

Active Voice: How does Exercise Improve Immune Bioenergetics?

By Jong-Shyan Wang, Ph.D.

Natural killer (NK) cells, which are found in the blood, are crucial in the prevention and treatment of cancer. They function by eliminating malignant tumors in an innate immune manner. NK cells express an array of activating and inhibitory receptors that recognize cancer cells without the need for immunization. Cytotoxicity is a process that results in damaging or destroying cells. The antitumor cytotoxicity of NK cells depends on their ability to recognize cancer cells and the production of cytotoxic proteins. Mitochondrial bioenergetics is essential for optimizing NK cell effector functions, including increased cytotoxic potential and cytokine production.

Regular exercise reduces mortality associated with most cancers. An acute bout of exercise mobilizes NK cells that enter the bloodstream from peripheral tissues. They can modulate the antitumor cytotoxicity of NK cells by altering cellular protein contents in an intensity-dependent manner. However, patients with malignancies experience gradual declines in muscle strength and cardiorespiratory fitness which can influence their ability to exercise. This may lead to a more sedentary lifestyle. High-intensity interval training (HIIT) has been shown to be a more effective modality for improving cardiorespiratory fitness than moderate-intensity continuous training in both healthy individuals and patients with cardiovascular disease.

Our study, published in the May issue of *Medicine and Science in Sport and Exercise*, involved 60 sedentary males who were randomly assigned to engage in either HIIT or moderate-intensity continuous training, or were assigned to a control group that did not receive exercise intervention. We observed that HIIT was superior to moderate-intensity training for enhancing exercise performance by increasing peak pulmonary ventilation and work-rate. Notably, both types of exercise training improved two cytotoxic characteristics that involved the increases in cytotoxic protein expressions and proliferative capacity of NK cells in the blood. Moreover, the two exercise regimens effectively elevated membrane potential and depressed cell matrix oxidant burden in mitochondria of NK cells. This was associated with an increased oxygen uptake efficiency in NK cells.

On the other hand, NK cells are also important antiviral white blood cells that can rapidly respond to pathogens before an adaptive immune response occurs. Clinical studies in patients with COVID-19 have shown decreased NK numbers and function, resulting in decreased clearance of infected cells and increased tissue inflammation. Our previous and present studies indicate that moderate-intensity exercise training downregulated the senescent and inhibitory receptors on NK cells, thereby increasing clonal expansion and simultaneously improving the efficiencies of NK cells in

recognizing and cytotoxic action against virus and cancer cells.

Our experimental findings could help to determine the effective exercise regimens for simultaneously improving cardiorespiratory fitness and the bioenergetic efficiency of NK cells in people living a sedentary lifestyle.

About the Author:

Jong-Shyan Wang, Ph.D. is a professor at the Graduate Institute of Rehabilitation Science at Chang Gung University, Taiwan. Prof. Wang was named in the Stanford University names World's Top 2% Scientists in 2021. His research focuses on developing exercise prescriptions for inflammatory/immunity, thrombotic, and cardiovascular disorders.

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美國運動醫學會重要報導：運動如何改善免疫細胞生物能量效率？

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如何調節血液中自然殺手細胞功能，在增進癌症的防治成效，至關重要。自然殺手細胞能藉由先天免疫方式，執行清除惡性腫瘤的作用；它們能表達一系列刺激和抑制受體，無需經由免疫調適，即可識別並毒殺癌細胞。自然殺手細胞的抗腫瘤細胞毒殺作用，取決於它們識別癌細胞和產生細胞毒殺蛋白的能力；而其粒線體生物能量特性，在調控細胞毒殺能力和產生細胞激素效率扮演關鍵角色。

規律而適度的運動可以降低大多數癌症的死亡率。急性運動能動員自然殺手細胞從周邊組織進入血液之中。並且，執行運動的強度與其影響自然殺手細胞毒殺蛋白表現，有其密切的相關性，並藉此調節抗腫瘤細胞毒殺效應。然而，惡性腫瘤患者會因肌肉和心肺適能逐漸下降，影響身體活動能力，導致他們處於更靜態的生活方式。我們發表在五月份《美國運動醫學會》之官方期刊 *Medicine & Science in Sports & Exercise* 的研究指出，高強度間隔式運動訓練能藉由提高心肺適能來增進個體的運動表現，而其效益更優於傳統的中等強度持續性運動訓練。值得注意的是，這兩種類型的運動訓練皆能改善自然殺手細胞之免疫功能，包括增加毒殺蛋白生成和細胞增殖能力。此外，這兩種運動訓練皆能有效提升自然殺手細胞粒線體的膜電位，改善其基質耐受氧化負載的能力，進而增進此免疫細胞的有氧代謝效率。

另一方面，自然殺手細胞也是重要的抗病毒免疫細胞，能在適應性免疫反應發生之前，迅速對病原體作出反應。在針對 COVID-19 患者的臨床研究顯示，自然殺手細胞數量和功能減少是導致降低清除感染細胞能力和增加組織發炎程度的重要因素。我們的研究指出，適度的運動訓練能有效降解自然殺手細胞的衰老和抑制性受體，增進其增殖效益程度，提高自然殺手細胞識別病毒或癌細胞的能力，進一步強化其細胞清除效率。

我們的實驗結果將有助於確立抗病毒與防治癌症的有效運動方案，除能改善靜態生活者的心肺適能外，同時亦能提升自然殺手細胞的生物能量效率，進而增進對病毒與癌細胞毒殺功能。

王鐘賢博士為台灣長庚大學復健科學研究所教授。王教授為史丹佛大學評為 2021 年全球前 2%「終身成就科學影響力」頂尖科學家。他的研究重點為針對發炎/免疫、血栓形成和心血管疾病，發展最適化的運動處方。這項研究計畫獲得台灣國家科學委員會和長庚醫學研究計劃的支持。