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Effects of low dose radiation exposure and ageing on T cell receptor beta chain (TCRβ) repertoire in human and mice

Doctoral Dissertation
by

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2022

Gliwice, Poland

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Abstract

T cell receptor (TCR) coding genes are created during the V(D)J recombination process, which ensures an efficient immune response against a variable collection of pathogens. During this process, discrete V, D, and J gene segments are assembled to create a coding exon of the variable domain of these receptors. V, D, and J gene ends during the assembly are subject to random nucleotide deletion or addition. This random nature of the V(D)J recombination process assures the creation of unique TCR sequences in every cell.

The T cell receptor repertoire diversity is the most commonly measured immune system property. This dissertation aimed to provide an analytical pipeline to investigate the TCR diversity based on high-throughput sequencing and flow-cytometry data. The amount of data produced with these methods is huge. Thus, supporting classical statistical methods with effect size statistics allowed for performing the comprehensive study of TCR diversity. Moreover, the impact of age, sex and ionising radiation on this property of TCR repertoire was investigated, focusing on cross-sectional and longitudinal data for humans and mice. The radiation effects were estimated using data from Atomic bomb survivors in Hiroshima and Nagasaki as well as data from irradiated mice. Machine learning techniques applied to the data allowed for constructing the models that explain sex-dependent dynamics of TCR diversity in time It was shown that TCR diversity decreases with age. However, the average diversity is different for men and women, and distinct patterns may be observed for age categories. Moreover, the proportions of productive and non-productive TCR sequences change with age. Interestingly, low-dose radiation accelerates the ageing of the immune system. On the other hand, higher doses of radiation affect the usage of specific V genes.

Applying empirical probability models of nucleotide insertions revealed unknown before properties of the V(D)J recombination process. New cryptic recombination signal sequences were observed and validated in mice, as well as, rare germline DNA retentions within the rearranged TCR sequences were noticed. The consequences of such errors are yet to be investigated.

Finally, considering the rapid development of long-read sequencing methods, their application to TCR identification was evaluated. Multiple algorithms were applied to Oxford Nanopore sequencing data, and their performance was investigated. It was shown that nontargeted long-read RNA-sequencing data might be utilised for the V and J gene repertoire analysis.