Peripheral T cell receptor repertoire features predict durable responses to anti-PD-1 inhibitor monotherapy in advanced renal cell carcinoma

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Abstract

Immune checkpoint inhibitors (ICIs) had benefits to cancer patients via systemic T cell-mediated anti-cancer immune response. Thus, we need to clarify the dynamic of peripheral T cell repertoires as non-invasive predictive biomarkers to select responders to ICIs.

We collected tumors and PBMCs from 25 advanced kidney cancers, before and after anti-PD-1 therapy. We applied a next-generation sequencing to characterize T cell receptor (TCR) alpha and beta repertoires, and found responders showed expansion of certain T cell clones in the peripheral blood as evidenced by the significant decrease of diversity index and increase in the number of expanded TCR clones at 1 month after treatment. We also found these expanded peripheral TCR clones were significantly shared with tumor-infiltrating T cells in responders, which may recognize cancer antigens. Expression analysis revealed significantly elevated transcriptional levels of *GZMB*, *Perforin*, *CD39*, and *PD-1* in responders, markers of cancer antigen-specific T cells.

In conclusion, TCR repertoire analysis can be a potential tool for personalized immunotherapy to identify peripheral surrogate markers for predicting clinical responses to ICIs.

Background & Results

Immunotherapies such as immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment. However, the clinical effect of ICIs is still limited and identification of a predictive biomarker is critically important for the precision medicine, which can select patients likely to have clinical benefit from ICIs.

In our study, a total of 25 advanced kidney cancer patients treated with PD-1 antibody (Nivolumab) were enrolled and defined as the patients of responder (CR, PR and long SD, n = 15) and non-responder (short SD and PD, n = 10) by RECIST criteria. We collected tumor tissues and peripheral blood mononuclear cells (PBMCs) before and 1, 3, 6 months after starting treatment. We applied a next generation sequencing approach to characterize T cell receptor (TCR) repertoires using mRNA isolated from tumor tissues and PBMCs. To assess clonality of T cells, the diversity index of TCR was calculated according to complementarity-determining region 3 sequences. In addition, we calculated the number of expanded T cell clones in PBMCs after starting PD-1 antibody.

Through TCR repertoire analysis, in the PBMCs 1 month after starting PD-1 antibody, we found that significant decrease of diversity index in responder group. We also found that the number of expanded T cell clones in PBMCs was significantly higher in responder group, suggesting that PD-1 antibody could induce strong immune reactions in PBMCs with oligoclonal expansion of T cells. Interestingly, some of abundant TCR clonotypes in PBMCs were also detected in tumor tissues, indicating that these TCR clonotypes might recognize cancer-specific antigens.

Significance of the research and Future perspective

Our findings revealed that the changes of diversity index of TCR and expanded T cell clones in PBMCs by TCR repertoire analysis can be early and concise markers to predict favorable response for ICIs. In the future, we can identify T cell clones that are significantly increased in responders, leading to the development of neoantigen-specific cytotoxic T cells therapy as personalized immunotherapy.

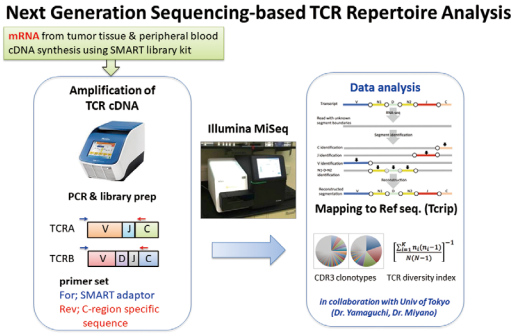

Figure 1: For TCR repertoire analysis, we have a novel platform to read T cell receptor using next-generation sequencing approach. We extracted mRNA from tissue and peripheral blood, and amplified TCR legion with specific primer. And then, we read TCR cDNA with next-generation sequencing and obtained data will be analyzed with our own developed algorism Tcrip.

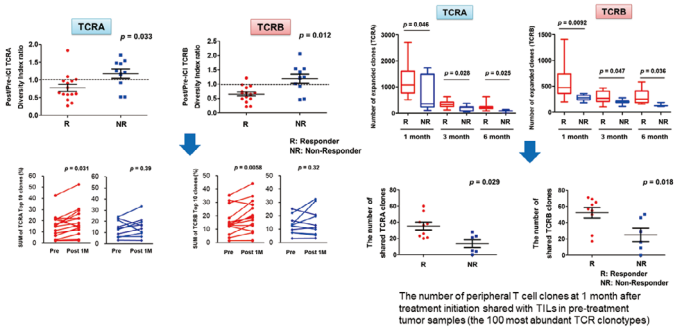

Figure 2: Diversity index for TCR alpha and TCR beta were significantly decreased at 1 month after the treatment in responders compared to that in non-responders, suggesting that responders had expansion of certain T cell clones even in blood samples, not in tumor tissues. These expanded clones at 1 month were significantly sustained at 3 and 6 months after treatment in responders, suggesting responders had long-lasting anti-cancer immune response.

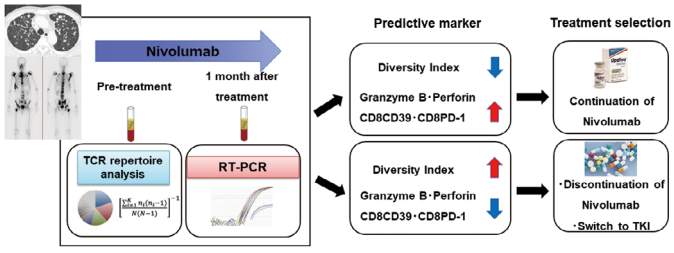

Figure 3: Graphical abstract

Patent

Treatise Kato, Taigo; Kiyotani, Kazuma; Tomiyama, Eisuke et al. Peripheral T cell receptor repertoire features predict durable responses to anti-PD-1 inhibitor monotherapy in advanced renal cell carcinoma. Oncoimmunology. 2021 Jan 19; 10(1): 1862948. doi: 10.1080/2162402X.2020

URL

Keyword renal cell carcinoma, immune checkpoint inhibitor, t cell receptor, next-generation sequencing, biomarker