ANNALS OF RESEARCH IN SPORT AND PHYSICAL ACTIVITY

Effect of moderate physical exercise on leukocyte profile in tumor microenvironment and melanoma growth in mice on a high-fat diet

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Publicado por: Imprensa da Universidade de Coimbra

URL persistente: URI:<http://hdl.handle.net/10316.2/44139>

DOI: DOI:https://doi.org/10.14195/2182-7087_ex2018_76

Accessed : 26-Apr-2023 10:30:15

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EFFECT OF MODERATE PHYSICAL EXERCISE ON LEUKOCYTE PROFILE IN TUMOR MICROENVIRONMENT AND MELANOMA GROWTH IN MICE ON A HIGH-FAT DIET

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KEYWORDS: cytokines, M1 macrophages, B16F10 cells, cancer and obesity.

Obesity leads to a systemic chronic inflammation promoting an increase in the risk of cancer development. Scientific evidences suggest that moderate physical exercise can be used to modulate the control of inflammation. Therefore, the aim of this study was to evaluate the alterations in leukocytes in tumor microenvironment of animals under high fat diet and moderated physical exercise in a murine melanoma model. Female mice were divided into 8 groups: 1) normal-fat control (N); 2) normal-fat + melanoma (NM); 3) high fat control (H); 4) high fat + melanoma (HM); 5) normal-fat control + moderate exercise (NE); 6) normal-fat melanoma + moderate exercise (NEM); 7) high fat control + moderated exercise (HE); 8) high fat melanoma + moderate exercise (HEM). After eight weeks of diet treatment and application of moderate physical exercise protocol (60 min., 5 days per week), the melanoma was induced by applying B16F10 cells, or phosphate buffered saline (PBS) in the control group. Initially, animals were followed until the death to establish the survival curve. Afterwards, another group of mice were analyzed and euthanized 21 days after injection of tumor cells. Food consumption, body weight, growth, physical performance, gastrocnemius and soleus muscle citrate synthase activity, tumor growth, tumor weight and adipose

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tissues weight were determined. Histological analysis of the tumor microenvironment was also performed. T regulatory (Treg) cells (CD4⁺/CD25⁺/FoxP3⁺) and Th17 cells (CD4⁺/IL-17A⁺), M1 and M2 macrophages infiltrated into the tumor was determined by flow cytometry. Cytokine profile (IL10, IL12, MCP-1, IFN-gamma, TNF-alpha and IL6) in tumor tissue was assessed by CBA assay. We observed that animals subjected to high fat diet had higher energy consumption (30% on average) and body weight gain (H and HE vs N and NE 37%, HM and HEM vs NM and NEM 73%, respectively). Animals subjected to exercise training showed higher physical performance (N and NM vs NE and NEM 35%; H and HM vs HE HEM and 26%, respectively). Animals from HM group presented higher tumor growth in comparison to all groups. Physical exercise promoted a lower tumor development. In tumor microenvironment, we observed higher M1 macrophage infiltration in animals from HM group. Exercised mice presented lower M1 macrophage percentage and an increase of M2 macrophages. These data indicate that moderate physical exercise can attenuate the inflammatory response from macrophages induced by high fat diet leading to a decrease of tumor growth.

ACKNOWLEDGEMENTS:

FAPESP, CNPq and CAPES