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Personalized Medicine in Pancreatic Cancer: Prognosis and Potential Implications for Therapy

Christine A. Iacobuzio-Donahue
Departments of Pathology, Oncology and Surgery, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins Medical Institutions, Baltimore, MD 21231, USA

Pancreatic cancer is a highly lethal disease. In 2010, an estimated 43,140 patients were diagnosed with pancreatic cancer and 36,800 died of their disease, making pancreatic cancer among the most lethal of all solid tumors.[1] The major reason for the lethal nature of pancreatic cancer is that it is commonly diagnosed in the final stages of the disease.[2] For example, Yachida et al. recently found that although there is a long window of opportunity for early detection of pancreatic cancers while still in the curable stage, most patients are diagnosed after metastatic dissemination has occurred.[3] Thus, the development of biomarkers for early detection of pancreatic cancer remains the most important hurdle towards cure of this disease.[4]

In an effort to better understand pancreatic cancer at its most lethal stage, in 2003, we instituted a rapid autopsy program for patients with end-stage pancreatic cancer.[5] This program has not only indicated that a rapid autopsy protocol for procurement of pancreatic cancer tissues is feasible, but has also led to novel insights into the biology of this tumor type that underlie its propensity to metastasize.[6] Perhaps the most surprising observation was that, contrary to common perception, not all pancreatic caners are metastatic. Twelve percent of patients had no metastatic disease at autopsy, and an additional 18 % of patients had limited metastatic burden, leading us to define these patients as having oligometastatic disease (defined as ≤10 gross metastases) that did not directly contribute to their cause of death. In many of these patients, death occurred due to complications of carcinoma infiltration by the primary carcinoma into surrounding vital structures. Second, we found that the status of the *DPC4* gene in the primary carcinoma is highly correlated to these patterns of failure. Loss of Dpc4 immunolabeling, signifying a deletion or mutation of the gene,[7] was correlated with widespread metastatic disease, whereas retention of Dpc4 immunolabeling correlated with the locally destructive/oligometastatic phenotype. Of interest, mutations of the *TP53* tumor suppressor gene also correlated with these patterns, although not to the extent of Dpc4. Thus, pancreatic cancer seems to be represented by to two phenotypes that differ not in their morphologic differences at diagnosis but in their metastatic efficiencies for which Dpc4 immunolabeling status is a marker. The significance of *DPC4* inactivation is further supported by a large study of 114 surgically resectable patients in which genetic inactivation of *DPC4*, whether by deletion or mutation, was

C.A. Iacobuzio-Donahue, Department of Pathology, GI/Liver Division, 1550 Orleans Street, CRB2 Rm 343, Baltimore, MD 21231, USA, ciacobu@jhmi.edu.

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associated with a worse overall survival compared to patients in which this gene is intact within their resected carcinoma tissues.[8]

A logical question raised by this data is to determine the functional mechanisms targeted by *DPC4* inactivation in pancreatic cancer cells that may promote metastatic efficiency. This is important to know as it will stimulate the formation of novel therapeutics that targets these prometastatic mechanisms. *DPC4* is a central mediator of the TGFβ signaling pathway that plays a role in cell growth and differentiation, extracellular matrix remodeling and immune regulation.[9] Loss of *DPC4* thus disrupts the tumor suppressive properties of canonical TGFβ signaling such as G1 cell cycle arrest and apoptosis leading to cancer cells with enhanced proliferation, growth, and migratory abilities.[10] However, because some of the growth inhibitory properties of TGFβ signaling do not require *DPC4* but rather alternative pathways downstream of a ras effector,[11–15] a full determination of the significance of *DPC4* in pancreatic cancer progression is needed. This notion is supported by experimental data indicating that the ability of cancer cells to undergo epithelial–mesenchymal transition is reliant on non-*DPC4* dependent TGFβ signaling pathways such as phosphatidylinositol-3-kinase (PI3K) signaling.[16–18]

In our autopsy series to date, Dpc4 in a surgically resectable carcinoma corresponds to a relative risk of 3.3 for development of widespread metastasis compared to those with intact Dpc4 labeling.[1] However, although Dpc4 loss is highly correlated with metastasis, it is important to note that metastasis formation is not an absolute occurrence in Dpc4 negative carcinomas. Recent studies from our lab indicate that irrespective of *DPC4* genetic status, many years may pass before the development of metastatic subclones suggesting that additional factors are required for metastasis to occur.[3] Thus, while it takes time for metastatic clones to develop, the genetic inactivation of *DPC4*, and hence disruption off canonical TGFβ signaling, may simply increase the efficiency of metastatic dissemination when it finally occurs.

The most implications of this work are its significance for clinical management of patients with pancreatic cancer.[19] For example, patients with borderline resectable carcinomas that has loss of Dpc4 expression in diagnostic biopsies may indicate a relatively higher risk of widespread distant recurrence and thus be prioritized for systemic rather than locoregional therapy. By contrast, retention of Dpc4 may indicate that particular patient is a better candidate for adjuvant chemoradiation, a treatment option that remains debatable for controlling locoregional disease.[20,21] Dpc4 status may also have implications for disease recurrence. For example, the development of a solitary metastasis years after surgical resection that is Dpc4 intact (indicting a wild type gene) may signify a more indolent biology and prompt discussions among clinicians as to the potential benefit of surgical resection of the metastasis. Ultimately, more studies will be needed to best understand the significance of Dpc4 in pancreatic cancers in the context of each patient's disease and at each clinical stage of diagnosis.

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