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Monitoring the TCR repertoire in cancer

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The T cell receptor (TCR) repertoire holds clues to the functioning of the immune system. Profiling the repertoire can provide a systemic view of the health of an individual. T-seq, our novel method of sequencing the T cell receptor (TCR) repertoire, enables its unbiased sampling. This has enabled inexpensive, deep profiling of the TCR repertoire in both mouse and human T cells. The method does not require T cell isolation and can be used to study infiltrates in tissues. By applying it to a variety of samples from mouse and human, we have improved the annotation of the TCR loci in both genomes. We have also characterized the RSS signals and identified evolutionary constraints, as well as their potential to shape the statistics of segment usage. We describe methods of characterizing the usage of V and J segments in the alpha and beta chains and comparing TCR repertoire data across samples. This study enhances our understanding of the "normal" TCR repertoire, and provides the tools and annotations needed to characterize disease states, in order to help identify biomarkers and potential targets of therapy. We propose methods of identifying signatures of repertoires in cancer and the potential implications of this signature for outcomes of cancer immunotherapy. We are using these tools to study the role of the TCR repertoire in disease progression and potential for use of the diversity of the TCR repertoire as a prognostic indicator.

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Heteroplasmy as a biomarker and therapeutic target in cancer

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It is increasingly appreciated that heteroplasmy, the occurrence of multiple mtDNA haplotypes in a cell, plays an important biological role, but its features are not well understood. Accurately determining the diversity of mtDNA has been difficult, due to the relatively small amount of mtDNA in each cell (<1% of the total DNA), the intercellular variability of mtDNA content and mtDNA pseudogenes (Numts) in nDNA. To understand the nature of heteroplasmy, we developed Mseek, a novel technique to purify and sequence mtDNA. Mseek yields high purity (>90%) mtDNA and its ability to detect rare variants is limited only by sequencing depth, providing unprecedented sensitivity and specificity. Using Mseek, we have established that heteroplasmy is ubiquitous and stable, through experiments in cell lines and several human samples. We have determined that heteroplasmy is maintained at the level of the single cell. Applying Mseek to several normal-tumor samples from breast cancer patients, we have demonstrated that selection of specific haplotypes occurs in tumors, compared to the normal cells. The restriction of haplotype diversity arises through selection at the level of mtDNA, since cellular selection cannot steer mtDNA haplotypes. The haplotypes provide a biomarker that is easy to monitor for the effects of treatments by monitoring the mtDNA released by dying cells. We are developing methods of targeting selected mtDNA haplotypes, as a therapeutic intervention in cancer.

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