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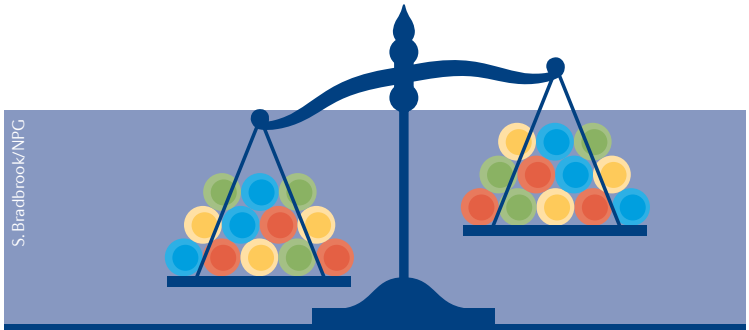

IMMUNOTHERAPY

Clonal neoantigens and immune response: a balancing act

Intratumour heterogeneity (ITH) is observed across many cancer types, including lung cancer. While ITH can have an impact on patient response to cancer treatments, such as targeted therapies, the impact of ITH on antitumour immunity and sensitivity to immunotherapy is not well established. Now, a study co-led by Charles Swanton, Sergio Quezada, Nicholas McGranahan, Andrew Furness, and Rachel Rosenthal, shows that "neoantigen ITH may play a role in determining antitumour immunity both in the context of immunotherapy naïve tumours as well as those subject to immune-checkpoint blockade".

To explore neoantigen heterogeneity, the relevance of neoantigen burden, and the importance of clonal versus subclonal neoantigens, patients with early stage non-small-cell lung cancer (NSCLC) included in The Cancer Genome Atlas (TCGA) project were assessed. In the immunotherapy naïve setting, these patients were found to have significantly longer overall survival if their tumours contained a high number of clonal neoantigens and exhibited low levels of neoantigen heterogeneity. Gene-expression analysis revealed a subset of immune-related genes that were upregulated in the high clonal neoantigen group, indicating an inflammatory tumour microenvironment (as noted by higher expression levels of genes encoding CD8α/β, IFN-γ, and granzymes A, B, and H). Expression of these genes was countered by upregulation of immunosuppressive regulators, such as PD-1, PD-L1, and PD-L2. Consistent with these data, the researchers "could also identify tumour-infiltrating $CD8^+$ T cells reactive to clonal neoantigens in patients with both homogenous and heterogeneous early-stage NSCLC tumours". Characterization of these cells demonstrated high expression of co-inhibitory immune-checkpoint molecules, including PD-1 and the effector molecule granzyme B.

Further analysis of a separate cohort of patients with NSCLC treated with the anti-PD-1 agent pembrolizumab showed that those deriving durable clinical benefit had "a significantly larger and more homogeneous predicted neoantigen repertoire than those patients without clinical benefit". Among the treated NSCLC cohort and a patient cohort with melanoma treated with anti-CTLA-4 therapy, patients with a high clonal neoantigen burden and low level of neoantigen ITH exhibited significantly longer overall survival than patients who had low clonal neoantigen burden or a high level of neoantigen ITH. Interestingly, subclonal neoantigens induced by alkylating agents that increased the mutational load were noted in some patients with a poor response, highlighting that total neoantigen burden is enhanced by such therapy, but might not induce an effective response.

"These findings pave the way for therapeutic strategies directed against clonal neoantigens, which are present in every tumour cell, and may contribute to future efforts to identify patients more likely to derive benefit from immune-checkpoint blockade. Our results also highlight the need to further determine the impact of current standard-of-care therapies, particularly cytotoxics, on clonal architecture", concludes Swanton.

Lisa Hutchinson

ORIGINAL ARTICLE McGranahan, N. *et al.* Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science* http://www.dx.doi.org/10.1126/science.aaf1490 (2016)