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Train the lymphocyte!: exercise affects T cell life cycle throughout life

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TRAIN THE LYMPHOCYTE! EXERCISE AFFECTS T CELL LIFE CYCLE THROUGHOUT LIFE

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T cells life cycle begins with hematopoiesis, a process in which all red blood and immune cells are generated. Hematopoiesis mainly occurs within the bone marrow (BM) and, under certain conditions, in peripheral tissue compartments such as spleen. Regarding the development of lymphocytes, their progenitors are known as hematopoietic stem and progenitor cells (HSPCs). Function, differentiation, and mobilization of these self-renewing and pluripotent cells is mainly regulated by the secretome of mesenchymal stromal cells in the bone marrow niche through release of cytokines and hematopoietic growth factors. Acute exercise transiently mobilizes progenitor cells into the circulation. Thereby, numbers of HSPCs in BM remains stable because both acute and chronic exercise training also stimulate proliferation of HSPCs to ensure a stable HSPC number in the BM compartment. Highest mobilizing effects were shown in response to acute and intensive endurance exercise bouts. Mediators of exercise-induced progenitor cell mobilization are the increased expression of granulocyte colony-stimulating factor (G-CSF), stem cell factor, vascular endothelial growth factor (VEGF), angiopoietin-1, and the interaction of CXCL4 and stromal derived factor 1 (SDF-1)^(1,2). In response to regular exercise training, it is suggested that HSPC quantity, availability, and colony-forming capacity is stimulated suggesting an important function of these cells for regeneration and adaptation of the immune system and potentially other organs and tissues. While direct exercise effects on differentiation stages from HSPCs to common lymphoid progenitors and differentiated lymphocytes remain to be shown, it is suggested that the increased release of HSPCs into circulation relatively increases the circulating pool of lymphocytes which shows tendencies to be higher in regularly active individuals compared to sedentary subjects^(2,5).

During normal conditions, the circulating pool of T cells is differentiated during the gradual release of naive cells from the thymus. Thymic output is more efficiently during

• 37

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young life followed by a progressive involution of this organ. Accordingly, the release of naive T cells declines to low levels during aging. Subsequently, the relative amount of terminally differentiated cells and clones of viral specific T cells increases throughout life. This aging processes are assumed to increase susceptibility to infection with novel pathogens in older individuals and was demonstrated to represent a clinical relevant immune risk factor during aging^(1,4,5). Some data from animal studies indicated that regular exercise slightly restores thymic function. Accordingly, exercise training increases the relative amount of naive T cells and lowers proportions of terminally differentiated CD4⁺ and CD8⁺ T cells. Murine studies indicated that these processes might not only account for blood lymphocytes, but also for splenic T cells. During each bout of acute exercise primarily senescent T cells are mobilized into the circulation making the contact with potentially apoptosis-inducing factors like reactive oxygen species (ROS) more probably. Accordingly, exercise seem to stimulate programmed cell death process mainly in highly differentiated and senescent T cells. Some studies indicated that apoptotic processes create signals for the production of HSPCs to produce naive T cells. Mediators of this increased cell-turnover might be microparticles, such as apoptotic bodies, which represent signaling molecules expressed by dying cells^(3,4).

CD4⁺ cells are important cytokine producers which can be further subdivided into Th1 and Th2 cells. Th1-type cells tend to produce mainly potent proinflammatory cytokines like interferone- γ , while Th2 cells express cytokines which evoke antibody responses or anti-inflammatory cytokines such as IL-10. Moderate bouts of exercise affect Th1/Th2 balance by increasing relative proportion of Th2 cells in blood. This process is supported by the increased appearance of regulatory T cells (T_{regs}, FoxP3⁺) in blood of regularly active subjects. Both processes are assumed to affect the anti-inflammatory potential of exercise training. Exercise also stimulates the vascular egress of effector T cell subtypes followed by redistribution of cells into peripherhal sites of antigen encounter like lungs and gut^(1,3,4). Thereby, exercise training seems to stimulate also several functional aspects of T cells like intracellular calcium signals and immunometabolism such as glutamine, β -alanin, and glucose metabolic pathways. During aging, an accumulation of T cells which express markers of immunosenescence is documented. Exercise seems to delay immunosenescence by an increase of CD28⁺ cells in active elderly subjects. In addition, telomere lengths of T cells from trained subjects seem to be longer compared to untrained subjects leading to an increased proliferation capacity of these cells^(4,5).

Taken together, acute or chronic exercise seem to affect T cell life cycle during genesis, differentiation and maturation, and aging. Nearly almost these adaptations seem to positively stimulate immune function as long as exercise is performed at moderate intensities and regularly. While many aspects of the effects of exercise on the differentiated T cell subpopulations remain to be shown, others seem to be represent a robust physiological basis for the lower susceptibility to infections of regularly active people.

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