Molecular pathology selected abstracts

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Ability of recurrent somatic mutations to predict response to immunotherapy

October 2022—Immune checkpoint inhibitors are cancer treatments that function as an immune checkpoint blockade, strengthening a person's immune response to a tumor. These medications have revolutionized the treatment of patients with metastatic or unresectable cancers, significantly improving life expectancy. However, the response rate is variable, and costs and toxicity are major impediments to more widespread adoption of these treatments. Previous studies have used several biomarkers to predict immune checkpoint blockade (ICB) response, including tumor mutations in candidate genes, mutations found via immune profiling by whole exome sequencing (WES), transcriptomics, tumor mutational burden (TMB), T-cell diversity/clonality, and neoantigen production. Although it is not consistently correlated with ICB response, PDL-1 IHC is widely used as a predictive biomarker. In addition, TMB, patient age, and tumor type are routinely used in clinical practice to determine whether applying immune checkpoint inhibitors would benefit patients. TMB generally is determined from targeted gene or exome sequencing data—calculating the number of nonsynonymous somatic mutations in the analyzed genomic DNA length—and is associated with ICB response. Higher TMB is thought to be associated with production of neoantigens by the tumor, generating a more robust immune response. The FDA recently approved TMB as a companion diagnostic in the clinical setting for predicting immune checkpoint inhibitor response. In the study described herein, the authors aggregated WES and clinical data from six published immunotherapy studies encompassing 319 patients with various tumor types to identify gene and pathway markers of ICB response. They focused on recurrently mutated genes and pathways, determining their ability to predict response. These features were integrated with other baseline predictive markers, such as age, tumor type, and TMB, to create the Cancer Immunotherapy Response Classifier (CIRCLE). To evaluate the role of this new classifier in ICB response, the authors categorized patients as responders and nonresponders and placed somatic mutations into high, moderate, low, and modifier classes. A significantly higher number of high and moderate impact mutations were found in the responder group. Responders were, on average, 4.5 years older than nonresponders. Furthermore, patients with melanoma and non-small cell lung cancer (NSCLC) were more responsive to ICB. A positive response trend was also observed in patients with bladder and head and neck cancers. Mutations in the *BCLAF1, TP53, KRAS,* and *BRAF* genes were significantly associated with ICB response. *BCLAF1* and *TP53* mutations were enriched in nonresponders, and *BCLAF1* mutations were more prevalent in older patients with melanoma. In contrast, *KRAS* and *BRAF* mutations were common in the responders with a tendency toward having NSCLC and melanoma, respectively. Twenty-one biochemical pathways were associated with ICB response, including nine pathways containing *TP53*, seven containing *BRAF* or *KRAS*, and five with none of the aforementioned genes. Combining the associated genes and pathways with the routinely used predictive factors of age, tumor type, and TMB (CIRCLE score) resulted in a 10.5 percent increase in sensitivity and 11 percent increase in specificity for predicting response to immunotherapy treatment compared to TMB alone. The authors concluded that this new integrated biomarker algorithm is superior to TMB alone in predicting response to immunotherapy. However, larger cohorts are needed to validate these findings.

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Association of *DOCK2* suppression with severe COVID-19 in an East Asian population

The SARS-CoV-2 virus displays heterogeneous clinical manifestations, ranging from a lack of symptoms to multi-organ failure and death. Since the beginning of the COVID-19 pandemic in early 2020, the scientific community has been assessing risk factors for severe disease to better protect more vulnerable populations. Genetic background is a risk factor for susceptibility to a variety of infectious diseases. However, high-risk genetic traits and associated disease susceptibilities vary greatly based on ethnicity. For example, a variant at *LZTFL1* on 3p21 has been associated with severe COVID-19 disease in Europeans but is rarely found in East Asians. The authors reported the results of a comprehensive genomewide association study of COVID-19 susceptibility in Japan and compared the results to those for Europeans. The study included 2,393 patients who were hospitalized with severe COVID-19 at some point between April 2020 to January 2021, the first through third waves of the pandemic in Japan. It also included 3,289 people, who represented the general Japanese population, as control subjects. To confirm their findings, the authors conducted a replication study using 1,243 COVID-19 patients who were hospitalized from February to September 2021, the fourth and fifth waves of the pandemic in Japan, and 3,769 controls. The findings confirmed the previously reported severe COVID-19–associated risk alleles in *LZTFL1, FOXP4, TMEM65, ABO, TAC4, DPP9,* and *IFNAR2*. When stratified for different ethnic populations, *FOXP4* had notably higher allele frequency in East Asians than in Europeans. In contrast, the *LZTFL1* risk allele was rare in the Japanese population. Interestingly, O blood type demonstrated a protective effect, particularly against severe disease and in younger patients. AB blood type, which is more common in the Japanese population, was a risk factor for severe COVID-19. Obesity showed a significant causal effect across all populations. At the genetic level, a locus on 5q35, near the *DOCK2* gene (rs60200309), was associated with severe COVID-19 in younger patients. The authors also looked up COVID-19 risk of the *DOCK2* variant in other ancestries. The variant exhibited the highest frequency in the Japanese and to a lesser extent in Native Americans. To further assess the function of the *DOCK2* allele, bulk and single-cell RNA sequencing was performed on peripheral blood and identified reduced expression of *DOCK2* in patients with this risk allele, particularly in innate immune cells, such as nonclassical monocytes. Immunohistochemistry for *DOCK2* was negative in lymphocytes and macrophages in the lung samples taken from COVID-19 autopsy cases. These findings were confirmed in vivo in a study of *DOCK2* inhibition in Syrian hamsters infected with SARS-CoV-2, which showed impaired migration of CD68 macrophages in the lung. The authors concluded that *DOCK2* downregulation in COVID-19 pneumonia impairs immune response and the ability to eliminate the SARS-CoV-2 virus and prolongs lung inflammation. These findings further confirm the importance of genetic background in disease susceptibility to COVID-19 and may better inform public health strategies to mitigate the pandemic.

Namkoong H, Edahiro R, Takano T, et al. DOCK2 is involved in the host genetics and biology of severe COVID-19. *Nature*. 2022. https://www.nature.com/articles/s41586-022-05163-5

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