Editorial



# Uncovering the role of immunosuppressive dendritic cells in pancreatic cancer

**Dwayne L. Thomas II[1,2,3], Adrian G. Murphy[1]**

[1]Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, [2]Department of Pathology, [3]Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

*Correspondence to:* Adrian G. Murphy. Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA. Email: amurph39@jhmi.edu.

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Pancreatic ductal adenocarcinoma (PDAC) is a debilitating disease that continues to have rising incidence and mortality rates. In 2018, it is estimated that nearly 56,000 individuals will be newly diagnosed with pancreatic cancer (1). Surgical resection remains the only possible curative measure as pancreatic cancer is notoriously resistant to systemic chemotherapy, has high rates of recurrence, and is associated with a 5-year survival rate of 8.5 (1). Increasingly, current research focuses on the immune system's interactions within the tumor microenvironment and exploring different ways to prime that environment to stimulate an immune response. Novel immunotherapies have the potential to harness the patient's innate immune system to help combat pancreatic cancer (2,3). This has led to numerous exciting discoveries and the development of novel therapies targeting different immune checkpoint pathways and the microenvironment.

The inherent complexity of the immune system results in certain immune components protecting against cancer (tumor infiltrating lymphocytes) (4) where as others function by promoting immune suppression such as myeloid-derived suppressor cells (MDSC) and tumor-derived macrophages (TAM) (5,6). The relatively poor response rates to immunotherapy in pancreatic cancer compared to lung cancer and melanoma, have prompted efforts to further elucidate the specific components of the immune system's response in the tumor microenvironment including the immune response at sites of metastasis.

Kenkel *et al.* investigated how the immune response at secondary/metastatic sites affected the metastatic behavior of pancreatic cancer in a preclinical model of PDAC (7). Using an immune competent orthotopic mouse model and Pdx1-*Cre*; *Kras*; *Trp53* mutated murine pancreatic cancer cells, $CD11b^+$ myeloid cells were found to have accumulated in the liver, surrounding early metastatic sites. Upon further characterization, these $CD11b^+$ ($CD11b^+$ $CD11c^{hi}$ MHC-$II^{hi}$) cells were categorized as dendritic cells (DCs), which secreted high levels of pro-tumoral mediators such as IL6, TNFα, and CCL2. DCs in tumor-bearing mice showed higher levels of expression of the immune checkpoint molecules PD-L1, PD-L2, and ICOSL when compared to normal liver DCs. The $CD11b^+$ DCs expressed multiple immunosuppressive factors resulting in the protection of metastases from immune elimination. This specific population of $CD11b^+$ DCs expressed monocyte/macrophage marker CD115, suggesting that they were derived from monocytes. Kenkel *et al.* further tested this theory by performing adoptive transfer of bone marrow monocytes that were congenically marked (CD45.1) into tumor-bearing mice. Before the transfer, these monocytes had high expression levels of Gr1/Ly6C, but five days post transfer the cells no longer expressed Gr1. This finding indicated that these monocytes were observed to traffic directly to the liver and had differentiated into $CD11b^+$ DC. As $CD11b^+$ DC accumulated in the liver, they were shown to increase regulatory T-cells in comparison to the poor response of $CD8^+$ T-cells. Additionally, $CD11b^+$ DCs uniquely expressed PD-L2 and anti-PD-L2 blocking antibodies lead to reduced metastatic progression via regulatory T cells expansion, which was mediated, by $CD8^+$

T cells (7). This research suggested a potential pathway for future targeting in an effort to enhance $CD8^+$ T cell activity resulting in growth at secondary/metastatic sites.

DCs are a unique subset of antigen presenting cells that capture, internalize, and process antigens *in vivo* (8-12) allowing for presentation on major histocompatibility complex (MHC) molecules and recognition by T cells (9-12). To date, their role in PDAC has been limited to their involvement in passive immunotherapy approaches (13).

This study demonstrates the potential for targeting key components in the innate immune system which can have favorable effects on tumor growth and metastasis. It also highlighted the specific influence of GM-CSF producing tumor cells which facilitated DC accumulation at metastatic sites. GM-CSF is increasingly known for its role in DC maturation (14) and directly upregulates major signaling pathways including JAK/STAT, MAPK and PI3K. Given the frequent use of recombinant G-CSF in patients with PDAC, the role of exogenous G-CSF on this specific DC subset is of particular interest (15).

This paper highlights the significance of how the immunosuppressive $CD11b^+$ DCs play a critical role in the early metastasis of pancreatic cancer at metastatic/secondary sites. In particular, these cells expressed MGL2 and PD-L2 and inhibiting these molecules resulted in the depletion of this DC subset thereby enhancing tumor immunity and inhibiting metastasis. MGL (macrophage galactose type C-type lectin) is expressed in human DCs and macrophages and has been shown to bind to epithelial mucins (MUC1) in colon cancer. Further study is required to elucidate the role of MGL (16,17) and its interactions with MUC1 in pancreatic cancer. This study also confirmed that this specific DC subset does exist in human PDAC where $CD11c^+HLA^-DR^+$ cells were observed to accumulate near $PD\text{-}L2^+$ stromal cells in cases of human PDAC liver metastases. These stromal cells were also observed to express MGL (the human homolog of MGL2). To date, there has been more focus on PD-1/PD-L1 interactions with anti-PD1 therapies, although there is emerging evidence that PD-L2 expression may play a role in disease response suggesting that therapies, which target both PD-L1 and PD-L2 may be more beneficial (18).

While the molecular targets of CD11b+ DCs have been established in this preclinical model, the challenge remains to translate these findings into therapeutic strategies targeting immunosuppressive DCs for patients with PDAC. This study suggests that the differential immune responses at metastatic sites vs. primary sites merits further attention, particularly to explain the underlying mechanism of immune suppression in PDAC.

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