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IMMUNOTHERAPY

HLA-1 genotype influences response to checkpoint inhibitors

The introduction of immune-checkpoint inhibitors has dramatically improved the survival outcomes of certain patients with advanced-stage cancers; however, the tumour or patient characteristics that confer sensitivity to this treatment approach remain largely unknown. Now, an analysis of the HLA class 1 genotypes of 1,535 patients with advanced-stage cancer receiving immune-checkpoint inhibition reveals associations between specific germline HLA genotypes and outcomes.

On the rationale for this approach, co-lead author Tim Chan explains "HLA diversity has been linked to an improved ability to fight off certain infections. We wanted to know if the same diversity can affect the ability of the immune system to fight off cancer in patients treated with immune-checkpoint inhibitors." on the rationale for this approach.

To investigate HLA heterozygosity, researchers conducted HLA class I genotyping of DNA samples from nonmalignant cells obtained from patients with advanced-stage cancers (predominantly melanoma or non-small-cell lung cancer) receiving immune-checkpoint inhibition in clinical trials. Patients were assigned to one of two cohorts on the basis of availability of exome-sequencing data (cohort 1) or next-generation sequencing data (cohort 2), in addition to clinical outcomes. Statistically significant associations were observed between HLA homozygosity, even at a single HLA locus, and inferior overall survival outcomes in both cohorts of patients. Similarly, patients with a loss of HLA heterozygosity observed in tumour DNA also had inferior outcomes.

Researchers then classified each HLA-1 allele into a specific subset (or 'supertype'), based upon similar peptide-binding characteristics, in order to explore the clinical relevance of these alleles. In patients with advanced-stage melanoma in cohort 1, those with HLA-B alleles of the B44 supertype had superior survival outcomes in response to anti-CTLA-4 antibodies, while those with alleles of the B62 supertype had inferior outcomes. This observation was confirmed in cohort 2. Further investigations revealed no association of HLA-1 alleles of the B44 supertype with disease prognosis.

"We found that germline HLA genes — the genes that patients are born with — can influence your likelihood of response to immune-checkpoint inhibition. The more diverse your HLA genes, the better you will do," summarizes Chan, adding that "certain HLA superfamilies are associated with an exceptional response, such as HLA B44."

These findings highlight the importance of genetic factors, in addition to immune cell phenotypes, in determining which patients are most likely to respond to immune-checkpoint inhibition. Furthermore, stratification of patients by HLA subtype might lead to improved response rates in future clinical trials.

Peter Sidaway

> "The more diverse your HLA genes, the better you will do"

ORIGINAL ARTICLE Chowell, D. *et al.* Patient HLA class I genotype influences cancer response to checkpoint blockade immunotherapy. *Science* http://dx.doi.org/10.1126/science.aao4572 (2017)