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Potentials of "stem cell-therapy" in pancreatic cancer: An update

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ABSTRACT

In recent times, cell-therapies like T-activated cells, dendritic cells and natural killer cells have shown increasing promise in treating cancers as evidenced by both animal and human studies in the literature. In addition, stem cells are also being considered as potent anti-cancer agents since they act through multi-pronged approaches (chemokines, cytokines, paracrine action). In this review, we have attempted to discuss the inferences of studies that have used different sub-types of stem cells namely mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs) and neural stem cells (NSCs) in *in-vitro/in-vivo* mice and/or human studies as a treatment modality for pancreatic cancer. Pancreatic cancers are diagnosed in late/metastatic stages hence limiting its progress to partial/disease-free status. Recent literature supports evidences of stem cell therapy in pancreatic cancer with promising results; yet their impact remains inconclusive due to limited studies in human subjects.

With reference to the treatment options for pancreatic cancer, the most studied sub-type of stem cells was HSCs as evident from the available clinical trials. The suggested mechanism of the HSC-transplantation is presumably via the graft-versus-tumor effect that elicits an anti-tumor immune response activated by the T-cell repertoires. On the other hand, the property of MSCs like tropism, migration to tumor site and activation of host immune cells by its secretome, appear to be able to regulate pancreatic tumor microenvironment. Further, drug delivery potential could be mediated via engineered MSCs to enhance the bioavailability of drug/prodrug at tumor site. Conclusively, stem cells have shown great potentials as next-generation therapeutic options.

Introduction

Pancreatic cancer is an aggressive malignancy which is seldom diagnosed in its early stage. Most of the patients have metastatic disease at presentation which results in an over-all survival (OS) of 5–8% [1,2]. It is also being observed that incidence of pancreatic cancer is increasing over the years [3,4]. Pancreatic cancer has been broadly classified in to two major subtypes: exocrine and endocrine. Tumors of exocrine cells i.e., pancreatic ductal adenocarcinoma (PDAC) is more common (>85%) than tumors of endocrine cells [5]. More than 50% of PDAC are diagnosed when the tumor has locally advanced and/or already metastatic. It has been observed that the treatment efficacy ranges from 3 to 34% in different stages of PDAC treated with approved drugs [6].

This marginal benefit of treatment is due to the heterogeneity and complex tumor micro-environment (TME) of PDAC. Therefore, there is an urgent need for alternative therapeutic options for better management of PDAC. One such option is use of stem cell therapy which has shown treatment efficacy in solid tumors such as prostate, lungs and breast carcinomas [7–9]. The principle of its success is due to the stem cell's unique properties of self-renewability, capability to differentiate, migration to the site of injury and release of diverse cytokines, chemokines and growth factors. These cells have shown to target/modulate immune pathways of cancer cells and thus are being exploited as "cell therapy" for cancer [10,11]. It must however be borne in mind that the effect of stem cells as an anti-cancer therapeutic agent largely depends on its sub-type.

This review will assist investigators to better understand the impact of adult somatic stem cells in pancreatic cancer and its

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challenges to derive its applicable outcome. The three types of stem cells discussed here are: Mesenchymal Stem Cells (MSC), Neural Stem Cells (NSC) and Hematopoietic Stem Cells (HSC). This article has reviewed available *in-vitro* studies and studies carried out in mice model with respect to MSCs/NSCs and human clinical trials using HSCs. As per our knowledge, this is the first review to discern stem cell therapy outcomes for pancreatic cancer.

Pancreatic cancer

Pancreatic ductal adenocarcinoma is one of the leading causes of cancer deaths world-wide presenting only a 9% 5-year survival rate as per the recent reports in 2019 [12,13]. The rate of incidence, however, presents variations amongst continents like America, India and Africa, with maximum rate being reported from the United states [14].

The recent advances in the field of genetics have been able to categorize pancreatic cancer into several sub-types based on their diverse mutations [15–20] (Table 1). Interestingly, mutations in specific genes and their signalling pathways appear to play role in the diversity of pancreatic cancer development. The vast array of genes involved in genesis and progression of pancreatic cancer makes it difficult to be targeted by a single or even multi-drug chemo-therapeutic agent.

Fig. 1 provides a glimpse of drug development from 1997 to 2015. FOLFIRINOX alone has shown a marginal OS improvement (10.9 months), but it is known to present side-effects. The most recent FDA approved treatment option of combining gemcitabine with nab-paclitaxel has shown lesser side-effects but the OS is only 9 months compared to 10.9 months when treated with FOLFIRINOX [1,21].

Development of next generation of drugs needs to focus and understand the tumor cell kinetics and communication/interactions within the tumor as well as its microenvironment so that a better OS can be achieved. Literature does support the hypothesis that various cell types are involved to form a complex co-existence of tumor and its surrounding [22]. These cells are pancreatic stellate cells, myeloid derived suppressor cells, cancer-associated fibroblasts, tumor-associated macrophages [23]. Such desmoplastic microenvironment helps the tumor cells to escape the immune check-points (PD-1/PD-L1) and result in proliferation and progression of the disease [1]. But clinical studies have shown that targeting the immune checkpoints alone (Colony-stimulating factor 1 receptor/CXCL12/CXCR4 axis/CD40 monoclonal antibody) does not show any benefit in O.S status [24]. In fact, Takeuchi et al., suggest that chemotherapeutic drugs such as gemcitabine have shown to re-structure the TME via employment of myeloid-derived suppressor cells in presence of increased secretion of GM-CSF [25]. The myeloid derived suppressor cells accumulate in the tumor microenvironment which leads to decrease in T cell activation and increase in angiogenesis contributes to tumor progression and acquiring chemo-resistant phenotype. Cisplatin has also shown to induce tumor associated macrophages via secretion of cytokines, IL-6 and PGE-2 [26].

As evident, PDAC progression is challenging with the available chemo-therapeutic drugs wherein the disease recurrence and further progression to metastasis is a highly common phenomenon. As an alternative, cell-based therapy could be a promising approach. Firstly, the properties of the stem cells such as their homing capability, targeting potential could be an advantage over

Table 1
Sub-types of cells and their related genes identified in Pancreatic Cancer.

S.No.	Sub-types	Related genes	Reference
1	Classical	TMEM45B, TFF1, MUC13	[15]
2	Quasi-mesenchymal	GPM6B, NT5E	
3	Exocrine-like	REG1B, PNLIPRP2, CFTR	
4	Normal stroma	ACTA2, VIM, DES	[16]
5	Activated stroma	ITGAM, CCL13, CCL18, SPARC, WNT2, WNT5A, MMP9, MMP11	
6	Basal	VGLL1, UCAI, S100A2	
7	Squamous	TP53, KDM6A	
8	Pancreatic progenitor	FOXA2/3, PDX-1, MNX-1	[17]
9	Immunogenic	Wnt pathway, TGFβ pathway	
10	Aberrantly differentiated endocrine exocrine (ADEX)	KRAS, NR5A2, RBPJL, NEUROD1, NKX2-2	
11	Stable	KRAS, SMAD4	[18]
12	Locally rearranged	KRAS, SOC9, GATA6, ERBB2, MET, CDK6, PIK3CA, PIK3R3	
13	Scattered	Non-random chromosomal damage	
14	Unstable	BRCA	
15	Immune escape	p62, KRAS, TP53, CDK2NA, SMAD4, PIK3CA	[19]
16	Immune rich	GNAS, IDH2, STK11, ATM, SMARCB1	
17	Immune exhasuted	PIK3CA, JAK3	
18	pure basal like	CDK2A, TP53	[20]
19	Stroma activated	MET, GLI1, HENT1	
20	Desmoplastic	CD276, HAVCR2	
21	Pure classical	KRAS, HENT1	
22	Immune classical	HENT1	

(TMEM45B:Transmembrane Protein 45B; TFF1:Trefoil Factor 1; MUC13:Mucin 13; GPM6B:Glycoprotein M6B; NT5E:5′-Nucleotidase Ecto; REG1B:Regenerating Family Member 1 Beta; PNLIPRP2:Pancreatic Lipase Related Protein 2; CFTR:Cystic fibrosis transmembrane; ACTA2:Actin, Alpha 2, Smooth Muscle, Aorta; VIM: vimentin; DES: desmin; ITGAM: Integrin Subunit Alpha M; CCL13:C-C Motif Chemokine Ligand 13; CCL18:C-C Motif Chemokine Ligand 18; SPARC: Secreted Protein Acidic And Cysteine Rich; WNT2:Wingless-Type2; WNT5A:Wingless-Type5A; MMP9: Matrix Metallopeptidase 9; MMP11:Matrix Metallopeptidase 11; VGLL1:Vestigial Like Family Member 1; S100A2:S100 Calcium Binding Protein A2; TP53:tumor protein p53; KDM6A:Lysine Demethylase 6A; FOXA2/3:Forkhead Box A2/3; PDX-1:Pancreatic And Duodenal Homeobox 1; MNX-1:Motor neuron and pancreas homeobox 1; KRAS: Kirsten rat sarcoma 2 viral oncogene homolog; NR5A2:Nuclear Receptor Subfamily 5 Group A Member 2; RBPJL: Recombination Signal Binding Protein For Immunoglobulin Kappa J Region Like; NEUROD1:Neuronal Differentiation 1; NKX2-2:NK2 Homeobox 2; SMAD4:SMAD Family Member 4; SOX9:Transcription Factor SOX-9; GATA6:Transcription Factor GATA-6; ERBB2:v-erb-b2 erythroblastic leukemia viral oncogene homolog 2; MET:MET Proto-Oncogene; CDK6:Cyclin-dependent kinase 6; PIK3CA:Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha; PIK3R3:Phosphoinositide-3-Kinase Regulatory Subunit 3; p62:Nucleoporin p62; CDK2NA:cyclin-dependent kinase Inhibitor 2A; GNAS: Guanine Nucleotide Binding Protein (G Protein), Alpha Stimulating Activity Polypeptide 1; IDH2:Isocitrate Dehydrogenase (NADP(+)) 2; STK11:Serine/Threonine Kinase 11; ATM: Ataxia telangiectasia mutated; SMARCB1:SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily B, Member 1; JAK3:Janus Kinase 3; GLI**1**:GLI Family Zinc Finger 1; HENT1:Human equilibrative nucleoside transporter 1; HAVCR2:Hepatitis A Virus Cellular Receptor 2).

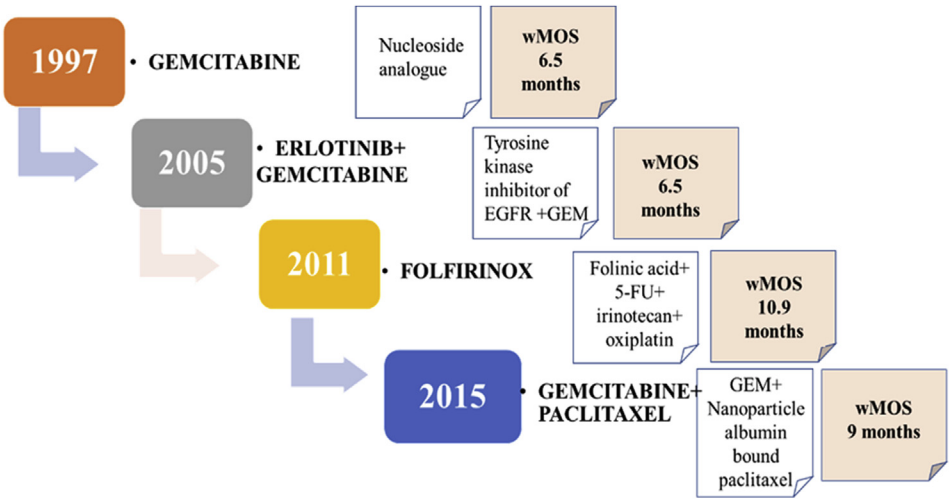

Fig. 1. List of US FDA approved drugs for treatment of pancreatic cancer and weighted months of survival (w MOS) from year 1997–2015. Gemcitabine (approved in 1997) is a nucleoside analogue with wMOS of 6.5 months. Similar result is shown with erlotinib (a tyrosine kinase inhibitor of EGFR) +gemcitabine (approved in 2005). In 2011, folfirinox (folinic acid+5-FU+irinotecan+oxiplatin) showed the best results with wMOS 10.9 months but had major side-effects such as diarrhoea, fatigue and neuropathy. Recently, gemcitabine in combination with paclitaxel was approved in 2015 which showed wMOS of 9 months. 5-FU: 5-fluorouracil; EGFR: epidermal growth factor receptor.

the conventional treatment modality. Additionally, secretory factors of stem cells such as CCL2/MMP1; CXCL12/CXCR4 are also known to cause anti-tumor effect [27,28].

Secondly, engineered stem cells capable of carrying cytotoxic agents such as pro-drugs, miRNA, siRNA is more stable and can enhance the primary immune reaction leading to better efficacy and lesser side-effects [29].

Stem cells

Stem cells are known to be able to modulate inflammatory microenvironment through release of paracrine factors (cytokines, growth factors) and more recently stem cell derived extracellular vesicles have shown to promote tissue regeneration [30].

To understand the status of cell therapy in cancer, an extensive search of the clinical trial database was carried out [31]. Presently, 544 clinical trials are recruiting patients (aged 18–64 years) for stem cell therapy in patients diagnosed with various cancers (inclusive of solid tumors and leukemia). Most of these studies are in phase 2 (n = 283) and only 8/544 are in phase 4. Among the different types of stem cells, more than 500 clinical trials are presently recruiting cancer patients for use of HSC, 12 clinical trials for use of MSC and only 4 clinical trials for use of NSC. Fig. 2 depicts the phase-wise distribution of studies undertaken using MSC, HSC and NSC in cancer. These studies have evaluated outcome measures such as better OS duration, achievement of both partial/complete disease-free status and reduced severe adverse events. But only a very few stem cell therapy-based studies have been undertaken in pancreatic cancer. Only 4 studies using HSC have been registered in www.clinicaltrials.gov and none using either MSC or NSC. Most of the studies using MSC and NSC are at proof of concept or being undertaken as research studies that uses models of cell line/xenografts/animal.

Mesenchymal stem cells (MSCs) therapy: naïve and engineered

Mesenchymal stem cells [somatic (adult) stem cells] are known for their pro- and anti-inflammatory properties as well as their ability to home and migrate towards inflammatory environment [32,33], although this mechanism of tropism is poorly understood. It has been suggested that this tropism may be dependent upon cellular adhesion molecules (SDF-1, CXCR4, HGF, c-met) and cytokine receptor pairs such as SDF-1/CXCR4, HGF/c-met, VEGF/VEGFr, PDGF/PDGFγ, MCP/CCR2, SCF/c-kit and others [32]. However, this migration towards tumor is non-specific as observed in several reports [34–40]. It is known that MSCs when administered *in-vivo*, initially migrate to the local site of inflammation such as lymph nodes and hence delivery to the targeted site may be affected [41–43]. Zachar et al. [44] succinctly explained the immunomodulatory role of MSCs and their targets in different conditions. The tumor microenvironment is pro-inflammatory and under this condition, MSCs are able to produce several immune modulatory factors such as TGF-β, IDO, PGE-2, TNF-α and many others [45–47]. These factors are capable of modulating the tumor microenvironment of the tumor. Further, MSCs are also able to inhibit T helper cell proliferation as well as modulation of dendritic cells (DCs) [43,48] and cytotoxic T cell induction through multiple pathways. Apart from these factors, chemokines such as CXCR2, CXCR3, CXCR4 and CCL5 are also involved in the MSC homing capacity towards inflammatory microenvironment. Thus, MSC homing capabilities are dependent on the local inflammatory microenvironment of the tumor. Fig. 3 illustrates the modulatory and co-modulatory factors and their targets in microenvironment of both MSCs and tumor cells.

Studies using naïve MSCs

A study by Cousin et al. [49] explored the potentials of human adipose-derived MSCs in PDAC cell-line and mice models. This study has been designed elegantly using G1/S transition blocker and Rb (tumor suppressor protein) pathway inhibitor. The authors suggest MSCs cause inhibition of cell cycle at G1 phase thus promoting cell death (*in-vitro)* and further in an *in-vivo* mice model showed CDK4 and cyclin D1 to be downregulated. Their results suggest an efficient and feasible approach to treat non-resectable locally advanced PDAC.

In-vivo studies using mouse peritoneal model was carried out to determine the ability of umbilical cord derived MSCs to attenuate growth of murine pancreatic cancer cells [50]. The results obtained showed UCMSC to cause G0/G1 arrest of PAN02 (murine pancreatic carcinoma cells) and significantly decreased the proliferation rate. Thus, suggesting UCMSC as a potential tool to target pancreatic

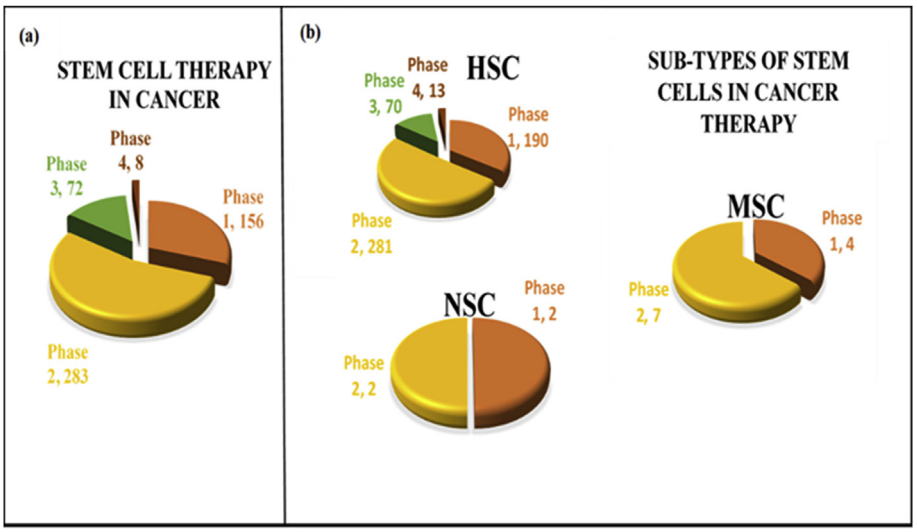

Fig. 2. Accrual of cancer patients in clinical trials. Enrolment of patients undergoing stem cell therapy in different phases of clinical trials. (a) Stem cell therapy: majority of the studies are at phase 2 (n = 283), followed by phase 1 (n = 156), phase 3 (n = 72) and phase 4 (n = 8) (b) Sub-types of stem cells: HSC (phase 1–190; phase2-281; phase 3–70; phase4-13), MSC (phase 1–4; phase2-7) and NSC (phase-1:2; phase-2-2). HSC: Hematopoietic stem cells; MSC: mesenchymal stem cells; NSC: neural stem cells.

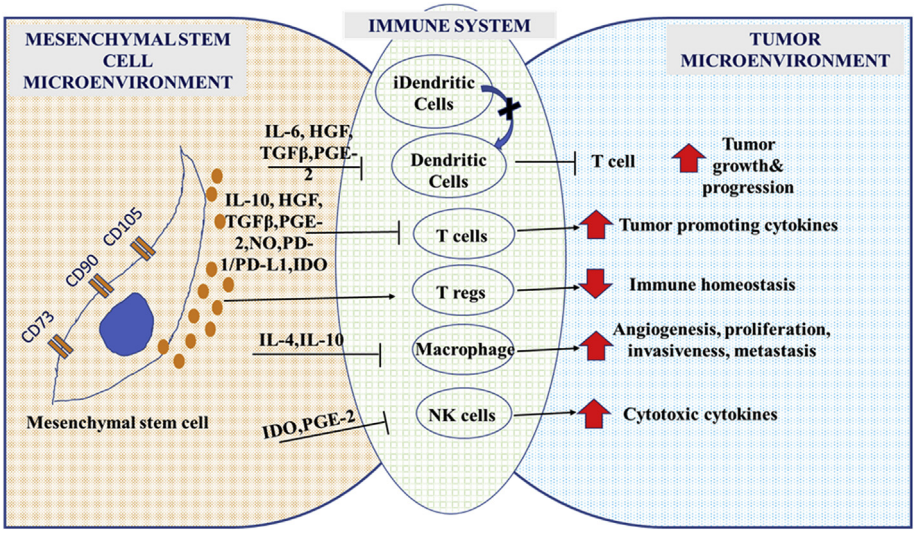

Fig. 3. Representative status of immune cells in mesenchymal stem cells and tumor microenvironment.
CD73, CD70 and CD105 are highly expressed by MSCs and secrete majorly growth factors, cytokines and chemokines. MSCs modulate immune status by suppressing T helper and cytotoxic T cells as well inducing T regulatory (T reg) cells via IL-10/HGF/TGFβ/PGE-2/NO/PD-1/PD-L1/IDO. Further, IL-6/HGF/TGFβ/PGE-2 released by MSCs inhibit maturation of immature dendritic cells (idendritic cells). MSCs can also limit secretion of cytokines via inhibition of natural killer (NK) cells and macrophages via IDO, PGE-2 and IL-4, IL-10 respectively. In the tumor microenvironment, an up-regulation of tumor growth and progression is due to inhibition of T cells via the dendritic cells. Inhibition of t-reg cells causes down regulation of immune homeostasis and macrophages promote angiogenesis, proliferation, invasion & metastasis. NK cells modulate release of cytotoxic cytokines. IL-10: interleukin 10; HGF: hepatocyte growth factor; TGFβ: Transforming growth factor beta; PGE-2: Prostaglandin E2; NO: nitric oxide; PD-1: Programmed cell death protein 1; PD-L1: programmed death-ligand 1; IDO: indoleamine 2,3-dioxygenase; IL-6: interleukin 6; IL-4: interleukin 4.

cancer.

Another study by Brini et al. [51], utilized oral MSCs obtained from routine dental procedure to target PDAC. The researchers herein emphasized on using human-gingival tissue as a source of MSC, owing to its non-invasive isolation procedures compared to bone marrow (BM) and adipose (AD). This study showed gingival derived MSCs could be used as a vehicle to carry anti-angiogenic drug Paclitaxel (PTX), to target CFPAC-1 pancreatic cell line, thereby, suggesting other sources of MSCs to be as effective as commonly derived MSC sources (BM, AD, Umbilical Cord).

Wnt signalling pathway is a commonly activated pathway known to be involved in PDAC pathogenesis. Naive-MSCs (N-MSCs) have been shown to target Wnt pathway by upregulating the expression of dickkop-related protein1 (DKK-1), which then ultimately affect the tumor cell cycle in breast cancer [52]. Similar studies targeting or inhibiting Wnt signalling using MSCs have not been reported in PDAC. N-MSCs have also shown to interact and enhance angiogenesis and proliferation of fibroblast cells in prostate and colon tumor cells. Thus, it appears that N-MSCs may act as a double-edged sword while interacting with tumor cells [53].

Studies using engineered MSCs

To further improve the efficacy of MSC as a stem cell-therapeutic

agent targeting tumor cells, the last decade has seen several studies being published that showed promising potential of genetically engineered MSCs (E-MSCs) [54]. These E-MSCs express anti-proliferative, pro-apoptotic, anti-angiogenic properties targeting diverse types of cancer cells. As early as 2008, Chen et al. [55] engineered the MSCs to express IL-12 in a mice model that had metastasis of melanoma, breast and hepatoma tumors and showed increased tumor cell apoptosis. Around the same time, Xu et al. [56] transplanted E-MSCs secreting IL-18 and showed enhanced T cell infiltration and long term anti-tumor immunity in non-invasive and invasive gliomas in a mice model. Similar results have been obtained in mice bearing renal cell carcinoma and cervical tumors [57,58]. Thus, evidences from the animal studies have shown E-MSCs can inhibit and/or modulate tumor growth. Agents such as interferon γ/β, CX3CL1, Flt3, TRAIL, HGF can also be incorporated into MSCs as a drug cargo to induce anti-tumor activity in various tumors such as prostate, melanoma, lungs, glioma as extensively reviewed by Shah K et al., 2012 [29].

In 2009, Zischek et al. [59], conducted a mice study using BM-derived E-MSCs for expression of suicide gene thymidine kinase (TK). The expression of TK was controlled using RANTES (CCL5) promoter that specifically expressed the carrier gene in inflammatory microenvironment. These E-MSCs showed 50% reduction of primary tumor burden, indicating a positive implication of E-MSCs as a gene carrier. In the following year, a study by Kidd et al. [60] showed that IFN-β engineered MSCs could alter the pancreatic TME of SCID mice by downregulating NF-κB, VEGF, IL-6 as well as chemokines such as CCL3 and CCL25. Although the literature provides enough evidence in *in-vitro* and in animals suggesting that E-MSCs can be used as anti-tumor vehicle in pancreatic cancer, but there is a lack of human studies. Thus, we suggest that human clinical trials should be undertaken to validate the outcomes achieved in the animal models.

Pro-tumorigenic effect of mesenchymal stem cells

Contrary to the reports supporting anti-tumorigenic effects of MSCs (naïve and engineered), studies reporting their pro-tumorigenic effects need to be critically reviewed as well. A report by Niibe et al. [61] showed BM-MSCs to promote progression of PDAC via Notch pathway. The authors herein suggested MSC-derived myofibroblast can regulate epithelial to mesenchymal transition (EMT), augment stemness associated genes, enhance sphere forming activity in a co-culture model (tumor: MSC). Subsequently Zhou et al. [62] showed that pancreatic adenocarcinoma invasion could be promoted when MSCs were pre-stimulated with TNF-α and IFN-γ. This study further suggested that EMT mediated invasion could be promoted by TGF-β1 when co-cultured with MSCs. A very recent study carried out by Saito et al. [63], also strengthens the role of MSCs in facilitating pancreatic cancer progression. Saito and team showed that production of amphiregulin and MMP3 were the driving force for BxPc3 invasiveness suggesting MSCs to play a critical role in cellular interaction.

Apart from the effect that MSCs may exert on tumor, it is important to ascertain the role of the source from which MSCs have been derived. Mathew et al. [64], carried out a study in mice model with an aim to decipher the functionalities of MSCs derived from healthy, carcinogenesis associated pancreas (neoplastic pancreas) and BM derived MSCs. The results indicated progression of tumor were comparable between BM-MSCs and MSCs derived from healthy pancreatic tissue. MSCs derived from neoplastic tissues, on the other hand, presented with relatively higher progression of tumor compared to its other counterparts. Such results urge researchers to functionally characterize MSCs from different sources (tumor/non-tumor) and report their effect on tumor progression.

The studies cited herein suggest that MSCs can influence both adaptive and immune responses by induction of regulatory T cells, modulation of DCs, anergy & apoptosis (cell-cycle and immune checkpoints) and secretion of soluble factors to create immunomodulatory microenvironment. TNF-α, IL-1β and IFN-γ are important MSC priming factors that manifest its immunosuppressive roles [65,66]. Thus, interaction with various factors (chemokines, pro-inflammatory growth factors and others) shows diverse modulatory and reprogramming capability of MSCs. In the last decade, MSCs have also been engineered specifically to act as a "Drug Carrier" of wide range of anti-tumor agents (schematically represented in Fig. 4). Such engineered MSCs have shown promising prospects for clinical translation.

Hematopoietic stem cells (HSCs) transplantation

In solid tumors, HSC transplantation is dependent on the graft-versus-tumor (GVT) effect rather than creating an anti-tumor cytotoxic effect [67]. The mechanism of GVT, though poorly understood, might be similar to graft-versus-host (GVHD) phenomenon [68]. The postulated hypothesis is that a new repertoire of donor T cell reacts with tumor associated antigens (TAAs) to elicit an immune response against the tumor [69-71]. Thus, patients showing higher GVT effect demonstrated longer survival when treated with HSCs. This could be achieved by inducing alloreactive donor derived T cells from bone-marrow [72]. In addition, HSC transplantation could be useful post chemo/radio therapy inductions. In PDAC, the anti-tumor immune responses are sequestered by immune cells ($CD8^+$ and NK cells) and their chemokine/cytokine factors including TGF-β. Till date, the studies carried out using HSC transplantation for treatment of patients with pancreatic cancer has been performed in very small numbers of patients either in resectable or non-resectable cases, thus, providing insufficient evidence for HSC transplantation to be used in PDAC treatment.

Takahashi et al. [72], conducted a pilot study in 5 patients diagnosed with unresectable pancreatic cancer. 2/5 patients showed tumor reduction, pain relief and also developed GVHD. Those who developed GVHD were treated with immunosuppressive drug and these patients showed elevated levels of tumor marker. Thus, suggesting that GVT effect was induced by non-myeloablative allogenic stem cell transplantation (HSC). Kanda et al. [73], enrolled 7 patients with advanced pancreatic cancer to test the feasibility and efficacy of allogenic reduced-intensity hematopoietic stem cell transplantation (RIST). With respect to

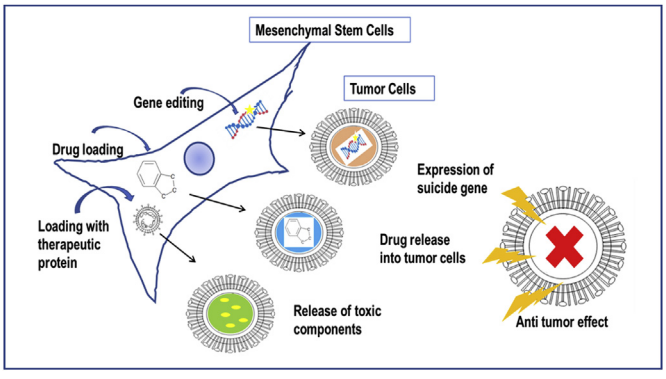

Fig. 4. Schematic representation of diverse types of MSC engineering and their impact on tumor cells.
MSCs can be engineered via gene editing to express suicide genes which can lead to anti-tumor effect. MSCs can also be used as a drug delivery vehicle to deliver drugs at tumor site. Loading of therapeutic protein in the MSC can lead to release of toxic components in the tumor cells resulting in tumor cell apoptosis.

transplantation-related mortality and survival 1/7 patient died within 100 days due to pneumonia (day 83), another patient died due to bacterial cholangitis (day 192), rest of the patients died with a median survival of 229 days (after RIST) but, this difference was not significant in comparison to non-treated patients. Achievement of tumor response post HSC transplantation in this study showed that 2/7 showed minor response as observed by CT scan (192 and 262 days respectively) and another patient achieved partial tumor marker response. 2/7 patients were free from all analgesics on achieving tumor regression. Effect of chemotherapy was observed with increase in CA-19-9 and long-term effect (~200 days) was observed with increased serum anti-CEA antibody levels. These results suggest that the anti-tumor effect was caused by GVT effect and not a chemotherapy effect. The authors in this study showed that RIST is a feasible treatment for advanced pancreatic cancer patients.

Similarly, in 2009, Abe and team [74] also undertook a study to investigate the response of 5 patients using allogenic HSCs as an immunotherapy option. These patients were treated with low-dose (2 Gy) total body irradiation and chemo-drugs, however, this study did not show any significant correlation with respect to ant-tumor effect. Post-transplantation, 3/5 patients achieved complete donor chimerism of peripheral T cells by day 42. 3/5 patients showed active GVHD and amongst these 2/5 patients achieved tumor regression. Complete disappearance of tumor was observed in one patient and the other patient showed only 20% tumor reduction. The levels of serum TNF-α were elevated in patients who responded to NST. Thus, suggesting its role in induction of anti-tumor effect mediated by NST.

Very recently, Omazic [75] and colleagues also enrolled 8 resectable PDAC patients to evaluate the effect of HSC transplantation after Whipple's surgery. HSC was derived from HLA identical siblings for 2/8 male patients. Another 2/8 patients did not undergo treatment since no HLA identical siblings were available. 4/8 patients did not consent for HSC therapy. The 6 patients who were not treated with HSCs had a mean survival of 33.6 months. Interestingly, the two patients treated with HSC following surgery had a recurrent free survival for 9 years. This study also identified cell cycle regulators INO80E and UCHL3 as molecular markers that showed clinical association with patient outcomes. Table 2 summarizes the total number of responders in each study and the cause of their effective mechanism.

Treatment with HSCs are most efficacious in leukemias and lymphomas as it enhances the host immune response post chemotherapy. However, in case of solid tumors, only a few non-cancerous cells reside in the tumor microenvironment and thus replacing these myeloablative (chemotherapy/radiation) cells by HSCs is a challenge.

On the other hand, treatment with non-myeloablative allogenic HSCs appears to be a promising treatment modality. This treatment option is based on the GVT effect which is mediated predominately by CD8 cytotoxic T lymphocytes. One of the major limitations of treating with NST is its short duration of tumor regression which ultimately causes the tumor to progress and hence leading to high mortality rate. In addition, there is also need to undertake toxicity studies in case of high dose HSC administration. As mentioned above, most of the studies are preliminary using a very small number of patients. Thus, there is a need to validate HSC treatment for PDAC in larger cohorts to asses both the risks and benefits in terms of relapse and/or resistance. Available clinical practice guidelines such as UpToDate reviews and national comprehensive Cancer network's clinical practice guidelines on "pancreatic cancer" (v2.2016) does not mention HSC as a therapeutic option.

Neural stem cells (NSCs)

Neural stem cells are multi-potent progenitor cells which demonstrate the property of tumor tropism and hence, have been investigated for their potential as a therapeutic delivery agent.

Similar to MSCs, NSCs can also be manipulated to deliver a variety of anti-cancer agents specifically to the tumor foci and has limited off-target effects and hence results in lower toxicity to the normal tissues. These cells have shown migration across the blood-brain barrier and so most studies have been conducted in tumors of the brain (glioma). However, recent evidences suggest that NSCs could also be employed in other tumors as well (Fig. 5).

Till date NSC mediated therapies have shown significant improvement in quality of life, before and after treatment in cancer patients. Pre-clinical mouse model studies have been mainly carried out for cancers of breast, glioma, medulloblastoma, pancreas, melanoma and ovarian [76]. Approaches for NSC mediated therapies include delivery of enzyme/pro-drug, oncolytic virus, protein, nanoparticles and oligonucleotide to the tumor site.

As evident from the clinical trials (Fig. 5), there are about 4 trials undertaken and these target recurrent high-grade gliomas. Since NSCs have high expansion rate and can efficiently transduce genes, Choi et al. [77]., evaluated the therapeutic efficacy of immortalized human NSC encoding v-myc gene and HB1.F3 (F3.CE) in pancreatic cancer mice model. Choi and colleagues observed a marked growth inhibition and increased apoptosis when BxPc3 (human pancreatic cancer cell line) was treated with F3.CE. The F3.CE model can activate the pro-drug CPT-11 to an active drug SN-38. The authors demonstrated for the first time that F3.CE cells could successfully exert therapeutic efficacy on BxPc3 cells.

Conclusion

Pancreatic ductal adenocarcinoma being a difficult and

Table 2
Clinical trials using hematopoietic stem cell transplantation in pancreatic cancer.

S.No.	Year	Title of study	Number of patients enrolled	Number of responders	Technique	Effect via	Reference
1	2004	Nonmyeloablative allogeneic stem cell transplantation for patients with unresectable pancreatic cancer.	5	2	CT, Tumor markers	Graft versus tumor (GVT)	Takahashi T et al.[72]
2	2005	Graft-versus-tumor effect against advanced pancreatic cancer after allogeneic reduced-intensity stem cell transplantation.	7	1 (tumor marker response) 2 (objective response) 4 (median survival of 229 days)	CT, Tumor markers	Graft versus tumor (GVT)	Kanda Y et al.[73]
3	2009	Nonmyeloablative allogeneic stem cell transplantation for patients with unresectable pancreatic cancer.	5	2	CT	TNF-α	Abe Y et al.[74]
4	2017	A Preliminary Report: Radical Surgery and Stem Cell Transplantation for the Treatment of Patients with Pancreatic Cancer.	2	2	Protein profiling	INO80E, UCLH3	Omazic B et al.[75]

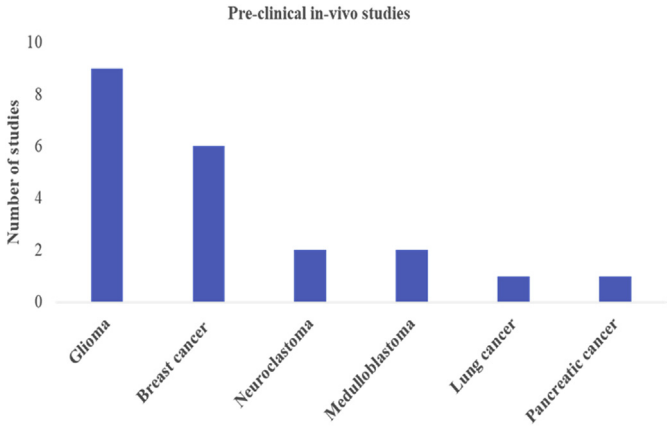

Fig. 5. Number of *in-vivo* pre-clinical studies undertaken using neural stem cells in solid tumors. The number of studies undertaken ranges from a single study (pancreatic cancer and lung cancer) to maximum of 9 studies (glioma). In case of breast cancer, 6 studies were undertaken, neuroblastoma and medulloblastoma 2 studies each.

challenging malignancy, necessitates multiple therapeutic approaches specially to breach its complex TME to lower its resistance to chemotherapeutic agents. In this direction, literature, however limited, does support (*in-vitro* and *in-vivo)* that stem cells could be the ideal candidates because of their tumor homing capabilities, its intrinsic immunomodulatory potential and can act as a delivery vehicle of multiple bioactive factors. Stem cell mediated antitumor effect following their transplantation can trigger immune responses such as chimeric antigen receptor response, T cell receptors directed against tumor response and functionally impair tumor cell adhesion, intra cell communication and its cell cycle. On the other hand, stem cell therapy has also shown to promote tumor growth. Therefore, factors like the source, dose, mode and route of administration plays a pivotal role in tumor targeting.

Till date, the mechanisms of action used by stem cells to target pancreatic cancer are poorly understood though several clinical trials are being undertaken using allogenic and autologous stem cells. The reason could be attributed to the differential potentials of stem cell subsets, their effect on multiple cellular targets and/or their activation of diverse signalling pathways. Future studies should be designed comprehensively to re-look into the existing knowledge (single/specific targets) and if the results thus obtained validate the clinical usefulness, it should be scaled-up for future applications. However, a few open questions remain to be elucidated as follows:

1. What is the best model to study the effect of stem cell therapy in pancreatic cancer?
2. Is cell therapy a viable treatment option for pancreatic cancer? If yes, what does stem cell target?
3. How will it be delivered and at what dosage?
4. Will this biological cell therapy react with the immune status of the host and cause adverse events (safety concern)?
5. Most importantly, which type of stem cells will give a better clinical outcome i.e, improved over-all survival?

Future research and/or clinical trials should be designed based on these above questions to elucidate the potential of stem cells. In this review the authors would like to emphasize firstly that clinical trials should be categorize based on their mutational landscape and histological staging. Secondly, efficacy, safety and over-all survival status should be the foremost questions addressed in the clinical trials using stem cells as therapeutic option in pancreatic cancer. Thirdly, other components of stem cells like “nano-carriers exosomes” and their secretome should also be explored for their effect on pancreatic tumors. However, it is extremely important to validate the safety profile of these biological agents before they could be used in clinics or be known as “off-the-shelf” treatment options.

In conclusion, the cited literature herein elucidates the mechanism of action of the three major sub-types of stem cells i.e., MSC, HSC and NSC. NSC is an attractive proposition to treat pancreatic cancer, but their isolation and purification from human source is a challenge. With respect to MSCs, although its mechanism has been extensively studied, yet the GVT effect of HSCs appear to be more promising mechanism that could provide better clinical outcome in cancers of pancreas.

Declaration of competing interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Neha Chopra: Data curation, Formal analysis, Investigation, Writing - original draft. **Sangeeta Choudhury:** Conceptualization, Supervision, Funding acquisition, Writing - review & editing. **Seema Bhargava:** Formal analysis, Writing - review & editing. **Saima Wajid:** Supervision, Writing - review & editing. **Nirmal Kumar Ganguly:** Supervision, Writing - review & editing.

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