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Classification of Pancreatic Cancer – Ready for Practical Application?

Danny N. Khalil^{1,2,3} and Eileen M. O'Reilly^{1,3,4}

¹Department of Medicine, Memorial Sloan Kettering Cancer Center

²Parker Institute for Cancer Immunotherapy

³Weill Cornell Medical College

⁴David M. Rubenstein Center for Pancreatic Cancer

Summary

There is great interest in an ability to categorize pancreas cancer and understand and classify the significant heterogeneity that exists in this disease. Such classifications based on morphologic, genetic, and immunologic features are emerging and the application of this information to provide both prognostic and predictive information is highly desired.

In this issue of Clinical Cancer Research, Wartenberg and colleagues offer a novel approach to classifying patients with pancreatic cancer (1). Traditionally, pancreatic cancer has been considered a disease with a uniformly poor outcome. Nonetheless, as with every other malignancy there is substantial heterogeneity in its behavior and clinical course. Recent classifications have begun to refine how we stratify this disease based on pathologic, genomic and more recently immunologic criteria. To date, these classifications have limitations and are not used on a day-to-day basis for patient decision making. A hope for the proximate future is the reality of a usable classification system with an ability to provide both prognostic and predictive information to the treating physician.

Historically, tumor immunologists have classified cancers into those considered immune responsive and those that are not. This distinction was often based on clinical, sometimes anecdotal, observations rather than strict criteria used in immunobiology. As a result, this classification was largely driven by the availability of immunotherapeutics (e.g., interleukin-2, interferon- α) in an era when the efficacy of such agents was mostly modest. Limitations to such a classification came to the forefront in the current era of checkpoint blockade when malignancies traditionally thought not to be immune responsive, such as non-small cell lung cancer, demonstrated sensitivity to anti-PD-1 therapy manifesting as profound and durable responses in a subset of patients.

Corresponding Author: Eileen M. O'Reilly, M.D., Memorial Sloan Kettering Cancer Center, 300 East 66th street, Office 1021, New York, NY 10065, Tel: 646 888-4182, Fax: 646 888-4254, oreillye@mskcc.org.

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Pancreatic cancer has remained in the non-responsive category, prompting the question of whether this reflects a fixed property of disease biology or merely the constraints in our current treatment armamentarium. In support of the latter possibility, there is a wealth of preclinical data suggesting that pancreatic cancers employ multiple means of immune evasion that are amenable to therapeutic intervention (2). These include the recruitment of regulatory immune cells (e.g., so-called myeloid-derived suppressor cells and M2 macrophages), the secretion of chemical messengers (e.g., the chemokine CXCL12, and the cytokines TGF β and GM-CSF), and the expression of cell-surface proteins (e.g., PD-L1 and CSF1R) that mediate immunosuppression. Which of these pathways drive tumor progression in humans, and thus offer attractive targets for intervention, is currently under active investigation. To date, treatment with single or combination checkpoint inhibitors in patients with pancreatic cancer have shown very limited efficacy outside of the small subset of individuals with microsatellite unstable/mismatch repair deficiency (1-2%). Multiple combination strategies to augment immunity are currently being evaluated with checkpoint inhibition, cytotoxic therapy, vaccines, and many other immunomodulatory approaches.

In this issue of CCR, Wartenberg and colleagues take an important step towards elucidating the role of immune cells in human pancreatic cancer that is not restrained by considering only the efficacy of current cancer immunotherapy. By parsing out three ways the immune system can interact with pancreatic cancers, independently of existing immune interventions, the authors shed light on what future immunotherapies might achieve in this disease (Table 1).

Through a combination of morphologic (tumor budding), genetic (50 “cancer-related” genes are interrogated) and immunologic (staining for CD3, CD4, CD8, CD30, PD-L1, and other surface markers is integrated with prior data on FOXP3 expression) studies the authors segregate pancreatic cancers into three immunologic categories. These categories (designated as ‘immune escape’, ‘immune rich’, and ‘immune exhausted’) are found to correlate, in some cases, with clinical outcomes. Using a retrospective data set, the authors find that patients in the immune rich category demonstrate superior overall, and progression-free survival as compared to patients in the immune escape or the immune exhausted category. In contrast to previous pancreatic cancer classification systems that separate tumors into two (ref. 3), three (ref. 4), or four (ref. 5) subsets based primarily on genetic features of the malignant cells, Wartenberg and colleagues have focused on immunity, suggesting that their approach may be more useful for guiding the use of immunotherapies rather than genetically targeted therapies.

Important limitations of the current study, which are not unique, include the small set of immunologic, morphologic, and genetic features that were analyzed. For instance, it is possible that if a different set of immune cell markers were studied, alternate classifications may have emerged. Other limitations are the sample size (110 patients) and fact that the entire data set was derived from patient with resectable disease.

Future studies of interest would link these clinical classifications to the reported biology from preclinical models. For instance, by including marker such as PD-1, TIM3, LAG3, 2B4, and EOMES, one could determine whether tumors in the ‘immune exhausted’ subset

show evidence of T-cell exhaustion. If that is the case, then many immunotherapies that potentially reverse T-cell exhaustion including anti-TIM3 and anti-LAG3 monoclonal antibodies (as will be studied in the upcoming phase I studies NCT03489343 and NCT03489369) may have critical relevance. Alternatively, one can ask whether active T cell exclusion (2) accounts for the paucity of T cells in the 'immune escape' subset. If that is the case, then blockade of pathways that mediate this effect (with CXCR4 antagonists for example, as in the ongoing phase I/II study NCT03193190), will provide further insight.

From the perspective of the past decade, there is both an abundance of investigational agents being developed for pancreatic cancer, and an abundance of diagnostic tools and putative biomarkers that could distinguish between different subsets based on fundamental biology. The challenge will be in combining these tools in as unbiased and thoughtful a manner as possible. With their current work, Wartenberg and colleagues take an important step forward along this path by proposing three distinct categories to describe the intra-tumoral immune status of patients with pancreatic cancer. The next step will be to broaden the immunologic, genetic, and morphologic variables under consideration. This will allow the field to better associate pathologic findings with specific biological processes, and to discover new pathways relevant in human pancreatic cancer by moving beyond the immune populations and markers that are judged important based on our current knowledge. The ultimate validation of this approach will come when patients treated with therapeutics tailored to their disease biology achieve outcomes surpassing what was possible in the previous generation. Based on the work described above, and on that of many other researchers, we are optimistic that such validation is a tangible future actuality.

Acknowledgments

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Table 1

Immune characterization of pancreatic cancer

Wartenberg Subset	Selected characteristic	Potentially analogous biology	Reference	Open question
Immune escape	Low T-cell infiltrate	T-cell exclusion	Feig et al., PNAS, 2013	Are mediators of T-cell exclusion (e.g., CXCL12) present?
Immune rich	Rich T-cell infiltrate	Cytolytic phenotype	Hamid et al., J Translational Medicine, 2011	Are cytolytic genes (e.g., granzyme B) expressed?
Immune exhausted	PD-L1 upregulation, or microsatellite instability	T-cell exhaustion	Wherry et al., Immunity, 2007	Are markers of T-cell exhaustion (PD-1, EOMES) present?