The intratumoral TCR dynamics under immunotherapy vs. targeted therapy

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The current standard of care for metastatic melanoma patients utilizes either the MAPK pathway inhibitors (MAPKi) or immunotherapies based on the blockade of the inhibitory checkpoints on T cells (immune checkpoint inhibitors or ICI). MAPKi is currently approved for patients whose tumors harbor an activating mutation at the V600 position of the BRAF gene (BRAF mutant melanoma) while ICI is approved for all melanoma genotypes. Interestingly, the efficacy of both MAPKi and ICI were reported to be dependent on the activity of antitumoral T cells and, indeed, both therapies increased T cell (and TCR) abundance in the tumor parenchyma. However, it is unclear whether the increased T cell numbers by MAPKi and ICI are of the same nature. This is an important question to address especially when one considers the fact that almost every patient treated with best MAPKi therapy will relapse in a median of one year. A small subset of ICI-treated melanoma patients, on the other hand, may experience prolonged tumor control. T-cell receptor (TCR) repertoire profiling has been utilized to analyze intratumoral or peripheral T cells in order to monitor the enrichment of certain T cell clones in the tumor, which may indicate enrichment of tumor-specific T cell populations. TCR diversity was found to be associated with progression-free survival (PFS) and thereby may be a prognostic biomarker for the therapeutic effect in advanced colorectal cancer. In a recent report by Marais group (UK), peripheral TCR expansion or contraction was shown to predict response to ICI treatment after one single dose. The overarching goal of our study is to compare the TCR repertoire dynamics and their associated tumor microenvironment (TME) phenotypes in melanoma tumor pre- and post-ICI vs. MAPKi treatment. We hypothesize that long term responder to ICI have a robust expansion of intratumoral T cells accompanied with activation of interferon signaling in the microenvironment as a result of the T cell activation. We further posit that the activation of immunosuppressive signaling such as VEGFA and TGFB negatively affects the activity of tumor-specific T cells.