Does diversity of T cell receptors functionality depend on age and sex?

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***Short Abstract* — T lymphocytes play an essential role in defence of an organism against pathogens and cancers through their clonally distributed T cell receptors (TCR). TCR gene sequences, which are randomly assembled during T lymphocyte ontogeny, can be either functional or nonfunctional. Here we examined effects of age on the functional status of TCR genes in men and women separately. Our results show that the diversity of functional rearranged TCR sequences significantly decreases with age only in women. The similar, but not significant trend was observed among men.**

***Keywords* — TCR repertoire, ageing, immunosenescence**

I. INTRODUCTION

T lymphocytes are one of the cells responsible for an adaptive immune response. Each of them expresses a unique heterodimeric T cell receptor (TCR) able to recognize a unique set of antigens. TCR genes are assembled from discrete V, D and J gene segments in developing lymphocytes. Due to the random nature of the V(D)J recombination process, only one-third of the rearranged TCR genes are functional. The remaining 2/3 are non-functional because of the loss of an open reading frame between the V and J genes, or the introduction of a stop codon. Hence, the TCR gene repertoire comprises functional and non-functional genes. Upon T cell activation, naïve T cells proliferate and differentiate into memory T cells. The production of naïve T lymphocytes declines with age [1], causing decreased TCR repertoire diversity and impaired immunity [2]. On the other hand, the size of naïve T cell clones increases in the elderly [3]. Even though the optimal size of TCR repertoire required to maintain efficient protection is not known, a decrease of TCR diversity is associated with impaired immune defences in mice [4]. Age-associated constriction of the TCR repertoire most probably participates in the increased susceptibility to infectious and non-infectious diseases in the elderly.

Here we intend to determine the impact of age on the functional status of TCR sequences. Due to the different ageing of men and women [5] and the influence of sex hormones on the immune system [6], we model the TCR repertoire status diversity for men and women separately.

Acknowledgements: This work was funded by SUT grants BKM/508/RAU1/2017t.27(JM) and BK-204/RAU1/2017/9.

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II. METHODS

We used a collection of 587 human TCRB repertoires obtained from healthy donors [7] publically available on the Adaptive Biotechnologies website [8], and a dataset of TCR repertoires obtained from 6 donors sampled three times 10 years apart [9]. Previously proposed analysis pipeline, including usage of Pielou's J index, was used to determine functional status diversity [10]. Weighted linear regression was employed to model functionality status diversity in age, with total counts of sequences serving as weighs. Separate models were created for men and women for two datasets. T-test compared regression slopes of created models.

III. RESULTS

We observed a negative correlation between age and diversity index among women. The age has a very small, but significant, effect on the functional status of TCR genes; the slope coefficients vary from -0.0006 to -0.0007 depending on the model. Furthermore, the rate of decline of the diversity index in women for the two datasets was not different (p-value = 0.64). The similar dependence was not detected among men, although the decreasing trend was also noticed.

These results illustrate a new aspect of the differences in biological ageing of the immune system in men and women.

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