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OBM Genetics

Review

Potential Use of Human Mesenchymal Stem Cells (hMSCs) in Pancreatic Damage/Cancer

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Academic Editor: Lunawati L Bennett

Special Issue: Gene Therapy on Cancer

OBM Genetics
2024, volume 8, issue 3
doi:10.21926/obm.genet.2403252

Received: March 13, 2024
Accepted: July 08, 2024
Published: July 17, 2024

Abstract

Pancreatic damage and pancreatic cancer pose significant challenges due to their complex pathogenesis, limited treatment options, and poor prognosis. In recent years, the potential use of human Mesenchymal Stem Cells (hMSCs) has been explored to address these complex pancreatic conditions and develop novel therapeutics. hMSCs, known for their regenerative and immunomodulatory properties, offer a novel therapeutic avenue for repairing damaged tissues and possibly inhibiting cancer progression. This communication discusses current research findings on the application of hMSCs in pancreatic damage and cancer treatment while evaluating hMSC-mediated gene therapy in pancreatic disorders. Moreover, the challenges and considerations associated with hMSC-based therapies and the potential best

therapeutic approaches are discussed. Furthermore, the current scientific evidence regarding hMSCs in revolutionizing the management of pancreatic damage and cancer, offering future perspectives for improved therapeutic strategies for patients facing these daunting conditions, is critically discussed.

Keywords
Pancreatic cancer; human mesenchymal stem cells; gene therapy; tumor-targeted therapy

1. Introduction

The pancreas regulates critical biological functions, including digestion and blood sugar [1]. Pancreatic damage can occur by an injury or harm to the pancreas. Some of the significant factors associated with pancreatic damage are pancreatitis, autoimmune disorders, severe infections, trauma, and obstruction. Pancreatitis is a condition characterized by the acute or chronic inflammation of the pancreas due to causes such as gallstones, certain medications, infections, and alcohol abuse. While recent studies have shown the gene mutations associated with the digestive protease-antiprotease pathway, stating that pancreatitis could be an autodigestion disease, the severity of pancreatitis is mainly driven by the local and systemic immune responses by the immune cells [2].

In some cases, autoimmune disorders may initiate pancreatic damage, i.e., autoimmune pancreatitis, leading to the immune system attacking the pancreas. Moreover, the pancreas can also be damaged by severe infections such as mumps, as well as by physical injuries and by blockages in the pancreatic duct or bile duct, leading to dysregulated digestive enzymes. Pancreatic trauma is injury or damage to the pancreas in which the severity of the damage can range from minor contusions to pancreatic ruptures. Overall, pancreatic damage may result in serious complications, including digestive problems, diabetes, pancreatic cancer, and organ failure [3]. Pancreatic inflammation, which is characterized by upregulated pro-inflammatory pathways, is shown to be one of the contributing factors to pancreatic cancer development [4, 5]. Therefore, the critical evaluation and treatment of pancreatic damage cases is vital.

Pancreatic cancer (PC) is among the most aggressive types of cancer, and its incidence rate has been steadily increasing over the years, with a poor prognosis [6]. The National Cancer Institute (NIH) in the United States has reported a 12.5% five-year relative survival rate of PC from 2013 to 2019. In 2023, the estimated number of deaths from PC is 50,550 [7]. Early detection of PC with imaging approaches poses a challenge because of the abdominal location of the pancreas and may not cause any symptoms at the beginning of the disease; thus, significant symptoms typically do not manifest in patients until the cancer has progressed to an advanced stage [1]. Pancreatic cancer has been classified into two main categories: exocrine and endocrine. Exocrine cell tumors, i.e., pancreatic ductal adenocarcinoma (PDAC), are more common than the endocrine-cell-originated tumor types. Despite recent advances in the treatment of pancreatic cancer, existing approved therapies for PDAC have only about 3-34% efficacy, depending on the stage of the tumor [8]. The current therapeutic strategies often have limited success due to the heterogeneity and complexity of the tumor and its microenvironment (TME), which hinders the delivery of therapeutics and

usually results in drug resistance. Although there are also surgical resection opportunities for the early stages of PC, most of the patients can not undergo surgical treatments owing to their cancer's silent and rapid progress, making it challenging to treat by surgery [9]. Moreover, a combination of chemotherapies has also been studied, which often failed with a survival rate of less than a year [10]. Hence, more effective treatment strategies for this compelling cancer must be developed urgently.

Human mesenchymal stem cells, or mesenchymal stromal cells (MSCs or hMSCs), are adult stem cells with self-renewal and multilineage differentiation capabilities [11]. These cells can be expanded *ex vivo* following their isolation from different tissues, such as bone marrow, placenta, dental pulp, and adipose tissues [12, 13]. hMSCs provide supportive stroma for the growth and differentiation of hematopoietic stem cells (HSC) and hematopoiesis. Moreover, MSCs can differentiate into various cell types, including osteoblasts, chondrocytes, and adipocytes, demonstrating their versatile nature and allowing for their extensive use in research and therapeutic applications [1]. Thus far, there has been a broad spectrum of diseases and conditions in which the MSCs are investigated as a therapeutic strategy. Due to their plasticity, self-renewal, ability to induce tissue repair, and tumor homing and immunomodulatory properties, MSCs possess considerable potential for developing therapeutics in PC. MSCs possess immunomodulation, affecting immune responses through interactions with various immune cells and local microenvironmental factors [2]. Hence, the immunomodulatory effects of MSCs make them a valuable target for the treatment of immune-related diseases and for promoting tissue regeneration [2-4].

Furthermore, MSCs are used as an upcoming tool, particularly in transdifferentiation, due to their differentiation potential, ease of isolation, and readily transduction by various vectors. Thus, they are used as vehicles for both long/short-term gene therapy [5]. Therefore, the therapeutic potential of MSCs includes their utilization as potent candidates in gene therapy for various medical conditions, including cancer [14]. This study summarizes current research findings on the application of hMSCs in pancreatic damage and pancreatic cancer treatment while evaluating hMSC-mediated gene therapy in PC. Furthermore, this paper will address the challenges and considerations associated with hMSC-based therapies and examine potential therapeutic approaches.

2. Understanding Pancreatic Damages and Cancer

Pancreatic damage can be classified into two main categories: trauma-related injuries and damage from inflammation. Despite its location in a protected environment, the pancreas is open to trauma. These trauma-related injuries are called blunt trauma (motor vehicle accidents, falls, or direct physical assaults). Mechanistically, blunt trauma induces a localization shift in the abdominal cavity organs, which puts pressure on the pancreas, resulting in injury. Pancreatic discoloration occurs due to blunt trauma and may lead to inflammation initiation. More severe traumatic injuries can generate pancreatic lacerations in which, depending on the tears in the pancreatic tissue, damage can cause internal bleeding and infection. Bleedings because of pancreatic trauma can lead to hematomas [15, 16]. More severe types of bleeding, such as pancreatic hemorrhage, are the primary cause of pancreatic trauma-related deaths and necessitate urgent medical intervention.

On the other hand, some injuries can disrupt the exocrine function of the pancreas, resulting in digestive enzyme transportation problems due to pancreatic duct injury. While trauma-related

pancreatic injuries are not familiar, these types of injuries, which can be challenging to diagnose, can lead to severe and potentially hazardous outcomes [15]. Inflammation-induced pancreatic damages are the pathologies characterized by inflammation of the pancreatic tissue prominently represented by the condition known as pancreatitis. Pancreatitis manifests in acute and chronic forms, driven by different etiological factors. The risk factors of pancreatitis may include excessive alcohol consumption, certain medications, infections, and gallstones, i.e., obstruction of the pancreatic duct by gallstones is observed in acute pancreatitis. Pancreatitis leads to the production of chemokines from damaged pancreatic tissue, which attracts inflammatory cells. The systemic action of the inflammation primarily determines the severity of the disease. In severe cases, it can result in the progressive disruption of multiple organ systems, leading to systemic inflammatory disease and multiorgan dysfunction syndrome [17, 18].

The development of the PC involves a series of stages that progress rapidly. This transformation originates from noncancerous precursor lesions known as pancreatic intraepithelial neoplasia (PanIN) lesions and evolves into invasive carcinoma. PanIN lesions are categorized by the extent of cellular and nuclear changes, ranging from low-grade (PanIN-1A/B) to high-grade (PanIN-3) lesions. Over time, many genetic changes accumulate and propel the histological progression through the PanIN stages (PanIN-1 to PanIN-3). These changes encompass genetic mutations, alterations in various genes that promote or suppress tumors, and microRNAs (miRNAs). In the early stages of low-grade PanIN lesions (PanIN-1), mutations in the Kirsten rat sarcoma oncogene homolog (KRAS), overexpression of oncogenic miRNAs, and activation of stromal-associated factors are present. Intermediate lesions (PanIN-2) are marked by Mucin 1 (MUC1) overexpression and inactivating mutations in the p16/CDKN2A gene. Finally, advanced lesions (PanIN-3) are associated with inactivating mutations in several tumor-suppressor genes such as tumor protein p53 (TP53), breast cancer type 2 susceptibility protein (BRCA2), and mothers against decapentaplegic homolog 4 (SMAD4) [17, 19, 20] (Figure 1A).

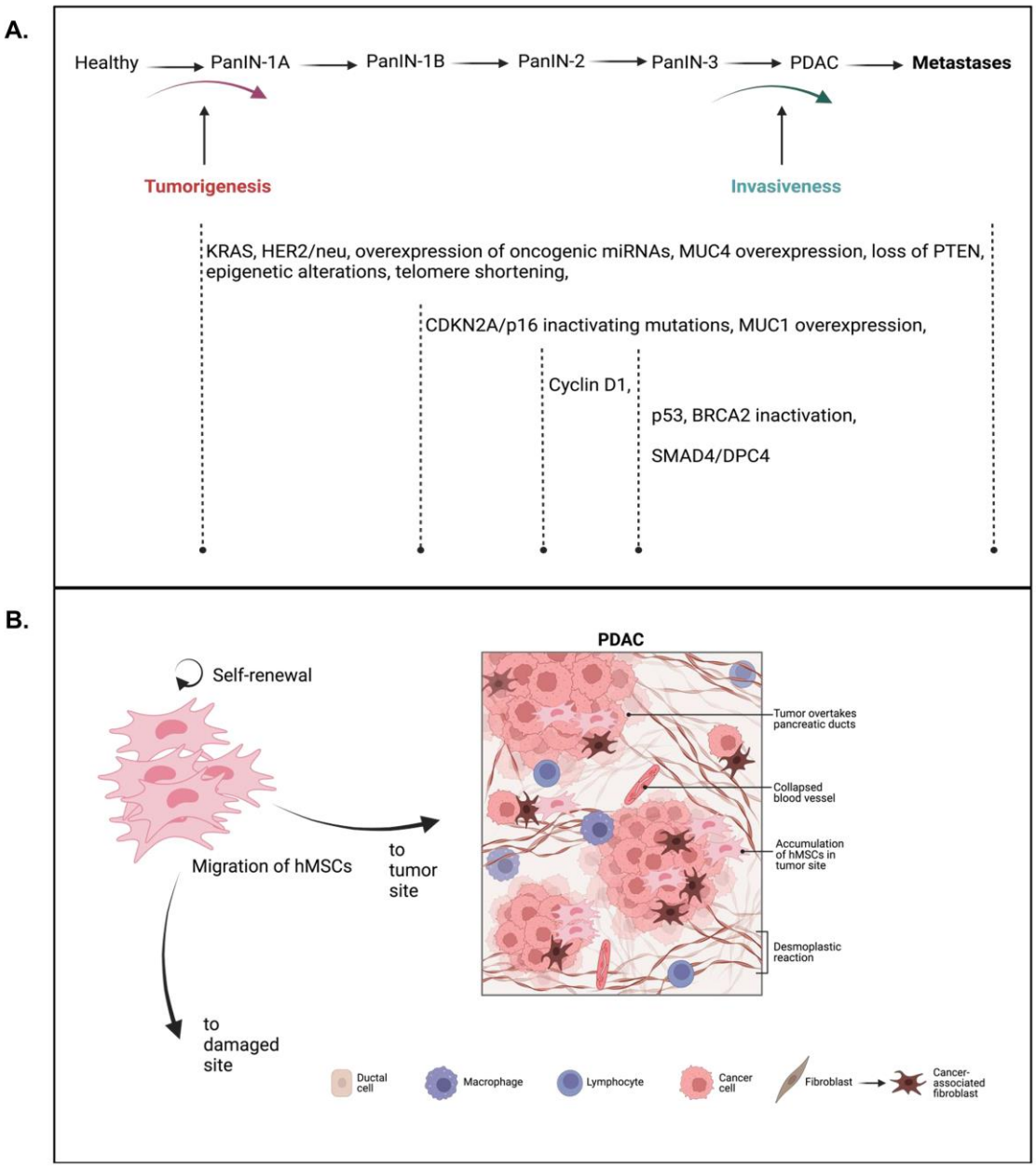

Figure 1 The Multistep Progression of PDAC (A). The illustration describes several molecular and histopathological changes involved during the development of PDAC. PanIN: pancreatic intraepithelial neoplasia; KRAS: Kristen rat sarcoma oncogene homolog; HER2/neu: Human epidermal growth factor receptor 2; MUC4: Mucin 4; PTEN: Phosphatase and tensin homolog; CDKN2A/p16: Cyclin-dependent kinase inhibitor 2A; BRCA2: Breast cancer type 2 susceptibility protein; SMAD4/DPC4: Mothers against decapentaplegic homolog4/Deleted in pancreatic cancer-4. The migration of hMSC to PDAC niche (B). hMSC homes to the tumor site accumulate there and contribute to tumor stroma. hMSC acts as a feeder layer for cancer-associated fibroblasts (CAFs), promoting their effects on the tumor site. hMSC accumulates in the TME and eventually leads to increased cancer progression, inhibition of anti-tumor immune response, angiogenesis, and provoke metastatic spread. The illustration was created with BioRender.com.

PDAC is characterized by a heterogeneous stroma comprised of cancer-associated fibroblasts (CAFs), neoplastic cells including cancer stem cells (CSCs), pancreatic stellate cells (PSCs), immune cells (primarily immunosuppressive subtypes i.e. regulatory T cells (Tregs), T-helper (Th)17 cells, tumor-associated macrophages (TAMs)), cytokines, extracellular matrix (ECM), growth factors and ligands [21]. PDAC is characterized by an immunosuppressive microenvironment with pro-tumoral inflammation [22]. Besides, the dense TME is a barrier to developing effective therapeutics and promotes the development of drug resistance and metastasis [8, 21, 22]. Crucially, hMSCs can migrate to the TME, where they can crosstalk, modulate the immune response, and contribute to ECM remodeling [23]. It is worth mentioning that cancer-associated fibroblasts (CAFs) are one of the major players driving the dense TME in PDAC. Considering the unique role of CAFs in PDAC, one should not rule out their origin, mesenchymal stem cells (MSCs). Recent studies have made progress in suggesting the biological role of MSCs in cancers of several origins. Previous studies have reported that bone marrow-derived MSCs were preferentially accumulated in pancreatic cancers *in vivo,* [24] promoting tumor growth, metastasis, angiogenesis, etc. Moreover, Kabashima-Niibe *et al.* reported that MSCs play a pivotal role in the induction of epithelial-mesenchymal transition (EMT) of PDACs [25]. In PDAC progression, CAF subpopulations contribute to TME heterogeneity and drug resistance. However, understanding the molecular mechanisms underlying CAF subtypes in PDAC progression requires more research. Miyazaki et al. showed that adipose-derived MSCs were shown to be differentiated into CAF subtypes *in vitro.* Hence, the investigation of MSCs' effects on CAF differentiation and TME regulation both *in vitro* and *in vivo* will shed light on our better understanding of the molecular mechanisms of the heterogeneous TME in PC [22, 26] (Figure 1B).

Since PDAC is diagnosed in the late stages of the disease, surgery options for its treatment can only be applied to a minority of PDAC patients. Therefore, available treatment strategies often include radiation and traditional chemotherapy drugs like gemcitabine, and, more recently, combination regimens such as FOLFIRINOX (combining 5-FU, Folinic Acid, Irinotecan, Oxaliplatin) and nab-paclitaxel. However, while GEM + nab-paclitaxel and FOLFIRINOX can provide clinical stabilization, they do not offer long-term effectiveness and can cause toxicity in patients. Chemotherapy resistance is the main obstacle in the treatment of pancreatic cancer, and thus, new therapeutic interventions are needed [22, 27]. In addition to these conventional treatments, targeted therapies such as PARP inhibitors and immunotherapy are also considered, depending on the patient's ability to tolerate the treatment. However, owing to the PC's complex microenvironment, current immune checkpoint- inhibitors such as anti-PD-1/PD-L1 therapy have limited effect on the PC. The rapid progress of this malignancy with poor prognosis requires alternative and more effective therapeutic strategies [6, 27].

Gene therapy can be considered a novel approach to the treatment of pancreatic cancer, especially for patients with unresectable or metastatic pancreatic cancer. Gene therapy might overcome therapy resistance frequently seen in conventional treatments by incorporating personalized medicine approaches with reduced side effects. While gene therapy has the potential to become a long-term treatment option, transforming pancreatic cancer into a manageable disease, further research is needed to confirm its effectiveness in PC [22, 27].

hMSCs are gaining popularity as a potent treatment strategy due to their unique properties, including targeted drug-gene delivery, interactions with tumor stroma, sensitization to traditional treatments, and immune modulation. They have been proposed as promising candidates for gene therapy due to their ability to act through multiple mechanisms [8]. Their application in PC has a

dual perspective as they still have unresolved concerns regarding their bench-to-bedside translation [8, 27].

3. Therapeutic Potential of hMSCs in Pancreatic Damage and Pancreatic Cancer

Stem cells attract significant interest in regenerative medicine and cancer owing to their multi-dimensional mode of action comprising chemokines, cytokines, and paracrine action. Although emerging supportive literature research demonstrates promising results, there have been limited clinical studies on the utility of stem cells in pancreatic diseases [8].

hMSCs are adult stem cells characterized by multilineage differentiation immunomodulatory and regenerative properties [23]. They can be isolated from distinct organs, including the adipose, bone marrow, and menstrual blood [28, 29]. MSCs have been reported to migrate to specific tissues in the human body, including injured tissue and tumors [23, 30]. Subsequently, MSCs reduce inflammation in the target tissues by releasing molecules such as cytokines, chemokines, growth factors, and stem cell-derived extracellular vesicles (i.e., exosomes). These immunomodulatory effects of MSCs are also observed in cancer and TME through the regulation of immune pathways [23, 31]. The immunomodulatory microenvironment produced by MSCs is accomplished through the influence of immune responses through the induction of regulatory T cells (Tregs), Dendritic cell (DC) modulation, and the secretion of immunomodulatory molecules [8].

Cell-based therapies such as stem cell therapy have been demonstrated to be an alternative option for pancreatic cancer. Compared to conventional treatments, stem cells display distinct tumor-homing abilities for primary and metastatic tumors, making them a significant candidate for targeted cancer therapy [11, 31, 32]. This capability of stem cells to target tumors might be simply due to the cooperation of their secretome. For instance, cytokines such as tumor necrosis factor-alpha (TNF-α), Interleukin-6 (IL-6), IL-1β, and interferon-gamma (IFN-γ) are involved in facilitating the adhesion and passage of MSCs through the vascular endothelial layer. Moreover, other functional molecules and chemokines, such as the stromal cell-derived factor-1 (SDF1), trigger cell chemotaxis, directing MSCs toward tumor locations through the CXCR4-SDF1 pathway [28].

3.1 Promising Research in hMSC-based Therapies

Various studies evaluate the role of hMSCs as regenerative and anti-cancer therapies in pancreatic diseases. Even though the reports underline the multifaceted effects of hMSCs, more recent research is anticipated to address these constraints [33-35]. In a recent study, MSCs derived from buccal fat pads were shown to have antidiabetic activity in the diabetic rat model through the regeneration of damaged pancreatic beta cells [36]. Furthermore, bone marrow-derived MSCs were shown to eliminate oxidative stress and reduce inflammation by inhibiting the NF-κB pathway, thereby improving acute pancreatitis in a rat model [37]. Besides, human adipose tissue-derived MSCs were also reported to preserve pancreatic acinar cells during severe acute pancreatitis by inhibiting ER stress and inflammation in a mouse model [38]. The secretome of human amniotic MSCs has immuno-modulatory and extracellular matrix-modulatory effects [6], contains angiogenic factors, and includes proteins related to cell motility and wound healing [7, 8]. Studies showed that the secretome of human amniotic MSCs has an anti-tumor effect on the Panc-1 pancreatic cancer cell line by regulating apoptosis, autophagy, invasion, and EMT [9-11].

Moreover, the secretome of human amniotic MSCs had hampered effects on the pancreatic cancer cells *in vitro* by suppressing the expression of essential molecules in cell signaling, including EGFR, c-Src, and SGK223 [39]. An analysis of hMSCs derived from adipose tissues has established their potential as an anti-tumor strategy and inducer of tumor cell death in PDAC, both *in vitro* and *in vivo*. The inhibitory effects of adipose tissue MSCs were further elucidated, showing that they induce cell cycle alterations, resulting in tumor growth inhibition [40]. On the other hand, MSC secretome has enormous effects on regulating cellular processes in PC [41, 42]. A recent study by Huo et al. revealed that PDAC progression was suppressed by the conditioned medium derived from K-Ras-proto-oncogene-overexpressing MSCs [42]. More importantly, bone marrow MSC-derived exosomes were shown to regulate pancreatic cancer cell stemness, proliferation, and migration through their cargo molecules, including circulatory RNAs (Exosomal circ_0030167), [41, 43] and microRNAs (Exosomal microRNA-143) [44]. In a study published by Kamerkar et al., engineered exosomes derived from MSCs were shown to target KRAS and inhibit cancer growth *in vivo* with increased overall survival [45].

Additionally, MSC-derived extracellular vesicles have been used as targeted therapy and drug delivery strategies to transfer molecules, including pro-drugs, miRNA, and siRNAs for PC, to enhance immunotherapy, promote the regulation of TME, and inhibit tumor growth [46, 47]. These recent studies establish the ability of MSC-derived extracellular vesicles to be utilized in a way to specifically target the tumor cells and also provide anti-tumor effects in the TME with greater stability, improved effectiveness, and reduced adverse effects [8, 48].

The primary characteristic of the hMSCs that could be used in cancer therapy is their ability to home to the primary and metastatic tumor sites. Recent studies have shown that stem cell use from adult tissue may be a novel vehicle for stem cell-mediated cancer therapy with improved anti-tumor effects. Stem cells have been used as vehicles to deliver various agents to tumor sites, which has been shown to decrease tumor size. Previously, our group has demonstrated that the homing ability of hMSC can turn into vehicles to deliver and release the therapeutic agent into the tumor cell mass, causing death in tumor cells. Combining target genes and self-suicide genes minimizes tumor size [11, 49, 50] (Figure 2). In various studies, genetically modified MSCs have been shown to increase apoptosis and decrease growth and angiogenesis in solid tumors [12].

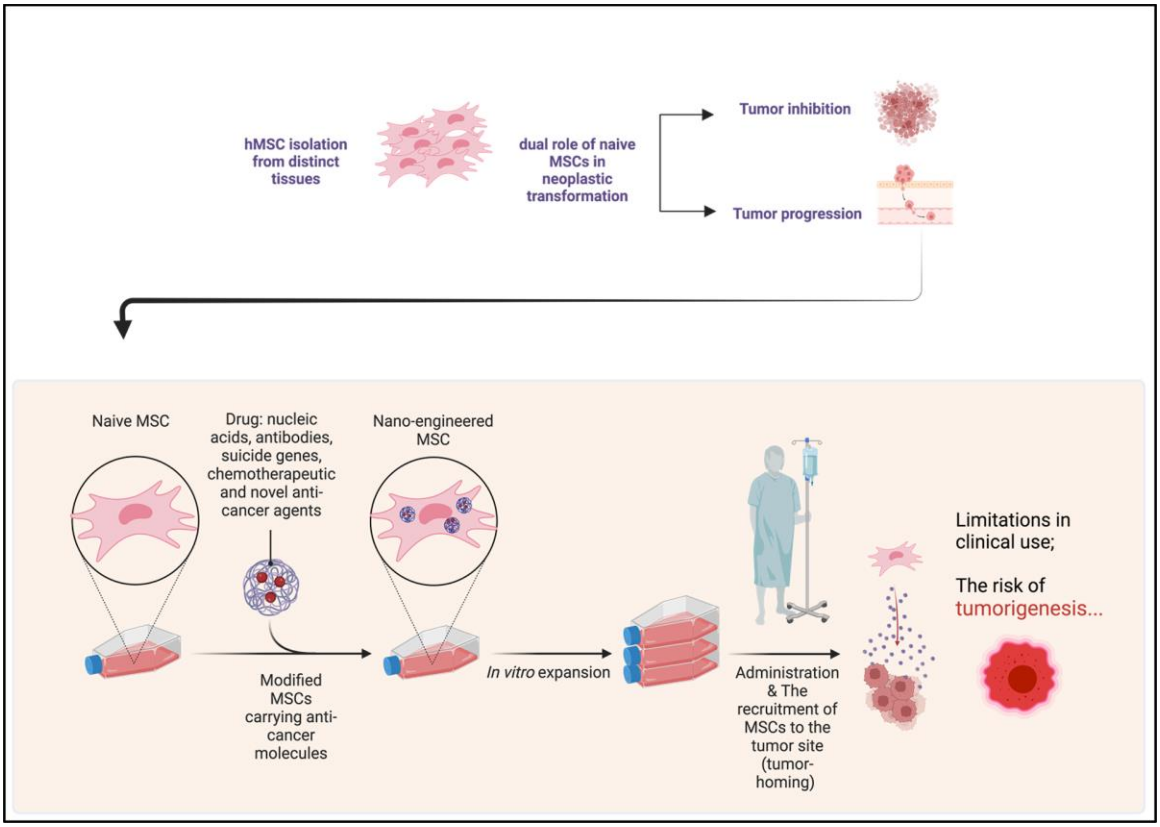

Figure 2 Utilization of engineered hMSC for targeted delivery of anti-cancer therapeutics. The illustration was created with BioRender.com.

In summary, MSCs from different cellular origins were investigated as a potential treatment approach for suppressing excess inflammation and repairing damaged tissue in pancreatic diseases, which also have non-toxicity against normal tissues [51-56]. However, the current literature does not have a consensus on the standardized protocol for the efficacy evaluation of isolated MSCs from various sources. It does not address the limitations regarding their application in the clinic [4, 12].

3.2 Discouraging Findings in hMSC-based Therapies

As mentioned earlier in the present communication, several studies have demonstrated the anti-tumorigenic effects of MSCs with tumor growth inhibitory roles in distinct malignant cells. Nevertheless, there has been accumulating evidence suggesting that MSCs have double-edged roles [33, 57]. For instance, native MSCs have been shown to interact and crosstalk with the tumor cells, representing both pro- and anti-oncogenic properties [57]. In the study by Ren et al., tumor-resident MSCs, especially in inflammatory environments, were shown to promote tumor growth by recruiting monocytes/macrophages. These MSCs had more tumor-promoting effects than normal tissue-derived MSCs [58]. Another study also demonstrated the pro-tumorigenic effects of stroma-derived MSCs through the secretion of monocyte/macrophage chemoattractant and alternative macrophage polarization [59]. In addition, MSCs were shown to promote pancreatic cancer cells' invasion and tumor growth by regulating epithelial-to-mesenchymal transition and VEGF production by MSCs [24, 25, 60]. Another study also shows that Secreted mucin 5AC (MUC5AC) acts as an oncogene in pancreatic cancer by facilitating the mobilization of adipose tissue-derived MSCs, contributing to the integrity of stromal heterogeneity [61]. Therefore, the potential application of

MSCs and their derived extracellular vesicles/exosomes in PC should be explored and monitored thoroughly before and during clinic application. Yet, tumor-associated MSCs displaying tumor-promoting manifestations could be of note as potential therapeutic targets to be inhibited in developing pancreatic cancer treatment. Finally our group previously showed that epigenetic alterations, such as hypermethylation of specific genes, could contribute to the tumorigenicity of hMSCs, suggesting that the use of hMSC in clinical applications requires close monitoring and targeting these alterations may be a strategy to protect against the neoplastic transformation of hMSCs [62].

4. Gene Therapy in Pancreatic Cancers: hMSCs as a Gene Therapy

Gene therapy is considered among the innovative strategies for inherited genetic diseases such as sickle cell anemia and acquired pathologies, including cancers. Gene therapy involves the genetic manipulation of the cells using nucleic acid to 'correct' the disease at the gene level [14]. To date, several gene therapy approaches, including adoptive immunotherapy (such as chimeric antigen receptor T-cells/CAR-T technology), viral vector-based therapies, and therapeutic vaccines, are being studied in pre-clinical and clinical phases for the treatment of various cancers, including pancreatic cancer [22, 63-66].

In a very recent work conducted by Barbey et al., a gene therapy product known as CYL-02, which encodes somatostatin receptor 2, deoxycytidine kinase, and uridylate monophosphate kinase and is complexed with a polyethyleneimine non-viral vector, was developed and shown to exhibit anti-tumor effects in the context of PC [67]. This study subsequently formulated a combinatorial approach with Gemcitabine, which was tested in a Phase 1 trial, and promising results were obtained for further investigation in a Phase 2 trial [68]. The CAR-T cell therapy approach is also being studied in various cancers to specifically target the tumor cells and reverse the immunosuppressive TME in cancer [64, 69, 70]. However, its application and efficacy are challenged by the limited presence of cancer-specific expressed antigens in solid tumors, such as PC. In Posey Jr et al., an abnormal glycoform of membrane mucin MUC1, Tn-MUC1, a neoantigen, was established as a cancer-specific target in CAR-T cell therapy in pancreatic cancer and leukemia xenografts. Since normal healthy cells do not express detectable levels of Tn-MUC1, abnormally glycosylated antigens are essential to be considered targets for CAR-T cells [71, 72]. In a case study conducted by Leidner et al., metastatic PC was treated with a single administration of autologous T cells. In this study, T-cells were engineered to have specific T-cell receptors (TCRs) on their surface to target driver mutation, KRAS G12D, expressed by the tumors. This neoantigen TCR gene therapy led to the regression of cancer in this patient [73].

The genetic profile of PDAC is well-established, characterized mainly by inactivated tumor suppressor pathways (INK4a/ARF (p16), TP53, DPC4/Smad4), activated oncogenic KRAS, and an increase in telomerase activity in the later stages of the tumor [22]. More recently, protein-protein interaction network analysis revealed eight differentially expressed genes (ADAM10, COL1A2, FN1, P4HB, ITGB1, ITGB5, ANXA2, and MYOF) as genomic biomarkers in PC development [74]. The study also performed molecular docking studies and suggested five repurposable drug molecules for the identified genes. Overall, these molecules govern significant interest as primary targets in developing gene therapies for PC.

Moreover, the induction of somatostatin receptor subtype(s) expression has gained popularity as a gene therapy target due to its anti-tumor effects in PC [75-77].

MSCs have been shown to express several chemokine receptors, including CCR1, CCR7, CCR9, CXCR3, CXCR4, CXCR5, and CX3CR1, which make them migrate towards the damaged tissues in response to the chemokine-attractive molecules produced by the injured tissues and inflamed TME [8, 14]. Moreover, MSCs are non-immunogenic, representing low or complete lack of MHC I and II expression, important costimulatory molecules for the adaptive immune system. Due to MSCs' homing abilities to migrate to the damaged tissue sides, including the tumors, avoiding the activation and clearance of the immune system cells makes them promising candidates in cellular and gene therapies. Also, due to their 'immune privilege' nature, MSCs serve as a vector for gene therapy [12, 78, 79]. MSCs isolated from distinct biological sources can be genetically manipulated *in vitro* and employed to transfer therapeutics such as prodrugs or bioactive molecules [79, 80]. Hua et al. demonstrated the effects of angiopoietin-1 gene-transfected MSCs in rats with severe acute pancreatitis. It was shown that this treatment reduced pancreatic injury and inflammation with lower levels of proinflammatory cytokines in the serum [54].

Furthermore, human umbilical cord blood-derived MSCs were transduced with a lentivirus vector expressing murine IL15, and this therapy resulted in the regression of the pancreatic tumor in syngeneic mice [81]. The proapoptotic and tumor-selective protein tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a crucial anti-cancer agent [82-84]. Casari et al. showed that adipose tissue-derived MSCs were engineered to release TRAIL [82]. In another study by Spano et al., adipose tissue-derived MSCs were genetically modified to release a soluble trimeric and multimeric variant of TRAIL as a gene therapy strategy for PDAC [85]. Based on the MSC gene therapy strategy, Rossignoli et al. have established a combinatorial therapeutics utilizing MSC-delivered soluble TRAIL and Paclitaxel (a chemotherapeutic agent), demonstrating an efficient treatment strategy in a mouse model of PC [86].

Cancer development may resemble the process of wound healing, and both share similar developmental processes, including the formation of new blood vessels, the activation of fibroblasts, and the modification of the ECM [27]. MSCs have been shown to migrate toward injured/cancer tissues [87]. The migration process highly includes the interactions of MSCs with endothelial cells, various receptors, and chemokines. This recruitment of MSCs to the target tissue requires the movement of the MSCs toward chemoattractants, then adhesion by surface receptors to eventually reach the injured/cancer tissue through blood flow. In the case of tumors, high amounts of inflammatory chemokines and growth factors are released by the tumor cells and immune cells located in the TME [56]. Among the growth factors (i.e., VEGF-A, GM-SCF, TGF-b), CXC chemokine receptor 4 (CXCR4) is considered significant for the recruitment and tumor tropism of MSCs [56, 88]. Hence, MSCs are potential candidates for targeted drug/gene delivery, with high cellular interactions in the targeted microenvironment.

Last but not least, genetically modified MSCs for example with hTERT shown to have expanded life spans while allowing maintenance of their distinct characteristics. This gene manipulation enabled cells to bypass cell cycle checkpoints that balance the state between cell proliferation, senescence, and carcinogenesis. The manipulation of telomere-telomerase activity to increase the proliferative capacity of stem cell populations is a crucial step in using MSCs for therapeutic applications. Still, close monitoring is required simply due to their neoplastic potential. This may also increase the risk of carcinogenesis due to the uncontrolled proliferation of stem cells [13].

5. Challenges and Considerations

hMSCs have been studied for their potential roles in diverse pathologies, including regenerative medicine and cancer. Yet, several challenges and considerations regarding their use in clinics remain elucidated. Of note, no standardized protocols exist for MSC isolation and expansion in cell culture. It has been shown that the extensive replicative history of MSCs in cell culture makes them vulnerable to damage from both intracellular and extracellular influences. Therefore, the extended replication of MSCs in cell culture carries the risk of spontaneous transformation, potentially leading to a carcinogenic phenotype. Consequently, the biosafety profile of MSC therapies should be closely monitored [27, 89]. Although genetic engineering can boost the therapeutic potential of MSCs, it also brings about risks such as unintended genetic alterations and immune reactions. Senescence hampers the cells' ability to proliferate and function, a process hastened by factors like replicative and oxidative stress. Extended culture periods and high passage numbers can cause MSCs to lose their original characteristics and functionality. This underscores the importance of carefully managing culture conditions and passage techniques to maintain cell quality. Addressing these challenges is essential for successfully applying MSCs in regenerative medicine and clinical therapies.

Different subtypes of MSCs could be considered the best option for distinct disease classes; therefore, it is essential to know which stem cell types would be the best therapeutic option for distinct diseases with specific clinical manifestations. There is an urgent need for research on the characterization and utility of these stem cell subtypes [56]. Moreover, the number of cells (dose), treatment duration, site, and route of administration vary in distinct biological circumstances, including pancreatic diseases. These should be considered thoroughly before being applied to the clinic [27]. Also, the persistence and pancreas-targeted distribution of MSCs still requires more research. For instance, intravenous (IV) and Intraperitoneal (i.p.) injections are considered the standard route of administration of MSCs in animal models [27, 90]. However, the majority of the systemically injected MSCs are shown to be initially trapped in the lungs as emboli [27, 91, 92]. Therefore, the optimal timing and dosing regimen and the best delivery route require further investigation to eliminate the side effects and enhance the therapeutic efficacy of MSCs.

Overall, the main challenges underlying the failure of MSCs' clinical development may include the poor-quality control and contradictory characteristics of MSCs (i.e., stability, heterogeneity, biodistribution, and migration capacity), contributing to inconsistent findings from large-scale clinical trials [93, 94].

Besides these challenges, applying MSCs as gene therapy is considered a powerful strategy, yet it still has limitations. In pancreatic disease, the MSCs can be used as drug/gene delivery systems [11]. Also, modifying MSCs' genetic makeup can be accomplished through different delivery methods, with viral vectors being the most commonly employed. Nevertheless, viruses in this context may raise concerns related to cancer development and immune system activation, which could limit their applicability in clinical settings. Consequently, non-viral vectors have emerged as an alternative to overcome these challenges [80].

Ethical and regulatory considerations for the usage of hMSCs have a variety of aspects. These include the requirement of informed consent from donors and patients, ethical sourcing of hMSCs, stringent patient privacy and data protection, rigorous safety and efficacy assessments through preclinical and clinical trials, transparent reporting of findings, and avoiding harm to individuals.

Besides, the effects of MSC-based therapy in the long term should be considered carefully, as these cells may contribute to the formation of new blood vessels (angiogenesis) and aid tumorigenesis. These unwanted side effects are not limited to angiogenesis; differentiation into bone and cartilage is also reported for MSCs. Notably, in a study where adipose-derived stem cells were used to treat macular degeneration, participants experienced irreversible vision loss [95]. Collectively, these factors should aim to protect ethical standards and patients' long-term well-being in the realm of hMSC research and clinical use. Lastly, regulating the biological standards of the MSCs may also contribute to their potential manufacturing practices to be utilized in clinics.

6. Future Directions and Research Prospects

Numerous studies have evaluated the potential applications of hMSCs in distinct diseases, including pancreatic disease. The efficacy of hMSCs isolated from various biological sources has been assessed as a potential therapeutic approach. However, their application in PC has a dual perspective as they still have unresolved concerns regarding their bench-to-bedside translation [8, 27]. Nevertheless, in the past few decades, the amount of MSC-focused research has grown exponentially in both preclinical and clinical trials of either autologous or allogeneic MSCs.

PDAC is a very aggressive cancer type; therefore, treatment strategies using gene delivery systems, mainly systemic delivery, possess difficulties, as in the case of chemotherapy. For instance, the number of transfected cells in the in situ approach is unknown. In contrast, natural barriers such as the bloodstream, nucleases, capillaries, or tumor stroma can hinder *in vivo* gene therapy. Regardless of the route of gene delivery, it is also challenging to reach all tumor cells. Nonetheless, among the classical gene therapy approaches, the *in situ* gene transfer seems promising in PDAC [22].

Moreover, the PDAC microenvironment is highly immunosuppressive, fostering resistance to single-agent immunotherapy, including gene therapy. Thus, combinatorial treatment approaches targeting multiple pathways simultaneously while providing sufficient specificity to cancerous cells possess a better option for this rapidly progressing malignancy. In addition, while several studies investigate the components of TME, understanding the PDAC's multi-faceted TME heterogeneity and the interplay within their molecular/cellular composition is yet to be further investigated. Further research is needed to understand this complexity and establish the signaling network within the TME from the functional and mechanical points of view [21]. Moreover, MSCs can be engineered as gene and cellular therapies. A better understanding of the crosstalk between the cancerous cells and MSCs will provide mechanistic insight to develop MSC-based effective treatment strategies for pancreatic diseases. Indeed, the PC microenvironment drives the invasive and metastatic characteristics of the tumor through the tight signaling between cancerous cells and pancreatic cells with the ECM [22, 27]. Yet, the limitations inhibiting MSCs therapeutic efficacy remain to be elucidated.

On the other hand, MSC-derived extracellular vesicles/exosomes are emerging as a cell-free therapy approach as an alternative to MSCs. Although these vesicles have been shown to have diverse effects in various physiological and pathological circumstances, they have been shown to mimic the cell of origin. Despite using an MSC-derived exosome characterization, further clarification is needed for their utilization in the clinic [96]. Indeed, MSC-derived extracellular vesicle use has good potential, as demonstrated by effects similar to those of MSCs. Nonetheless, they have

remarkable safety profiles, which are the main obstacles in cellular therapies, including MSC-based strategies [96, 97]. Therefore, exosomes could serve as a safer alternative for drug delivery, avoiding the tumorigenesis risk associated with the direct use of MSCs. This approach could have broader therapeutic applications in treating various diseases. It's worth noting that research in this field is promising to fully understand and harness the potential of exosomes for clinical use (Figure 3).

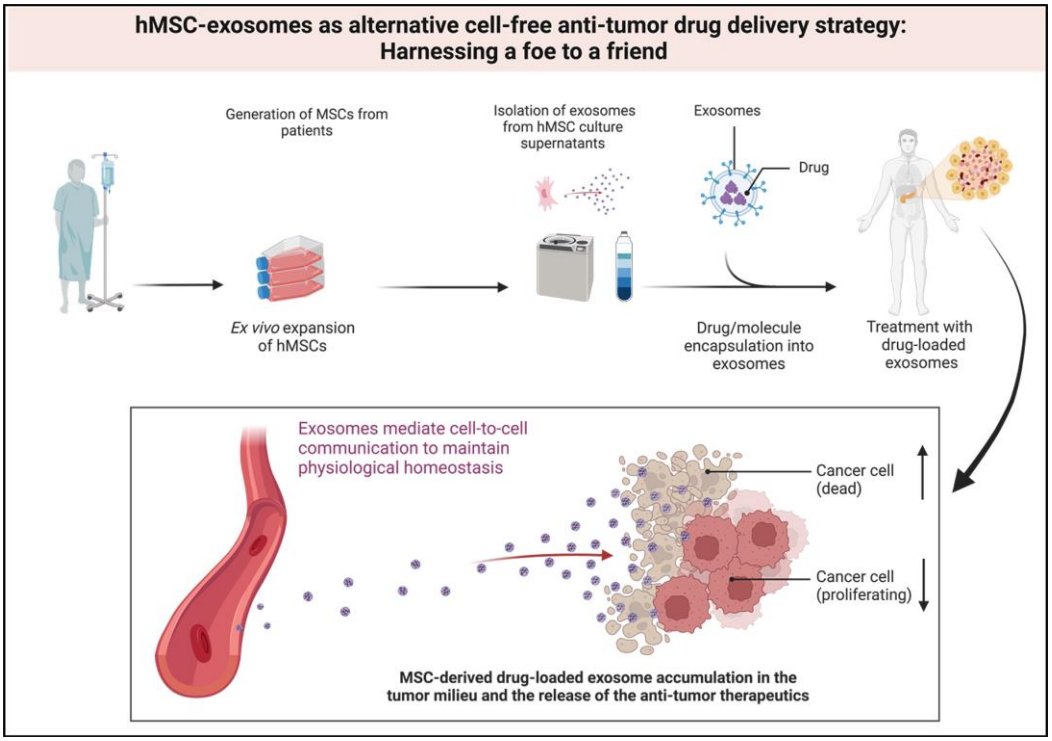

Figure 3 Utilization of hMSC-derived exosomes as alternative cell-free targeted drug delivery platform. The illustration was created with BioRender.com.

Additionally, MSCs have been demonstrated to be engineered for enhanced therapeutic success. In this regard, targeting the MSC metabolism through a genetic engineering approach may improve the MSC functionality, quality, and therapeutic efficiency in pancreatic diseases [94, 98].

Overall, hMSCs exhibit substantial promise as anti-tumor therapy strategies. Although the use of hMSCs in cancer therapy remains an active field of investigation, there has been evidence that further research, particularly for unraveling their precise mechanisms of action and addressing challenges that impede their therapeutic effectiveness, will promote their translation to the clinical phase. Additionally, the advancement of next-generation technologies will contribute to our understanding of how MSCs operate in diverse pathological contexts.

7. Conclusion

Due to their accessibility in human tissues, ease of expansion *ex vivo,* and characteristics, hMSCs are the focus of ongoing research, with potential applications in various medical conditions, including pancreatic diseases. Accumulating evidence demonstrates the potential of MSCs in regenerative medicine and cancer; however, a finding also points to their limitations. Therefore, further research, mainly through clinical trials, is essential for developing practical hMSC-based therapeutic approaches for pancreatic disorders. Nevertheless, clinical trials involving MSCs as gene

therapy demonstrate these cells' wide-ranging and promising uses in treating various diseases. By altering MSCs to express therapeutic genes, scientists seek to boost their regenerative, anti-inflammatory, and anti-cancer capabilities. These trials underscore the potential of MSC-based gene therapies to provide novel treatments for cardiovascular diseases, neurological disorders, musculoskeletal conditions, cancer, genetic disorders, and immune-related diseases, paving the way for future advancements in gene therapy.

Last but not least, upcoming studies should prioritize the long-term monitoring of MSC treatment in animal models and patients with pancreatic diseases. Investigating the biosafety aspects linked to MSC plasticity and pro-tumorigenic effects is vital. Further clinical investigations should consider combinatorial approaches, including genetically engineered MSCs and conventional therapies for treating fast-growing PC. In brief, MSC-based targeted therapies are evolving to revolutionize the management of pancreatic damage and cancer, offering promising future perspectives for improved and innovative therapeutic strategies for patients.

Author Contributions

N.S. conceived of the presented idea. H.O.E. and E.E. took the lead in writing the manuscript. All authors contributed to the final manuscript by reviewing, editing, and providing feedback.

Competing Interests

The authors have no conflict of interest to declare.

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