

Acute exercise enhances the expansion of cytotoxic T-cells specific to leukemia and melanoma antigens: implications for adoptive transfer immunotherapy?

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ABSTRACT

INTRODUCTION: The *ex vivo* expansion of tumor-associated-antigen (TAA)-specific cytotoxic T-cells from healthy donors for adoptive transfer in cancer patients has been used successfully to prevent relapse after hematopoietic stem cell transplantation (HSCT). However, this therapy is limited by the difficulty in priming and expanding sufficient numbers of functional TAA-specific T-cells, as T-cells recognizing TAA are usually low in frequency and avidity in healthy donors. Furthermore, monocyte-derived dendritic cells (Mo-DC) are used for TAA-presentation, but their manufacture is limited by low blood monocyte numbers. Therefore, large and impractical numbers of blood cells are required to successfully expand TAA-specific T-cells. Acute exercise is well-known to transiently activate and increase the numbers of T-cells and monocytes in peripheral blood. We therefore hypothesized that the immune-enhancing effects of exercise could be harnessed to enhance the *ex vivo* expansion of TAA-specific T-cells for adoptive transfer immunotherapy. **AIMS:** To examine the effects of acute exercise on (1) the number and function of TAA-specific T-cells expanded *ex vivo*, and 2) the generation and function of mo-DC. **METHODS:** 12 healthy adults (mean \pm SD: Age 27 \pm 2.6-yrs) completed an acute bout of stair-running exercise (time: 104 \pm 17sec; max HR: 172 \pm 14 bpm; lactate 9.51 \pm 1.9 mmol). Mo-DC were generated from pre and post exercise blood samples and were pulsed with the melanoma-associated-antigens MAGE-A4 and PRAME, the common tumor-antigen survivin, and the leukemia-associated-antigen WT-1. Autologous DC were used to expand TAA-specific T-cells obtained before and after exercise over 14-days. T-cells were enumerated and phenotyped by flow cytometry and function was assessed by ELISPOT and antigen-specific cytotoxicity. **RESULTS:** A greater number of mo-DC were generated from post-exercise blood samples (pre: 2.0 \pm 1.0 X10⁶cells, post: 5.2 \pm 2.6 X10⁶cells). This was due to the 1.7-fold increase in blood monocytes post-exercise, as the number of mo-DC generated per input CD14+cell did not differ (pre: 0.40 \pm 0.25, post: 0.59 \pm 0.36). Total T-cell expansion was increased post-exercise (fold-increase: pre: 2.48 \pm 0.75, post: 2.90 \pm 0.74). ELISPOT revealed that the majority of donors had enrichment in TAA-specific T-cells post-exercise, as T-cell lines expanded from post-exercise samples exhibited an increased interferon-gamma response to TAA compared to T-cell lines expanded from pre-exercise samples. ELISPOT revealed that 66% of donors had a greater number of T cells specific to at least one TAA post-exercise. Exercise had no effect on T-cell phenotype or antigen-specific cytotoxicity in the expanded cells. **CONCLUSION:** These data indicate that a single bout of exercise enhances mo-DC generation and the expansion of TAA-specific T-cells *ex vivo*. Exercise may therefore serve as a simple behavioral adjuvant to enhance the expansion of TAA-specific T-cells in healthy donors and improve the efficacy of adoptive transfer therapy in cancer patients, after allogeneic HSCT.

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