

Explore the impact of immune health on cancer outcome

Master's Thesis (30 ECTS)

Naja Lange 201906591

Aarhus University | Bioinformatic Research Center (BiRC) | spring 2024

Supervisor: Nicolai Juul Birkbak

Associate Professor

Department of Molecular Medicine

Aarhus University



AARHUS
UNIVERSITY

Abstract

Immunosenescence refers to age-related changes that impact the immune system, increasing susceptibility to age-related diseases. T cells, which are key effector cells in the adaptive immune system, play a central role in the defense against pathogens. However, T cells undergo functional decline with age due to immunosenescence. This study includes eight T cell receptor (TCR) sequencing datasets from both healthy individuals and cancer patients to explore the dynamics of the TCR landscape. In both healthy individuals and cancer patients, the TCR- β landscape changed with age, showing a decrease in the proportion of non-expanded clones and an increase in expanded clones as age increased. Analyses of TCR- β diversity revealed sex differences in the diversity of individuals over 30 years of age. Cancer patients with low TCR- β diversity experienced worse survival outcome. Longitudinal analysis of melanoma patients showed changes in TCR- β diversity after immunotherapy treatment. Additionally, investigating the relationship between tumor stage and TCR- β diversity revealed a potential association, indicating that lower diversity correlates with more advanced tumor stages. The TCR- α landscape exhibited similar trends to those observed in the TCR- β landscape.

Table of contents

Abstract	2
1. Introduction	4
1.1 <i>Immunosenescence</i>	4
1.2 <i>The formation of T cells and T cell receptors</i>	5
1.3 <i>T cell repertoire diversity</i>	6
1.4 <i>Immune health and potential applications</i>	8
1.5 <i>Sexual dimorphism in immune responses</i>	8
1.6 <i>Immune health and cancer</i>	8
2. Methods	11
2.1 <i>Datasets</i>	11
2.1.1 <i>Healthy samples</i>	11
2.1.2 <i>In-house datasets</i>	12
2.1.3 <i>ImmunoSEQ datasets</i>	13
2.1.4 <i>TRACERx</i>	14
2.1.5 <i>Nishida</i>	14
2.2 <i>TCR data analyses</i>	15
2.3 <i>Calculation of TCR diversity</i>	15
2.4 <i>Statistical analysis</i>	16
3. Results	17
3.1 <i>Exploring the TCR-β landscape in healthy individuals</i>	17
3.1.1 <i>Exploring the CDR3 overlap between individuals</i>	23
3.2 <i>Exploring the TCR-β landscape in cancer patients</i>	24
3.2.1 <i>Survival outcome analysis</i>	28
3.2.2 <i>Disease status analysis</i>	30
3.3 <i>Investigating public clones in the TCR-β repertoire</i>	32
3.4 <i>Investigating longitudinal samples in the MOMA Melanoma cohort</i>	34
3.5 <i>Exploring the TCR-α landscape in breast cancer patients</i>	37
4. Discussion	40
5. Conclusion	46
6. References	47
7. Supplementary	51