Abstract

Understanding melanoma biology to improve patient responses to therapy.

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While patient-derived materials helped us understanding the dynamic interactions between the tumour and the immune system, the numerous variables within the human population limit the detection of subtle changes that might impact the response to therapy. Conversely, tractable and easy to manipulate models, such as transplantable mouse tumours, xenografts and organoids, have low heterogeneity, lack the co-evolved inflammatory environment and TME. In recent years, we reported that our $BRAF^{V600E}$/UVR mouse melanoma model recapitulates the cardinal genomic features of human melanoma including a UVR-induced mutational signature, high C-to-T load and recurrent mutations in the same top 10 genes as occur in human cutaneous melanoma. This model retains the key features of the native immune system and TME, while additionally allowing control of the genomic and environmental variables that cannot be controlled when working with human-derived samples. We used this model to evaluate the biological features of durable response to PD-1 blockade and identified a 10-gene set defining stroma remodelling consistently upregulated and a 7-gene proliferation signature downregulated in tumours responding to therapy. We validated these responses in two independent early on-treatment ICI cohorts of patients (Figure 1), thus showing that features of lasting response derived from our preclinical model provide insights into human responses that are otherwise difficult to identify due to the complexity of the human population.

T cell receptors (TCR) are generated by somatic rearrangements of the *TCR* locus to create the diversity needed for effective immune function. We sequenced *TCR* in peripheral blood mononuclear cells (PBMC) and plasma cell-free DNA (cfDNA) in melanoma patients receiving immunotherapy. We used the data to infer T cell clonal expansion and contraction observed dynamic awakening of the immune system after one cycle of anti-PDL1 and anti-CTLA4 drugs. Importantly, these early changes in the TCR and peripheral T cell repertoire identified which patients would go on to respond to treatment, so could be used as biomarkers to deliver personalised immunotherapy to melanoma patients. We also found that the expansion of a particular subset of immune-effector peripheral T cells that we call immune-effector T cells (T_{IE} cells) correlated with response. Specifically, T_{IE} expansion occurred in the patients who went on to respond, but not in the patients who presented progressive disease. Our data suggest that minimally invasive liquid biopsies can be used to determine which patients will go on to respond to immunotherapy early during their treatment cycle, allowing melanoma patient treatment to be tailored to deliver better responses.