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Role of the immune system in pancreatic cancer progression and immune modulating treatment strategies

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ABSTRACT

Traditional chemotherapeutics have largely failed to date to produce significant improvements in pancreatic cancer survival. One of the reasons for the resilience of pancreatic cancer towards intensive treatment is that the cancer is capable of high jacking the immune system: during disease progression the immune system is converted from a system that attacks tumor cells into a support structure for the cancer, exerting trophic actions on the cancer cells. This turn-around of immune system action is achieved through mobilization and activation of regulatory T cells, myeloid derived suppressor cells, tumor-associated macrophages and fibroblasts, all of which suppress CD8 T cells and NK cells. This immune suppression occurs both through the expression of tolerance-inducing cell surface molecules, such as PD-L1, as well as through the production of "tolerogenic" cytokines, such as IL-10 and TGF-β. Based on the accumulating insight into the importance of the immune system for the outcome of pancreatic cancer patients multiple new immunotherapeutic approaches against pancreatic cancer are being currently tested in clinical trials. In this review we give an overview of both the immune escaping mechanisms of pancreatic cancer as well as the new immune related therapeutic strategies currently being tested in pancreatic cancer clinical trials.

Introduction

Pancreatic cancer is the 5th leading cause of cancer related death in the developed world with more than 260,000 deaths annually worldwide [1]. Due to its aggressive nature and late presentation 5-year survival is a dismal 6%. Research efforts have mainly focused on improvements in surgical technique, radiation therapy and chemotherapeutics. However, advancements in traditional chemotherapeutics have been especially slow, and despite the recent success of the FOLFIRINOX regiment in metastatic disease long term significant benefit has not materialized.

Recently, research efforts have focused on the role of the immune system in the development and progression of cancer. It is now known that both the innate and the adaptive immune system are active against human cancers [2]. Effective anticancer function of the immune system requires cytotoxic CD8 T cells, T helper-1 (Th1) cells, mature dendritic cells (DCs), activated pro-inflammatory macrophages (M1) and NK cells. However, cancer cells induce both local and systemic immune dysfunction thus avoiding detection by the immune system [3]. Under the tumor induced immunosuppressive environment T helper cells acquire a T helper cell type 2 phenotype (Th2), which does not support cytotoxic CD8 T cell responses and is tolerant toward tumors, macrophages switch to the immunosuppressive M2 state, while T regulatory cells (Tregs) and myeloid derived suppression cells (MDCS) inhibit effector immune responses (Fig. 1).

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Tumor immune modulation and evasion starts at the level of the cancer cell. Cancer cells use at least three mechanisms to modulate the immune system and avoid detection by effector immune cells: contact dependent factors (expression of immune system checkpoint ligands such as PD-L1), secretion of soluble immunosuppressive factors (such as IL-10, TGF-β and VEGF) and interference with MHC class I peptide presentation (through down-regulation of MHC class I expression or disabling of the antigen degradation or antigen insertion into the MHC class I grove). Despite the fact that downregulation of MHC class I makes cancer cells the target of NK cells, cancer cells influence the cytotoxic activity, the presence of activating receptors, and the numbers and proliferation of NK cells, thus further avoiding detection and destruction. Through these mechanisms cancer cells have a profound local and systemic immunomodulating effect which leads to general immunosuppression and tumor progression.

It is safe to predict that immune modulation strategies in pancreatic cancer will be widely explored in the years to come in view of the increasing scientific knowledge in the field, the success of immunotherapeutic strategies in other cancers, and the evident inadequacy of competing treatment modalities. In this review we describe the immune escape mechanisms of cancer, with a primary focus on pancreatic cancer, and we discuss immune modulating treatment strategies tested in pancreatic cancer clinical trials. We focus primarily on recent scientific insights, as well as clinical trials that are characteristic of the given treatment strategies.

In pancreatic cancer a dysfunctional immune system aids rather than controls cancer

Immune cells in pancreatic cancer promote an immunosuppressive and anti-inflammatory environment (Fig. 1)

T regulatory cells

Of all the different types immune cells, Tregs have gotten the most attention in tumor immunology research. They are generally defined as $CD4^+CD25^+FoxP3^+$ cells and they are found in the tumor microenvironment at increased numbers. By expression of CTLA-4 and secretion of IL-10 and TGF-β, among others, Tregs suppress exaggerated immune responses and are essential in the prevention of auto-immune diseases. In cancer however, they produce a local immunosuppressive environment ideal for tumor growth [4,5]. Patients with pancreatic cancer have increased numbers of Tregs both in the circulation and at the tumor site. Moreover, the presence of Tregs at the tumor site correlates with more advanced presentation of disease [6,7], a lower chance of surgical resection and a worse survival after resection [8], while low Treg percentage in the circulation one year post resection correlates with improved survival [8]. In addition, as levels of Treg cells increase, levels of the $CD8^+$ effector cells decrease [7]. Hence the Treg compartment represents an attractive target in pancreatic cancer.

Myeloid derived suppressor cells

MDSCs are immature myeloid cells that suppress both innate and adaptive immunity [9]. Factors contributing to their action in immunity include sequestration of cysteine (an essential amino acid for T cell activation), expression of high levels of arginase (resulting in depletion of L-arginine which is required by T cells for protein synthesis), increased production of reactive oxygen species, impairment of T cell homing to lymph nodes and secretion of TGF-β. These factors inhibit the function of effector T cells and NK cells and promote the development of Tregs. In a mouse model of spontaneous pancreatic cancer development the extent of immune suppression induced by MDSCs increased during the progression from premalignant lesions to pancreatic cancer [10]. Patients with pancreatic cancer have increased MDSCs in the circulation compared to healthy controls, and MDSCs levels correlate with levels of the Th2 cytokine IL-13 and Treg cell numbers [11]. Increased levels of circulating MDSC is an independent poor prognostic factor in patients with pancreatic cancer [11].

Tumor associated macrophages (TAMs)

TAM tumor infiltration is associated with worse prognosis in multiple cancers. Macrophages, due to stimuli from the tumor microenvironment such as IL-10, TGF-β and other cytokines, switch their differentiation from M1 (pro-inflammatory or

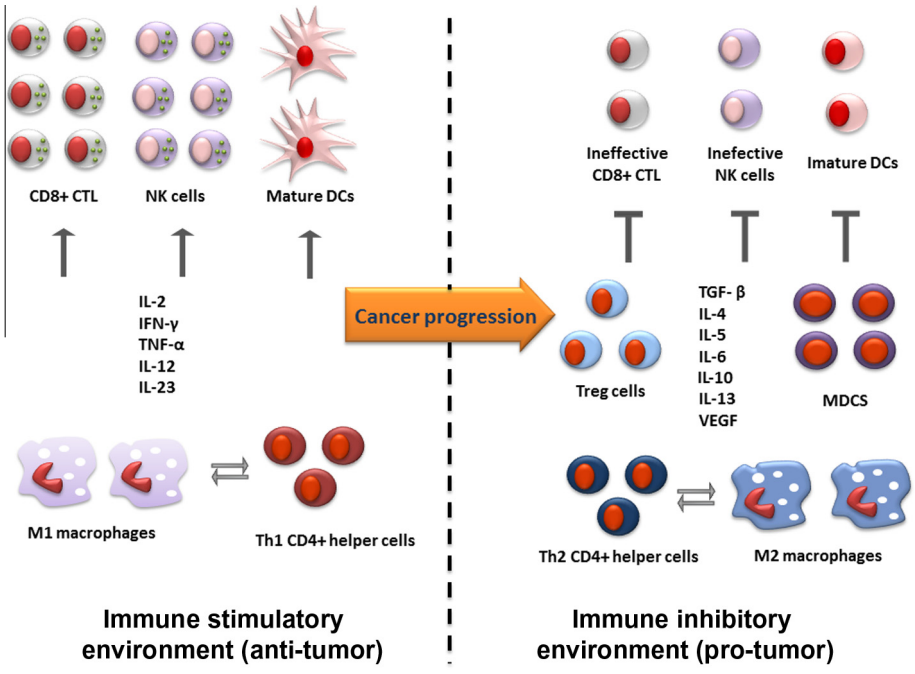

Fig. 1. Changes in the tumor immune microenvironment during cancer progression.