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Mini-review

Macrophages and pancreatic ductal adenocarcinoma

Aida Habtezion [a,*], Mouad Edderkaoui [b], Stephen J. Pandol [b]

[a] Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA 94305, USA
[b] Departments of Medicine and Biomedical Sciences Cedars-Sinai Medical Center, Veterans Affairs Greater Los Angeles Healthcare System & University of California at Los Angeles, Los Angeles, CA, USA

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ABSTRACT

Monocytes and macrophages make up part of the innate immune system and provide one of the first defenses against variety of treats. Macrophages can also modulate the adaptive immune system. Efficient sensing and response to tissue environmental cues highlights the complexity and dynamic nature of macrophages and their plasticity. Macrophages may have divergent roles depending on their polarity and stimulus received. Accumulating evidence demonstrates the critical role played by macrophages in tumor initiation, development, and progression. In this review, we discuss the characteristics of tumor-associated macrophages (TAMs) and their role in pancreatic adenocarcinoma. In addition, we give an overview on recent advances related to the therapeutic implication associated with targeting TAMs in pancreas cancer.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive tumors and the fourth leading cause of cancer-associated death in the United States [1,2]. PDAC develops by an adenoma to carcinoma sequence as a result of accumulating genetic alterations, which provide signals (e.g. TGFβ via SMAD4) that promote recruitment of immune cells [3–5]. Histologically, microscopic pancreatic intraepithelial neoplasms (PanIN) progress from intraepithelial to invasive pancreatic cancer and parallel the accumulating genetic alterations in the adenoma to carcinoma succession of PDAC [3,6,7]. Macrophages are one of the early infiltrating immune cells in PanIN lesions and continue to persist through the invasive cancer [8]. Moreover, recent studies showing macrophage involvement even at the early stages of acinar cell dedifferentiation to ductal cells or acinar-to-ductal metaplasia (ADM) underscores the critical role these cells play in pancreatic cancer initiation, progression, and metastasis. Tumor macrophage infiltration is associated with poor outcome. Analysis of human pancreatic cancer tissues showed that the number of infiltrating macrophages in tumor tissue from patients with metastases was significantly greater compared to patients with no metastasis [9].

The tumor environment is rich in immune cell infiltrates yet tumors are able to circumvent interference through mechanisms that inhibit immune cell mediated anti-tumor effects. Such modification of immune cell functions creates a favorable microenvironment that allows tumor progression (Fig. 1). This review attempts to summarize the knowledge gained during the last few years on the role of macrophages in pancreatic cancer.

Characteristics of tumor associated macrophages (TAMs)

Macrophages are efficient phagocytic cells of the innate immune system originating from bone marrow derived monocytes that constantly reconstitute most of the gastrointestinal tissues including the pancreas under homeostatic and inflammatory conditions [10–12]. In addition, local proliferation also contributes to maintain tissue resident macrophages. As a result of their plasticity, macrophages make up a heterogeneous population of immune cells with distinct functional and phenotypic characteristics [10]. More recently, classification of macrophages based on their functions, namely host defense, wound healing, and immune regulation, has been suggested [13]. More broadly and for simplicity, macrophages have been classified as classically activated (M1; commonly activated by IFN-γ and TLR ligands, express higher levels of IL-12, IL-23, TNFα, MHCII, IL-6, and inducible nitric oxide synthase or iNOS) or alternatively activated (M2; commonly activated by IL-4 and IL-13, express higher levels of IL-10 and TGFβ) [14,15]. M1- and M2-polarized macrophages predominate in acute and chronic pancreatitis respectively [12,16], with tumor-associated macrophages (TAMs) infiltrating solid tumors including PDAC thought to bear similarities to M2s and associated with poor prognosis [5,17].

TAMs have been studied in different cancer types, play an immunosuppressive role, and are frequently associated with poor prognosis due to their abilities in promoting tumor growth, invasion, angiogenesis, and metastasis as discussed below [18,19]. In addition to general macrophage markers (F4/80 in mouse, CD68 in human), scavenger receptors such as CD163, CD204, and CD206 have

* Corresponding author.
E-mail address: aidah@stanford.edu (A. Habtezion).

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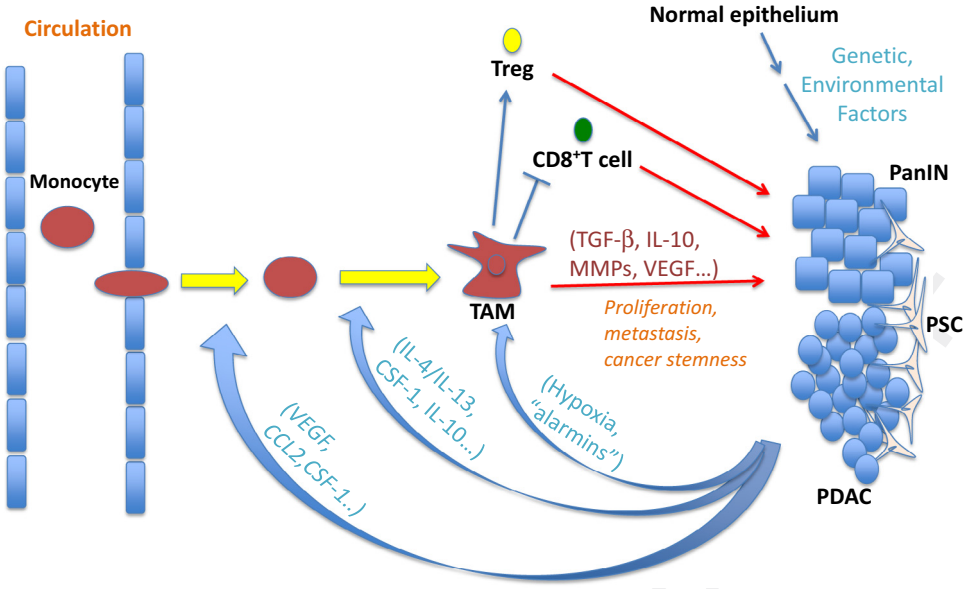

Fig. 1. Tumor associated macrophages (TAM) in pancreatic cancer. Macrophages play an important role in pancreas cancer development and progression. CCL2, chemokine (C-C motif) ligand 2; CSF-1, colony stimulating factor 1; IL, interleukin; MMPs, *matrix metalloproteinases*; PDAC, pancreatic ductal adenocarcinoma; PanIN, pancreatic intraepithelial neoplasia; TGFβ, transforming growth factor beta; Treg, regulatory T cell; VEGF, *vascular endothelial growth factor.*

been used to identify TAMs in cancers [20]. Functional properties of TAMs include production of IL-10 and matrix *metalloproteinases* (MMPs), as well as M1-associated iNOS suggesting heterogeneous or mixed characteristics amongst tumor infiltrating macrophages [21,22]. Recent study found that TAMs were predominantly M2 and associated with poor prognosis, whereas M1 predominated in the non-tumor inflammatory region surrounding the cancer cells, highlighting the importance of spatial localization of TAMs [23].

The importance of TAMs in PDAC is emphasized by the results coming from several groups showing relationships between number and location of TAMs in surgically resected tumors and patient outcome. Of note, the 5 year survival rate after surgery performed with curative intent is only about 20% [24]. Thus, the correlation between disease recurrence and survival after surgery represents opportunities to determine factors associated with disease recurrence and survival. Examples include findings that metastasis to lymph nodes found in surgical specimens is highly associated with M2s in the primary tumor and poor outcome [17]; and that high level of M2s in tumors as mentioned above is associated with shorter survival times while a greater ratio of M1s to overall macrophage number is associated with a longer survival after surgery [23]. It is known that extra-pancreatic nerve plexus metastasis of PDAC is associated with a poor outcome. One study showed that there is an association between a high number of M2s in the extra-pancreatic nerve plexus and decreased disease free survival and overall survival in patients undergoing resection of PDAC [25]. These studies confirm the long-standing findings in PDAC that a poor prognosis is associated with neural invasion and lymph node metastasis, and show that these biomarkers of outcome are associated with greater numbers of M2 type of macrophages.

Tumor microenvironment/evasive mechanisms recruiting and promoting TAM

The tumor microenvironment includes proliferating tumor cells, tumor-associated stromal fibroblasts (pancreatic stellate cells or PSCs in the case of PDAC), immune cells, blood vessels, and other tissue cells. The tumor microenvironment is enriched by factors that recruit circulating monocytes and favor generation of TAMs resembling M2 (Fig. 1). Such factors include colony-stimulating factor (CSF)-1, chemokines and cytokines such as IL-4, IL-13, TGFβ, and IL-10 [14,26–29]. CSF-1 promotes myeloid progenitor differentiation into monocytes and macrophages; and regulates proliferation, function, survival and migration of macrophages [30]. CSF-1 has also been implicated in promoting generation of alternatively activated macrophages or M2 [31,32]. In experimental PDAC models CSF-1/CSF-1R inhibition depleted CD206^{hi} TAMs and altered residual TAMs to support anti-tumor responses [33]. Thus, tumor-derived cytokines and chemokines not only promote macrophage recruitment and survival but also TAM functional properties that enhance tumor growth. In addition, other tumor-derived factors such as vascular endothelial growth factor (VEGF) also promote TAM infiltration as discussed below [34]. Dineen et al. showed in an animal model of pancreatic cancer that TAMs express *epidermal growth factor receptor* (EGFR) 2 whereas, macrophages from the animals without tumors did not express the receptor. They also found that VEGF recruits TAMs to the tumor microenvironment and that inhibition of VEGF prevented this effect [35].

CCL2/CCR2 axis is important for monocyte egress from the bone marrow and their recruitment into tissues under homeostasis and inflammation [36–38]. Of the chemoattractants identified to play a role in tumor monocyte/macrophage recruitment, the CCL2/CCR2 axis has been the best studied. Bone marrow monocyte mobilization and tumor infiltration was shown to depend on CCR2 in PDAC model, and increased bone marrow monocyte mobilization correlated with increased PDAC infiltration with CCR2+ macrophages and was associated with poor survival in patients with PDAC [39]. In addition, CCR2 inhibition led to a decrease in monocyte recruitment, tumor growth and metastasis in an orthotropic model of PDAC. Results from this study have led to the ongoing Phase Ib trial testing CCR2 blockade in combination with chemotherapy in patients with advanced PDAC (NCT01413022).

TAMs are found in high concentration in hypoxic and avascular areas of the tumor [40]. Presence of large areas of hypoxia has been correlated with poor prognosis and resistance to anti-tumor therapies [41]. In a mammary tumor model, TAMs were shown to up regulate VEGF expression in areas of hypoxia [40]. In addition, increased TAMs were present in poorly vascularized areas VEGF-positive

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