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NEWS

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CONSERVED INTERFERON-G SIGNALING DRIVES CLINICAL RESPONSE TO IMMUNE CHECKPOINT BLOCKADE THERAPY IN MELANOMA

Tumor-infiltrating T cells are widely recognized as a predictive biomarkers for the effect of checkpoint inhibitors (CPI) in several solid tumors. In an interesting article published in *Cancer Cell* by Grosso et al.,[1] the authors analyzed the transcriptome of 101 paired pre- and post-treatment biopsies from patients diagnosed with advanced melanoma enrolled into the CheckMate038 trial to receive nivolumab as single agent versus the combination of nivolumab + ipilimumab. To complete the analysis, they also performed a functional study across 58 melanoma cell lines. In the tumor samples, they were able to confirm that sensitivity to CPI, as single agent or in combination, can be explained by the development of a strong T-cell response, surrounded by a pre-existing level of T-cell tumor infiltration and the expression of interferon-γ response genes.[2]

In both preclinical models and tumor samples, the combination of anti-PD-1 and anti-CTLA-4 worked as a stronger immune stimulation than either therapy alone, thereby shifting the balance in favor of an antitumor immune response in a greater number of cases. The interferon-γ release from T cells recognizing cognate antigen on cancer cells serves to amplify the nascent antitumor immune response causing the inhibition of immune exclusion cancer signatures. Across the 58 cell lines evaluated, the data on the interferon-γ response divide them into two subpopulations. The ones unable to signal had mutations in *JAK1* or *JAK2*, rarely present in CPI-naive melanoma patients. Among patients, baseline and on-therapy biopsies of patients without a response to CPI therapy had a higher expression of signatures of T-cell exclusion, with the relevant feature that biopsies from responding patients displayed decreased expression of *WNT* and *MYC* genes on therapy, related to resistance to CPI, while the ones from nonresponding patients continued to express the immune exclusion genes.

All these data suggest the presence of feedback loops between the tumor and CD8 T cells mediated by interferon-γ that modulates immune exclusion secondary to WNT signaling. T-cell infiltration and expression of interferon-γ-regulated genes increased in biopsies of patients receiving CPI therapy regardless of clinical response, whereas the degree of human leukocyte antigen (HLA) upregulation on therapy and the decrease in expression of genes associated with immune exclusion were related to response. In most cases, CPI modified the transcriptome of melanoma biopsies changing towards a more antitumoral microenvironment, particularly when the combination of nivolumab plus ipilimumab was administered, achieving a higher response rate. As a future perspective, the authors suggest that analogous responses could be achieved with the use of oncolytic viruses or other inhibitors, such as WNT signaling, the adenosine pathway, or the release of other inhibitors tackling LAG-3, TIM-3, TIGIT, and so on. However, further validations are clearly needed.

MULTIMODAL IMMUNE LANDSCAPE MAPPING OF PANCREATIC CANCER

Immune checkpoint inhibitors are widely used as treatment for an increasing number of solid tumors. Pancreatic ductal adenocarcinoma (PDA) is characterized by an extensive and complex immune-suppressive tumor microenvironment that makes it largely refractory to immunotherapy. However, recent clinical trials using a combination of immune regulatory agents have shown positive initial results, highlighting the need to better understand the immune landscape of human PDA. In an article recently published in *Nature Cancer* by Steele et al.,[3] a multimodal analysis approach was presented, combining mass cytometry (cytometry time of flight immune phenotyping), multiplex fluorescent immunohistochemistry, and single-cell RNA-sequencing to investigate the immune landscape of pancreatic tumors.

The authors aim to provide a robust and detailed portrait of the network of immune-suppressive cellular interactions in and around PDA. Thus, they map the immune infiltration as well as the systemic immune response through both surgical and fine-needle biopsy samples of tumor and nonmalignant tissue and matched patient blood in human PDA. It was shown that immune landscapes were heterogeneous among individual patients, although some common features emerged. An inverse correlation between the infiltration of myeloid and CD8+ T cells was reported. Furthermore, increased markers of CD8+ T-cell dysfunction were shown in advance disease stages. Multiple and redundant potential immune-suppressive interaction within the PDA microenvironment were described. However, the specific combinations of immune checkpoint genes expressed in each patient's CD8+ T cells were unique.

Interestingly, Steele et al. found differential expression of the immune checkpoint *T cell immunoglobulin and ITIM domains* gene (*TIGIT*) in patient tumor-infiltrating CD8+ T cells, both at the gene and protein level. These findings should be taken into account as combination immunotherapy becomes available for PDA. This is a promising study including fine-needle biopsy samples, which allows the study of immune infiltration in unresectable advanced stage disease patients. These tumors have CD8+ T cells with a more pronounced exhaustion signature, which may indicate its progressive immune dysfunction. Moreover, researchers found that *TIGIT* expression in patient's blood corresponded with TIGIT activity in the tumor, suggesting a noninvasive approach to assess target therapy candidates.

Spatial information is lost in single-cell analysis and to overcome this issue, the authors used single-cell methodology in combination with immunohistochemistry, which allowed the identification of multiple cell types within a tissue, while preventing the position of tumor cells relative to components of the microenvironment. Immunotherapy in PDA is challenging due to the complex immune landscape. Thus, the authors, using a multimodal approach, point toward the diversity of immune response in PDA and therefore the importance of future translational studies and clinical trials, with the ultimate goal of being able to implement personalized treatments. This work, therefore, will be important for ongoing initiatives in precision medicine and immune-oncology. Moreover, further validation in prospective trials is clearly needed.

CLINICAL UTILITY OF CIRCULATING TUMOR DNA SEQUENCING IN ADVANCED GASTROINTESTINAL CANCER: SCRUM-JAPAN GI-SCREEN AND GOZILA STUDIES

Next-generation sequencing can identify novel targets for patients with cancer. However, genomic heterogeneity may limit responsiveness to matched targeted therapies. Moreover, it is challenging to differentiate driver from passenger molecular alterations in tumors, considering that each origin has distinct therapeutic implications. Circulating tumor DNA (ctDNA) assessment may better reflect the genetic profile of all tumor cells present in a patient, unlike tissue biopsies, which are obtained from only one tumor region. In the era of precision medicine, cancer patients have the opportunity to be included into clinical trials with specific targeted agents. However, patient recruitment is one of the most difficult aspects of clinical trials, especially because many actionable targets are present in only a small fractions of patients and screening of a huge number of candidates is needed for a single study. Additional limitations may include extended screening periods, requirements for sequential tissue biopsy, and lengthy genotyping duration, which lead to low screening efficiency. Therefore novel tools are needed to overcome these barriers and maximize patient participation in clinical trials. As such, analysis of ctDNA has the ability of detecting genomic alterations at high accuracy compared with tumor tissue analysis.

Nakamura et al.[4] recently published an interesting article in *Nature Medicine* that demonstrates that ctDNA-based genotyping improved the screening success rate, shortened screening duration, and hastened trial enrollment, while maintaining high concordance with tissue genotyping and comparable response rates and survival. This study compared trial enrollment in GOZILA, which used ctDNA-based screening, versus GI-SCREEN, which used tissue in the first 1787 patients with advanced gastrointestinal cancer. GOZILA and GI-SCREEN genotyping results were used to enroll those patients into matched clinical trials. Screening test findings were significantly improved in GOZILA compared with GI-SCREEN, including sample unavailability (0.3% versus 1.5%), failure rate (0.1% versus 10.6%), sample acquisition duration (median, 4 versus 14 days), test duration (median, 7 versus 19 days), and proportion of successfully tested patients eligible for tailored therapy (7.9% versus 6.0% for variants associated with evidence level 1 or 2 recommendations); all $P < 0.0001$. Likewise, ctDNA genotyping both increased the relative proportion of patients enrolled by 132% (9.5 versus 4.1%, $P < 0.0001$) and reduced the time from screening study enrollment to clinical trial recruitment by 83% (median, 1.0 versus 5.9 months, $P < 0.0001$). The objective response rate for patients enrolled by ctDNA (20.0% versus 16.7%, $P = 0.69$) and progression-free survival (median, 2.4 versus 2.8 months) were similar to those enrolled by tissue, demonstrating the accuracy of ctDNA screening identifying eligible patients.

The authors also describe the genomic profiles of ctDNA and the different clonal distribution of ctDNA mutations. Overall, ctDNA was detected in 91.4% (1.438/1573) of patients showing similar actionable aberrations to those from previous published reports in this setting, including *KRAS*, *NRAS*, *BRAF,* and *PIK3CA* mutations; *ERBB2*, *FGFR1-2,* and *MET* amplifications; *FGFR2-3, ALK, NTRK1,* and *RET* fusions and MSI. ctDNA identified pathogenic germline *BRCA* mutations in 1.5% (26/1.687) of patients being the most common presentation (42%, 11/26) in pancreatic ductal adenocarcinoma, where 3.0% (11/363) had a previously unknown pathogenic *BRCA* variant. In conclusion, the present article underscores that ctDNA genotyping has advantages over tissue genotyping, with shorter turnaround time and higher sequencing success and actionable alteration detection rate, which are associated with improved clinical trial enrollment without compromising the efficacy.

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