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INFLUENCE OF PHYSICAL ACTIVITY ON CANCER DEVELOPMENT, TREATMENT AND PROPHYLAXIS

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Abstract

Activation of the growth factors pathways is involved in cell growth and proliferation and is associated with carcinogenesis. Many studies have shown an increase in blood growth factors concentrations after training. On the other hand, numerous organisations recommend physical activity in cancer therapy and prophylaxis. This two phenomena may actually cause confusion. The aim of this paper was to present findings on the significance of physical

activity in course of neoplastic disease and dispel doubts concerning its role in cancer treatment.

Keywords: physical activity, IGFs, growth factors, carcinogenesis, cancer

Short article full-text:

Cancer is not only a growth of autonomously proliferating cells but other, non-malignant structures also are a functional part of the disease. Immune cells, fibroblasts, specialized mesenchymal cells and microvasculature together build up the tumour microenvironment and have functional interactions with neoplastic cells. Through metabolic interactions, involving machinery consisted of hormones, cytokines and further signalling molecules, healthy cells and tissues actively participate in tumour proliferation. Normal cells affect a tumour via signalling pathways. Aberrations in homeostatic regulation exert a significant influence on the course of the disease. Research conducted on aforementioned relations leads to their potential employment in therapy. [1, 2]. In this paper, we will focus on growth factors secreted under the influence of increased physical activity and their potential effects on carcinogenesis and tumour proliferation processes.

Growth factors are relatively small proteins that exhibit activity as promoters of cell proliferation. They regulate the embryonic development as one of the main stimuli for tissue differentiation. Subsequently, they have a regulatory influence on growth throughout all ontogenesis. Unlike the hormones secreted by the specialised organs, growth factors are produced by almost all known cells of the human body. The binding of growth factors to specific membrane receptors (in some cases - nuclear) initiates the activation of numerous signalling pathways leading to the transcription of genes responsible for processes of proliferation and differentiation. The complexity of the signalling action is determined by the abundance of pathways that modulate the stimulus. Due to aforementioned features, as well as involvement in acute phase of inflammation and other immune-derived pathways they are considered important tumour growth modulators [1-3]. Insulin-like growth factors (IGFs) present well-known mechanism of action among the numerous signal molecules, accordingly we will focus on their input in physical activity potential impact on cancer development and prophylaxis.

IGFs are endocrine, autocrine and paracrine stimulators of mitogenesis, survival and cellular transformation, therefore they are considered as important regulators of the cell cycle. Their actions are mediated through the type 1 IGF-receptor (IGF-1R), a tyrosine kinase that resembles the insulin receptor. The bioavailability of free IGF for interaction with the IGF-1R

is modulated by the insulin-like growth factor-binding proteins (IGFBPs). IGFBPs, especially IGFBP-3, also have IGF-independent effects on cell growth. IGFBP-3 also constitutes a component of cycles that result in subsequent inhibition of growth or implication of a block on the path to programmed cell death [3, 4]. Other IGFBPs are involved in regulation of signalling axis. Not all mechanisms are understood. Their multitude of functions makes them an interesting research field, especially in oncology. For example: IGFBP5 is a specific inhibitor of angiogenesis stimulated by VEGF - vascular endothelial growth factor. By slowing down the angiogenesis, IGFBP5 inhibits tumour growth [INHI3]. IGF-1 and IGF-2 are the only known proteins in the family of insulin-like growth factors. The gene encoding them evolved from a common precursor by duplication. The vast majority of IGF is produced in hepatocytes as a response to growth hormone (GH) stimulation. Significant pool of IGFs is synthesized in the bone by stimulation with parathyroid hormone. IGFBPs are also produced in the liver. Because of the structural analogy with the insulin, free IGFs induces a hypoglycaemic effect. Interaction with insulin receptors does not occur while the agent is bound to its transporting protein. More than 90% of circulating insulin-like growth factors are bound with IGFBP-3. The remaining pool is associated by other transport proteins, and only 1% circulate in free form. This is due to the short half-life of the free IGF, which ranges from 10 minutes to several hours. There is a correlation between the amount of bioavailable IGFs (ie associated with the carrier) and the growth of tissues - especially muscle tissue, which is the most responsive to physical activity and nutritional deficiencies. IGF stimulates collagen synthesis and induces the development of oligodendrocytes. Numerous studies have demonstrated the stimulating effect of IGF on tumour cells cultured in vitro [2-5].

Studies conducted in a randomized population of healthy subjects have shown an increase in bioavailable IGF concentrations after training. Exercises were based on the standard physical preparation program for US soldiers. After a period of eight weeks of regular activity, significant increases in IGFBP-3 and IGFBP-2 concentrations were observed in the serum of subjects [5]. However, what should be noted is that the concentration of IGFBPs in the blood stream decreases in the state of energy shortage. Malnutrition, fasting, and pathological conditions exert a significant influence on homeostasis of growth factors. In these circumstances catabolic processes dominates the metabolome which results in release of substrates necessary for survival. The example of the phoenomenon is exhaustion of the body in cachexia, when the serum IGF levels in the patient are significantly reduced. The analogy in the construction of IGF and insulin is not accidental and the mutual regulatory pathways are closely linked [5, 7, 9].

Physical activity is most often defined as an increase in energy expenditure of the body resulting from increased skeletal muscle function. Its metabolic effect is the energy consumption, utilisation of reserves and the proliferation of tissues - mainly muscular and connective - occurring with proper access to the nutritious resource. Physical activity is an important health-promoting behavior, but its association with cancer therapy remains poorly understood [7].

International Agency for Research on Cancer stated that obesity is the leading cause of one third of colorectal, 4ast, endometrial, esophageal, and renal cancers. The studies that gave rise to the above statements are based on statistical data including BMI and lifestyle of oncological patients [8]. A review of more than 70 studies on the impact of physical activity on the prevention of 4ast cancer has made it possible to estimate a 25% reduction in the incidence of the disease. The problem of type, quantity and dosage of exercises was also discussed. The recreational activities, which do not cause excessive burdens on the body, are considered the best. The authors recommend conducting further research to better understand the mechanisms of the positive effect of exercise on disease prevention. Very similar results were obtained when analyzing the effects of moderate exercise in the prevention of colorectal cancer (mean reduction in risk of disease estimated above 20%). For the contrast, studies tracking the potential impact of physical activity on the onset of renal, testicular and bladder cancer have shown little or no effect on disease prevention. In addition, intensive physical training seems to be a factor promoting the development of prostate cancers. Mechanisms remain unclear, most probable is organ physical stimulation, impact of growth factors is also taken into account. The difficulty in conducting research on physical activity in the occurrence of lung cancer was related to the effects of cigarette smoking. Recreational training has an impact on the potential reduction of the risk, but it mainly concerns subjects who have never smoked. So far there is an inadequate scientific evidence on the impact of exercise in the prevention of hematologic diseases [7].

Physical activity is very often recommended in the cancer treatment process. Organizations such as the World Health Organization, the American Cancer Society, the American Institute for Cancer Research, the Australian Association for Excercising and Sports Science, and the American College of Sports Medicine have issued guidelines in which they postulate the inclusion of exercise in prevention programs and oncological treatment. Its undoubted benefit is the regulation of the psycho-somatic welfare of the patient, especially in prophylaxis and complete remissions of the disease [4, 7]. On the other hand, there is a direct correlation between tumour proliferation and insulin-like growth factors. Many pharmaceutics

work by cutting down the IGF pathway and thereby allowing tumour cells to enter apoptosis, autophagy or other programmed death processes [2, 5, 6, 9]. Despite the fact of IGFs direct influence on proliferation of tumours, high levels of IGF and IGFBP3 have been found to be positive prognosis predictors for some cancers. Attention was paid to the reduction of insulin resistance, endorphin ejection, increased prostaglandin production, decreased adipocytic reserve, and improved overall immune function [4, 8, 10]. Essential energy competition between neoplasms and normal tissues may be crucial in understanding complicated relationships in human metabolome. The tumour tissue significantly differes from normal one in the scope of presented receptors. It is therefore difficult to predict its response to growth factors present in the bloodstream. This unpredictability may be the reason for the inhibitory effect of IGF and IGFBP in the carcinogenesis process in some tumours [1, 3].

Systemic defects presented by neoplastic cells cause not only changes in secretion of growth factors, but also aberrations in the reception of the signal carried by the molecule. According to this hypothesis, IGFs are not the cause of cancer, but only a potential modulator of its growth [1, 3, 7].

Concerning the general homeostasis of the body, it seems that the benefits of balanced physical exercise outweigh the potential risks caused by the secretion of growth factors. Individual adverse cases confirm the need for personalized treatment of each patient - careful monitoring of changes in the therapeutic process and rapid and effective response. In order to achieve this goal, careful comprehensive diagnostics are essential.

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