Commentary

Are there any differences in genomic characterization of non-small cell lung cancer between African Americans and Whites?

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Lung cancer is the most common cancer and the leading cause of cancer-related deaths worldwide; in 2012, around 1.82 million new cases were diagnosed and 1.59 million patients died of the disease globally (1). It remains essentially incurable despite recent advances in conventional treatment, including surgical resection, radiotherapy, and drug therapy. African Americans have especially been reported to have poorer prognosis when compared with Whites (2-4).

Recent randomized controlled trials demonstrated that lung cancers with epidermal growth factor receptor (*EGFR*) mutations (5-10) and those with anaplastic lymphoma kinase (*ALK*) translocations (11,12) were effectively treated with specific inhibitors that targeted these mutated gene products. Thus, the discovery of new oncogenic driver mutations exerts a great influence on novel drug development strategies as well as on the treatment of patients who harbor tumors with novel mutations. Early studies have suggested that the prevalence of *EGFR* mutations in patients with non-small cell lung cancer (NSCLC) differs among different national and ethnic origins (13,14). Subsequent studies showed that the frequency of *EGFR* mutations was high in Asians (50–60%) and low in Whites (10–20%), but their frequency in African Americans varied with reports (15-17). The nature and frequency of other oncogenic driver mutations in NSCLC among African Americans have been rarely reported (18,19).

Araujo and colleagues studied the spectrum of genomic alterations in NSCLC specimens from 99 African Americans and 283 Whites (20). The marked advantage of this study is a comprehensive and exhaustive analysis using targeted massively parallel DNA sequencing that covers all the exons of 81 genes relevant to NSCLC. In total, 227 non-silent variants were identified in the coding sequences of these 81 genes, the majority of which were located in conserved and possibly active domains. Of the 99 African American patients, 24 (24.2%) had an activating driver mutation, including a mutation of *KRAS* in 21 patients, *EGFR* in 5 patients, and *NRAS*, *ALK*, and *PIK3CA* in one patient each. The frequencies of these classic driver mutations and the frequency as a whole were not significantly different from those observed in Whites; driver mutations were found in 90 (31.8%) of the 283 White patients included in this study. Amplification of several oncogenes was also observed especially in the classic driver-negative tumors. These included *SOX2*, *TP63*, *PIK3CA*, *FGFR1*, *MCL1*, *FGFR3*, *TNFAIP3*, *MLL2*, and *WHSC1L1*. Furthermore, an NSCLC-related pathway analysis showed that 67 (67.7%) tumors resected from African Americans had at least one alteration (mutation or amplification) in survival and proliferative signal transduction pathways, including the receptor tyrosine kinase, RAS/MAPK/ERK, phosphatidylinositol 3-kinase, and WNT pathways. The cell cycle control pathway was also frequently affected; 52 (52.5%) tumors presented with at least one alteration.

The authors hypothesize that African Americans could present with different subtypes of NSCLC with a high frequency of oncogenic driver mutations or unknown gene alterations that endow tumors with a more aggressive phenotype, considering that African Americans have higher lung cancer incidence and mortality than Whites. However, an absence of survival and associated clinical data such as tumor stage and performance status is a crucial disadvantage of this study. Another limitation is

that more than 90% of the patients included in this study were smokers. Since smoking is the strongest external causal factor of lung cancer that can conceal the relatively small racial effects on lung carcinogenesis, non-smoking patients with NSCLC may be more appropriate subjects for the purpose of this study. However, the results from non-smokers would be applicable to a limited number of African Americans with NSCLC, because such patients are uncommon. Lastly, there was no sample calculation to identify the difference in the frequency of driver mutations between African Americans and Whites under the control of the beta-error. The frequency of mutations in any classic driver oncogenes, which was 24.2% in African Americans and 31.8% in Whites, would be statistically significant if sufficient number of patients were analyzed. Indeed a pooled analysis performed subsequently by the same study group (n=260 for African Americans and n=283 for Whites) showed that the frequency was statistically lower in African Americans than in Whites (21). Bollig-Fischer *et al*. reported that the frequency of a mutation was decreased for African Americans than for Whites (32% *vs*. 41%; odds ratio 0.58; 95% confidence interval, 0.36–0.93; P=0.025) when investigating the mutations in 26 oncogenes identified in NSCLC (n=137 for African Americans and n=335 for Whites) (19). Steuer *et al*. recently reported the results from the Lung Cancer Mutation Consortium (n=60 for African Americans and n=838 for Whites), which were similar to those of this study. They noted a lower frequency of oncogenic driver mutations in African Americans patients than in Whites after adjusting for smoking by a multivariate analysis, although the sample size of their study was also too small to obtain statistical significance (odds ratio 0.69; 95% confidence interval, 0.41–1.18; P=0.176) (18).

In summary, although no statistically significant genomic difference in NSCLC between African Americans and Whites was identified against the initial hypothesis, this study clearly confirmed potential therapeutic targets in African Americans, for which tumor genomics has not been extensively investigated.

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Footnote

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