Distinct features of the T cell receptor repertoire in human regulatory T-cells

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Regulatory T-cells (Treg cells) is a subset of T-lymphocytes, which suppress inflammatory response and maintain self-tolerance. T-cell receptor (TCR) is crucial both for the suppressive function and for thymic progenitor differentiation to Treg cell when strong TCR signalling in the thymus allows Treg cells to avoid apoptosis and form the first distinct T-cell subset.

Massive parallel sequencing of the most variable epitope recognising CDR3 region of the TCR transcript allows estimating the required repertoire diversity for healthy immune responses. For the search of the optimal therapeutic TCR clones we need to dissect the TCR repertoire features varying between functional T-cell subsets. Here we compare the beta chain TCR repertoires of human naïve and memory helper T-cells and naïve and memory regulatory T-cells. TCR sequencing data was obtained from previous publications: naïve and memory Treg cells [1], naïve and memory helper T-cells from [2]. Raw reads were processed uniformly with MiXCR software. TCR repertoire post-analysis was performed with the software VDJtools [3]. We performed the analysis of TRBV12.3/18/20.1-bearing repertoires to avoid batch effect from separate raw data sources.

The diversity of the TCR repertoire differs between helper and regulatory T-cells: Treg cells are significantly less diverse then helper T-cells. Entering the memory pool, Treg cells become less diverse in the TCR repertoire, which reflects the specific antigen recognition-driven selection. In average Treg cells have longer N-insertions and shorter D-segments than helper T-cells. Increased N-insertion length with the same distribution of CDR3 length suggests distinct TCR rearrangement pattern during Treg subset generation in the thymus. Treg cell repertoires from unrelated healthy individuals are less similar to each other than T helper TCR repertoires, when share of common clonotypes with same CDR3 aminoacid sequence, V- and J-segment usage was considered. The share of public clonotypes in memory Treg TCR repertoire is significantly lower than in memory T-helper cells (p-value= 0,013) or in naive T-helpers (p-value= 0,0075).

We used the profiling of biophysical properties of aminoacids composing the CDR3 region and showed that central CDR3 aminoacids have ability for strong interactions in Treg cells with maximum in naïve Treg cells, but such strong interaction is not met among T helper TCR clonotypes. Aminoacid hydrophobicity disrorder and other properties contribute to this integral strength parameter for the naive Tregs. The analysis of selected V-gene families highlighted the importance of strong hydrophobic aminoacids for naïve Treg selection but the appearance of voluminous and charged aminoacids in CDR3 instead of hydrophobic in the memory Treg subset. This difference can be explained with the notion that memory Treg pool consists both of the thymic-born nTregs, e.g. former naïve Tregs and iTregs, which arise from T-helpers in the immune system periphery and the memory Treg pool of the most frequent V-genes may consist mostly of the iTreg cells.

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3. Shugay M. et al. (2015) VDJtools: Unifying Post-analysis of T Cell Receptor Repertoires. PLoS Comput Biol, **11**(11):e1004503.

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