Pancreatic Cancer Immunotherapy: Progress, Challenges and Opportunities

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Pancreatic ductal adenocarcinoma (PDAC) remains a treatment refractory malignancy, characterized by a highly complex tumor microenvironment (TME) which contributes its aggressive phenotype and is a major determinant of therapy resistance. Unlike other cancers, immunotherapy has shown limited promise in PDAC due to several impediments. PDAC is typically immunologically quiescent due to low mutational load resulting in limited neoantigens, and highly immunosuppressive TME owing to infiltration of immunosuppressive T- cells, B-cells and MDSCs. Even in the presence of immune checkpoint blockade agents, the recruitment of CD8+ CTLs is compromised. To design effective immunotherapies for PDAC it is thus paramount to: a) evaluate tumor-specific antigens capable of eliciting potent anti-tumor response; b) understand the underlying mechanisms of immunosuppression orchestrated by cancer cells; c) abrogate immune checkpoints that inhibit the activity of CTLs; and, d) investigate the “druggable” signaling cascades to promote the recruitment of effector CTLs, and abrogate immunosuppressive immune cells in the TME. Due to their aberrant overexpression and functional involvement, mucins have emerged as promising candidates to targeted therapies of pancreatic cancer. From the standpoint of vaccine development, aberrant glycosylation and extensive splicing of mucins in cancer can potentially generate more neoantigens. Our efforts are directed towards developing a mucin-based immunotherapeutic strategy and evaluating its efficacy in conjunction with checkpoint-blockade agents and pharmacological modulation of TME in pancreatic cancer.

Biography

Dr. Jain received his Masters in Biochemistry in 1996 from Devi Ahilya University, Indore and received his Ph.D in Biotechnology in 2002 from the Institute of Microbial Technology, Chandigarh India. Subsequently he completed his post-doctoral training at the University of Nebraska Medical Center (UNMC) in 2007 in Cancer Biology and later joined the Department of Biochemistry and Molecular Biology as a faculty member. The overall objective of his research is to improve the delivery and distribution of therapeutic agents for solid tumors, particularly pancreatic cancer. Jain’s team is studying the role of signaling pathways involved in the complex cellular crosstalk in the tumor microenvironment with a goal to selectively modulate the obstructive effects of stroma. His laboratory is also interested evaluating in biomarkers for early diagnosis, and developing targeted therapeutic approaches (radioimmunotherapy, immunotherapy) that exploit differential overexpression of mucins in pancreatic cancer.