ImmunoTools *special* Award 2018

Tim Konstantin Boßlau, PhD-student

Supervisor: Prof. Dr. Karsten Krüger

Leibniz-University Hannover, Institute of Sports Science, Department of Sports and Health, Am Moritzwinkel 6, 30167 Hannover, Germany

Effect of a combined endurance/resistance training on immunosenescence and hematopoietic progenitor cell functionality in the elderly

The aging process underlies physiological changes in various systems of the human body. Specifically the functional decline of the immune system, referred to as immunosenescence, evoked a great interest for over the past decade. During aging, considerable shifts in T cell subpopulations occur with a reduction of undifferentiated naïve and an increase in the exhausted senescent T cell phenotypes. These and other age-related alterations cause an impaired capacity to combat novel antigens, leading to a higher susceptibility to infections, an increase of autoimmune diseases, and an increase of age-related diseases such as cancer. Recent studies suggest that senescent T-lymphocytes produce a significant amount of pro-inflammatory cytokines due to their self-reactivity, which contributes to a condition of chronic low-grade inflammation at old age. This process has a high clinical relevance due to the role of inflammation in the formation of many metabolic, cardiac and neurodegenerative diseases.

Similar to the differentiated immune cells, also their hematopoietic progenitors underlie an age-related decline in functionality, including a diminished migration and proliferation capacity as well as an altered potential for differentiation. Gene expression profiling revealed that hematopoietic stem cell aging is accompanied by the systemic down-regulation of genes mediating lymphoid specification and function in parallel to an up-regulation of genes involved in specifying myeloid fate and function. These data support the hypothesis for an age-dependent alteration in gene expression at the stem cell level, which presages downstream developmental potential and thereby contributes to the formation of immunosenescence.

Regular exercise has been shown to have rejuvenating properties. With regard to immunosenescence, a recent cross-sectional study demonstrated reversible effects of exercise on age-related changes of T cell subpopulations. In addition, investigations in a mouse model exhibited functional improvements of hematopoietic progenitor cells after a regular endurance training program. However, longitudinal intervention studies on humans, which examine the effect of exercise on both immunosenescence and

hematopoietic progenitor cell functionality, are still lacking and further research in this field is required to understand the cellular mechanisms of an aging immune system.

With this background, we hypothesize that physical training has a positive impact on hematopoietic progenitor cell function and *thereby* causes a rejuvenating effect on immunosenescence in so far untrained elderly persons.

To test this hypothesis, 30 previously untrained subjects, aged between 60 and 70 years, will complete a twelve-week combined endurance/resistance training program (twice a week, 60% 1RM, individual increase). An age-matched group without training is used as control. Blood samples will be collected before and after the exercise period for flow cytometry analyses and cell culture experiments.

FITC, PE, and PerCP conjugated anti-human antibodies will be used to analyse immunosenescence by flow cytometry (CD3, CD4, CD8, CD25, CD27, CD45RA, CD45RO, CD57, CD62L). Additionally, T cell apoptosis and activation status will be determined by using Annexin V and CD69 markers. Hematopoietic progenitor cells will be quantified and subsequently isolated via positive magnetic cell separation (CD34, CD45). In order to assess their migration and proliferation capacity, as well as their differentiation potential, cell culture experiments will be conducted. In a next step, the observed exercise-induced changes of T cell subpopulations and hematopoietic progenitor cell function will be correlated to examine any associations. Finally, changes of pro-inflammatory cytokine levels will be measured by human ELISA-sets (IL-1ß, IL-6, IL-15, and TNF alpha).

Summarized, we know that human aging is accompanied by functional deteriorations of the immune and the hematopoietic system. The aim of our longitudinal intervention study is now to verify the postulated positive effect of exercise on both conditions, and thereby implicating a link between the two. Getting the **ImmunoTools** *special* Award would greatly help me to implement this proposal as it provides many of the required reagents.

ImmunoTools *special* AWARD for **Tim Konstantin Boßlau**

includes 23 reagents

FITC - conjugated anti-human CD3, CD27, CD57, Annexin V

PE - conjugated anti-human CD4, CD45RO, CD62L, CD69

PerCP - conjugated anti-human CD8, CD45, CD45RA

human ELISA-set (for one 96 plate): human IL-1beta, human IL-6, human IL-15

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