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IDENTIFY IMMUNE CELL TYPES AND BIOMARKERS ASSOCIATED WITH IMMUNE-RELATED ADVERSE EVENTS USING SINGLE CELL RNA SEQUENCING

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Background Recent advancements in immunotherapy are revolutionizing the landscape of clinical immuno-oncology and have significantly increased patient survival in a range of cancers. Notably, immune checkpoint blockade therapies have induced durable responses and provided tremendous clinical benefits to previously untreatable patients. However, unleashing immune system against cancer also disrupts the immunologic homeostasis and induce inflammatory responses, resulting immune-related adverse events. The precise mechanisms underlying immune-related adverse events (irAEs) remain unknown. Furthermore, it is unclear why immune checkpoint blockade therapies only induce irAEs in some patients but not the others. In this study, we systematically characterize the functional impacts of immune checkpoint blockade on the patient immune system at single-cell resolution.

Methods The peripheral blood mononuclear cells (PBMCs) from seven cancer patients with melanoma, non-small cell lung cancer, or colon cancer (MSI-H) receiving immune checkpoint inhibitors (CPIs), i.e. anti-PD-1+anti-CTLA4 combo or anti-PD-1 single agent, were collected at three serial time points (T1, T2, and T3). During the immunotherapy, four patients developed irAEs, including colitis (2X), pneumonitis (1), hyper/hypothyroidism (1), while three patients showed no signs of irAEs. In total, we generated and characterized single cell gene expression profiles for more than 65,000 cells from 21 PBMC libraries. Furthermore, we simultaneously measured TCR and BCR from nine selected samples, thus generating a comprehensive profile of Immune repertoire upon CPIs.

Results We systematically characterized T cells, B cells, monocytes, NK cells, and platelets from PBMCs. Both checkpoint blockade and patient comorbidity affect PBMC populations. We found that irAEs are often associated with an acute increase in monocytes and decrease in T cells. After repeated CPI treatment, PBMC populations remained relatively stable. We characterized specific subsets within each cell type that are associated with CPI treatment as well as patient clinical conditions, and identified signature genes for each subset. For example, Mucosal-Associated Invariant CD8 T cells were strongly enriched in the PBMC population of the colon cancer patient. In the melanoma patient who received anti-PD-1 +anti-CTLA4 combo but didn't develop colitis, we found enriched NK cell subsets expressing chemokine such as XCL1 and CCL4. Furthermore, we found prominent T cell clonal expansion in this patient compared to the two melanoma patients who developed colitis. The administration of steroids after irAEs led to massive anti-inflammatory responses in PBMCs, often characterized by the prominent expression of AREG.

Conclusions Our study characterized the functional impact of CPIs on patient PBMCs. Our data demonstrated that single cell RNA sequencing provides a powerful tool to dissect and identify clinically actionable biomarkers for response prediction and side effects alleviation in patients receiving immunotherapy in the era of precision medicine.

Ethics Approval This study was approved by the Institutional Review Board (#1050678) at Intermountain Healthcare (Salt Lake City, UT USA)

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0062>

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MICROSATELLITE INSTABILITY/MISMATCH REPAIR BIOMARKER TESTING DISPARITIES IN PATIENTS WITH ADVANCED COLORECTAL CANCER: IMPLICATIONS FOR IMMUNE CHECKPOINT INHIBITORS

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Background Immune checkpoint inhibitors have revolutionized outcomes for patients with a spectrum of cancer types, including the first tissue/site-agnostic FDA approvals (in 2017 for 2nd-line and 2020 for 1st-line) for advanced cancers with DNA microsatellite instability-high/mismatch repair deficiency (MSI-High/MMRd). However, the factors associated with patients' access to MSI/MMR testing are unknown.

Methods Patients ≥ 20 -years-old who newly presented with histopathologically-confirmed stage 4 colorectal adenocarcinoma from 2010–2016 were identified from the National Cancer Database, which comprises $>70\%$ of all newly-diagnosed cancer patients in the U.S. Patients were excluded if they lacked data about MSI/MMR testing or were initially diagnosed at another institution. The primary outcome was receiving MSI/MMR testing, either via immunohistochemistry or molecular diagnostic. Patient demographic, socioeconomic, and care setting characteristics were evaluated for association with MSI/MMR testing, as well as between MSI/MMR testing and immunotherapy receipt, using multivariable logistic regression.

Results Of 45,326 newly-diagnosed stage 4 colorectal adenocarcinoma patients, only 26.5% (n=11,998) received MSI/MMR testing – rising from 14.4% in 2010 to 41.1% in 2016 (adjusted odds ratio [aOR] 1.26/year, 95% confidence interval [95%CI] 1.25–1.29, $p < 0.001$). Overall, patients who were older (referent 60–69-years-old; 70–79-years-old aOR 0.83, 95%CI: 0.77–0.89, $p < 0.001$; 50–59-years-old aOR 1.25, 95%CI: 1.16–1.33, $p < 0.001$), male (aOR 0.94, 95%CI: 0.90–0.99, $p = 0.01$), or of Black non-Hispanic race/ethnicity (aOR 0.87 vs. White non-Hispanic, 95%CI: 0.82–0.94, $p < 0.001$) were independently less likely to receive testing. Additionally, patients who were either uninsured (referent private insurance, aOR 0.78, 95%CI: 0.70–0.86, $p < 0.001$), Medicaid-insured (aOR 0.87, 95%CI: 0.80–0.94, $p = 0.001$), or Medicare-insured (aOR 0.87, 95%CI: 0.81–0.93, $p < 0.001$); or diagnosed at community (referent academic/NCI-comprehensive cancer program, aOR 0.60, 95%CI: 0.56–0.66, $p < 0.001$) or comprehensive community (aOR 0.76, 95%CI: 0.72–0.80, $p < 0.001$) cancer programs, were also significantly less likely to be tested. Even for patients diagnosed in 2016, untested patients received independently less immunotherapy than tested patients (aOR 0.61, 95%CI: 0.53–0.68, $p < 0.001$).

Conclusions MSI/MMR testing rates for stage 4 colorectal cancer patients have dramatically improved in recent years, but appeared underutilized in patients that were older, of Black non-Hispanic race/ethnicity, uninsured or Medicaid-insured, or diagnosed at community programs. Our findings suggest that socioeconomic and care setting opportunities exist for improving access to testing of this important predictive biomarker for immune checkpoint blockade.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0063>