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EFFECTS OF LIFELONG TRAINING ON T LYMPHOCYTES SENESENCE

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KEY WORDS: immunosenescence, masters athletes, inflammation

Aging has profound impact on the immune system, mainly on T-cells. The characteristics of immunosenescence from T cell pool, include poor vaccination responses and an inverted CD4:CD8 ratio, low numbers and proportions of naïve T-cells (that would impair the capacity of the immune system to deal with new pathogens), larger numbers of effector memory T-cells in late stage of differentiation. Also, persistent infections, such as cytomegalovirus (CMV), would further reduce the naïve T-lymphocyte repertoire and drive effector T- cells into senescence⁽¹⁾. These senescent T-cells are apoptose resistant, incapable of dividing and thought to be the major cause of the chronic low-grade inflammation seen with age⁽²⁾. Older persons with more pronounced chronic low-grade inflammatory profile are more prone to frailty and mortality⁽³⁾. Furthermore, age-related loss of Treg function would contribute to a greater risk of autoimmune disease while the age-related increase in Treg numbers could result in compromised immune responses, increasing the risk of malignancies and infections. A recent model proposed that regular bouts of exercise can trigger preventive and/or restorative mechanisms of T-cell immunosenescence by inducing the apoptosis of senescent and functionally exhausted late stage differentiated T-cells and thus preventing overcrowding of the immune space^(4,5) which increases infection susceptibility to novel pathogens. Physical exercise preferentially mobilizes senescent T cells from the peripheral tissues into the blood, which might facilitate their subsequent apoptosis and create "vacant space" for newly functional T cells to occupy and expand the naïve T-cell repertoire.", "author" : [{ "dropping-particle" : "", "family" : "Simpson", "given" : "Richard J", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Exercise and sport sciences reviews", "id" : "ITEM-1", "issue" : "1", "issued" : { "date-parts" : [["2011", "1"]] }, "page" : "23-33", "title" : "Aging, persistent viral infections, and im-

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munosenescence: can exercise “make space”?”, “type” : “article-journal”, “volume” : “39” }, “uris” : [“http://www.mendeley.com/documents/?uuid=7d444808-8a79-407b-9737-e7c3d971d57a”] }, { “id” : “ITEM-2”, “itemData” : { “DOI” : “10.1159/000270905”, “ISBN” : “1423-0003 (Electronic. Briefly, a 3 stage process is proposed: firstly, T-cells in a late differentiated stage are mobilized into the peripheral blood during exercise; Then, these cells leave the bloodstream to peripheral and/or inflamed tissues 1-2 h after exercise and a portion of these senescent T cells subsequently undergo apoptosis, thus creating vacant space; Consequently, lowered T-cell numbers drive the positive feedback loop, increasing naive T-cell output, filling the vacant space and contributing to an expanded naive T-cell repertoire. Repetitions of this process in response to exercise would reduce the frequency of senescent T cells over time, lowering infection risk and increasing healthy longevity. Master athletes represent an interesting sub-demographic group to test this theory since they maintain a high training load and frequency throughout life, and represent an “exceptionally successful aging” process. The aim of this study was to evaluate the effects of lifelong training on senescent T lymphocytes and their response to acute exercise.

MATERIAL AND METHODS

Nineteen master athletes (53.5 ± 8.94 yrs.) who regularly participated in training and competitions for more than 20 years and a control group of 9 healthy individuals (53.7 ± 6.04 yrs.) participated in this study. All subjects performed a progressive test to exhaustion on a cycle ergometer. Blood samples were obtained before (Pre), 10 min after the test (Post) and 1 h after the test (1h). Phenotypic study of peripheral blood T-cells was performed by flow cytometry. Expression of genes of interest was done on T-cells purified by cell sorting. Group comparisons were assessed using the Mann–Whitney *U* test. Alpha level was set at 0.05. For the analyses of change, accounting for the multilevel design of the study (level 1 units (intra-individual) within each level 2 unit (individuals of different groups)), hierarchical random effects models (REM) were constructed using a multilevel modeling approach.

RESULTS

$\text{VO}_{2\text{max}}$ was higher for master athletes when compared to the control group ($P < 0.001$). No differences were founded for CD4^+ and CD8^+ T-cells and their subsets between master athletes and the control group at all times of measurement. Also, total CD3^+ , CD4^+ and CD8^+ T-cells percentages did not increase with exercise. There were no significant differences in the proportion of Tregs either within the total lymphocyte population or within

the CD4 T-cell population, between the two groups at baseline. There was no significant effect of acute exercise on the proportion (%) of Tregs within total lymphocytes and CD4⁺ T-cells. However, acute exercise induced a significant increase in the number of Tregs at Post and returned to pre-exercise values at 1 h post for both groups. FoxP3, TGF- β and IL-10 mRNA expression was similar for both groups. For FoxP3 and TGF- β after exercise the number of detected cases was different between groups, with higher results for master athletes ($P < 0.05$). IL-10 mRNA expression remained unchanged at all times of measurement for masters (Pre = 61.1%; Post = 66.7% and 1 h Post = 50% of all subjects), while in the control group there was a tendency for fewer cases expressing mRNA for IL-10 (Pre = 22.2%; Post = 55.6% and 1 h = 22.2%). Senescent CD4⁺ and CD8⁺ T-cells were higher in the control group when compared to masters before and 1 h after exercise. At baseline, masters had significant less percentage of senescent T lymphocytes ($-6.7829 \pm 3.06\%$), CD4⁺ T-cells (-5.8145 ± 2.42) and CD4⁺ senescent naive (-5.3182 ± 2.5761) and effector memory ($-4.3505 \pm 1.93\%$) T-cells. Regarding the CD8⁺ T-cells, masters had significant less senescent CD8⁺ T-cells (-13.0661 ± 4.95), senescent T CD8⁺ naive (-9.3624 ± 2.09), central memory (-7.0282 ± 3.065) and effector memory (-12.0034 ± 5.49) cells. No significant effect of sports participation (controls vs masters) was noted for the % of senescent CD45RA expressing effector memory cells (EMRA) CD4⁺ and CD8⁺ T-cells. Senescent CD4⁺ T-cells were mobilized by exercise only in the masters and returned to Pre-values in 1h. Senescent CD8⁺ T-cells, CM and EM CD8⁺ T-cells were also mobilized by exercise in the masters. These values return to Pre-values in 1h after the end of the protocol. In the control group, only the senescent CD8⁺ CM T-cells increased at Post and their values remained elevated 1h after the test. The senescent EMRA CD8⁺ T-cells did not increase at Post but decreased in 1h to values below those observed at Pre and Post, in the masters. Age had a negative effect on the naive CD8⁺ T-cells. VO_{2max} associated negatively with the percentage of total lymphocytes and positively with the proportion of naive CD4⁺ T-cells. The mRNA expression of the CCR7 gene for naive CD8⁺ T-cells and the Fas-L gene for effector-terminal CD8⁺ T-cells was not different between masters and controls and did not change in response to the maximal protocol test.

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CONCLUSION

Master athletes have elevated anti-inflammatory markers and maintain the number and markers of activation of regulatory T cells as adaptive responses to exercise. Lifelong training decreased the percentage of senescent naive, CM and EM CD8⁺ T-cells and senescent naive and CM CD4⁺ T-cells. In both CD4⁺ and CD8⁺ T-cell subsets, the percentage of senescent EMRA T cells was also lower in the master athletes. Maintaining high levels of aerobic fitness during the natural course of aging may help prevent the accumulation of senescent

T-cells and the maintenance of function and number of T regs, hallmarks of a younger immune system.

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