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Biology of human anti-tumor effector T cells studied by next generation sequencing (NGS) of their transcriptome

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Immunological therapies for human cancers have shown impressive results. Thesetherapies usually work through the activation and expansion of tumor antigen specific T cells. Unfortunately, these T cells are subject to a number of extrinsic and intrinsic regulatory mechanisms that stand as constraints against better outcomes. While much effort is underway to define and then deal with these regulatory pathways, currently available sets of immunological assays, unfortunately, have turned out to be quite inadequate for a fuller understanding of the biology of the tumor antigen specific T effector cells. In this context, given the power of RNA-Seq by NGS technology and the opportunities that this technology offers, we carried out NGS using the melanosome associated MART-127-35 epitope specific TCR-engineered (TCReng) human primary CD8+ and CD4+ T cells as a model to obtain a comprehensive understanding of the transcriptional signatures underlying their biology. Data analyses revealed approximately 30,000 transcripts, a sizeable number of which showing up- or down-regulation covering virtually all relevant aspects of T cell biology (i.e., effector functions, differentiation, proliferation, apoptosis, etc.) when they were stimulated by the epitope. The transcriptional profiles of the TCReng CD8+ and CD4+ T cells were found to be remarkably similar. Additionally, 72,000 known isoforms and about 20,000 previously undescribed isoforms were detected. Interestingly, a number of long non-coding RNAs (lncRNA) - some with known functions (e.g., NEAT1 and MALAT1 implicated in RNA editing, were up-regulated in the two cell types), and others with unknown function (e.g., GAS5, MIAT, and FTX showing modulations in expression), were also detected in both cell types. Although a comprehensive knowledge of the transcriptional signatures and a clear understanding of the spliced variants, the novel isoforms, and the lncRNAs in T cell biology will require further work, our study shows that NGS of specific epitope reactive T cells will be a very useful tool in deciphering the transcriptional controls underlying the function and the fate of epitope specific anti-tumor T cells.

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