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Editorial Note on Pancreatic Cancer Subtypes

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Editorial

Pancreatic Ductal Adenocarcinoma (PDAC) is the most common form of pancreatic cancer and has often been viewed as a disease with a poor prognosis and few clinically useful molecular subtypes. However, over the last decade multiple groups have characterized the complex molecular landscape of PDAC to reveal several distinct classes of disease. In this issue of Gastroenterology, multicenter study examining gene expression programs in resected PDAC specimens and define 5 transcriptomic subtypes. Their robust stratification system corroborates key features of previous studies, while establishing an integrated classification that defines subtypes by gene expression features from both tumor and stromal compartments. Recent studies have defined numerous molecular subtypes of PDAC. Genome sequencing has elucidated classes of tumors based on mutations in key signaling pathways, including KRAS, DNA damage repair, transforming growth factor-beta, chromatin remodeling, and others. Several studies have examined gene expression using microarrays or RNA sequencing and have identified distinct RNA signatures of PDAC. Collisson originally described 3 PDAC gene expression subtypes, including classical, quasimesenchymal, and exocrine-like subtypes. Moffitt later used a "virtual microdissection" approach on data from primary and metastatic PDAC tumors to digitally separate tumor, stromal, and normal cell gene expression. They identified 2 tumor-specific signatures, including a classical subtype and a basal-like gene expression program that resembled the basal subtype of breast and bladder cancers. Moreover, they also identified 2 stroma-specific gene expression signatures and demonstrated that combinations of the stroma and tumor-specific subtypes represent distinct biology with different prognostic implications.

The International Cancer Genome Consortium subsequently defined 4 major gene expression subtypes of PDAC, including a pancreatic progenitor class that showed strong overlap with the Collisson and Moffitt classical subtypes, as well as a squamous classification that closely resembles the Moffitt basal-like subtype. Additionally, the International Cancer Genome Consortium study also described an aberrantly differentiated endocrine exocrine subtype and a novel immunogenic subtype that was associated with evidence of a significant immune infiltration. The Cancer Genome Atlas project subsequently provided further data suggesting that the aberrantly differentiated endocrine exocrine/exocrine-like subtype and the immunogenic subtype likely represented gene expression from non-neoplastic cells. Beyond these messenger RNA subtypes, noncoding RNAs as well as protein expression have also been used to molecularly stratify PDAC specimens. More recently, Tuveson Q3 performed drug sensitivity profiling of PDAC organoid models and elucidated novel functional subtypes that were used to define gene expression signatures that predict chemotherapy sensitivity.

Now report an impressive analysis of gene expression data from 309 resected PDAC tumors that were consecutively collected across 4 academic centers. They rediscovered the classical/pancreatic progenitor and basal like/squamous subtypes in higher cellularity tumors and used unsupervised consensus clustering of all tumors in the cohort to define 5 distinct subtypes comprised of both tumor-specific and microenvironment-derived signatures. Two of these classes showed low stromal signals, including pure classical and pure basal-like subtypes. The other 3 classes were defined by the impact of high stromal content, including the immune classical, desmoplastic, and stroma activated subtypes. Although the Puleo classification has similarities with the Moffitt classification, the authors argue that their 5-subtype stratification incorporates more information about immune cell and proinflammatory signals and propose that tumor and microenvironment expression features must be integrated to define optimal clinically prognostic subtypes of PDAC. The demonstration of robust gene expression signatures from a large cohort of formalin fixed paraffin embedded specimens (standard in clinical practice) is a novel and important contribution to the literature.

Additionally, the authors provide an impressive online histogenomics application allowing the correlation of histology with transcriptomic signatures. An important limitation of the study is its focus only on primary resected tumors rather than metastatic disease, which may harbor distinct tumor and stromal features. With several well-done studies now proposing multiple gene expression classifications of PDAC, how does the field make sense of these subtypes to benefit patient care? These classifications are more similar than different, and several common themes have emerged. The classical/ pancreatic progenitor and the basal-like/squamous neoplastic subtypes have been validated across multiple studies in primary and metastatic samples. Basal-like/squamous tumors harbor a significantly worse prognosis than classical/ progenitor tumors. These basal-like/squamous tumors also display more frequent TP53 mutations a higher pathologic grade and a poorer response to modern chemotherapy regimens [1-5].

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