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An Unbiased Profiling of Immune Repertoire via Sequencing and Analyzing T-Cell Receptor Genes

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Abstract : Adaptive immune system recognizes a wide range of antigens via expressing a large number of structurally distinct T cell and B cell receptor genes. The distinct receptor genes arise from complex rearrangements called V(D)J recombination, and constitute the immune repertoire. A common method of profiling immune repertoire is via amplifying recombined receptor genes using multiple primers and high-throughput sequencing. This multiplex-PCR approach is efficient; however, the resulting repertoire can be distorted because of primer bias. To eliminate primer bias, 5' RACE is an alternative amplification approach. However, the application of RACE approach is limited by its low efficiency (i.e., the majority of data are non-regular receptor sequences, e.g., containing intronic segments) and lack of the convenient tool for analysis. We propose a computational tool that can correctly identify non-regular receptor sequences in RACE data via aligning receptor sequences against the whole gene instead of only the exon regions as done in all other tools. Using our tool, the remaining regular data allow for an accurate profiling of immune repertoire. In addition, a RACE approach is improved to yield a higher fraction of regular T-cell receptor sequences. Finally, we quantify the degree of primer bias of a multiplex-PCR approach via comparing it to the RACE approach. The results reveal significant differences in frequency of VJ combination by the two approaches. Together, we provide a new experimental and computation pipeline for an unbiased profiling of immune repertoire. As immune repertoire profiling has many applications, e.g., tracing bacterial and viral infection, detection of T cell lymphoma and minimal residual disease, monitoring cancer immunotherapy, etc., our work should benefit scientists who are interested in the applications.

Keywords : immune repertoire, T-cell receptor, 5' RACE, high-throughput sequencing, sequence alignment
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