CellPress

Review

Exercise-Dependent Regulation of NK Cells in Cancer Protection

Manja Idorn[1] and Pernille Hojman[2,*]

Natural killer (NK) cells are the most responsive immune cells to exercise, displaying an acute mobilization to the circulation during physical exertion. Recently, exercise-dependent mobilization of NK cells was found to play a central role in exercise-mediated protection against cancer. Here, we review the link between exercise and NK cell function, focusing on circulating exercise factors and additional effects, including vascularization, hypoxia, and body temperature in mediating the effects on NK cell functionality. Exercise-dependent mobilization and activation of NK cells provides a mechanistic explanation for the protective effect of exercise on cancer, and we propose that exercise represents a potential strategy as adjuvant therapy in cancer, by improving NK cell recruitment and infiltration in solid tumors.

Exercise is Beneficial for Cancer Patients–A Role for NK Cells

Circulating immune cells were first shown to be regulated by exercise in 1893 by Schulte, who described how lymphocytes were recruited to the blood stream during physical exertion [1]. Through such immune cell recruitment, exercise may directly stimulate the immune system to combat disease. Within the past 30 years, focus on getting patients across a number of diseases out of bed and into active rehabilitation early in the disease trajectory has emerged [2]. In cancer, the benefits of engaging patients in an active lifestyle despite their disease are becoming increasingly evident. At present, more than 100 exercise intervention studies in cancer patients have reported favorable effects on both patient-reported outcomes (Box 1) and **physical functioning** (see Glossary) when exercise is performed during or after antineoplastic therapy [3]. In addition, accumulating evidence suggests that exercise has a direct effect on tumor growth. Early evidence from observational studies has shown that physical activity reduces the risk of disease recurrence in colorectal, prostate, and breast cancer patients [4–6] (Box 2). Moreover, a 2-year training intervention study has recently shown that high intensity endurance training can increase **PSA doubling time**, a surrogate marker for delayed tumor progression in prostate cancer patients [7].

Accordingly, several preclinical studies have shown that voluntary wheel running can inhibit tumor growth across a range of experimental animal tumor models, including both genetic and transplantable tumor models [8]. In line with this, our laboratory has recently shown that voluntary wheel running in mice could induce an exercise-dependent increase in intratumoral immune cell infiltration in various genetic and transplantable murine tumor models [9]. Intratumoral infiltrates included natural killer (**NK**) **cells**, and exercise-mediated induction of intratumoral NK cells contributed to a 50–60% reduction in tumor growth. Further mechanistic analyses demonstrated that tumor control could be achieved through an epinephrine-dependent mobilization of NK cells, together with subsequent IL-6-induced redistribution and activation of NK cells. These recent findings have linked exercise, epinephrine ('fight or flight' response), and IL-6 to NK cell mobilization and

Trends

Exercise controls tumor growth through epinephrine-dependent mobilization of NK cells, stressing the importance of intensity driven exercise in tumor control.

Muscle-derived exercise factors, known as myokines, can regulate NK cell proliferation, maturation, and activation, representing a muscle-to-immune cell crosstalk axis during exercise.

Exercise promotes additional effects within tumors, including improved vascularization and perfusion, resolution of hypoxia, and increased body temperature, all contributing to a microenvironment that promotes NK cell responsiveness.

Exercise is being increasingly prescribed to cancer patients to mitigate treatment-related side effects, as well as to improve quality of life and physical functioning. Yet, the cumulative effects of exercise may translate into both improved tumor control and enhanced treatment efficacy.

[1]Centre for Cancer Immune Therapy, Department of Hematology, Copenhagen University Hospital, Herlev, Denmark
[2]Centre of Inflammation and Metabolism and Centre for Physical Activity Research, Rigshospitalet, Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark

*Correspondence: phojman@inflammation-metabolism.dk (P. Hojman).

Box 1. Exercise and Depression in Cancer Patients

Many patients diagnosed with cancer suffer from depression, yet exercise may comprise an effective intervention. Several Cochrane systematic reviews have documented beneficial effects of exercise on patient-related outcomes, including depression, in patients with cancer both during and after completed anticancer therapy [96,97]. While depression may arise from multifactorial causes, kynurenine-mediated tryptophan degradation has been proposed as a mechanism, whereby stress induces depression. Ruas and colleagues recently showed that exercise training could decrease kynurenine levels through increased kynurenine metabolism in the muscles, proposing a mechanistic link between exercise training and reduced depression [98].

Box 2. Exercise and Cancer Prevention

Over the past 10 years, epidemiological studies have demonstrated that exercise and physical activity are associated with markedly reduced cancer-related, and overall mortality, across the 'big' cancer diagnoses, that is, breast, colon, and prostate cancers [5,99,100]. The Centers for Disease Control and Prevention (CDC) has summarized the scientific evidence stating that: 'physical active people have a lower risk of developing colon or breast cancer than people who are not active'; and 'physical active people may have a lower risk of developing endometrial and lung cancer, although the scientific evidence is not final yet' (http://www.cdc.gov/physicalactivity/basics/pa-health/index.htm#ReduceCancer).

redistribution, and ultimately, to control of tumor growth in mice [9]. In light of this, we review the current knowledge on exercise-mediated regulation of NK cells, seeking to improve our understanding of the role of exercise and exercise factors in the mobilization and activation of NK cells in tumor control. The review is mainly focused on human findings, yet, to provide additional insight into relevant mechanisms, animal studies are also discussed. The ability to further our insight into the mechanistic pathways regulating NK cell antitumoral activity and cytotoxicity are timely, as they may facilitate additional approaches–including physiology-based ones–to improving potential cancer treatments.

Basic NK Cell Biology

NK cells were originally described as a subset of lymphocytes with a 'natural killing' ability towards cancer cells without previous priming [10], classifying them within the innate immune system of fast responders. Recent classification groups NK cells within the emerging population of innate lymphoid cells (ILCs) [11]. NK cells develop in the bone marrow from $CD34^+$ hematopoietic precursor cells and are subsequently distributed widely throughout the body including the bone marrow (BM), lymph nodes (LNs), spleen, peripheral blood, lung, and liver (Figure 1) [12]. In healthy adult individuals, NK cells constitute 5–15% of all circulating lymphocytes [13]. Upon activation, the main function of NK cells is to kill infected (e.g., virus) or transformed (malignant) cells, and, to trigger the adaptive immune response through cytokine release. For further characterization of NK cell phenotype and function, see Box 3.

Exercise and the Control of NK Cell Mobilization

Characterization of exercise-mediated changes in circulating immune cells began in the 1980s, with technological advancements in flow cytometry. Now, a general model of exercise-driven modulation of immune cell distribution in tissues has been proposed, describing how NK cells, T cells, and to a lesser extent, B cells, are mobilized to the circulation during exercise (Figure 2) [14]. This mobilization appears to represent a recruitment of stored immune cells, rather than a generation of new cells [15].

Kinetics and Intensity of NK Cell Mobilization

Exercise-mediated mobilization of NK cells is a very rapid phenomenon. As little as 70 s of stair climbing has been shown to increase the frequency of NK cells in the blood by 6-fold [16]. Subsequently, several studies have shown mobilization of NK cells within minutes with exercise, when performed with an intensity associated with breathlessness, increased heart rate, and elevated plasma epinephrine levels [17–19]. In general, maximal mobilization of NK cells is

Glossary

Antibody-dependent cell-mediated cytotoxicity (ADCC): mechanism of immune-mediated killing of antibody coated target cells. Binding of IgG antibodies to the FcRγIII receptor expressed on NK cells leads to NK cell activation and subsequent lysis of the antibody coated target cell.
AMPK (5′ AMP-activated protein kinase): enzyme playing a central role in cellular energy homeostasis, regulating energy pathways involved in both glycolytic and oxidative metabolism.
Catecholamines: group of monoamines, including dopamine, epinephrine, and norepinephrine. The latter two being hormones commonly associated with a 'fight or flight' response.
γδ T cells: constitute a small fraction (1–5%) of all human T cells and are defined by the genetic composition of their T cell receptor. They have been described as a link between adaptive and innate immunity.
Immunoscore: the immune context characterizes the location, density, organization, and functional orientation of tumor-infiltrating immune cells, and can be used as a tool to help predict patient prognosis.
M1 macrophages: regarded as the classically activated macrophages, which promote inflammation.
Myocytes: muscle cells in cell culture systems.
Myokines: are proteins and peptides, which are released from skeletal muscle in response to muscle contraction or other stimuli.
Myotubes: fully differentiated muscle cells in cell culture systems.
NK cells: natural killer cells are cytotoxic lymphocytes of the innate immune response.
PBMC: peripheral blood mononuclear cells are blood cells that include lymphocytes (NK, NKT, T and B cells), as well as monocytes.
Physical functioning: a common outcome in exercise intervention studies, comprising physiological evaluations such as muscle mass and strength and fitness levels, or functional capacity, which includes functional tests such as sit–stand test, 6 min walk test, or hand grip strength.
PSA doubling time: prostate specific antigen (PSA) doubling time refers to an algorithm used to predict