IN THE SPOTLIGHT

Chemotherapy and Tumor Evolution Shape Pancreatic Cancer Recurrence after Resection

Filip Bednar1,2 and Marina Pasca di Magliano1,2,3

Summary: Most patients with pancreatic cancer who undergo curative resection and systemic chemotherapy still relapse with local or systemic recurrence. In this issue, Sakamoto and colleagues use advanced genomic tools to investigate the evolutionary origins of pancreatic cancer recurrence and discover an increased mutational burden that might be promoted by therapeutic intervention and might provide an opportunity for therapeutic intervention.

See related article by Sakamoto et al., p. 792 (1).

Pancreatic ductal adenocarcinoma (PDA), the most common form of pancreatic cancer, remains one of the deadliest cancers due to late diagnosis and only modest effectiveness of existing treatments. Only 10% to 15% of patients present with a primary tumor that is surgically resectable. The standard of care for these patients has been to combine resection with 6 months of systemic chemotherapy to maximize their chance of a cure. Unfortunately, the vast majority of these patients eventually relapse and die of their disease. This clinical course suggests that most patients already carry micrometastases undetectable by current diagnostic tests at the time of resection. Until now, it has been unclear how the recurrent tumors evolve from the primary tumor and how or whether the treatment course affects this evolution. The current work by Sakamoto and colleagues in Cancer Discovery begins to define these evolutionary links and highlights key areas for future study in this subset of patients with pancreatic cancer (1).

Significant genomic intratumoral heterogeneity and complex phylogenetic relationships between primary tumors and metastases have been described in other solid organ malignancies including lung, breast, and kidney cancers (2–4). In pancreatic cancer, Iacobuzio-Donahue and colleagues had previously performed whole-genome sequencing in patients with stage IV metastatic disease who were untreated, and described intratumoral heterogeneity, with the coexistence of geographically and genomically distinct subclones within the primary tumor. Intriguingly, in those same patients, the genomic data supported polyclonal seeding of metastases (5, 6). It is important to note that in the current study, all patients had stage I/II resectable disease and underwent surgery and adjuvant chemotherapy.

Using targeted and whole-exome sequencing and phylogenetic analysis of 10 resected tumors and associated recurrences, Sakamoto and colleagues now identify two modes of PDA relapse after primary tumor resection and systemic chemotherapy (Fig. 1). In the first scenario, a single dominant subclone serves as the source for the relapse, a monophyletic recurrence. In the second scenario, a combination of distinct subclones within the primary tumor leads to multiple recurrences, a polyphyletic recurrence (1). This observation is in line with the genomic and evolutionary complexity seen in other solid organ tumors. In addition, by analyzing the mutational signatures present in primary versus recurrent disease, the authors demonstrate that adjuvant systemic chemotherapy produces treatment-specific mutational signatures most often marked by platinum therapy–based double-strand DNA breaks within the relapsed tumors. The additional mutational stress and concurrent evolution lead to potential new driver mutations in a number of oncogenic pathways including the MAP/ERK kinase signaling pathways, the PI3K/AKT/mTOR pathway, MYC/MAX-driven transcription, chromatin remodeling, DNA damage repair, and nuclear export in the metastases (1). This chemotherapy-driven evolutionary links contrasts with the findings in treatment-naïve metastatic PDA, where the primary tumors and metastases have a limited and similar complement of driver mutations (6). The authors also observe a trend for improved recurrence-free survival in patients exhibiting the monophyletic origin of their disease relapse compared with those with polyphyletic evolutionary trees. This is consistent with the scenario where polyclonal seeding provides genomic diversity to the micrometastases to allow for a quicker emergence of resistant subclones during the evolutionary pressure of systemic therapy. These results highlight the interplay between the genomic diversity of PDA and treatment-driven selection pressure to drive disease relapse.

Genomic evolution in PDA is often marked by complex genome rearrangement patterns consisting of a combination of focal amplifications, whole-genome duplications, and loss of heterozygosity at multiple loci. Transcriptional signature analysis of resected PDA tumors within The Cancer Genome Atlas and other datasets has also defined two primary transcriptional subtypes of PDA, the classic and the squamous/basal-like type (7). Recent work, including the current article, has now begun to integrate these genomic and transcriptomic

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characterizations into a unified model of PDA biology. A key observation has been that genomic rearrangements partly drive wild-type allele loss and mutant allele gain at the KRAS locus (1, 8, 9). The altered KRAS signaling correlates with and likely contributes to the progression from the classic to the squamous/basal-like subtype and is associated with the presence of metastases (8, 9). Similar observations are made by Sakamoto and colleagues, where a variety of complex genomic rearrangements lead to mutant KRAS allele gain in the metastases compared with the resected primary tumors (1). The KRAS allelic imbalance also combines with chromatin regulator disruption and transcription factor expression changes, including GATA6 and MYC among others, to drive PDA transcriptional subtype evolution and behavior (1, 7–10). A key question arising from the current work is how monophyletic versus polyphyletic spread relates to the presence of the functional classic and squamous PDA subtypes. Recently published work has identified frequent coexistence of the two transcriptional subtypes by histology and at single-cell transcriptional level in most patients (9, 10). Phylogenetic analysis suggests that squamous differentiation arises within classic glandular tumors during PDA evolution, but metastases can still arise from clones of either subtype, suggesting that the acquisition of the metastatic phenotype does not have to be preceded by evolution of a squamous/basal-like subclone in the primary tumor (10). The emerging picture is that of a pancreatic tumor undergoing parallel intratumoral polyclonal development until one or more of the subclones develop the ability to metastasize. The timing of a curative resection during the process of tumor evolution might then determine whether monophyletic or polyphyletic recurrence will occur (Fig. 1). The presence, prevalence, and heterogeneity of any micrometastases at the time of resection of the primary tumor control the rate of therapeutic resistance and recurrence during the evolutionary sweep imposed on the neoplastic cells by systemic chemotherapy. The findings reported in this article support the notion that posttreatment sampling might be important to devise therapeutic approaches for relapsed disease, which is intrinsically different from the primary, prechemotherapy tumor. Given the increased mutational burden of postchemotherapy disease, an intriguing question is whether the relapsed tumor would have a higher prevalence of neoantigens and potentially be more susceptible to immunotherapy. To evaluate this possibility, examining changes in the microenvironment pre- and post-treatment, as well as the patient’s systemic immune status, will be important in future studies.

The results of this study allow us to place our current treatment approaches to resectable pancreatic cancer within an evolutionary framework. A key clinical question under intense scrutiny is whether patients with resectable tumors should be treated with chemotherapy before or after resection. Within the context of a constantly evolving heterogeneous tumor, any systemic therapy is a form of selective pressure and additional mutation drive to allow the development of therapy-resistant subclones. The only difference between a neoadjuvant (chemotherapy before surgery) or adjuvant (chemotherapy after surgery) scenario is whether this selective pressure is applied on the intact primary tumor. How this affects clinical outcomes is currently unknown and under intense investigation. However, it is clear we need to understand the mechanisms regulating tumor evolution on the genomic and functional level and their interaction with our systemic therapies to define how treatment resistance and relapse occur. This work by Sakamoto and colleagues lays a key foundation for this. It is time for us to begin translating this understanding to our patients.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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**REFERENCES**

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