Cancer Cell
Article

Depletion of Carcinoma-Associated Fibroblasts and Fibrosis Induces Immunosuppression and Accelerates Pancreas Cancer with Reduced Survival

Berna C. Özdemir,[1,2] Tsvetelina Pentcheva-Hoang,[3] Julienne L. Carstens,[1] Xiaofeng Zheng,[1] Chia-Chin Wu,[4] Tyler R. Simpson,[3] Hanane Laklai,[5] Hikaru Sugimoto,[1,2] Christoph Kahlert,[1,2] Sergey V. Novitskiy,[6] Ana De Jesus-Acosta,[7] Padmanee Sharma,[3] Pedram Heidari,[8] Umar Mahmood,[8] Lynda Chin,[4] Harold L. Moses,[6] Valerie M. Weaver,[5] Anirban Maitra,[9] James P. Allison,[3] Valerie S. LeBleu,[1,2] and Raghu Kalluri[1,2,*]

[1]Department of Cancer Biology, Metastasis Research Center, University of Texas MD Anderson Cancer Center, Houston, TX 77054, USA
[2]Division of Matrix Biology, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA 02115, USA
[3]Department of Immunology, University of Texas MD Anderson Cancer Center, Houston, TX 77054, USA
[4]Department of Genomic Medicine, University of Texas MD Anderson Cancer Center, Houston, TX 77054, USA
[5]Department of Surgery, University of California, San Francisco, San Francisco, CA 94143, USA
[6]Department of Cancer Biology, Vanderbilt University School of Medicine, Nashville, TN 37232, USA
[7]Department of Medical Oncology, Johns Hopkins Hospital, Baltimore, MD 21287, USA
[8]Department of Radiology, Massachusetts General Hospital, Boston, MA 02114, USA
[9]Departments of Pathology and Translational Molecular Pathology, Ahmad Center for Pancreatic Cancer Research, University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
*Correspondence: rkalluri@mdanderson.org
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SUMMARY

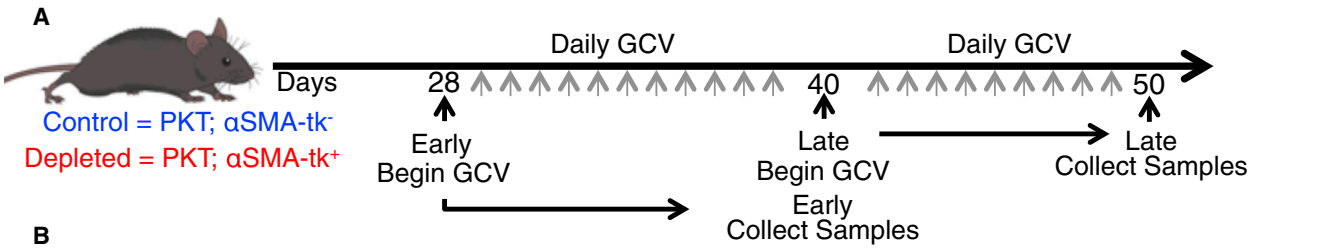
Pancreatic ductal adenocarcinoma (PDAC) is associated with marked fibrosis and stromal myofibroblasts, but their functional contribution remains unknown. Transgenic mice with the ability to delete αSMA$^+$ myofibroblasts in pancreatic cancer were generated. Depletion starting at either noninvasive precursor (pancreatic intraepithelial neoplasia) or the PDAC stage led to invasive, undifferentiated tumors with enhanced hypoxia, epithelial-to-mesenchymal transition, and cancer stem cells, with diminished animal survival. In PDAC patients, fewer myofibroblasts in their tumors also correlated with reduced survival. Suppressed immune surveillance with increased CD4$^+$Foxp3$^+$ Tregs was observed in myofibroblast-depleted mouse tumors. Although myofibroblast-depleted tumors did not respond to gemcitabine, anti-CTLA4 immunotherapy reversed disease acceleration and prolonged animal survival. This study underscores the need for caution in targeting carcinoma-associated fibroblasts in PDAC.

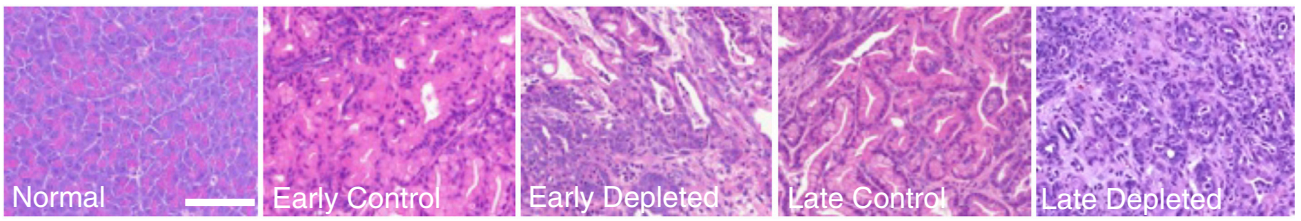
INTRODUCTION

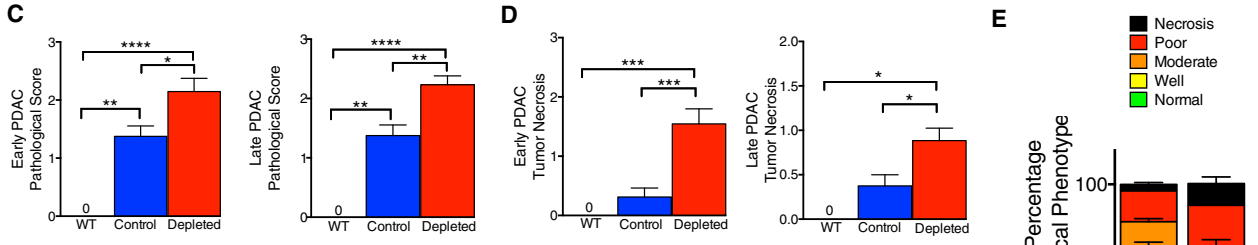
Pancreatic ductal adenocarcinoma (PDAC) is a near uniformly lethal disease with a dismal median survival of 4 to 6 months (Hidalgo, 2010; Korc, 2007). Despite years of efforts to design therapeutic approaches for pancreatic cancer, the use of conventional chemotherapy combination regimens with modest benefit remains the only option for the overwhelming majority of patients who present with advanced neoplasms. Revisiting the complex biology of PDAC in an unbiased manner is thus urgently required if we are to develop more effective therapies. The progress in generating genetically engineered mouse models faithfully mimicking human PDAC provides a unique opportunity to interrogate the functional contribution of the desmoplastic stromal reaction in PDAC, a defining feature of this carcinoma, which accounts for the majority of the tumor tissue volume

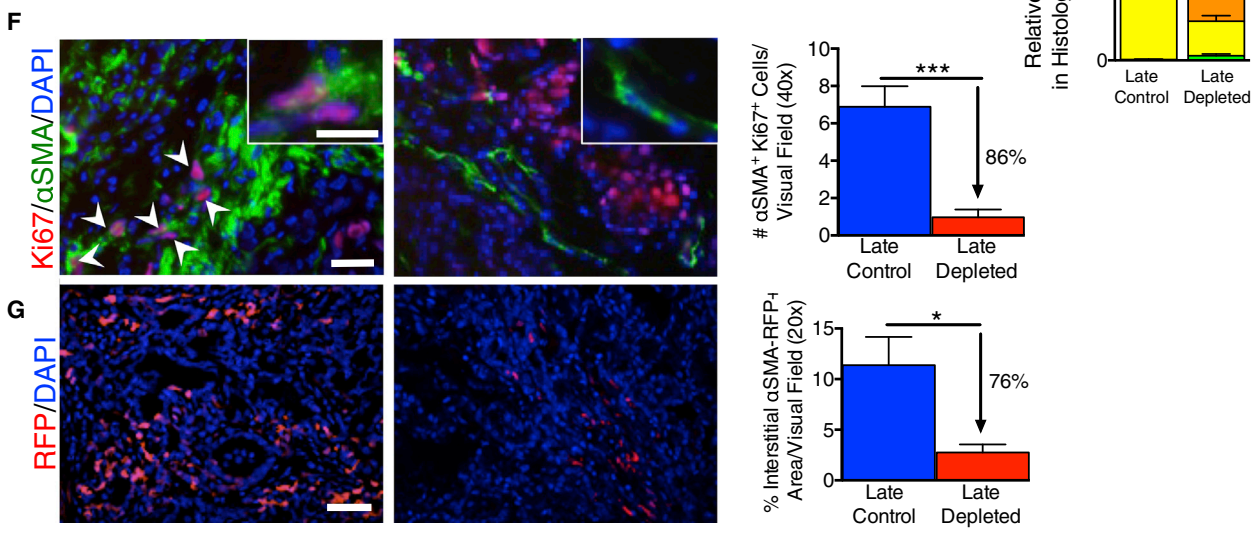
Significance

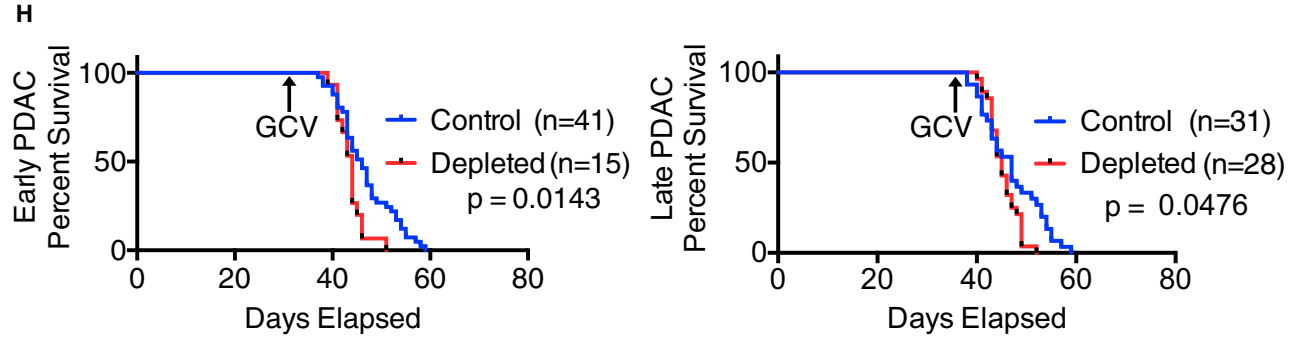
Pancreas cancer is associated with large amounts of stroma composed of collagen I and myofibroblasts, but their functional contribution remains unknown. Specific depletion of myofibroblasts using compound genetic mouse models of PDAC leads to aggressive tumors with diminished animal survival. Fewer myofibroblasts in human PDAC also correlate with reduced patient survival. Detailed studies show that myofibroblast loss decreases the ability of the immune system to control cancer associated with the persistence of regulatory T cells. Myofibroblast depletion did not improve gemcitabine's efficacy, but immunotherapy to revive immune attack prolonged mice's survival. This study demonstrates a protective role of myofibroblasts and suggests that targeting carcinoma-associated fibroblasts in pancreas cancer should be approached with caution.











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