The distinct genetic features of pancreatic cancer in Chinese population

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers with unclear genetic foundation. Genetic association studies with large cohort were extensively performed but not for East Asian population especially for Chinese Population. To date, little is known about racial disparities in the genetic landscape of PDAC. Significantly higher rate of EGFR mutation in Chinese lung cancer patients bring about a new era of lung cancer treatment, leading to a remarkably improved survival. Therefore, understanding the distinct genetic features of PDAC in Chinese population is warranted and could possibly change the paradigm of PDAC management.

With the rapid development of NGS technology, a lot of studies regarding the germline and somatic mutations of pancreatic cancer came forth. Shindo et al. reported the germline mutations commonly identified in 854 patients with sporadic pancreatic cancer.[1] Large cohort studies like TCGA (The Cancer Genome Atlas) revealed the complex somatic molecular landscape of pancreatic cancer and paved the way for precision medicine.[2] For studies in Chinese population, our previous work[3] summarized the germline mutations in 1009 pancreatic cancer patients and performed comparative analysis with cohorts of other races. We found that pathogenic sequence variations were detected in 6.2% of patients with PDAC. SPINK1 and CFTR variations were significantly associated with higher risk of pancreatic cancer. Guo et al.[4] profiled the genomic alteration of PDAC with 408 Chinese patients, showing a relatively higher mutation rates of DNA damage repair-related genes.

In the current study by Zhang et al.,[5] DNA-sequencing of commercial panel were performed for blood and tissue samples from 1080 Chinese PDAC patients. It was shown that KRAS mutation rate (83.2%) in Chinese cohort were significantly lower than those in Western cohorts. However, extra caution should be taken when interpreting this result because lower mutation rate could be caused by low cellularity of core needle biopsy or ambiguous pathological diagnosis. An NGS study based on resected PDAC samples in Chinese population showed KRAS mutation of 94.7%.[6] Further studies with microdissection of tumor samples are needed to prove this point. This study also showed that KRAS wild-type patients were detected with more uncommon gene fusions and were with younger age as reported in an earlier study.[7] For the KRAS mutation spectrum, it seems that Chinese PDAC may have higher proportion of KRAS G12V mutation.[2,6] KRAS G12C mutation was detected in only 2.6% of PDAC patients, which might limit the application of AMG510 in Chinese PDAC patients. This study also showed a higher rate of CDKN2A mutation in metastatic lesions, which was formerly considered to be an early event for PDAC evolution (PanIN-1 to PanIN-2). The metastatic lesions in this study were not matched with primary tumor, which might limit the significance of the finding. It is to be determined if there is difference among races regarding the molecular alterations during PDAC evolution.[8]

To be noticed, it was observed that 23.3% patients had DDR gene germline or somatic mutations in this cohort, as the potential beneficiary of platinum-based chemotherapy or PARP inhibitor. Germline variants were also discussed in this study, indicating that ATM, BRCA2, SMARCA4, and ATRX were the most frequently mutated genes in Chinese patients, which was slightly different from a large cohort from USA with ATM, BARD1, BRCA1 and BRCA2 as the top 4 mutated genes.[9] Unfortunately, formal comparative analysis cannot be performed due to the absence of family history information and survival data in this cohort.

This study is the largest Chinese cohort so far discussing the somatic mutations of pancreatic cancer, which indicated that the racial disparities of pancreatic cancer on the somatic mutation landscape existed, but were also limited. It seems unlikely that pancreatic cancer would achieve revolutionary progress of treatment based on racial disparities in cancer genome. Also, DNA-seq studies of Chinese PDAC patients were mostly commercial panel-based instead of whole exome

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sequencing or whole genome sequencing.[6,10] Other mutations in non-hotspot genes or non-coding regions could be concealed by the current discovery of Chinese population.

In the past 2 decades, advances in genomics have provided important information on the genetic basis of tumorigenesis and progression. Next-generation sequencing has now penetrated into all aspects of tumor research. Individualized interpretation of the genomic and epigenomic information of each cancer patient, taking into account both germline and somatic variations, will fundamentally change the paradigm of tumor biology research. In the future, integrating comprehensive genome sequencing data of tumors into clinical decision-making paradigm is warranted and more genetics based clinical trials are needed for precision medicine of PDAC.

Contributors

YM and KJ participated in the conceptualization. LY, JW, and ZL participated in drafting and revising the manuscript.

Declaration of interests

The authors report no conflict of interests.

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