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Stem Cell Therapies on Pancreatitis

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1. Introduction

Pancreatitis is an inflammatory acute or chronic disease of the pancreas. Although etiology of acute and chronic pancreatitis remains poorly defined, so far a variety of environmental, hereditary and immunological factors and bile duct obstructions have been described. Treatment of patients suffering from severe acute pancreatitis (AP) remains challenging, and despite improved strategies, mortality is still between 30 and 50 % [1]. The prognosis of patients with acute pancreatitis is largely determined by the presence of organ failure and infected pancreatic necrosis with associated mortality rates of 15%-30% [2].

AP is an inflammatory disease of the pancreas characterized by edema, acinar cell necrosis, hemorrhage and severe inflammation of the pancreas [3,4] and some of the other organs including liver [3,5]. Some inflammatory factors including interleukin (IL)-1, IL-6, IL-8, C-reactive protein, tumor necrosis factor (TNF), nitric oxide (NO) and endothelin are suggested to be involved in the genesis and progression of AP as well as in the progression from slight AP to severe AP [6]. By electron microscopic observation, dilatation of irregularly arranged cisternae of rough endoplasmic reticulum and of some of the cisternae of Golgi apparatus are prominent. The mitochondria with increased translucence of the matrix, partial destruction or loss of the cristae are edematous. Sometimes myelin figures are observed within the mito-chondrial matrix. Numerous, large autophagosomes containing amorphous, membranous or granular masses and zymogen granules are present within the cytoplasm (Figure 1,2). Nuclear chromatin clumping and margination indicating apoptosis are present [4] (Figure 2).

Chronic pancreatitis (CP) characterized by fibrosis, and pain is a long-standing inflam-mation of the pancreas that alters its normal structure and functions. Regions of the pancreas are transformed from glandular tissue to a mass of almost complete fibrosis. The secretory parenchyma is destroyed by processes such as necrosis/ apoptosis, inflam-mation or duct obstruction. Pancreatic stallate cells present in the periacinar space and
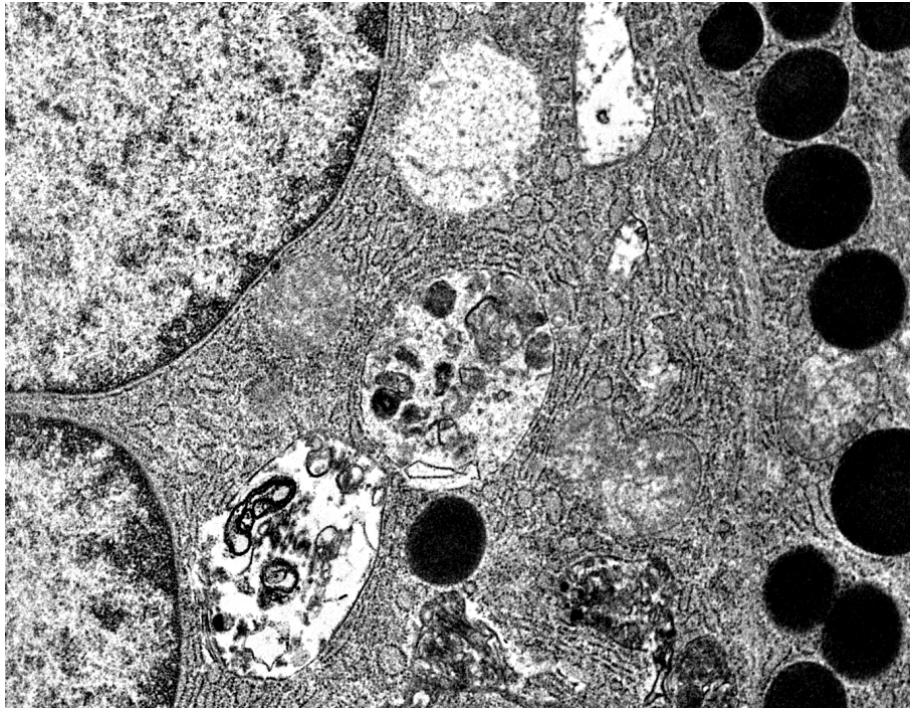
Figure 1. Mitochondral edema and degeneration, and accumulation lysosomes containing identifiable cytoplasmic elements, amorphous, membranous or granular masses are observed in the cytoplasm of an acinar cell in cerulein-induced experimental acute pancreatitis. X 10.000
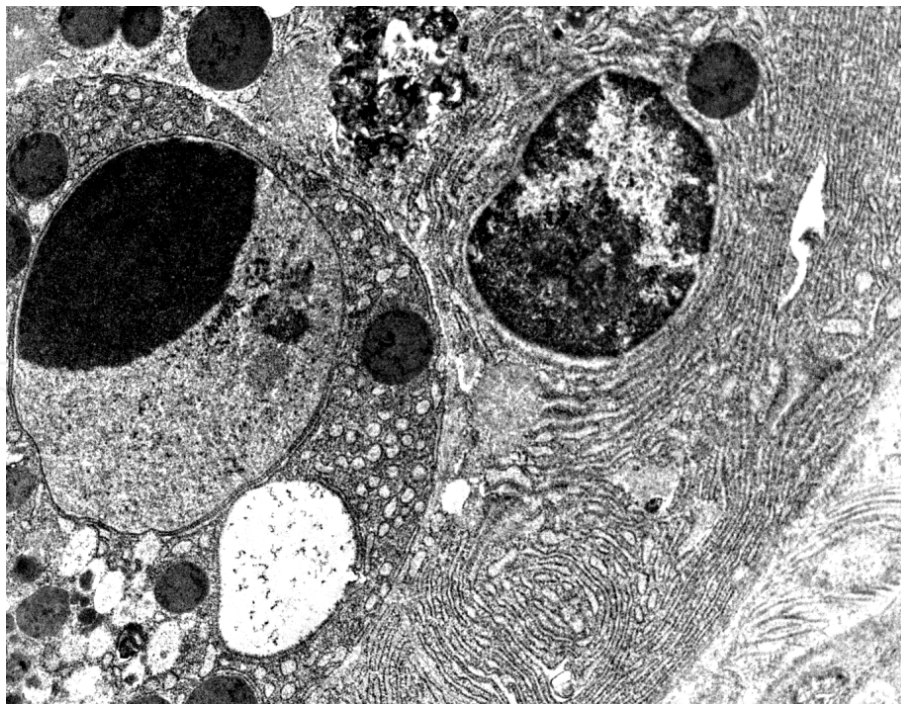

Figure 2. Nuclear chromatin clumping and margination indicating apoptosis, and organelle degeneration as well as lysosome accumulation are observed in the cytoplasm of acinar cells in cerulean-induced experimental acute pancreatitis. Note that apoptotic cell is engulfed by a neighboring acinar cell. X 8.000

have long cytoplasmic processes that encircle the base of the acinus are strongly in‐volved not only in the pathogenesis of CP but also in pancreatic cancer. They are lo‐cated in the periacinar, perivascular and periductal regions of the pancreas [7, 8].

Over the past decades, our understanding of the pathogenesis of pancreatitis has significantly improved. Animal models including caerulein, taurocholate, L-arginine studies are important in order to understand the pathogenesis of pancreatitis, however none of them are fully satisfactory. It is now widely accepted that AP is triggered by premature activation of proen‐zymes within pancreatic acinar cells, thereby leading to autodigestion of the pancreas. Esrefoglu *et al* [3,4,9] emphasized the role of oxidative stress on the pathogenesis of careulein-induced pancreatitis. They showed potent therapeutic effects of some antioxidant agents including melatonin, ascorbic acid and N-acetyl cysteine on AP in rats. In fact, in recent years, valuable data on the efficiency of antioxidants against oxidative damage have been obtained from experimental studies with rodents. With the inspiration of the results of these experi‐ments, efficiency of some of these antioxidants has been tried on the patients with AP and found beneficial. However, at present there is insufficient clinical data to support the benefits of antioxidants, alone or in combination with conventional therapy, in the management of AP in humans [10]. The effects of stem cells transplantation on tissue oxidative stress level have been studied lately. In fact, stem cell transplantation helps to maintain tissue regeneration by replacing the degenerated cells as well as by regulating oxidative stress production. Stem cells have been shown to be able to scavenge reactive oxygene and nitrogen species, and to limit oxidative stress-induced tissue damage [11]. Recently, mesenchymal stem cells have been found beneficial in a traumatic brain injury in vitro model and myocardial ischemia/reperfu‐sion model decreasing oxidative stress levels by their paracrine effects [12,13]. Mesenchymal stem cells have been shown to increase tissue SOD, activity but decrease tissue MDA level on AP in rats [14].

Development of evidence based therapies for pancreatitis has lagged behind advances in understanding of the pathophysiology of the disease. Herein, no pharmacologic therapy has been shown to affect disease progression. Several potential reasons for the lack of progress in development of treatments for pancreatitis includes a lack of sustained effort to transition basic science findings into clinical trials and a lack of appropriate preclinical models for testing potential therapeutic agents. In recent years, the efficacy of stem cell transplantation applica‐tions is widely investigated in the course of several diseases in experimental animals and also in humans. In pancreatitis, stem cells might recover the damaged pancreatic tissue by their excessive proliferating and differentiating capabilities and regulatory functions on oxidative stress levels under the regulatory control of the microenviroment. Unfortunately, the results obtained from rodents studies might not be similiar to those obtained from human studies. Herein I tried to review the results of stem cell transplantation therapies obtained from rodent and human studies on AP and CP. However, I realize that although researchers agree about the therapeutic potency of transplanted progenitor and stem cells on acute and chronic pancreatitis, any clinical trial has been performed so far.

2. Catagorization of stem cells

Stem cells are different from the other cell types since they are unspecialized cells that are capable of changing themselves into various types of specialized cells. The main features of stem cells are the capability to divide, proliferate, and self-renewal; to differentiate to one or several cell types and to survive in an undifferentiated stage for a while. In fact, they may remain in such an undifferentiated state for long time periods. When the morphological as well as functional differentiation begins, these cells differentiate into multiple specialized cell lineages. One stem cell may divide into two identical stem cells by symmetrical division or it may divide into one stem cell and one progenitor cell by asymmetrical division. One progenitor cell also may divide into identical progenitor cells by symmetrical division. The committed progenitor cells exhibit a capacity to give rise to terminally differentiated cells under favorable influences which are not fully known yet.

Stem cells are classified depending on the potential for differentiation into specialized cell types. The most capable stem cells which are totipotent cells of the zygote within first 4 days of the intrauterine life are able to form a full organism in appropriate microenvironment. However, pluripotent cells, known as 'embryonic stem cells'(ESCs), principally derived from the inner cell mass of the embryo can form virtually any cell type derived from any of three embryonic germ layers; ectoderm, mesoderm or endoderm. Thus, an embryonic stem cell can form enterocyte (endodermal in origin), cardiomyocyte (mesodermal in origin), and kerati-nocyte (ectodermal in origin). Surplus embryos obtained from in-vitro fertilization laboratories are the main sources of the ESCs. However, some disadvantages including high immune reaction risk and some ethical concerns limit their applications. The third type of stem cells is multipotent stem cells which are also known as 'adult stem cells'. These cells with a relatively limited differentiation potential can form several cell types of the tissue. These cells reside together with the specialized cell types of the adult tissues and they are thought to be respon-sible for the tissue maintenance and repair. The exact mechanisms that affect them to stay in undifferentiated stage for a period of time and force them to differentiate into a specialized cell type are not fully known yet. The two major populations of adult stem cells are bone marrow mesenchymal and hematopoietic stem cells (HSCs). Hematopoietic stem cells have a predetermined fate to form all types of the mature blood cells. Mesenchymal stem cells can differentiate into multiple cell lineages, including tendon cells, muscle cells, osteocytes, fat cells etc. The term 'multipotent stromal cell' implies the multipotent stem cells of both bone morrow and of none-morrow tissues such as umbilical cord blood, adipose tissue, muscle tissue, dental pulp etc. Important data obtained from mainly cell culture studies have provided clues about the ability of adult stem cells to differentiate into various cell types from different germ layers. For instance; the HSCs which are derived from mesoderm can transform into hepatocytes which are derived from endoderm or brain stem cells which are derived from ectoderm can form skeletal muscle fibers which are derived from mesoderm. Multipotent cells are genetically identical to their hosts, thus they don't cause any immune reaction. However, these cells are restricted in their ability to form different cell types in comparison with ESCs. Moreover, they have some disadvantages including slow rate of cell division and difficulties to isolate in sufficient numbers for application because of their sparsity within the tissues. The

last type of stem cells is unipotent stem cells that have a very limited capacity for differentiation and can give rise to only one type of cell under normal conditions. For instance; unipotent stem cells of colony forming unit of erythrocytes (CFU-E) can only give rise to mature erythrocytes of blood.

In recent years stem cells are widely studied for their promising potential therapeutic use in both rodents and humans. However, some of the human studies failed to be successful. Researchers agree that as well as isolation of adequate numbers of healthy stem cells, selection of most convenient transporting route, regulation of stem cell differentiation into a special cell type, and obtainment of the usual functions of the differentiated cells are very important regarding the benefit of stem cell applications. The most important risk of the transplanted stem cells is generation of tumors if cell division continues in an uncontrolled manner. Unfortunately, the stem cell transplantation therapy may be considered as a sort of two-edged sword.

2.1. Stem cells in exocrine pancreas

Identification of stem and/or progenitor cells in the adult pancreas has been an area of intense investigation in the past decades, but the results remain controversial [15]. Determined stem cells for pancreatic cell therapies have not been considered an option based on evidence that there are no or only rare pancreatic stem cells in postnatal tissues [16]. Rare stem cell populations have been identified within the pancreas and that express pluripotency genes (OCT4, SOX2) [17-19]. The few studies in which OCT4 and SOX21 multipotent stem cells have been identified in adult pancreas have indicated also their rarity [19]. Smukler *et al* [17] described pancreas-derived multipotent cells, which are rare (1/5000 pancreas cells) and form spheres in vitro. They can differentiate into multiple lineages, including several endocrine cell types and neurons. Gong *et al* [20], using stem cell marker nestin, reported experimental clues supporting the lack of primary stem cells in adult pancreas tissue. They suggested that the so-called pancreatic stem cells may actually originate from bone marrow stem cells. When pancreatic tissue is injured, bone marrow stem cells may participate in the repair.

The location of stem cells in each organ has been widely investigating. Wang *et al* [21] provide evidence that the biliary tree is a reservoir of stem cells for the pancreas. They present evidence to suggest the biliary tree and pancreatic networks are connected anatomically and functionally to comprise maturational lineages relevant to pancreatic organogenesis. They showed that determined stem cell populations, present throughout life, are precursors for pancreatic committed progenitors in the pancreatic duct glands (a novel ductal compartment that is gathered in gland-like outpouches), and are present in the ramifying, continuous network of ducts and associated glands of the biliary tree.

The postnatal pancreas has long been thought to contain only committed progenitors, found in pancreatic ducts [22,23] and, in the pancreatic duct glands [24]. These precursors are reported to be limited in their proliferative and self-renewal potential. A recent study of Stanger *et al* [25] suggested that the final size of the pancreas is also determined by the number of embryonic progenitor cells, each with an autonomous restriction on the amount of tissue it was capable of generating. Centroacinar cells and terminal duct cells lie at the junction between

peripheral acinar cells and the adjacent ductal epithelium. Both of these cell types are supposed to be candidate pancreatic progenitors. Specifically, these cells express high levels of Ptf1a, Sox9, Sca-1, SDF-1, c-Met, and Nestin [26]. Magliano *et al* [27] have reported that although Sox9 is expressed throughout the pancreas epithelium, pancreatic ductal cells in the adult pancreas, excluding acinar and centroacinar cells, it is reactivated in acinar cells that undergo de-differentiation after induction of pancreatitis with cerulein. The findings suggest that at least a subset of cells residing in a centroacinar/terminal ductal location is capable of progenitor function. The finding that this population undergoes dramatic expansion during an epithelial injury suggests that these cells are involved in pancreatic epithelial regeneration. Together with their location at the junction between peripheral secretory cells and more central ductal epithelium, these features suggest similarity between centroacinar/terminal ductal cells and hepatic oval cells which are progenitor cell type capable of multilineage differentiation in the event of any injury [28].

In the primary transition pancreas, primary stem cell type is multipotent stem cells, capable of contributing to all epithelial cell lineages of the pancreas parenchyma. These cells coexpress important transcription factors including Pdx1, Ptf1a, Nkx6.1, Hnf1β, and Sox9 [29-31]. During the secondary transition period, pancreatic epithelium forms finger-like projections into the surrounding mesenchyme generating a tree-like epithelial structure with recognizable 'tip' and 'trunk' segments [32,33]. The bipotential progenitor cell population within the trunk segment seems to be progenitors of both endocrine and duct lineages [31,34,35]. Solar *et al* [34] provided clues on the potency of these cells to contribute to the endocrine and ductal lineages by genetic lineage tracing of Hnf1β positivity. Following their specification, endocrine precursor cells leave the trunk compartment to form mature islets [36-38] whereas the remaining cells that remain within the trunk contribute to the pancreatic duct [39]. Recently we investigated prenatal and postnatal development of the rat pancreas as well as the other organs of the digestive system (Unpublished data). At prenatal 10th day pancreas premordium was composed of a few tubes lined with a simple epithelium and surrounding mesenchymal tissue rich in vessels. Many mitotic figures were observed within the epithelium (Figure 3A). At prenatal 14th day, branching of the tubes was prominent. The tips of the branhcing trunk were formed as primitive acini (Figure 3B). The epithelium was still rich in mitosis. At prenatal 17th day, further branches gave rise to increased number of acini (Figure 3C). Endocrine cell islets were observed at prenatal 17th day for the first time. However, at postnatal 15th day, it was so clear that the same trunk gave rise to both exocrine and endocrine compartments of the pancreas (Figure 3D).

Pancreatic regeneration involves two pathways; proliferation and differentiation of pancreatic progenitor cells, and replication of preexisting differentiated acinar, islet, and ductal epithelial cells [40]. Expression of transcription factors and cell differentiation are under the control of some regulating signalling factors either secreted from neighbouring tissues or pancreatic mesenchymal cells (e.g. fibroblast growth factors) [41,42] or are expressed on the surface of differentiating pancreatic cells (e.g. Notch) [43]. Mammalian pancreas displays a significant capacity for regeneration following injury. A variety of cell types have been proposed as possible pancreatic progenitors, including cells associated with ductal epithelium [19],
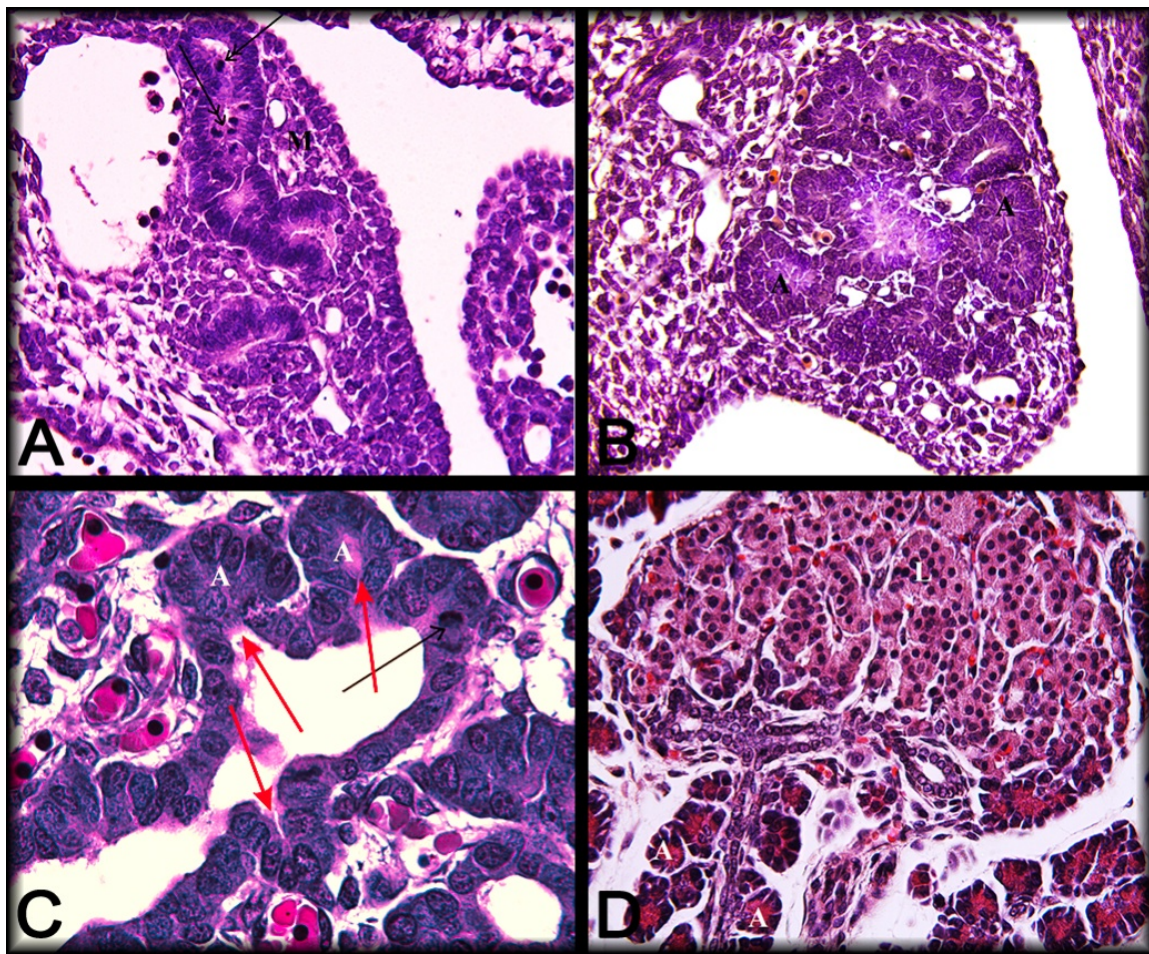
Figure 3. The histological features of the pancreas during development. A. Prenatal 10th day. Pancreas premordium is composed of a few tubes lined with a simple epithelium and surrounding mesenchymal tissue rich in vessels. Many mitotic figures are observed within the epithelium. B. Prenatal 14th day. Branching of the tubes is prominent. The tips of the branhcing trunk form primitive acini. C. Prenatal 17th day. Increased number of acini was formed by further branches (red arrows). Many figures of mitosis are present within the epithelium (black arrows). D. Postnatal 15th day. The same trunk gives rise to both exocrine and endocrine compartments of the pancreas.

mesenchymal-like nestin expressing cells [44] and preexisting acinar cells [45]. Centroacinar cells and terminal duct cells are frequently supposed to be candidate pancreatic progenitors. These cells are markedly enriched for transcripts encoding Sca1, Sdf1, c-Met, Nestin, and Sox9 markers which were previously associated with progenitor populations in embryonic pancreas. Fluorescent Activated Cell-Sorted centroacinar/terminal duct cells are shown to be able to form self-renewing "pancreatospheres" in suspension culture. The progenitor cells of the spheres have capacity for spontaneous endocrine and exocrine differentiation; additionally they have ability to glucose-responsive insulin secretion. Moreover, when injected into cultured embryonic dorsal pancreatic buds, these adult cells display capacity to contribute to the embryonic endocrine and exocrine lineages. Finally, the number of these cells is shown to be significantly increased in the setting of chronic epithelial injury [26].

Taguchi *et al* [40] observed newly formed acinar cells on day 7 following the induction of acute necrotizing pancreatitis in rats. They reported that proliferation started in the main and large

ducts at 24 h; marked mitotic activity was evident in small ductal epithelial cells and tubular complexes on day 3, and in acinar cells on day 7. The lobular structure returned to normal appearance on day 28. These results suggest that regeneration after necrotizing pancreatitis involves proliferation and differentiation of pancreatic progenitor cells. Ductal epithelial cells with duodenum homeobox protein 1 (PDX-1)-positive nuclei may contribute to the differentiation of the stem cells in the main duct of pancreas.PDX-1-positive cells in the main duct might be quiescent pancreatic stem cells. PDX-1 might be a marker of cells that regain their multipotency to differentiate into any pancreatic cell types [46], and is thought to be an intrinsic signal determining the region of gut endoderm that ultimately becomes the pancreas [47]. PDX-1 has an important role in the determination of pancreatic progenitors [48] and neurogenin-3 is required for determination of endocrine precursor [49].

3. Stem cell transplantation therapies

The use of stem cells for the treatment of various diseases in both humans and animals has been the focus of considerable interest. Stem cell technology gives hope of effective treatment for a variety of diseases through the rapid developing field that combines the efforts of cell researchers and clinicians. However; it seems to be early to carry out a Bench-to-Bedside program applying stem cell therapeutics in the clinical setting yet. Detailed researches are necessary to understand the optimal transplantation routes and doses as well as the mechanisms of stem cell interaction with the injured microenvironment as clues for realizing stem cell behavior.Stem cell therapy offers the possibility of repairing acutely or chronically injured tissue and has the potential to regulate immune function and reduce inflammatory changes.

Recently, I reviewed the role of stem cells in repair of liver injury and experimental and clinical benefit of transferred stem cells on liver failure [50]. I was suprised to recognize of how many fundemantal and clinical trial on stem cell transplantation have been performed on acute and chronic liver failure. In this chapter, I review cell types involved in pancreas regeneration and cell transplantation therapies for both acute and chronic pancreatitis, with an emphasis on regeneration. However, I realise that even fundamental studies are very limited. Adipose-derived, bone marrow-derived and umblical cord-derived mesenchymal stem cells (MSCs) have been subjected to the basic stem cell trials. To my knowledge any clinical trial has been performed so far.

3.1. Mesenchymal stem cells

The MSCs, belong to a class of mesodermal adult stem cells population are found in numerous living tissues including bone marrow, adipose tissue, amniotic fluid, liver, lung, skeletal muscle and kidney. It has been reported that among MSCs obtained from bone marrow, adipose tissue, umbilical cord blood and placenta could be expanded extensively in vitro. The studies have confirmed that MSCs could differentiate into a range of cell types. For instance; bone marrow derived MSCs could differentiate into a range of cell types such as adipocytes,

osteoblasts, nerve cells, and liver cells under different conditions [51-53]. Additionally, the experimental and clinical studies have shown that the MSCs could reduce the expression of a variety of inflammatory factors [54,55], inhibit immune responses [56,57], and promote the regeneration of various tissues and organs [58,59] including lung, kidney, liver and heart [60-63]. Imunomodulatory functions of MCSs include suppression of T cell and B cell prolif-eration, and suppression of terminal differentiation of B cells, and immune modulation of other cell of the immune system including NK cells and macrophages [64]. Here are the results obtained from various trials related with stem cell transplantations on acute and chronic pancreatitis.

3.1.1. Bone morrow derived MSCs

Bone marrow-derived MSCs harbor a biological basis which can be used as a candidate for severe AP therapy. Cui *et al* [65] found transplanted and mobilized bone marrow stem cells beneficial on mice with severe AP. They mobilized bone marrow stem cells by injection of granulocyte colony stimulating factor. The mortality rate and serum level of amylase were found to be significantly decreased in the mice pretreated with bone marrow-derived MSCs' transplantation or G-CSF injection. Chen *et* al [66] injected $1x10^6$ mL MSC via tail vein at 0th, 0th and 6th, 0th, 6th and 12th hours after AP induction by 5% sodium taurocholate injection to biliopancreatic duct. After treatment with MSCs, the damage was less severe than that in the untreated AP groups. Besides, MSCs therapy could improve renal injury in rats with severe AP, probably by reducing the damage to renal interstitial capillary endothelial barrier, and up-expression of AQP1 in kidney. Tu *et al* [14] reported that MSCs can effectively relieve injury to pancreatic acinar cells and small intestinal epithelium. MSCs were shown to be able to promote the proliferation of enteric epithelium and repair of the mucosa as well as to attenuate systemic inflammation in rats with severe AP. Serum malondialdehyde (MDA) level was reduced while superoxide dismutase (SOD) activity was increased the rats from AP + MSCs group. They concluded that MSCs transplantation could reduce pancreatitis-related oxidative injury by inhibiting lipid peroxidation, by protecting the stability of the membranes, and by improving the scavenging ability of oxygen-derived free radicals. Recently, Sun *et al* [67] intraperitoneally injected the third-generation bone marrow-derived MSC at a dose of 5×10(6) once daily for 3 days. All rats were sacrificed after 72 h. Compared with severe AP group, histomorphological alternations of small intestine were significantly lower in MSC injected group. The relative expression quantity of TNF-α mRNA and IL-1β mRNA in small intestine was both significantly higher in severe AP and MSC groups than those in control group. Compared with AP group, the expression quantity of TNF-α mRNA and IL-1β mRNA in pancreas was significantly lower in MSC group. The relative expression quantity of TNF-α mRNA and IL-1β mRNA in small intestine were both significant higher in severe AP and MSC groups than those in control group. The expressions of TNF-α mRNA and IL-1β mRNA in MSC group were lower than those in severe AP group. The beneficial effects of MSCs seem to be primarily mediated via indirect actions but not by their differentiation into target cells. Wang *et al* [68] showed beneficial effects of bone marrow-derived MSCs on AP-associated lung

injury in rats. Results showed that serum amylase activity was decreased and pulmonary edema and the expression of TNF-α was significantly diminished in MSC transplanted group.

It has also been reported that autologous bone marrow MSCs can be used for the treatment of CP.

It has been suggested that bone marrow-derived MSCs has a role in pancreatic tissue repair by contribute to the pancreatic stellate cell population. In the absence of preneoplastic lesions, these cells contribute at a very low level to the ductal epithelium of the chronically inflamed pancreas [69]. MSCs are thought to alleviate pancreatic edema and inflammatory infiltration by regenerating pancreatic cells. Jung *et al* [55] proposed that MSCs alleviate AP through specific accumulation in injured pancreatic tissue rather than through cell regeneration. In this study, inflammation was inhibited by promoting apoptosis of CD4+ T cells. Bone marrow-derived MSCs reduced expression of inflammation mediators and cytokines in rats with mild and severe AP. MSCs suppressed the mixed lymphocyte reaction and increased expression of Foxp3(+) (a marker of regulatory T cells) in cultured rat lymph node cells. Rats with mild or severe AP that were given infusions of hcMSCs had reduced numbers of CD3(+) T cells and increased expression of Foxp3(+) in pancreas tissues. MSCs might alleviate pancreatitis by regulating immune function rather than by regeneration of pancreatic tissue.

3.1.2. Adipose-derived MSCs

After in vivo administration, human adipose-derived stem cells (hADSCs) migrate into injured tissue, where they inhibit the release of pro-inflammatory cytokines, promote the survival of injured cells, and finally inhibit inflammation [70]. Baek *et al* [71] have shown that the migration of hADSCs into injured/inflamed sites in vivo is mediated by various factors including growth factors and chemokines. hADSCs would be a potential therapeutic strategy for AP, based on its properties that control inflammation, immune response, and tissue repair. Further research should focus on the interaction between hADSCs and pancreatic acinar cells, immune cells, pancreatic stellate cells, and fibroblasts [72]. Although reserachers agree about the potency of adipose-derived MSCs on tissue repair, to my knowledge, any related experimental and clinical study has been reported so far.

3.1.3. Umblical cord-derived MSCs

The studies about the umblical-cord derived stem cells (UCMSCs) are also limited. Yang *et al* [73] injected 5×10^4, 5×10^5 5×10^6 or 1×10^7 cells/kg of umblical cord stem cell suspension into the tail vein at 0 h, 1 h, 6 h and 12 h after the induction of severe AP by sodium taurocholate in rats. Mortality in rats receiving 5×10^6 cells/kg of UCMSCs at 0 h was 10% compared with 58% in the severe AP group. Ascites, serum amylase and wet-dry pancreatic weight significantly decreased. Pathologic injuries of pancreatic and pulmonary tissues were markedly alleviated. Administration of umblical cord-derived MSCs at the doses of 5×10^5, 5×10^6 and 1×10^7 cells/kg at 1 h or 5×10^6 cells/kg at 6 h significantly reduced the severity of AP. The data of the study of Yang *et al* [73] showed that UCMSCs cannot differentiate into other cells in 24 hours. The authors conclude that the prevention of damage has nothing to do with a differentiation of cells and that it seems to be a paracrine effect that can modulate immune function.

UCMSCs may also be a promising therapeutic intervention for human CP in the future. In the study of Zhou et al [74] a rat model of CP induced by dibutyltin dichloride (DB) was used. UCMSCs were administered intravenously on day 5 after the administration of DB. UCMSCs were detected in inflamed pancreatic tissues on days 14 and 28. Umbilical cord mesenchymal stem cell treatment reduced the histological scores of pancreas samples and improved the fibrosis. The expression of cytokines in the DB group was significantly higher than that of DB + UCMSC group. Pancreatic stellate cell activation was also inhibited by UCMSC treatment.

Stem cell types, dosages, application routes, main benefits and adverse reactions of stem cell therapies on acute and chronic pancreatitis are summarized in Table 1.

Source (Country)	Pancreatitis type	Experimental design	Species	Stem cell type	Dosage	Route	Sacrification time	Examined organ/organs	Main benefits	Adverse effects
Cui et al; 2003 China (Ref. no: 65)	Severe AP	L-arginin-induced	Female Balb/c mice	Bone marrow-derived MSC	2×10^7; 4 days prior to SAP induction	Tail vein	24th., 48th. and 72th. after induction of SAP	Pancreas	↓ Mortality rate Amylase level Pathological changes	😊
Chen et al; 2013 China (Ref. no: 66)	Severe AP	5% sodium taurocholate-induced	Male Sprague-Dawley rats	Bone marrow-derived MSC	1ml (1×10^6/mL) at 0. hour of SAP induction	Tail vein	6th. 12th. 24th. hours after induction of SAP	Pancreas Kidney	↓ Amylase level Creatine level BUN level Pathological changes US changes	😊
Tu et al; 2012 China (Ref. no: 14)	Severe AP	Sodium deoxycholate-induced	Male Sprague-Dawley rats	Bone marrow-derived MSC	2ml (1×10^6 cells/mL) 2 min after SAP induction	Caudal vein	6th. 24th. 72th. hours after induction of SAP	Pancreas cells (in culture) Small intestines	↓ Amylase LD level MDA content Pathological changes ↑ SOD activity	😊
Sun et al; 2013 China (Ref. no: 67)	Severe AP	L-arginin-induced	Male Sprague-Dawley rats	Bone marrow-derived MSC	5×10^6, once daily for 3 days	Peritoneal	72th. hour after induction of SAP	Pancreas Small intestines	↓ TNF-α mRNA IL-1β mRNA Pathological changes	😊
Wang et al; 2012 China (Ref. no: 68)	Severe AP	5% sodium taurocholate-induced	Male Sprague-Dawley rats	Bone marrow-derived MSC	1 ml (1×10^6/mL), 2 hours after SAP induction	Injection	1th, 3th, 6th, 12th and 24th hours after induction of SAP	Lung	↓ Amylase level MPO level TNF-α Substance P Pathological changes	😊
Marrache et al; 2008 USA (Ref. no: 69)	Severe CP	Cerulein-induced	Female C57BL/6 rats	Bone marrow-derived progenitor cells	Total 5×10^6 bone marrow cells, 4 weeks before CP induction	Tail vein	0, 6, 20, 30, 45 weeks after CP induction	Pancreas	↓ Pathological changes	Eosinophilic metaplasia (a reactive change to BMT)
Yang et al; 2013 China (Ref. no: 73)	Severe AP	Sodium taurocholate-induced	Male Sprague-Dawley rats	Umbilical cord-derived MSC	5×10^4- 5×10^6, 1×10^7 cells/kg of UCMSC suspension	Tail vein	48 hours after AP induction	Pancreas Lung	↓ Mortality rate Amylase level Ascite TNF-α Interferon-γ Pathological changes	😊
Zhou et al; 2013 China (Ref. no: 74)	Severe CP	Dibutyltin dichloride-induced	Male Sprague-Dawley rats	Umbilical cord-derived MSC	2×10^6 UCMSCs in 100 μL of PBS on day 5 after CP induction	Jugular vein	On days 14th and 28th after CP induction	Pancreas	↓ Amylase level Pathological changes Fibrosis	😊

AP: Acute pancreatitis, BMT: Bone marrow transplantation, BUN: Blood urea nitrogen, CP: Chronic pancreatitis, IL: Interleukin, LD: Lactate dehydrogenase, MDA: Malondialdehyde, MPO: Myeloperoxidase, MSC: Mesenchymal stem cell, SAP: Severe acute pancreatitis, SOD: Superoxide dismutase, TNF: Tumor necrosis factor, UCMSC: Umblical cord mesenchymal stem cell, US: Ultrastructural

Table 1. A brief summary of characteristics of included studies

As a conclusion, although stem cell transplantation to patients with acute or chronic pancreatitis has not been performed so far, it is clear that stem cell transplantation might be a promising therapeutic approach for acute and chronic pancreatitis in the very near future.

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