Immune Repertoire Profiling by High-Throughput Sequencing

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***Short Abstract* — We provide the first comprehensive and systematic measurement of B cell repertoire to study the influence of ageing, genetic background and vaccination history on the antibody repertoire by deep high-throughput DNA sequencing and informatics analysis.**

***Keywords* — High throughput sequencing, immune repertoire, antibody repertoire, B cell, vaccination, Roche 454.**

I. PURPOSE

Despite the many advances in personal genome analysis, the immunoglobulin repertoire of the genome, while central to human health, is in practice extraordinarily challenging to measure and analyze. There are several reasons for this, including the facts that each B cell contains a distinct antibody sequence encoded in its genome, that the antibody repertoire is not constant but changes over time, and the high similarity between antibody sequences.

II. METHODS

We have addressed this challenge by using high-throughput long read sequencing to perform immunogenetic characterization of expressed human antibody repertoires[1,2]. Children, adult and elder volunteers received influenza vaccines at day 0. Their blood samples were collected and immunoglobulin heavy chains were sequenced by high throughput sequencing at day 0, day 7 and day 28. Informatic analysis of large numbers of antibody heavy chain sequences from individual subjects allowed us to perform global characterizations of isotype distributions, clonal lineage structure of the repertoire and age-related mutational activity. With influenza vaccination as a specific stimulus, we used lineage analysis to measure the clonal structure and mutational distribution of individuals' repertoires;

III. RESULT

Analysis of this data showed that elderly subjects have a decreased number of lineages but an increased pre-vaccination mutation load in their repertoire and that some of these subjects have an oligoclonal character to their repertoire in which the diversity of the lineages is greatly reduced relative to younger subjects. In conclusion, we have shown that it is possible to make personalized individual-specific measurements of immune repertoire with high throughput DNA sequencing technology. These global repertoires contain a wealth of information and can be used to study individual-specific vaccine responses. By reconstructing the clonal structure of antibody lineages within the repertoire we discovered that elderly subjects can have an impaired oligoclonal structure relative to younger subjects. This approach to immune system characterization may be generally applicable to the development of new vaccines and may also help identify which individuals respond to a given vaccine.

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