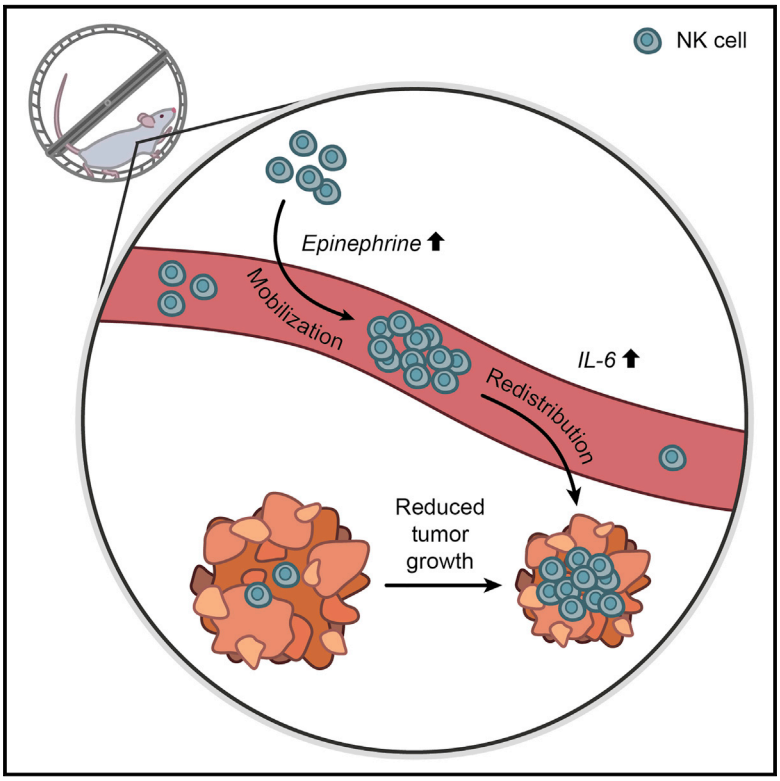
Short Article

Cell Metabolism

Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution

Graphical Abstract



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In Brief

The beneficial effects of exercise are countless. Pedersen et al. now link exercise, cancer, and immunity and reveal that exercise decreases tumor incidence and growth by over 60% across several mouse tumor models through a direct regulation of NK cell mobilization and trafficking in an epinephrine- and IL-6-dependent manner.

Highlights

- Exercise reduces tumor incidence and growth in several mouse models
- Exercise increases NK cell infiltration, thereby controlling tumor growth
- Epinephrine mobilizes NK cells and β-blockade blunts the tumor suppression
- Exercise-induced muscle-derived IL-6 is involved in NK cell redistribution

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Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution

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SUMMARY

Regular exercise reduces the risk of cancer and disease recurrence. Yet the mechanisms behind this protection remain to be elucidated. In this study, tumor-bearing mice randomized to voluntary wheel running showed over 60% reduction in tumor incidence and growth across five different tumor models. Microarray analysis revealed training-induced upregulation of pathways associated with immune function. NK cell infiltration was significantly increased in tumors from running mice, whereas depletion of NK cells enhanced tumor growth and blunted the beneficial effects of exercise. Mechanistic analyses showed that NK cells were mobilized by epinephrine, and blockade of β-adrenergic signaling blunted training-dependent tumor inhibition. Moreover, epinephrine induced a selective mobilization of IL-6-sensitive NK cells, and IL-6-blocking antibodies blunted training-induced tumor suppression, intratumoral NK cell infiltration, and NK cell activation. Together, these results link exercise, epinephrine, and IL-6 to NK cell mobilization and redistribution, and ultimately to control of tumor growth.

INTRODUCTION

Epidemiological data document that regular exercise protects against the development of certain cancers and lowers the risk of disease recurrence (Brown et al., 2012; Christensen et al., 2014), prompting extensive research into exercise interventions in cancer patients (Jones and Alfano, 2013). Across a range of cancer diagnoses, exercise has been shown to improve functional capacity and patient-reported outcomes (Mishra et al., 2012). However, exercise may also directly suppress tumor growth, as suggested by decreased risk of disease recurrence in physically active cancer patients (Ballard-Barbash et al., 2012). Little is known about the mechanisms behind this protection, but exercise-mediated changes in body composition, sex hormone levels, systemic inflammation, and immune cell function have been suggested as possible mediators (McTiernan, 2008).

Exercise training comprises of acute bouts of physical exertion, followed by periods of recovery. During these acute bouts of exercise, plasma levels of stress hormones and muscle-derived myokines increase dramatically (Catoire and Kersten, 2015). Myokines may have direct anti-proliferative effects on cancer cells, as shown for oncostatin M on hormone-sensitive breast cancer cells (Hojman et al., 2011) and SPARC in colon cancer (Aoi et al., 2013). Yet during exercise, an acute mobilization of immune cells to the circulation is also seen (Pedersen and Hoffman-Goetz, 2000; Bigley et al., 2014). Cells of the immune system play dual roles in cancer. The immune system has a powerful capacity to combat cancer, but chronic inflammation has also been linked to tumorigenesis in several conditions (Vivier et al., 2012; Imai et al., 2000; Grivennikov et al., 2010). On the protective side, infiltrating cytotoxic immune cells have been demonstrated as positive prognostic factors for disease outcome and overall survival in several cancers (Fridman et al., 2012; Remark et al., 2013). Thus, mobilization of cytotoxic immune cells during exercise might represent an indirect defense mechanism against cancer growth.

RESULTS AND DISCUSSION

Voluntary Wheel Running Significantly Reduces Tumor Incidence and Growth

First, we evaluated the effect of wheel running before and/or during tumor challenge in a subcutaneous B16F10 melanoma model in female mice (Figure 1A). Four weeks of wheel running