived from multiple tissues such as adipose tissue, amniotic fluid, BM, lung, liver, kidney, and skeletal muscle (9). Sources such as BM, umbilical cord blood, placenta, and adipose tissue are relatively easier to obtain and can yield an abundant amount of stem cells (9). They can give rise to a multitude of cell lines depending on the circumstances (9). They possess not only the capability to aid regeneration and repair of injured tissues but can also decrease inflammatory mediators and impede the immunological response (9). They hamper the proliferation of T and B cells as well as decrease the terminal differentiation of the B cells (9). They exert immunomodulatory effects on other cells such as macrophages and natural killer (NK) cells as well (9). The following is a brief overview of common sources of harvesting the MSCs:

Bone marrow: There are many studies on animals that have used MSCs derived from the BM for treatment in pancreatitis with resultant beneficial effects. Cui et al.

(36) recruited BM stem cells by use of granulocyte colony-stimulating factor (G-CSF) and then transplanted them into mice with severe acute pancreatitis (9). They noted that amylase level and mortality rates were lower in the mice that received stem cell therapy (9, 36). The ability of MSCs to ameliorate insult to the small intestinal epithelium as well as pancreatic acini was seen by Tu et al. (37). There was a decrease in widespread inflammation as well as stimulation of proliferation of small intestinal epithelium (9, 37). They also noted that MSCs could decrease oxidative stress by preventing lipid peroxidation, ensuring membrane stability and augmenting the activity of free radicals derived from oxygen (9, 37). Reduction in renal insult from the MSC therapy as a result of decreasing the disruption of the interstitial capillary endothelial barrier and increased expression of a marker called AQP1 (Aquaporin 1) was seen in the study performed by Chen et al. (9, 38). Sun et al. (39) injected BM-derived MSCs within the peritoneum of rats and saw that there was decreased expression of proinflammatory tumor necrosis factor alpha (TNFα) messenger Ribonucleic Acid (mRNA) and IL-1β mRNA (9). Their study suggests that therapeutic benefits that are derived from the use of MSCs are indirect and not by mere differentiation into particular cells (9, 39). Lung injury induced by acute pancreatitis was noted to be decreased when MSCs were used by Wang et al on a study conducted on rats (9,40). Pulmonary edema, as well as serum amylase levels along with TNFα expression, was decreased (9,40). BM MSCs may aid regeneration and repair of damaged pancreatic tissue by adding to the pancreatic stellate cell numbers (9). By regenerating the injured pancreas, they decreased edema and pancreatic infiltration of inflammatory cells (9). Jung et al, however, noted that MSCs were beneficial in acute pancreatitis as they localized to the site of damaged pancreatic tissue and decreased the inflammatory response by stimulating the apoptosis of CD4 + (cluster of differentiation 4) cells instead of through regeneration of cells (9, 41). The MSCs increased the expression of forkhead box P3-positive [Foxp3(+)] cells, which is a regulatory T cell marker and decreased CD3+ (cluster of differentiation 3) T cells within the pancreas (9, 30). Hence, this suggests that they exert beneficial effects in pancreatitis through immunomodulatory activities instead of regeneration.

Adipose tissue: These cells localize to injured tissue and they protect the injured cells by impeding the release of inflammatory mediators such as cytokines, hampering further inflammation (9). The migration of these stem cells to the areas of injury is facilitated by chemokines and growth factors as shown in the study by Baek et al (42). Another study was performed by Kim et al. (43) in which MSCs derived from canine adipose tissue were used therapeutically in cases of severe acute pancreatitis in rats. There was decreased edema of the pancreas, necrosis of acinar cells, and inflammatory cell infiltration (43). Expression of proinflammatory cytokines (tumor necrosis factor-α, IL-1β, IL-6, IL-12, IL-17, and -IL23 and interferon-γ) was reduced while that of antiinflammatory mediators was increased (IL-4 and IL-10) along with decreased CD3 (+) T cells and increased Foxp3 (+) cells (43). This emphasizes the immunomodulatory and anti-inflammatory effects of the MSCs.

Umbilical cord: Similar to other MSCs, those derived from the umbilical cord have also shown therapeutic benefit in pancreatitis. Yang et al. (44) conducted a study on rats using umbilical cord stem cells that showed a significant reduction in mortality rates in rats with severe acute pancreatitis (10% in those who received the MSC therapy vs 58% in those who did not) along with reductions in the pancreatic weight, serum amylase levels as well as ascites. The study also revealed that the umbilical cord-derived stem cells were not able to give rise to other cell lines within 24 hours and hence their protective benefit is likely due to immunomodulatory activities carried out via paracrine effects instead of via differentiation (9, 44). Umbilical cord stem cells can also be effective for chronic pancreatitis as evidenced by Zhou et al. (45) with decreased histological scores and fibrosis as well as prevention of pancreatic stellate cell activation (9).

Induced Pluripotent Stem Cells

Another form of stem cells, which have emerged fairly recently, are induced pluripotent stem cells (iPSCs). These were first postulated by researchers at Kyoto University to reprogram already-differentiated adult somatic cells (46). Early forms of approach to achieving this were through transfecting genetic material that codes for certain factors that are deemed to be essential in early embryonic development and maintaining pluropotentiality. Examples of genes include Oct4, Sox2, Klf4, Nanog, and Lin28. Using some combination of these genes, researchers have been able to create iPSCs very similar to embryonic stem cells in rat fibroblasts as well as human cells. Since then, further research has allowed for a better understanding of optimal conditions, including using certain kinds of somatic cells, viral factors used to transfect DNA data into desired cells, and controlling the expression of the aforementioned factors (47). These factors play a role in how the iPSCs differentiate into desired cell lines and this was demonstrated by Hu et al. (48) wherein

neural cells derived through iPSCs had a lower efficiency and a broader variability when compared with embryonic stem cells. This is shown by further studies that demonstrated similar problems in iPSC-derived cardiomyocytes compared with that of embryonic stem cells in both human-derived stem cells (49) as well as murine (50,51). In addition, for our focus of study, there is a lack of current basic research on iPSC used in amelioration of pancreatitis, acute or chronic. However, there is in vitro evidence of differentiation of iPSC into productive β cells of pancreas (52,53).

Clinical and Research Consequences

Stem cell therapy for both acute and chronic pancreatitis is promising as evidenced by several studies conducted on animals. Human studies have not yet been performed thus far. In both acute and chronic pancreatitis, there is intense localized as well as systemic inflammation, and as a result of this, the devastating complications and damage to the pancreas ensue. Hence, stem cells are now believed to play a potential therapeutic role in both types of pancreatitis. The stem cells can be harvested from various sources but the most readily available are those of the adipose tissue, BM, and the umbilical cord (9,54). Studies for acute and chronic pancreatitis have been carried out by inducing pancreatitis with various forms of chemicals. MSCs have numerous therapeutic benefits including the ability to dampen inflammatory response, apoptosis along with fibrosis even without the process of differentiation into cell lines, and aiding in regeneration (54). Unlike embryonic stem cells and inducible pluripotent stem cells, MSCs do not necessitate differentiation into various cell types to aid in tissue injury or disease processes (54). MSCs decrease the expression of proinflammatory cytokines (tumor necrosis factor-α, IL-1β, IL-6, IL-12, IL-17, and -IL23 and interferon-γ) and increase the expression of anti-inflammatory cytokines (IL-4 and IL-10), hence suppressing inflammatory response (43). They also serve to immunomodulate the cell populations as they increase Foxp3 (+) cells and decrease CD3 (+) T cells (43). The study by Yang et al. (44) also revealed that this ability to inhibit inflammation correlates with the dose and the timing of transplantation of the MSCs. The greater the dose and the earlier the MSCs are administered after the onset of pancreatitis, the more pronounced the anti-inflammatory effects (44). Other markers that indicate that MSCs limit the degree of pancreatic damage are serum amylase, lipase levels, and myeloperoxidase levels. These are all shown to be decreased in cases of pancreatitis treated with MSCs (55). There is a reduction in pancreatic edema and histological scores of fibrosis and damage (54, 55). The stem cells are recruited to the areas of pancreatic injury and the degree of recruitment is dependent on the amount of tissue damage that has occurred (41, 55). Studies such as those carried out by Sun et al and Kawakubo et al, among others, show benefits in cases of chronic pancreatitis. In the study by Zhou et al. (45), they noted that pancreatic fibrosis was reduced as a result of inhibition of proinflammatory cytokines (45). Sun et al. (56) recently revealed that the use of stem cells harvested from the adipose tissue in mice with chronic pancreatitis resulted in decreased pancreatic damage as well as fibrosis and apoptosis. The adipose tissue migrated to sites of injury in the pancreatic tissue and gave rise to amylase cells and aided in the retention of the pancreatic morphology and the prevention of damage as well as inhibition of fibrosis (56).

Immunogenicity/Tumorigenicity of MSC

Usage of MSCs as a therapeutic intervention for their tissue forming as well as their immunomodulatory potential, though promising, begets the question of safety. More specifically, allogenic or xenogenic sources of MSCs would be expected to have immunogenic potential (57-60). In vitro studies of the MSC demonstrate that they have very weak immunogenicity. Flow cytometry studies of obtained MSCs lack, as Grinemo et al. (57) put it, MHC (major histocompatibility complex) class II expression on the cell surface and co-1stimulatory molecules (example: B7-1, B7-2, CD40, or CD40L) that are necessary for immune response, which essentially makes them immunologically inert and even immunosuppressive. Le Blanc et al. (58) demonstrated that in vitro, both undifferentiated and differentiated MSC do not stimulate allogenic lymphocytes. However, in vivo, Poncelet et al. (60) demonstrated cellular as well as humoral responses to transplantation of allogenic (swine) MSC, which was also previously seen in allogeneic murine MSC transplants (61).

In vivo studies of xenogenic MSC transplant resulted in outright rejection as demonstrated by Grinnemo et al. (61) in multiple studies, which inoculated mice with human embryonic stem cells (HESC). In one particular study, this team demonstrated that xenogenic transplants of HESC resulted in rejection in six weeks in immune-incompetent mice who were also receiving tacrolimus (62).

In contrast, studies that explored the use of allogeneic stem cell transplant did show short-term survival and benefit before complete rejection. Intracardiac transplantation of allogenic BM MSC in rats with an induced MI (myocardial infarction) resulted in restored cardiac

function as long as three months. However, five weeks after transplantation, the rats had formed cellular and humoral defenses against the MSC, which resulted in rejection (62). Furthermore, in rats who received an allogeneic heart transplant that was also inoculated with BM MSC from the same host did not show any evidence of prolonged graft survival. In the same study, rats that were also immunosuppressed with cyclosporine A accelerated the graft rejection. Authors postulated that this may be due to the upregulation of MHC class I/II molecules that observed under immunohistochemistry (63). This was also observed in the study by Huang et al (64). In a slightly different scenario, irradiated mice that were transplanted with BM along with allogeneic BM MSC demonstrated a proliferative response of host spleen cells and subsequent BM graft failure (64).

One of the implications of the MSC therapy that has been explored is its ability to differentiate and essentially form new functioning tissue. However, their longevity is questionable. When looking at possible sources of MSC, xenogenic transplants have proved to be unworthy (57, 61). Furthermore, even allogeneic transplants have eventually been completely rejected as shown in studies by Huang et al. (64) and Nauta et al. (59). In the study by Huang et al. (64), allogeneic MSC was detected only as late as five weeks. Accordingly, B6 mice treated with BALB/b MSC (allogeneic transplant) were rejected within three days in the study by Nauta et al (59). Although syngeneic MSC survived longer and presumably exerted immunomodulatory effects longer (as seen by significantly higher BM engraftment), they were also ultimately eliminated (59). Autologous stem cell proliferation was attempted by Cui et al. (36) but did not reach the same level of localization and proliferation as direct inoculation of allogeneic stem cells.

Hence, the MSCs particularly those from allogenic or xenogenic sources can induce the development of immunological responses (65). These immune responses can be either an acute humoral or a cell-mediated immune response or a combination of both, hence resulting in rejection of the transplanted cells (65). There has also been a concern that they can have tumorigenic potential given their role in replication and proliferation of tissues. The route of administration of the stem cells can play a role in this process as well as administering the cells via the intravenous route has the potential for systemic exposure (65). Aside from that, host factors also need to be considered, especially if already immunocompromised or will be subjected to immunosuppressant medications posttransplant (65). Researchers have to be wary of this potential complication and it has been reported in several cases where stem cells are being used. Gastric cancer occurred in mice that were chronically infected with helicobacter and this infection led to the migration of BM-derived stem cells to the stomach subsequently causing malignancy (66). Another example is a study conducted using MSCs to ameliorate cisplatin-induced acute kidney injury in which there was the formation of a tumor in the lungs three months after stem cell therapy (65).

Recently, further studies have also emerged that allude to promising use of stem cells. Angiotensin-II was used to pretreat human umbilical cord-derived MSCs and when administered it, deceased the overall pancreatic damage in acute pancreatitis by limiting dysfunction of endothelial cells and improving angiogenesis (67). In another study, the BM-derived MSCs reduced pancreatic injury by regulation of microRNA-9 leading to a reduction in inflammation and ultimately lessening necroptosis (68). Another novel modality that is being researched in combination with stem cells is the use of N-acetylcysteine. When BM-derived MSCs were used in conjunction with N-acetylcysteine, the damage to the pancreas was reduced due to reduced oxidative damage and overall inflammation (69).

More research still needs to be conducted regarding the safety of stem cell transplantation. The regulation of the differentiation process is important and needs to be controlled as it can potentially give rise to tumors (9). Apart from that, the function of the differentiated cells that arise from the stem cells themselves needs to be assessed to ensure that they can carry out their destined role (9). Ethical concerns also arise when human subjects are involved with stem cell use. Hence, further studies and trials need to be undertaken, though stem cell transplantation does appear to carry significant therapeutic potential in both acute and chronic pancreatitis.

There are some animal studies that pertained to using MSCs in the treatment of acute and chronic pancreatitis. The findings of the studies are reported in a table format for ease of reference (Table 1). The studies are subdivided based on the chronicity of pancreatitis. Various offending agents of differing concentrations are used to induce injury to the system. Allogenic transplant of BM MSC (rat to rat) is the most popular with a few studies using human umbilical cord MSC (xenogenic). Kim et al. (43) opted for canine adipose tissue for the source of MSC. Cui et al. (36) explored the use of G-CSF to promote autologous

Table 1. 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. (37)	Bone marrow (rat)	Sodium deoxycholate	Rat	Caudal vein injection	1×10^6 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. (40)	Bone marrow (rat)	5% sodium taurocholate	Rat	Caudal vein injection	1×10^6 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. (39)	Bone marrow (rat)	L-arginine	Rat	Intra-peritoneal injection	5×10^6 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. (44)	Umbilical cord (human)	5% sodium taurocholate	Rat	Tail vein injection	Variable (5×10^6 cells/kg at 0 h, 1 h, 6 h and 12 h in one group and 5×10^4 cells/kg, 5×10^5 cells/kg, 1×10^7 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. (38)	Bone marrow (rat)	5% sodium taurocholate	Rat	Tail vein injection	1×10^6 cells/mL	Decreased blood urea nitrogen, creatinine, amylase levels Decreased damage of pancreatic tissue and renal interstitial capillary barrier Increased expression of aquaporin 1 in the kidney (helps promote renal reabsorption of water and hence circulating blood volume)
Cui et al. (36)	Bone marrow (mice)	L-arginine	Mice	Tail vein injection	2×10^7 cells	Decreased amylase levels, mortality rates Decreased gross and microscopic evidence of pathological pancreatic damage
Meng et al. (70)	Umbilical cord (human)	3% sodium taurocholate	Rat	Tail vein injection	1×10^7 cells	Decreased serum lipase and amylase levels Decreased features of pancreatic injury (edema, hemorrhage, necrosis, inflammatory cell infiltrate)

Table 1. Studies using stem cell therapy in acute pancreatitis. (Continue)

Study conducted by	Source of stem cells	Triggering agent	Animal	Mode of delivery	Stem cell quantity	Outcomes
Hua et al. (71)	Umbilical cord (human)	3% sodium taurocholate	Rat	Tail vein injection	2×10^6 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. (72)	Bone marrow (human)	Cerulein and lipopoly saccharide	Rat	Intra-peritoneal injection	1×10^6 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. (43)	Adipose tissue (canine)	3% sodium taurocholate	Rat	Injection into common biliopancreatic duct	1×10^7 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. (73)	Bone marrow (rat)	3% sodium taurocholate	Rat	Injection into biliopancreatic duct	$5\text{-}7 \times 10^7$ cells	Increased rates of survival Decreased expression of TNF-α and IL-1β mRNA
Kawakubo et al. (74)	Amniotic membranes (human)	Dibutyltin dichloride	Rat	Intravenous	1×10^6 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

stem cell proliferation as opposed to direct inoculation of MSC. Route and quantity of MSC differ among the studies as reported in the tables (Tables 1 and 2). The results are summarized in the final column.

CONCLUSION

Both Acute and chronic pancreatitides provoke severe inflammation and damage. They result in local and systemic complications and are associated with high rates

Table 2. Studies using stem cell therapy in chronic pancreatitis.

Study conducted by	Source of stem cells	Triggering agent	Animal	Mode of delivery	Stem cell quantity	Outcomes
Zhou et al. (45)	Umbilical cord (rat)	Dibutyltin dichloride	Rat	Intravenous	2×10^6 cells/kg	Inhibition of pancreatic stellate cell activation Enhanced histological scores Decreased fibrosis and expression of pro-inflammatory cytokines
Kawakubo et al. (74)	Amniotic membranes (human)	Dibutyltin dichloride	Rat	Intravenous	1×10^6 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
Marrache et al. (75)	Bone marrow (mice)	Cerulein	Mice	Tail vein injection	5×10^6 cells	Stem cells derived from the bone marrow may contribute to stellate cells in the pancreas (impacting tissue repair) Minimally contribute to pancreatic ductal epithelium

of morbidity and mortality. Thus far mainly supportive forms of therapy exist and despite early and aggressive treatment, the outcomes can be dismal at times. Hence any opportunities for therapy should be considered and explored as they may help to improve the overall prognosis and result. The use of stem cell therapy for both acute and chronic pancreatitis is gaining interest and recognition given the results of studies that have been conducted so far. It helps to prevent pancreatic damage, fibrosis, and suppresses inflammation along with a reduction in markers of inflammation and cell injury.

Some centers are performing beta-cell transplants in diabetic patients but the use of stem cells in patients with acute and chronic pancreatitis is scarce. Centers such as the Hope Medical Group in China and the Regeneration Center in Thailand are utilizing stem cell therapy for acute and chronic pancreatitis. Information regarding the outcomes and the number of procedures as well as how posttransplant patients are evaluated for success is not readily available. In the United States, the Food and Drug Administration (FDA) has not approved the use of stem cells for acute and chronic pancreatitis.

In addition, iPSC stem cells are not fully understood and before considering them as possible sources of stem cells therapy for acute or chronic pancreatitis, more trials must be conducted. Although initial evidence points to their inefficiency in truly developing into desired cell lines, they may still be beneficial for their immunomodulatory effects that were witnessed with MSCs and embryonic stem cells. Their advantages include the massive availability and that the ethical issues associated with harvesting embryonic stem cells do not apply to iPSCs (47).

The ARRIVE (Animals in Research: Reporting In Vivo Experiments) guidelines as outlined by Kilkenny et al. (76) provide a proper framework to report animal-based research. Published in 2010, the guidelines help ensure that all appropriate data are reported to mitigate possible discrepancies between preclinical research and clinical trials. They also help guide humane use of animals in scientific research in accordance with the "3Rs Principles" (i.e., Replacement, Reduction, and Refinement) (76). Further analysis of these animal studies under the context of these guidelines would allow for more detailed evaluation and more refined conclusions can be drawn. The scope of that is beyond the realm of this mini-review.

Hence, studies on humans are yet to be undertaken and even the animal model studies, though they show promising outcomes, need further exploration. Extrapolation of the results in the animal studies to humans is not feasible as the studies themselves have several variabilities. Further investigation still needs to be performed before data can ultimately be applied to patient populations.

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REFERENCES

1. Sarles H. Revised classification of pancreatitis--Marseille 1984. Dig Dis Sci 1985; 30: 573-4. [Crossref]
2. Bhatia M, Wong FL, Cao Y, et al. Pathophysiology of acute pancreatitis. Pancreatology 2005; 5: 132-44. [Crossref]
3. Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. Am J Gastroenterol 2006; 101: 2379. [Crossref]
4. Bhatia M, Brady M, Shokuhi S, et al. Inflammatory mediators in acute pancreatitis. J Pathol 2000; 190: 117-25. [Crossref]
5. Granger J, Remick D. Acute pancreatitis: models, markers, and mediators. Shock 2005; 24: 45-51. [Crossref]
6. Petrov MS, Shanbhag S, Chakraborty M, Phillips AR, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology 2010; 139: 813-20. [Crossref]
7. Eşrefoğlu M, Gül M, Ates B, Batçioğlu K, Selimoğlu MA. Antioxidative effect of melatonin, ascorbic acid and N-acetylcysteine on caerulein-induced pancreatitis and associated liver injury in rats. World J Gastroenterol 2006; 12: 259-64. [Crossref]
8. Eşrefoğlu M, Gül M, Ateş B, Selimoğlu MA. Ultrastructural clues for the protective effect of melatonin against oxidative damage in cerulein-induced pancreatitis. J Pineal Res 2006; 40: 92-7. [Crossref]
9. Esrefoglu M. Stem Cell Therapies on Pancreatitis. In: Rodrigo L, editor. Acute and Chronic Pancreatitis. Rijeka: InTech; 2015. p. Ch. 08. https://doi.org/10.5772/58883
10. Ben Nasr M, Frumento D, Fiorina P. Adipose Stem Cell Therapy for Chronic Pancreatitis. Molecular Therapy 2017; 25: 2438-9.
11. Karaoz E, Okcu A, Unal ZS, et al. Adipose tissue-derived mesenchymal stromal cells efficiently differentiate into insulinproducing cells in pancreatic islet microenvironment both in vitro and in vivo. Cytotherapy 2013; 15: 557-70. [Crossref]
12. Jung KH, Song SU, Yi T, et al. Human bone marrow-derived clonal mesenchymal stem cells inhibit inflammation and reduce acute pancreatitis in rats. Gastroenterology 2011; 140: 998-1008. [Crossref]
13. Schneider G, Saur D. Mesenchymal Stem Cells: Therapeutic Potential for Acute Pancreatitis. Gastroenterology 2011; 140: 779-82. [Crossref]
14. Pittenger MF, Mackay AM, Beck SC, et al. Multiline age potential of adult human mesenchymal stem cells. Science 1999; 284:143-7. [Crossref]
15. Smukler SR, Arntfield ME, Razavi R, et al. The adult mouse and human pancreas contain rare multipotent stem cells that express insulin. Cell Stem Cell 2011; 8: 281-93. [Crossref]
16. Xu X, D'Hoker J, Stangé G, et al. Beta cells can be generated from endogenous progenitors in injured adult mouse pancreas. Cell 2008; 132: 197-207. [Crossref]
17. Zhou Q, Law AC, Rajagopal J, Anderson WJ, Gray PA, Melton DA. A multipotent progenitor domain guides pancreatic organogenesis. Dev Cell 2007; 13: 103-14. [Crossref]
18. Gong J, Tian F, Ren J, Luo G. Experimental evidence supporting the lack of primary stem cells in adult pancreatic tissue. Pancreatology 2010; 10: 620-30. [Crossref]
19. Wang Y, Lanzoni G, Carpino G, et al. Biliary tree stem cells, precursors to pancreatic committed progenitors: evidence for possible life-long pancreatic organogenesis. Stem Cells 2013; 31: 1966-19. [Crossref]
20. Bonner-Weir S, Toschi E, Inada A, Reitz P, Fonseca SY, Aye T, Sharma A. The pancreatic ductal epithelium serves as a potential pool of progenitor cells. Pediatr Diabet 2004; 5: 16-22. [Crossref]
21. Inada A, Nienaber C, Katsuta H, et al. Carbonic anhydrase II-positive pancreatic cells are progenitors for both endocrine and exocrine pancreas after birth. Proc Natl Acad Sci USA 2008; 105: 19915-9. [Crossref]
22. Strobel O, Rosow DE, Rakhlin EY, et al. Pancreatic duct glands are distinct ductal compartments that react to chronic injury and mediate Shh-induced metaplasia. Gastroenterology 2010; 138: 1166-77. [Crossref]
23. Lynn FC, Smith SB, Wilson ME, Yang KY, Nekrep N, German MS. Sox9 coordinates a transcriptional network in pancreatic progenitor cells. Proc Natl Acad Sci U S A 2007; 104: 10500-5. [Crossref]
24. Maestro MA, Boj SF, Luco RF, et al. Hnf6 and Tcf2 (MODY5) are linked in a gene network operating in a precursor cell domain of the embryonic pancreas. Human Mol Genet 2003; 12: 3307-14. [Crossref]
25. Jensen J. Gene regulatory factors in pancreatic development. Dev Dyn 2004; 229: 176-200. [Crossref]
26. Villasenor A, Chong DC, Henkemeyer M, Cleaver O. Epithelial dynamics of pancreatic branching morphogenesis. Development 2010; 137: 4295-305. [Crossref]
27. Solar M, Cardalda C, Houbracken I, et al. Pancreatic exocrine duct cells give rise to insulin-producing β cells during embryogenesis but not after birth. Dev Cell 2009, 17: 849-60. [Crossref]
28. Seymour PA, Freude KK, Dubois CL, Shih HP, Patel NA, Sander M. A dosage-dependent requirement for Sox9 in pancreatic endocrine cell formation. Dev Biol 2008; 323: 19-30. [Crossref]
29. Anderson KR, Singer RA, Balderes DA, et al. The L6 domain tetraspanin Tm4sf4 regulates endocrine pancreas differentiation and directed cell migration. Development 2011; 138: 3213-24. [Crossref]
30. Cole L, Anderson M, Antin PB, Limesand SW. One process for pancreatic beta-cell coalescence into islets involves an epithelial-mesenchymal transition. J Endocrinol 2009; 203: 19-31. [Crossref]
31. Rukstalis JM, Habener JF. Snail2, a mediator of epithelial-mesenchymal transitions, expressed in progenitor cells of the developing endocrine pancreas. Gene Exp Patterns 2007; 7: 471-9. [Crossref]
32. Afelik S, Jensen J. Notch signaling in the pancreas: patterning and cell fate specification. Wiley Interdiscip Rev Dev Biol 2013; 2: 531-44. [Crossref]
33. Taguchi M, Yamaguchi T, Otsuki M. Induction of PDX-1-positive cells in the main duct during regeneration after acute necrotizing pancreatitis in rats. J Pathol 2002; 197: 638-46. [Crossref]
34.Kopp JL, Grompe M, Sander M. Stem cells versus plasticity in liver and pancreas regeneration. Nat Cell Biol 2016; 18: 238. [Crossref]
35. Rovira M, Scott SG, Liss AS, Jensen J, Thayer SP, Leach SD. Isolation and characterization of centroacinar/terminal ductal progenitor cells in adult mouse pancreas. Proc Natl Acad Sci U S A 2010; 107: 75-80. [Crossref]
36. Cui HF, Bai ZL. Protective effects of transplanted and mobilized bone marrow stem cells on mice with severe acute pancreatitis. World J Gastroenterol 2003; 9: 2274-7. [Crossref]
37. Tu XH, Song JX, Xue XJ, et al. Role of bone marrow-derived mesenchymal stem cells in a rat model of severe acute pancreatitis. World J Gastroenterol 2012; 18: 2270-9. [Crossref]
38. Chen Z, Lu F, Fang H, Huang H. Effect of mesenchymal stem cells on renal injury in rats with severe acute pancreatitis. Exp Biol Med (Maywood) 2013; 238: 687-95. [Crossref]

39. Sun XC, Wu JS, Wu JM, Huang ZM, Yu Z. [Effects of intraperitoneal injection of marrow mesenchymal stem cells on intestinal barrier in acute pancreatitis]. Zhonghua Yi Xue Za Zhi 2013; 93: 951-5.
40. Wang L, Tu XH, Zhao P, Song JX, Zou ZD. Protective effect of transplanted bone marrow-derived mesenchymal stemcells on pancreatitis-associated lung injury in rats. Mol Med Rep 2012; 6: 287-92. [Crossref]
41. Jung KH, Song SU, Yi T, et al. Human bone marrow-derived clonal mesenchymal stem cells inhibit inflammation and reduce acute pancreatitis in rats. Gastroenterology 2011; 140: 998-1008. [Crossref]
42. Baek SJ, Kang SK, Ra JC. In vitro migration capacity of human adipose tissue-derived mesenchymal stem cells reflects their expression of receptors for chemokines and growth factors. Exp Mol Med 2011; 43: 596-603. [Crossref]
43. Kim HW, Song WJ, Li Q, et al. Canine adipose tissue-derived mesenchymal stem cells ameliorate severe acute pancreatitis by regulating T cells in rats. J Vet Sci 2016; 17: 539-48. [Crossref]
44. Yang B, Bai B, Liu CX, et al. Effect of umbilical cord mesenchymal stem cells on treatment of severe acute pancreatitis in rats. Cytotherapy 2013; 15: 154-62. [Crossref]
45. Zhou CH, Li ML, Qin AL, et al. Reduction of fibrosis in dibutyltin dichloride-induced chronic pancreatitis using rat umbilical mesenchymal stem cells from Wharton's jelly. Pancreas 2013; 42: 1291-302. [Crossref]
46. Takahashi K, Yamanaka S. "Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors". Cell 2006; 126: 663-76. [Crossref]
47. Charles A. Goldthwaite, Jr. The Promise of Induced Pluripotent Stem Cells (iPSCs). [Stem Cell information] Bethesda, MD: National institutes of Health, 2016. stemcells.nih.gov/info/Regenerative_Medicine/2006Chapter10.htm.
48. Hu BY, Weick JP, Yu J, et al. Neural differentiation of human induced pluripotent stem cells follows developmental principles but with variable potency. Proc Natl Acad Sci USA 2010; 107: 4335-40. [Crossref]
49. Zhang J, Wilson GF, Soerens AG, et al. Functional cardiomyocytes derived from human induced pluripotent stem cells. Circ Res 2009; 104: e30-e41. [Crossref]
50. Kuzmenkin A, Liang H, Xu G, et al. Functional characterization of cardiomyocytes derived from murine induced pluripotent stem cells in vitro. FASEB J 2009; 23: 4168-80. [Crossref]
51. Mauritz C, Schwanke K, Reppel M, et al. Generation of functional murine cardiac myocytes from induced pluripotent stem cells. Circulation 2008; 118: 507-17. [Crossref]
52. Jacobson E, Tzanakakis E. Human pluripotent stem cell differentiation to functional pancreatic cells for diabetes therapies: Innovations, challenges and future directions. J Biol Eng 2017; 11: 21. [Crossref]
53. Southard S, Kotipatruni R, Rust W. Generation and selection of pluripotent stem cells for robust differentiation to insulin-secreting cells capable of reversing diabetes in rodents. PLoS One 2018; 13: e0203126. [Crossref]
54. Kawakubo K, Ohnishi S, Kuwatani M, Sakamoto N. Mesenchymal stem cell therapy for acute and chronic pancreatitis. J Gastroenterol 2018; 53: 1-5. [Crossref]
55. Hou YC, Huang CF, Wang HC, Wu Y, Shan YS. Therapeutic Efficacy of Spleen-Derived Mesenchymal Stem Cells in Mice with Acute Pancreatitis. J Stem Cell Res Ther 2015; 5: 318. [Crossref]
56. Sun Z, Gou W, Kim DS, et al. Adipose Stem Cell Therapy Mitigates Chronic Pancreatitis via Differentiation into Acinar-like Cells in Mice. Mol Ther 2017; 25: 2490-501. [Crossref]
57. Grinnemo K, Kumagai-Braesch M, Månsson-Broberg A, et al. Human embryonic stem cells are immunogenic in allogeneic and xenogeneic settings. Reprod Biomed Online 2006; 13: 712-24. [Crossref]
58. Le Blanc K, Tammik C, Rosendahl K, Zetterberg E, Ringdén O. HLA expression and immunologic propertiesof differentiated and undifferentiated mesenchymal stem cells. Exp Hematol 2003; 31: 890-6. [Crossref]
59. Nauta A. Donor-derived mesenchymal stem cells are immunogenic in an allogeneic host and stimulate donor graft rejection in a nonmyeloablative setting. Blood 2006; 108: 2114-20. [Crossref]
60. Poncelet A, Vercruysse J, Saliez A, Gianello P. Although Pig Allogeneic Mesenchymal Stem Cells Are Not Immunogenic In Vitro, Intracardiac Injection Elicits an Immune Response In Vivo. Transplantation 2007; 83: 783-90. [Crossref]
61. Grinnemo K, Månsson-Broberg A, Leblanc K, et al. Human mesenchymal stem cells do not differentiate into cardiomyocytes in a cardiac ischemic xenomodel. Ann Med 2006; 38: 144-53. [Crossref]
62. Inoue S, Popp F, Koehl G, et al. Immunomodulatory Effects of Mesenchymal Stem Cells in a Rat Organ Transplant Model. Transplantation 2006; 81: 1589-95. [Crossref]
63. Lin C, Lin G, Lue T. Allogeneic and Xenogeneic Transplantation of Adipose-Derived Stem Cells in Immunocompetent Recipients Without Immunosuppressants. Stem Cells Dev 2012; 21: 2770-8. [Crossref]
64. Huang X, Sun Z, Miyagi Y, et al. Differentiation of Allogeneic Mesenchymal Stem Cells Induces Immunogenicity and Limits Their Long-Term Benefits for Myocardial Repair. Circulation 2010; 122: 2419-29. [Crossref]
65. Večerić-Haler Ž, Cerar A, Perše M. (Mesenchymal) Stem Cell-Based Therapy in Cisplatin-Induced Acute Kidney Injury Animal Model: Risk of Immunogenicity and Tumorigenicity. Stem Cells Int. 2017; 2017: 7304643. [Crossref]
66. Houghton J. Gastric Cancer Originating from Bone Marrow-Derived Cells. Science 2004; 306: 1568-71. [Crossref]
67. Yang J, Su J, Xi S, et al. Human umbilical cord mesenchymal stem cells pretreated with Angiotensin-II attenuate pancreas injury of rats with severe acute pancreatitis. Biomed Pharmacother 2019; 117: 109052. [Crossref]
68. Song G, Ma Z, Liu D, et al. Bone marrow-derived mesenchymal stem cells attenuate severe acute pancreatitis via regulation of microRNA-9 to inhibit necroptosis in rats. Life Sci 2019; 223: 9-21. [Crossref]
69. Ma Z, Song G, Liu D, et al. N-Acetylcysteine enhances the therapeutic efficacy of bone marrow-derived mesenchymal stem cell transplantation in rats with severe acute pancreatitis. Pancreatology 2019; 19: 258-65. [Crossref]
71. Hua J, He ZG, Qian DH, et al. Angiopoietin-1 gene-modified human mesenchymal stem cells promote angiogenesis and reduce acute pancreatitis in rats. Int J Clin Exp Pathol 2014; 7: 3580-95.
72. Jung KH, Yi T, Son MK, Song SU, Hong SS. Therapeutic effect of human clonal bone marrow-derived mesenchymal stem cells in severe acute pancreatitis. Arch Pharm Res 2015; 38: 742-51. [Crossref]
73. Zhao H, He Z, Huang D, et al. Infusion of Bone Marrow Mesenchymal Stem Cells Attenuates Experimental Severe Acute Pancreatitis in Rats. Stem Cells Int 2016; 2016: 7174319. [Crossref]
74. Kawakubo K, Ohnishi S, Fujita H, et al. Effect of Fetal Membrane-Derived Mesenchymal Stem Cell Transplantation in Rats with Acute and Chronic Pancreatitis. Pancreas 2016; 45: 707-13. [Crossref]
75. Marrache F, Pendyala S, Bhagat G, Betz KS, Song Z, Wang TC. Role of bone marrow-derived cells in experimental chronic pancreatitis. Gut 2008; 57: 1113-20. [Crossref]
76. Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Animal research: reporting in vivo experiments: The ARRIVE guidelines. PLoS Biol 2010; 8: e1000412. [Crossref]