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TARGETING THE THERAPEUTIC EFFECTS OF EXERCISE ON REDOX-SENSITIVE MECHANISMS IN THE VASCULAR ENDOTHELIUM DURING TUMOR PROGRESSION

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I. SUMMARY

The American Cancer Society estimated 1.5 million new cancer cases in the US in 2012. Although the exact number is not known, it is estimated that brain metastases occur in 20–40% of cancer patients (NCI). Due to the complexity of development and the variation in tumor etiology, therapy options have been limited for a number of cancers while progressive treatments have been successful for some malignancies. Combining treatment strategies has shown potential to increase positive outcomes, however cancer remains a formidable diagnosis with no true cure. Many researchers have focused on alternative forms of cancer prevention or treatment to slow cancer progression. Studies have shown that with moderate, regular exercise signaling pathways associated with increased antioxidant activity and cellular repair are upregulated in vascular tissue, however the physiological mechanisms are poorly understood. The purpose of this review is to examine the current literature in order to better understand the impact of exercise on cancer progression and tumor metastasis and discuss potential redox related signaling in the vasculature that may be involved.

Keywords

Cancer; exercise; reactive oxygen species; brain microvasculature; metastasis; tight junction

II. INTRODUCTION

Cancer is a multidimensional disease that can arise from a variety of factors including age, genetic predisposition, environmental, and lifestyle choices. With a growing number of associations between daily activities and cancer development and progression, recent research has focused on understanding the contribution of lifestyle choices such as exercise. Several groups have demonstrated that exercise can have positive outcomes on activity, strength, aerobic capacity and emotional factors in humans (1). In rodents, exercise has been shown to alter primary tumor size and regulate factors involved tumor cell survival and growth (2). The types of exercise, intensity of training and cancer type are key factors that vary greatly between studies (3). Less is known about the effect of exercise on tumor progression and metastasis. Key steps in metastatic initiation and growth are determined by the tumor cells' ability to transverse the vascular membrane, enter the blood stream and penetrate the endothelium in a new site. In addition to metastasis, tumor development and maintenance require adequate blood supply and nutrients to grow. The role of the vasculature and vascular endothelial environment is critical in understanding how these

metastatic events unfold. Tumor cells can disrupt tight junction (TJ) protein expression (4). TJs are the main structural components that determine paracellular integrity in brain endothelium, and tumor cells extravasate and disseminate into the brain between disrupted TJs. It is known that exercise alters the gene expression of factors involved in angiogenesis as well as components associated with permeability of the vascular endothelium (5, 6). These processes are of particular consequence in the brain endothelium where tight junction protein complexes form an additional barrier that limits passage into the cerebrospinal environment. Activation of redox-sensitive small GTPases can lead to the disruption of TJs and promote tumor cell extravasation (7). There is evidence that exercise can alter the oxidation status of the microvasculature and thereby may offer protection against tumor cell invasion into the brain (8).

III. TUMOR DEVELOPMENT AND VASCULAR SIGNALING

Risk Factors

Cancer can arise from a variety of sources including genetic mutations or predisposition, environmental factors or toxins, as a result of lifestyle and behavioral choices, and as a consequence of the natural progression of aging. Mutations in tumor suppressor genes such as *p53*, *BRCA1/2*, *PER2* and others involved in cell growth and turnover can be inherited however familial predisposition does not guarantee cancer development (9–11). Industrial workers or those persons working shift-work or in transcontinental travel industries are also at a higher risk for cancer (12, 13). Diet and lifestyle choices also have strong connections to cancer development (14). Obesity and metabolic syndromes have been linked to increased incidence of cancer and challenges when managing tumor progression.

Progression

Three fundamental steps have been described in the process of tumor development and malignant progression (15). Initiation of cancer development begins at the cellular level where individual cells acquire the capacity to form malignant growth. Initiation can be triggered by the factors mentioned previously or can arise spontaneously during normal cell division. At this phase pathways that deter tumor initiation such as those that enhance DNA repair, promote detoxification or reduce reactive oxygen species (ROS) can slow or prevent tumorigenesis. Studies have shown that exercise is associated with an increase in antioxidant vitamins as well as enzymes glutathione peroxidase, catalase and superoxide dismutase (SOD) (16, 17). Once cells have gained the capacity for unabated growth a “promoting” stimulus is needed to maintain the cells and promote further development. Promotion involves the colonization of tumor cells and is often involved with environmental factors that promote development, such as circulating hormones (18). Some studies have also shown a relationship between exercise and reduced levels of circulating hormones, which may have anti-promotional/progressive effects on tumor growth (19, 20). The final fundamental step is progression (21). Progression involves the accumulation of more malignant cells and the development of a pro-growth environment within which the tumor can be self-sustained. Once the tumor has been established, progression can be characterized by the development of the primary tumor, metastatic growth, or both. Progression requires adaptation and compliance of the surrounding tissues including, very importantly, the vasculature (22). The effects of exercise with respect to vascularization and tumor maturation have been mixed. Studies have shown that exercise decreases angiogenesis in the tumor environment, decreases vascular endothelial growth factor (VEGF) and increases oxygen content (23) while others have reported that exercise increases tumor vascularization and lowers oxygen levels within the tumor mass (24). The following section will discuss contributions of specific signaling molecules in the context of vascularization and tumor development.

Cancer and vascular endothelium

The vascular system plays a critical role in the development and progression of cancer (25). By providing a “highway” for growing tumors to receive nutrients and travel to other sites in the body, the signaling and regulatory pathways in the vasculature are essential to understanding cancer progression (26). Several factors have been determined to be important for tumor vascularization and development of a pro-growth environment. VEGF signaling promotes angiogenesis and vascularization of the tumor environment (27). Multiple studies have shown that ROS may be involved in VEGF signaling and angiogenesis (28, 29). ROS are generated as result of normal physiological function (30). Increased ROS are associated with cell proliferation and migration (31, 32), increased VEGF (33), angiogenesis (34), and other signaling pathways (35, 36). Indeed ROS are also involved directly in cell signaling events including alteration of redox-sensitive modifiers such as phosphatases. The activation of these pathways in vascular endothelial cells leads to mobilization, rearrangement of the cytoskeleton, and tubular formation (31, 37). In addition to vascularization, ROS can stimulate small GTPase signaling pathways leading to cellular rearrangement and alterations in the vascular endothelial cells which may can promote tumor cell invasion (36, 38, 7).

IV. METASTASIS

Tumor metastasis is a complicated event that involves many variables and depends on both the tumor cells and the host. Normal healthy cells do not live long when detached from the connective tissues of the extracellular matrix, however tumorigenic cells must gain the ability to survive and translocate in order to recognize another location in the body. Metastatic growth is more common within the visceral cavity i.e. lungs, liver, or bone (NCI). Tumor cells can travel through lymphatic or blood vessels to gain access to these regions of the body. Brain metastases occur about ten times more frequently than primary brain tumors, and they manifest in approximately 30% of all other cancer types (NCI) (39). Because the central nervous system does not have any lymphatic vessels the only method of entry for tumor cells is the blood stream. Once inside the brain microvasculature tumor cells must cross the blood-brain barrier (BBB), which is reinforced with tight junctions (7). The mechanism of tumor cell extravasation into the brain is not well understood, however one hypothesis involves the activation of redox-sensitive pathways, which compromise tight junction protein integrity leading to tumor cell invasion (40). ROS are generated during tumor progression and metastasis within the tumor and surrounding tissue (41, 42). Tumor cells promote ROS generation which can lead to further DNA damage by increasing NADPH oxidase (NOX) activity and promoting redox-sensitive pro-growth pathways (43). Studies have also demonstrated that tumor cells often have a reduced sensitivity to ROS or may “hijack” ROS-mediated signaling in order to progress (41). Studies have shown that exercise has different effects on redox status depending on several variables (discussed below). Increased antioxidant activity can counterbalance heightened ROS levels in surrounding tissue (44). In the context of the vasculature and infiltration through the BBB, damage to the vessels and the TJs directly contribute to tumor cell invasion (Figure 1).

V. EXERCISE AND CANCER PROGRESSION

Exercise can be divided into two major categories, aerobic and anaerobic. Aerobic exercise occurs when oxygen is in ready supply and has the potential to generate more superoxides and hydrogen peroxide, which can cause harm to the organism (2). Anaerobic exercise or strength training can take place under low oxygen conditions or when ATP demand has exceeded oxygen availability. Anaerobic exercise is not as likely to generate free radicals but can lead to more cellular damage if performed incorrectly (45). Short-term, intense bouts of exercise also have the potential to generate more ROS however adaptive responses are

also upregulated to counteract the increase in ROS (21). In addition to ROS generation, studies have shown that exercise is associated with the upregulation of SOD (Figure 1), which are responsible for the dismutation of free radicals and the generation of hydrogen peroxide. Hydrogen peroxide can increase the activity of endothelial nitric oxide synthase (eNOS) (38). Indeed, vascular expression of eNOS is associated with increased vasodilatation, improved blood flow and vascular endothelial function (46).

Exercise Models

There are several key variables to keep in mind when evaluating the protective effects of exercise on cancer development. The type of exercise and duration are important. Studies have shown that anaerobic exercise can be protective for some types of lung cancer while aerobic activity (even 1 hour/week) could be beneficial to reduce the risk for colon cancer (47, 2). Intense physical activity has been associated with decreased risk for breast cancer and others have shown that regular moderate exercise, which is also connected with decreased levels of ROS, can exert positive effects for several types of cancers (48). Another factor to be aware of in several exercise and cancer studies is diet. While diet is not the topic of this review, it is important to note animals fed a high-fat or western diet showed less benefit (sometimes no benefit) with exercise when compared with animals on standard chow diet (2). Lastly, a potentially important distinction when evaluating the therapeutic benefit of exercise is “primary vs. secondary” effects of exercise treatment. Many cancer studies have reported positive outcomes with exercise based on the fact that regular activity improves muscle tone and mobility thereby increasing quality of life for some cancer patients. This is not surprising considering side effects of most cancer treatments include weakness and fatigue (49). The fact that regular activity can improve these secondary effects of cancer drug treatment are not surprising considering that skeletal muscle comprises approximately 40% of body mass in adults (50). The “primary” effects of exercise on cancer development and progression are less understood. These include biological changes in the tumor cells or the tumor environment that are a direct consequence of exercise, such as alterations in oxidative status, gene expression and signaling pathways that may influence tumor growth and/or survival. Several specific cancer types have been studied in the context of exercise. The most prevalent and well studied are discussed in the following sections.

Lung Cancer

Lung cancer has the highest mortality rate among all cancer types (69). In 2012 alone, there were an estimated 225,000 new cases of lung cancer in the United States (68). Primary lung tumors are also the most likely to form brain metastases (51). Several studies have focused on the effects of exercise and lung cancer development/progression. Paceli et al. demonstrated that anaerobic but not aerobic exercise decreased the number of tumor cell lesions in an experimental model of lung cancer development (52). Exercise was also associated with higher glutathione levels (53) and increased ROS scavengers (54, 55) in the lung. Interestingly each of these studies observed changes in oxidative measurements using methods of forced exercise rather than voluntary aerobic exercise suggesting that activity intensity somehow influences antioxidant mechanisms.

Hormone Sensitive Cancers

Prostate and breast cancer patients have been shown to gain significant benefit from regularly scheduled exercise. It has been shown that men had reduced risk for prostate cancer when they exercised at least 3 hours per week at a high intensity and women also had a protective benefit from regularly scheduled exercise (48). The incidence of brain metastases from primary breast tumors is second to lung cancer and studies show that BCRA1 mutations are associated with a greater risk for brain metastases (51). Indeed studies have suggested that exercise can modulate steroid hormone levels, estradiol, testosterone

and androstenedione thereby reducing the risk or progression of hormone sensitive tumors (56, 57). In addition to hormone sensitive mechanisms some data have shown that redox-sensitive pathways including small GTPases (Ras, Rac1 and RhoA) are altered in a model of breast cancer metastasis (58) and conversely antioxidant mechanisms are enhanced with exercise (59).

Gastrointestinal Cancer

Thus far, the neoplasm that appears to be the most influenced by exercise intervention is gastrointestinal cancer (47, 48, 2). Studies have shown that exercise can delay the onset of intestinal cancers and protect against the development of chemically induced carcinogenesis (60, 2). Increased levels of activity were associated with greater risk reduction (47) and also decreased tumorigenesis (61) or tumor progression (62). Several studies have shown a link between diet/exercise and metabolic and oxidative factors. Using a mouse model of “multiple intestinal neoplasia” *Apc^{Min}* (63) mice were given either standard or high-fat chow and exposed to exercise (64). The exercised mice on standard chow had a reduction in the number of polyps but the high-fat mice did not. Furthermore the high-fat fed mice had increased inflammation and immunosuppression that was not altered by exercise. However in high-fat fed rats exercise completely prevented carcinoma development (65). Disruption of cell cycle control genes and oncogenic mutations, which promote uncontrolled growth and angiogenesis were observed in gastrointestinal carcinomas (66). Finally, mice showed decreased inducible nitric oxide synthase expression (decreased cell growth and angiogenesis) following exercise in a chemical model of carcinogenesis (61). Data from these studies and others have lead some researchers to hypothesize that the positive effects of exercise maybe be related to increased gut motility or clearance of irritants/inflammatory factors and an inhibition of cell proliferation (57).

VI. CONCLUSIONS

Although many associations have been made between exercise and cancer prevention and progression, the mechanisms that underlie tumor progression and metastasis are poorly understood. Of the most prevalent cancer types, gastrointestinal (colon) has shown the most promise with respect to exercise as a treatment. Several biochemical pathways are believed to be involved with exercise and tumor development (3, 21). Alterations in redox status can modulate many processes in normal physiology as well as pathophysiology. In the initial stages of cancer development an increase in ROS can promote tumorigenesis through DNA damage and increased inflammatory response (21). Once the tumor cells begin to multiply, angiogenesis and enhanced cellular proliferation are necessary for the tumor to grow and establish. Tumor metastasis is a complicated phenomenon that can arise if the circumstances are favorable (3). In the brain, metastasis formation becomes more arduous due to the fortification of microvessels with tight junctions (4). With respect to exercise a variety of outcomes have been described in various cancer models. It appears that duration, intensity, and metabolic type (aerobic vs. anaerobic) are all important as well as the cancer cell type in understanding the effect of exercise on tumorigenesis or tumor progression (48, 2). Because oxidative status appears to play a role in cancer development and exercise can modulate redox-related components such as antioxidant enzymes and DNA repair mechanisms (21), it seems crucial that more work be done to further elucidate the molecules and pathways involved.

VII. Future Directions

Exercise is a multifaceted intervention, which can promote a variety of outcomes in a host-specific manner. At the present time evidence suggests that exercise can have variety of effects on the development and progression of cancer. However, many pathways involved in

cancer growth and metastasis can also be driven by exercise and may in fact be beneficial under normal physiological contexts such as aging (67). Therefore, more stringent research designs are advocated in order to better understand the protective effects of physical activity on tumor progression and metastasis development.

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Figure 1.

Balancing redox status. Tumor cells promote increased oxidation, tissue and DNA damage, and angiogenesis. Exercise can modulate some of these effects in specific tumor types. Tumorigenesis and tumor cell proliferation (black arrows) generate ROS, which can ultimately lead to cell damage and activation of downstream signaling (Ras). Redox-sensitive GTPase activation promotes tumor growth and phosphorylation of tight junction proteins leading to degradation. Exercise (white arrows) abrogates several of these outcomes in a tumor specific and activity-type dependent manner.

Ras- Ras sarcoma; Rac1- Ras-related C3 botulinum toxin substrate 1; RhoA- Ras homolog gene family, member A; GTPase- Guanosine triphosphate hydrolase; P- phosphate; NOX- NADPH oxidase; ROS- reactive oxygen species; SOD- superoxide dismutase; GPX- glutathione peroxidase; TJ- tight junction