Concise Review: Pancreatic Cancer and Bone Marrow-Derived Stem Cells

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Key Words. Bone marrow • Cancer • Pancreas • Stem cells

ABSTRACT

Pancreatic adenocarcinoma remains one of the most challenging diseases of modern gastroenterology, and, even though considerable effort has been put into understanding its pathogenesis, the exact molecular mechanisms underlying the development and/or systemic progression of this malignancy still remain unclear. Recently, much attention has been paid to the potential role of bone marrow-derived stem cells (BMSCs) in this malignancy. Hence, herein, we comprehensively review the most recent discoveries and current achievements and concepts in this field. Specifically, we discuss the significance of identifying pancreatic cancer stem cells and novel therapeutic approaches involving molecular interference of their metabolism. We also describe advances in the current understanding of the biochemical and molecular mechanisms responsible for BMSC mobilization during pancreatic cancer development and systemic spread. Finally, we summarize experimental, translational, and/or clinical evidence regarding the contribution of bone marrow-derived mesenchymal stem cells, endothelial progenitor cells, hematopoietic stem/progenitor cells, and pancreatic stellate cells in pancreatic cancer development/progression. We also present their potential therapeutic value for the treatment of this deadly malignancy in humans.

SIGNIFICANCE

Different bone marrow-derived stem cell populations contribute to the development and/or progression of pancreatic cancer, and they might also be a promising "weapon" that can be used for anticancer treatments in humans. Even though the exact role of these stem cells in pancreatic cancer development and/or progression in humans still remains unclear, this concept continues to drive a completely novel scientific avenue in pancreatic cancer research and gives rise to innovative ideas regarding novel therapeutic modalities that can be safely offered to patients.

INTRODUCTION

Pancreatic cancer remains one of the most challenging diseases of modern gastroenterology, affecting more than 330,000 patients worldwide annually, and is associated with an exceptionally high mortality rate. This dramatic prognosis can be explained by the fact that, for most patients, pancreatic cancer is diagnosed at the final (metastatic) stage of progression, whereas only few of the affected individuals are diagnosed at an early (local) stage of pancreatic adenocarcinoma. Unfortunately, the disease itself seems to be extremely aggressive. Even in patients subjected to the surgical removal of the cancerous lesions and intensive chemo/radiotherapy, the overall survival remains very low. Over the last few years, several clinical studies have highlighted multiple risk factors for pancreatic cancer, including age, male gender, smoking, and obesity [1]. Additionally, several precancerous lesions have recently been defined, and, owing to the progress in diagnostic imaging and laboratory measurements, the detection of pancreatic cancer at earlier stages became technically possible. Nevertheless, despite significant progress in and efforts being put into identifying the molecular mechanisms responsible for pancreatic cancer development and more aggressive treatment strategies, this disease remains deadly and is associated with an unclear pathogenesis.

CONCEPT OF CANCER (STEM) CELLS

Our current understanding of the pancreatic cancer pathogenesis is based on a long-term model of a step-by-step progression from a local pancreatic abnormality, termed pancreatic intraepithelial neoplasia, to the development of an adequate "clone" of aggressive immortal cancer cells that are responsible for the initiation, progression, and systemic spread of the disease [2]. According to experimental studies, among the several types of cancer cells that are present within the
pancreatic tumor microenvironment, only a very small proportion (<1%) possesses the unique molecular armament necessary for tumor initiation and metastasis. This cell population is generally termed “pancreatic cancer stem cells” and is believed to be atop the hierarchy of all cancer (stem) cells [3–7]. In pancreatic adenocarcinoma, the probable molecular characteristics of this cell population have already been proposed. Recent studies have shown that this highly tumorigenic cancer cell subpopulation expresses CD44, CD24, and epithelial-specific antigen and presents an upregulation of crucial genes responsible for self-renewal. However, others have highlighted that pancreatic cancer stem cells may express other/additional receptors and/or markers on their surface, such as CD133, PANC-1, CXCR4 (the receptor for chemokreceptor stromal-derived factor-1 [SDF-1]), and c-Met (the tyrosine kinase receptor for hepatocyte growth factor [HGF]), as well as intracellular molecules like aldehyde dehydrogenase-1. Taken together, these findings suggest that, at different molecular levels, biological factors protect these cells from death induced by chemotherapeutic agents and enable their (almost unlimited) proliferation and survival [3–14].

The preliminary identification of pancreatic cancer stem cells led to the development of innovative therapeutic concepts. Although this discovery has not resulted in any specific “anti-stem cell” therapy, it immediately stimulated researchers’ interest to develop and examine the efficiency of multiple substances that interfere with various molecular pathways defining the high aggressiveness and proliferation capacity of these cells. For example, recent analyses of reagents such as quercetin, Delta-like ligand 4 (DLL4) blocking antibodies, and γ-secretase inhibitors demonstrated promising results in preclinical studies [12–14]. However, the identification of pancreatic cancer stem cells also provided researchers with novel questions regarding the pathogenesis of this deadly disease. For example, very little is known about the exact origin of these cells. There is evidence demonstrating that various stem cells exist within both the exocrine and endocrine compartments in the pancreatic environment. Moreover, several types of pancreatic cells are capable of undergoing successful transdifferentiation and de-differentiation (reviewed in detail in [15–17]). Nevertheless, how and/or whether these cells may give rise to pancreatic cancer (stem cells) remains speculative. Whether they even originate from the pancreas itself or from other organs/sources, such as the bone marrow (BM) environment, also remains unclear.

**Bone Marrow-Pancreatic Cancer Axis**

The BM is known to be an extremely rich source of stem cells and, within its environment, different populations of stem and/or progenitor cells can be found, including endothelial progenitor cells (EPCs), mesenchymal stem cells (MSCs), and hematopoietic stem/progenitor cells (HSPCs). These play diverse roles in the regeneration of blood compartments and other connective tissues and organs, including those of the gastrointestinal (GI) tract. General characteristics of these bone marrow-derived stem cell (BMSC) populations are presented in supplemental online Figure 1.

The fact that different BMSC populations may play an important role in the development of a GI cancer has been revealed by Houghton et al. [18], who demonstrated in a mouse model of chronic gastritis that BM-derived cells egress from the BM environment, are mobilized to the inflamed gastric tissue and repopulate it, and may undergo all cardinal stages of histological transformation that lead to the development of gastric cancer. Within time, animal and experimental reports confirmed the significance of BMSCs in the pathogenesis of different types of neoplasm developing in various organs, such as the lung, brain, and/or GI tract malignancies [19–21]. Further translational evidence confirming the existence of BMSC mobilization toward the developing tumor in humans was provided through a detailed molecular analysis of tumor specimens derived from patients that underwent BM transplantation because of hematological malignancies. Using immunostaining and fluorescence in situ hybridization analysis for sex chromosomes sequences in sex-mismatched grafts, researchers found that, in such transplant recipients, multiple cell types, derived from the tumor microenvironment, are of donor (allogeneic) origin. Such donor-derived BMSCs were detected in multiple types of neoplasm in humans, including lung adenocarcinomas, laryngeal squamous cell carcinomas, glioblastomas, Kaposi sarcomas, and/or GI cancers [22, 23]. Interestingly, in our recent studies, we observed an intensified systemic trafficking of BMSCs in patients with gastric and pancreatic cancer. This process did not seem to be associated with the clinical stage of the disease and occurred in patients presenting with both early and advanced disease [21, 24].

The exact biochemical and/or molecular signals responsible for such crosstalk between the developing tumor (in the pancreas) and the BM environment that stimulate such systemic activation of BMSCs remain unknown. It has been proposed that the most important molecule orchestrating stem cells’ egress from the BM, their systemic mobilization, and anchoring within the side of a developing tumor, is a chemokine, SDF-1, also known as C-X-C motif chemokine 12 (CXCL12). This substance is synthesized in response to local hypoxia via upregulation of the HIF-1α transcription factor [25]. However, our and others’ reports revealed that during the development of pancreatic cancer in humans, SDF-1 systemic levels do not increase and do not correlate with the absolute number of circulating BMSCs [21, 24, 26]. Similar results were also observed for another powerful mobilizer of BMSCs, granulocyte-colony stimulating factor (G-CSF), which is commonly used as a pharmaceutical agent to stimulate BMSC systemic mobilization in hematological settings. In multiple studies, researchers found that systemic G-CSF levels are also comparable between healthy individuals and patients with different types of pancreatic neoplasm [27, 28]. This discrepancy may be explained by the presence of a high proinflammatory setting that accompanies pancreatic cancer development in humans. This is associated with higher activity of proteolytic enzymes such as metalloproteinases, which are present both at the systemic and local levels [29, 30] and may result in the inactivation of BMSC chemokreceptors. Thus, researchers focused their efforts on other substances—mainly immune-related molecules, bioactive lipids, and growth factors—because these are involved in the formation of an immune-modulated microenvironment in pancreatic cancer, contribute to the development and/or progression of pancreatic malignancies, and, therefore, might potentially affect BMSC homeostasis and function [24, 28, 31]. Based on these studies, several substances that seemed to participate in a biochemical crosstalk between the BM and the developing pancreatic cancer have been identified. These involved anaphylatoxins of the complement cascade and/or biopolymers, such as C5a and C5b-9/membrane attack complex (MAC), sphingosine- and ceramide-derivatives, HGF, and cytokines (mainly interleukin [IL]-6 and IL-8) [24, 28]. The exact function of these substances
on the regulation of BMSC homeostasis has not been fully examined. However, it is well established that these molecules influence the function and/or development of the (pancreatic) tumor microenvironment, local BM homeostasis, and BMSC metabolic/proliferative activity and/or survival, as well as the systemic immune balance at different levels—epigenetic, (intra)cellular, and/or systemic (Figs. 1, 2; Table 1) [32–60]. Given that (in translational and clinical studies) these substances exert a significant influence on pancreatic cancer development/progression, the fact that their levels correlate with absolute numbers of circulating BMSCs found in peripheral blood samples derived from patients with pancreatic adenocarcinoma is particularly important. Interestingly, several therapeutic inhibitors of these biochemical substances are currently tested in various experimental and/or clinical studies, bringing promising results. For example, great hopes are associated with a novel agent (drug XL184), which inhibits the HGF/c-met axis. This substance has already been demonstrated to reduce pancreatic tumor burden in experimental animals [8]. In addition, modulators of sphingosine-1-phosphate signaling are being tested as potential therapeutics for patients with cancer. Drugs such as fingolimod were proven to inhibit cancer growth and its invasiveness [61, 62]. Importantly, this drug is already being used for the treatment of patients with multiple sclerosis and, according to clinical results, is tolerated relatively well by patients and has quite limited side effects [63]. Moreover, complement cascade inhibitors, such as eculizumab, which is mainly used in the transplantation and/or hematological setting, are promising candidate drugs for use in patients with pancreatic malignancy. In fact, multiple experimental studies demonstrated that the inhibition of the action/generation of the complement cascade’s anaphylatoxins reduces the aggressiveness, growth, and metastatic potential of pancreatic cancer cells (reviewed in detail in [64]).

**CONTRIBUTION OF BMSCS TO PANCREATIC CANCER DEVELOPMENT AND THEIR POTENTIAL THERAPEUTIC USE**

Independent of the multiple mechanisms orchestrating systemic biochemical crosstalk between pancreatic cancer and the BM environment, the actual contribution of BMSCs to pancreatic cancer development remains unclear. The exact role of BMSCs in the pathogenesis of human malignancies in general and pancreatic cancer in particular has generated an intensive debate. Although this phenomenon has not yet been fully elucidated, it was proven that various BMSC populations possess different molecular properties, contributing to pancreatic malignancy development and systemic spread. For example, the pancreatic cancer stem cells share many similarities with BM-derived very small embryonic/epiblast-like stem cells (VSELs), which represent a very small percentage of BMSCs, possess high expression of “embryonic” genes (such as Oct-4 and/or Nanog) and are mobilized into the peripheral blood in patients with pancreatic cancer. Their absolute numbers also correlate with HGF levels [24]. Interestingly, intensified accumulation of such small Oct-4+ cells has already been detected in pancreatic cancer samples, and this has been associated with greater invasiveness and proliferation potential, as well as with the presence of extensive metastasis and multidrug resistance [65–67]. However, results suggest that not all BMSC...
populations may play a significant direct role in the development of human malignancies. Among the usually examined BMSC populations, researchers share a common view that the population of BM-derived MSCs seems to be especially involved into the development and progression of (pancreatic) cancer, whereas the contributions of EPCs and HSPCs remain less evident and are rather indirect (supplemental online Table 1) [68–76]. These experimental observations are in agreement with our previous clinical studies of patients with gastric neoplasms and pancreatic cancer, indicating a very selective mobilization of BMSCs, mainly of VSELs and MSCs, in patients with these types of cancers [21, 24].

MSCs in Pancreatic Cancer

MSCs possess the molecular potential to influence and direct several cardinal processes that are crucial for the development of malignancies, because these cells are a rich source of various biochemical mediators (growth-modulating factors and/or cytokines). These mediators may modulate the function of immune cells, both at the local and systemic level; provide the necessary signaling, promoting the development of tumor and its specific microenvironment; stimulate the formation of morphological structures that support the survival of cancer cells; and enable evasion from the immune system attack within the tumor environment (supplemental online Table 1). With respect to pancreatic cancer, it has been shown that MSCs preferentially migrate to the pancreatic cancer stroma and may support neoangiogenesis. Surprisingly, some studies demonstrated that both of these properties of MSCs may also be of potential therapeutic use. These SCs may be used as vectors for the successful delivery of proapoptotic and/or antiproliferative signals to pancreatic cancer cells/environment, resulting in the inhibition of tumor growth and/or limitation of new vessel formation in experimental animals [68–71].

EPCs in Pancreatic Cancer

In contrast, BM-derived EPCs do not seem to influence such diverse and numerous processes during carcinogenesis when compared with MSCs. These cells only seem to promote vasculo-genesis through different molecular pathways. This function has been observed in multiple types of malignancy (reviewed in detail.
However, HSPCs may indirectly modulate tumor growth via cells that do not give rise to pancreatic adenocarcinoma per se. In solid tumors, including pancreatic cancer, HSPCs seem to modulate tumor growth. Interestingly, intensified systemic mobilization of EPCs favoring immune tolerance toward a malignant microenvironment, and increase permeability of BM endothelium thereby enabling egress of BMSCs.

HSPCs in Pancreatic Cancer

In solid tumors, including pancreatic cancer, HSPCs seem to modulate the immune system function. It has been shown that these cells do not give rise to pancreatic adenocarcinoma per se. However, HSPCs may indirectly modulate tumor growth via differentiation into inflammatory cells and myofibroblasts, which, in turn, may promote (local) deregulation of the immune profile, favoring immune tolerance toward a malignant microenvironment and generate appropriate factors, promoting growth and/or proliferation of cancer cells (supplemental online Table 1).

Although HSPC transplantation is a commonly used therapeutic modality for the treatment of congenital blood disorders and/or leukemia, during the last decade, there have been some attempts to use (allo) transplanted HSPCs for the treatment of pancreatic cancer [78–81]. These first translational reports are based on the analysis of a total of 22 patients with locally advanced or metastatic disease, who, in most cases (21 of 22), received BM transplant from human leukocyte antigen-matched family relatives and underwent a reduced intensity conditioning before transplantation. After BM transplantation, a successful engraftment of such BM-derived SCs was observed in approximately 90% of patients with pancreatic cancer. For one patient, a complete response (defined as a lack of clinical evidence of a tumor mass in a computed tomography scan for at least 4 weeks) was observed, whereas in four individuals, a partial or minor response.
(defined as either >50% or 25–50% decrease in tumor size, respectively) was visible. Eight patients had stable disease. Unfortunately, the application of this experimental treatment did not translate into increased survival of these patients, which was approximately 139 days (median value), and, in most cases, tumor progression led to death of the affected individuals. Interestingly, the overall survival of these individuals after BM transplantation was not significantly associated with clinical or general laboratory parameters. However, the authors noticed that patients with pancreatic cancer, who developed chronic graft-versus-host disease after BM transplantation, tended to survive longer (the difference was close to statistical significance). They also identified two factors that were significantly associated with longer survival after BM transplantation—the number of transplanted cells over $4 \times 10^6$ cells per kg and an Eastern Cooperative Oncology Group performance status grade below 2 [81].

## Other Populations of BM-Derived (Stem/Progenitor) Cells

Finally, it seems important to highlight that, besides the aforementioned well-known populations of BMSCs, other less-defined types of (stem/progenitor) cells originating from the BM may also contribute to the development/progression of pancreatic cancer. For example, as mentioned before, we demonstrated that among various BMSCs, a population of recently discovered small SCs—VSELs—intensively egresses from the BM environment, and increased numbers of these SCs circulate in peripheral blood derived from patients with pancreatic cancer [24]. Currently the concept of VSELs is a matter of a lively debate, because some investigators challenged the existence of such SCs, whereas others provided further reports about the significance of VSELs in regeneration of various organs and cancerogenesis [21, 82–84]. Therefore, the eventual role of these BMSCs in pancreatic adenocarcinoma development/progression still needs to be defined and will undoubtedly be intensively examined within upcoming years. Furthermore, one cannot exclude the potential significance of another population of cells, pancreatic stellate cells (PSCs), in the development/progression of pancreatic cancer. It is estimated that approximately 5%–18% of PSCs participating in pancreatic regeneration after injury stimuli are derived from cells originating from the BM [85, 86]. Although it is generally believed that these cells contribute to the generation of pancreatic fibrosis during cancer development, still, recent reports suggest that action of these cells may be time- and context-dependent. Paradoxically, these cells seem to initially protect from pancreatic cancer development/progression and, at later stages, promote systemic spread of this disease. This occurs mainly because PSCs are involved in and influenced by a complex network of interactions from the side of immune, endothelial, and cancer cells, which may totally subvert PSC function (reviewed in detail in [87–89]). Nevertheless, further (clinical) studies are undoubtedly needed to confirm all these experimental observations and verify their significance for eventual therapeutic approaches.

## Conclusion and Further Challenges

In summary, the studies presented demonstrate that different BMSC populations contribute to the development and/or progression of pancreatic cancer, and they might also be a promising weapon that can be used for anticancer treatments in humans. Even though the exact role of these stem cells in pancreatic cancer development and/or progression in humans still remains unclear, this concept continues to drive a completely novel scientific avenue in pancreatic cancer research and gives rise to innovative ideas regarding novel therapeutic modalities that can be safely offered to patients. Unfortunately, many concerns and challenges still need to be addressed in this field. Currently, the main focus is on the precise molecular characterization of the origin and metabolism of pancreatic cancer stem cells, the identification and/or modulation of signaling orchestrating BMSC function and/or homeostasis in individuals affected by pancreatic adenocarcinoma, and the potential applications of genetically modified and/or (allo) transplanted BMSCs in the clinical setting. Hopefully, these new molecular and clinical approaches will deliver promising results and sufficiently increase our chances of successfully fighting off and curing pancreatic cancer in the next few years.

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## Author Contributions

W.B.: conception and design, literature search, manuscript writing, manuscript editing, final approval of manuscript; T.B. and T.S.: conception and design, literature search, manuscript editing, final approval of manuscript.

## Disclosure of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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