

Pancreatic Cancer: Targeted Therapy Holds the Promise

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Pancreatic cancer is one of the most lethal malignancies, with a 5-year overall survival rate of less than 10%, underpinning an unmet need for this devastating disease.¹ Delineation of the molecular subtypes is prominent to better understanding of both the intertumoral and intratumoral heterogeneity in pancreatic cancer, and ultimately pave the way for precision oncology. Perturbed genomic integrity and transcriptomic reprogramming play important roles in tumorigenesis. Homologous recombination (HR) is one of the major DNA damage repair (DDR) pathways that are crucial to maintaining genomic integrity. Loss of HR related genes, such as *ATM*, *BRCA1* and *BRCA2*, would result in HR deficiency, also known as “BRCAness”, which together with pathogenic germline or somatic mutations, would lead to the accumulation of DNA damage and the subsequent tumorigenesis. Studies on the transcriptomic profiles have advanced our understanding on the molecular subtypes of pancreatic cancer. But the landscape of copy number variation (CNV) in HR pathway in pancreatic cancer remains elusive.

In this issue of EBioMedicine, Zhan et al reported the largest single-institute cohort, to the best of our knowledge, of pancreatic cancer patients, that evaluated the correlation between prognosis and genomic alterations, especially CNV of HR pathways.² They found that the amplification of HR and receptor tyrosine kinase (RTK) related genes was associated with dismal prognosis in pancreatic cancer. Patients were categorized into two clusters (CNV-G₁, CNV-G₂) by utilizing unsupervised clustering, which showed deficient and proficient HR respectively. In order to stratify the patients more precisely, the authors took a further step. They analyzed the differentially expressed genes between the two clusters and established an elegant algorithm to calculate the CNV score. Based on this model, they were able to stratify patients into four subtypes, including repair-deficient (CNV-G₁ with low CNV score), proliferation-active (CNV-G₁ with high CNV score), repair-proficient (CNV-G₂ with low CNV score), and repair-enhanced (CNV-G₂ with high CNV score). The repair deficient subtype had the most favorable prognosis and might be

responsive to PARP inhibitors, while the repair-enhanced and repair-proficient tumors showed higher tumor mutation burden (TMB), suggesting they are more likely to respond to immunotherapy.

This study is significant in that it provided thoughtful insights into understanding the CNV landscapes and the role of CNV in HR genes in facilitating the intertumoral and intratumoral heterogeneity in pancreatic cancer. The comprehensive proof of concept results of this study indicated that this model could be a surrogate biomarker to predict treatment response to PARP inhibitor and immunotherapy. Additionally, the newly identified molecular subtypes may help to facilitate personalized therapeutic strategy for pancreatic cancer.

The POLO (Pancreas Cancer Olaparib Ongoing) trial has led to the approval of Olaparib, a PARP inhibitor, by the U.S. Food and Drug Administration (FDA), as first-line targeted therapy for metastatic pancreatic cancer patients with germline *BRCA* (*gBRCA*) mutation. This enabled us to tailor the therapeutic strategies for pancreatic cancer patients, especially those with specific genomic alterations, such as deleterious *gBRCA* mutation. Notably, heterogeneous responses to Olaparib are prevalent among those with identified *gBRCA* mutation, indicating other genomic events may also contribute to the heterogeneity.³

Chromosome imbalance can induce genomic instability. Delineation of the variation of chromosomal rearrangement has identified four subtypes, including locally rearranged, scattered, stable and unstable, the latter of which accounts for 14% of all pancreatic cancer.⁴ Most “stable” tumors exhibited unbalanced number of chromosomes, also known as aneuploidy, which is associated with decreased immune infiltration and suppressed immune surveillance. The “unstable” subtype is characterized by genomic instability, which suggests the defect of DDR. Intriguingly, a majority of unstable tumors exhibited deleterious *BRCA* mutation and were more responsive to PARP inhibitors than the stable counterparts.⁴ This classification partially explains how chromosome imbalance can increase intertumoral heterogeneity by inducing HR deficiency.

Furthermore, the pre-existed intratumoral heterogeneity may also contribute to treatment resistance.⁵ Basal-like and classical pancreatic cancer cells can coexist in the same tumor. The analysis of the evolutionary trajectory of CNV in mutant *KRAS* has identified *KRAS*

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imbalance as a crucial event in driving genome doubling and instability, which could contribute to pancreatic tumorigenesis and the switch from classical to basal-like phenotype.⁶ The plasticity of these subtypes leads to the spatial heterogeneity and highlights the necessity of further studies to understand the evolutionary trajectory in the context of cell lineage specific CNV alterations.

Although this study did not identify increased TMB in repair-deficient tumors, emerging data has shown that HR deficiency is associated with increased response to immunotherapy. For example, tumors with *BRCA2* mutation showed better treatment outcomes of immunotherapy.⁷ *ATM* deletion would also restore the innate immune surveillance and enhance the efficacy of immunotherapy for pancreatic cancer in preclinical models.⁸ Notably, *ATM* has the highest mutation rate (3.45% in this study) among all the HR related genes, which is consistent to the previously reported 4% in sporadic pancreatic cancer.⁹ Loss of *ATM* would increase the risk of pancreatic cancer in patients with Intraductal Papillary Mucinous Neoplasm (IPMN).¹⁰ These results provide a rationale for investigating immunotherapy in pancreatic cancer patients with HR deficiency. Indeed, several ongoing Phase I/II trials are evaluating the efficacy of combining PARP inhibitors with immunotherapy for pancreatic cancer (NCT03404960, NCT03637491).

In summary, this study reinforced that HR deficiency would render this subset of pancreatic cancer patients more vulnerable to PARP inhibitors. It incorporated the genomic alteration with mathematical algorithm and constructed a novel model to identify pancreatic cancer patients that are more likely to benefit from PARP inhibitors and immunotherapy. The implementation of this CNV model, together with some state-of-the-art technologies, such as liquid biopsy and single cell sequencing, could be a game changer for personalized therapy that would ultimately translate into clinical benefit for this otherwise devastating malignancy.

Declaration of interests

The authors declare no conflicts of interest.

Contributors

Both authors were equally involved in the overall design, literature search and writing of this commentary.

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