Clinical Oncology: Case Reports

OPINION

A SCITECHNOL JOURNAL

Examining Regulatory T Cells in Pancreatic Cancer

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Abstract

Regulatory T cells (Tregs) represent a prominent subset of immunosuppressive cells within the pancreatic tumor microenvironment. They exert influence on tumor growth by directly affecting cancer cells or by inhibiting effector immune cells. The mechanisms of Tregs interact within a partially redundant network with other immunosuppressive cells, such as Myeloid-Derived Suppressor Cells (MDSCs), contributing to the robustness of tumor immunosuppression and resistance to immunotherapy. The findings from preclinical studies, which indicate a simultaneous decrease in MDSCs when Tregs are depleted in early tumors, but an inverse relationship in advanced Pancreatic Cancer (PCa), underscore the importance of a comprehensive assessment of the immunosuppressive profile throughout the progression of PCa. An insightful context for the examination of these intricate compensatory mechanisms could be the tumors of patients who have undergone Neoadjuvant Therapy (neoTx). Our observations reveal a concurrent reduction in intratumoral Tregs and MDSCs following neoTx, even in cases of locally advanced PCa. NeoTx also results in diminished levels of αSMA+ myofibroblastic Cancer-Associated Fibroblasts (myCAFs) and an increased presence of CD8+ cytotoxic T lymphocytes within the tumor.

Keywords: Regulatory T cells; Pancreatic cancer; Neoadjuvant therapy

Introduction

Regulatory T cells (Tregs) constitute a significant subset of immunosuppressive cells within the microenvironment of pancreatic tumors. Tregs exert their influence on tumor growth through direct interactions with cancer cells or by inhibiting effector immune cells. These Treg cells establish a partially overlapping network with other immunosuppressive cell types, including Myeloid-Derived Suppressor Cells (MDSCs), contributing to the resilience of tumor immunosuppression and resistance to immunotherapies. Findings from preclinical studies, where Treg depletion led to a concurrent reduction in MDSCs in early-stage tumors but demonstrated an inverse relationship in advanced pancreatic cancer (PCa), underscore the need for a comprehensive analysis of the immunosuppressive profile across the spectrum of PCa tumorigenesis. One pertinent scenario for the investigation of these compensatory mechanisms might involve patients with locally advanced PCa who are undergoing Neoadjuvant Therapy (neoTx).

Pancreatic cancer

Pancreatic Cancer (PCa) stands as one of the most lethal human neoplasms, and it is anticipated to become the second leading cause of cancer-related fatalities worldwide by 2030. The therapeutic challenges in PCa are rooted in the low immunogenicity of cancer cells, the tumor's robust immunosuppressive mechanisms, or often a combination of both. In the case of PCa, the presence of immunosuppressive immune cells is observed even in the precursor stage, specifically around Pancreatic Intraepithelial Neoplasia (PanIN) lesions. As the tumor progresses, the prevalence of these suppressive cells continues to increase. The primary factors contributing to the pro-tumorigenic characteristics of the pancreatic tumor microenvironment encompass a highly fibrotic stroma and the accumulation of immune-suppressive cell populations, including regulatory T cells (Tregs), Tumor-Associated Macrophages (TAMs), and MDSCsPca.

Treg cells

Treg cells, characterized by the expression of CD4+ CD25+ Foxp3 +, constitute a specific lymphocyte subgroup that plays a crucial role in maintaining self-antigen and harmless foreign antigen tolerance under normal physiological conditions. However, tumor cells can hijack these Treg cells to evade the host immune response . Treg cells tend to gather around precursor lesions and tumor cells, hindering tumor-specific T cell responses and impeding the success of immunotherapy in various cancer types, including PCa . There are several proposed mechanisms by which Treg cells suppress effector T cell responses. These include directly eliminating effector T cells through substances like granzymes and perforines, secreting inhibitory cytokines like interleukin (IL)-10 or transforming growth factor (TGF)-β, inhibiting CD8+ effector T cells through membrane-bound TGF-β, and competing for access to Antigen-Presenting Dendritic Cells (DCs) . Additionally, Tregs impact effector T cell function by disrupting cell metabolism through IL2 deprivation and promoting adenosine production within the tumor microenvironment.

Immunotherapies in Cancers

Current immunotherapies are designed to augment the activities of effector T cells by targeting PD1/PD-L1 and/or CTLA-4 receptors. However, it's worth noting that Treg cells within the tumor microenvironment also express both PD-1 and CTLA-4, often at even higher levels than effector T cells. This becomes evident when examining the effects of PD-1 blockade, which notably enhances the proliferation of immunosuppressive PD-1+ effector Treg cells in gastric cancer patients with hyperprogressive disease following nivolumab treatment .In contrast, the CTLA-4 blockade with imilimumab results in the selective reduction of Treg cells and an increase in CD8+ T effector cell cytotoxicity, despite both of these functionally opposing T cell subpopulations expressing CTLA-4. These findings suggest that a combination of PD-1 and CTLA-4 inhibitors is likely to have a synergistic effect, activating intratumoral effector T cells by relieving them from PD-1/ PD-L1-m n an orthotopic implantation model, where primary KrasG12D-expressing pancreatic ductal epithelial cells were introduced into the pancreata of syngeneic Foxp3+ DTR mice, the removal of Foxp3+ cells through diphtheria toxin injection resulted in a significant reduction in tumor volume and an extended overall survival. There is an increasing focus on various translational immunotherapy strategies aimed at depleting or impairing Treg cells in solid tumors. These approaches involve targeting surface molecules expressed at higher levels in intratumoral Tregs compared to circulating Treg cells.Notably, the activation of

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Received: October 06, 2023; Manuscript No: COCR-23-118825; **Editor Assigned:** October 09, 2023; PreQC Id: COCR-23-118825 (PQ); **Reviewed:** October 18, 2023; QC No: COCR-23-118825 (Q); **Revised:** October 19, 2023; Manuscript No: COCR-23-118825 (R); **Published:** October 25, 2023; DOI: 10.4172/cocr.6(3).315

ICOS, 4-1BB, and GITR has been shown to hinder Treg suppressive capabilities and enhance the cytotoxic activity of effector T cells. Furthermore, researchers have explored targetable chemokines and chemokine receptors responsible for recruiting Treg cells into the pancreatic cancer microenvironment to improve ICI therapies in preclinical trials. Treg cells expressing CCR4 were observed to be attracted to CCL22, which is released by myeloid cells in ovarian cancer. The anti-CCR4 monoclonal antibody Mogamulizumab effectively triggered anticancer responses by depleting effector Treg cells in solid tumors. Another experimental approach to disrupt intratumoral Treg-mediated immunosuppression involves converting them into effector T cells by targeting the histone methyltransferase EZH2 and/or Helios.

Treg cells engage in close interactions with a subset of immature immune cells known as MDSCs, establishing a mutually activating functional crosstalk. These MDSCs possess a highly effective immune-suppressive machinery capable of dampening both innate and adaptive immune responses. For instance, MDSCs hinder the tumoricidal activity of effector T cells, resulting in the failure of robust anti-tumor responses. Soluble factors produced by both MDSCs and Tregs create positive feedback loops that foster the expansion of each cell population, amplifying the suppressive characteristics of the pancreatic tumor microenvironment. In a mouse model of colon carcinoma, IFN-γ-activated MDSCs were found to promote the de novo development, expansion, and recruitment of Treg cells. This effect could be attributed to the upregulation of MHC-II, IL-10, and TGF-β.

Furthermore, the expression of surface molecules by MDSCs, including CD40/CD40L, PD-1/PD-L, and CD80/CTLA-4, contributes to the accumulation of Tregs and is crucial for inducing T-cell tolerance. In a mouse model of ovarian cancer, MDSCs elevated the expression of CD80, which could bind to CTLA-4 on Tregs, further reinforcing the immunosuppressive phenotype . On the flip side, Tregs also play a role in modulating the expansion and pro-tumorigenic function of MDSCs. Tregs boost the proliferation of MDSCs through a TGF-β-dependent mechanism. Additionally, Tregs producing IL-35 enhance the suppressive functions of MDSCs via the PD-L1 pathway . Furthermore, in vivo depletion of MDSCs in a mouse model of orthotopically transplanted PCa led to a concurrent reduction in Treg infiltration within the tumor.

Tumor-infiltrating Tregs and macrophages have been demonstrated to collaborate, creating an immune-suppressive environment within the tumor. The functional and morphological characteristics of Tumor-Associated Macrophages (TAMs) in the pancreatic tumor microenvironment are subject to dynamic changes, often categorized as M1 or M2 polarization, representing proinflammatory and anti-inflammatory phenotypes, respectively . In the context of Pancreatic Cancer (PCa), TAMs tend to deviate towards the M2 phenotype, which has pro-tumorigenic effects, including the promotion of tumor progression, reinforcement of immunosuppression, facilitation of metastasis, and induction of resistance to chemotherapeutic drugs. Initially, macrophages can employ their innate immune functions to eliminate tumor cells, but this anti-tumorigenic role may shift as tumorigenesis progresses.In this context, cancer cells express the 'do not eat me' CD47-SIRPα molecule on their surface, which hinders macrophages' ability to phagocytose them. Pancreatic cancer cells can also impede the production of tumoricidal factors such as TNF-α and NO. M2-polarized macrophages are characterized by the secretion of immunosuppressive cytokines such as IL-10, TGF-β, IL-6, PGE, CCL2, CCL17, and CCL20. These cytokines inhibit CD8+ T cell-mediated anti-tumor immune responses and promote the differentiation and maturation of Treg cells from CD4+ T lymphocytes .

Considering the multifaceted role of TAMs in promoting PCa progression and their association with a poorer prognosis, macrophages present an appealing target for enhancing anti-tumor immunity and clinical therapy. In fact, therapies aimed at targeting TAMs in PCa have shown promise in preclinical studies, and some of these agents are currently undergoing clinical evaluation. Therapeutic strategies that focus on TAMs in PCa include macrophage depletion through the inhibition of CSF1R signaling, blocking the recruitment of macrophages into the tumor microenvironment by targeting CCL2/CCR2 signaling, and reprogramming macrophages towards a tumoricidal, classically activated phenotype using CD40 agonists or inhibiting the 'do not eat me' CD47-SIRPα signaling axis to enhance tumor cell phagocytosis. Conventional chemotherapy has also demonstrated its capacity to exert an immunomodulatory influence on various solid malignancies, including pancreatic cancer (PCa). In conditions like cervical and colorectal cancer, chemotherapy based on platinum agents resulted in a selective reduction in Foxp3+ T cells while preserving CD8+ T cell cytotoxicity. Additionally, the administration of gemcitabine led to a reduced frequency of circulating M- and PMN-MDSCs in patients with PCa. However, this decrease was reversed after a resting phase in which gemcitabine was not applied, highlighting the necessity for continuous gemcitabine treatment to maintain a lasting impact on intratumoral MDSC infiltration. Regrettably, this requirement for continuous administration is associated with an increase in chemotherapy-related side effects and a decline in patients' quality of life. A more profound comprehension of the intricate cellular interactions responsible for Treg- and MDSC-mediated immunosuppression within the pancreatic tumor microenvironment could pave the way for the development of combination therapies with fewer adverse effects compared to conventional chemotherapy.

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