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Research Progress on Molecular Mechanisms of Exercise-Regulated Immunity

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Abstract:
Physical exercise exerts bidirectional effects on human immune system. This essay is written to demonstrate significant molecular mechanisms of the opposite immune regulations by physical activity. Epidemiologic evidence indicates that regular exercisers experience reduced risk of upper respiratory tract infections (URTIs) and exhibit substantially lower incidence rates of certain cancers. Inversely, athletes who have undergone intense physical training, such as those who have participated in a marathon race. The incidence rate of URTI will increase significantly compared to that of ordinary people who did not participate in the competition during the same period. Through comprehensive literature review and analysis, this review synthesizes current knowledge on exercise-immune interactions. Main findings indicate the J model theory curve relationship between exercise intensity and infection risk of URTIs, demonstrating that moderate activity enhances immunosurveillance while prolonged high-intensity exercises may induce temporary immunosuppression. This article clearly explains the classic cellular pathways of immune regulation, achieving a combination of the macroscopic and the microscopic. Serving as the scientific basis for individualized exercise prescriptions.

Keywords: Immune system; MAPK pathway; PI3K-Akt pathway; Cortisol.

1. Introduction

Due to the impact of the past years' epidemic, people have started to pay attention to their own immune systems. Despite decades of investigation, the molecular mechanisms underpinning exercise-mediated immune regulation remain fragmented across disparate studies. Current literature frequently examines specific pathways in isolation, such as catecholamine-driven immune cell mobilization, the dual role of IL-6 in inflammation, or cortisol-mediated inhibition of nuclear factor-kappa B signaling, without integrating them into a coherent framework. Few reviews comprehensively synthesize neuroendocrine signaling molecules including epinephrine and cortisol, cellular effectors such as neutrophils and T and B lymphocytes, and intracellular pathways like PI3K-Akt and MAPK into a unified model that explains the bidirectional effects of exercise on immune function.

Acute or moderate-intensity physical activity usually enhances immune responds, mobilizes immune cells. Such as neutrophils and phagocytes, and upregulates cytokines, interleukin-6 and interleukin-15, signaling pathways such as mitogen-activated protein kinase or extracellular signal-regulated kinase and phosphatidylinositol 3-kinase-protein kinase B. Optimizing pathogen clearance. In contrast, prolonged or excessive exercise triggers an immune-suppressive cascade, mainly mediated by hypothalamo-pituitary-adrenal (HPA) axis activation, cortisol release, and subsequent interruption of pro-inflammatory signals, nuclear factor-κB. The established "J-shaped" model further elaborates on this dose-response relationship, linking exercise intensity with URTIs risk.

This review addresses these gaps by systematically consolidating recent advances in the molecular basis of exercise-regulated immunity. We first delineate pro-immunity mechanisms in section 2, detailing how exercise-induced mediators, Such as catecholamines and myokines and signaling cascades amplify immune cell function. Next, we examine suppressive mechanisms in section 3, focusing on HPA axis activation, glucocorticoid signaling, and their inhibition of cytokine production and leukocyte activity. Finally, we contextualize these findings within the "J-model," bridging molecular insights to real-world applications. By unifying fragmented knowledge, this work aims to inform evidence-based exercise strategies that harness immunoprotection while mitigating risks, ultimately advancing human health in clinical and public fitness settings.

2. The Molecular Mechanism of Exercise Promoting Effects on the Immune System

At present, there have been many studies on cytokines that affect the immune system. The following are some molecules and important pathways that promote the immune system.

2.1 Catecholamines

Catecholamines have a variety of functions, one of which is to increase the number of immune cells. According to relevant research, the level of catecholamines in the body will increase after exercise [1].

2.2 Neutrophils

Neutrophils are an important part of the human immune system, and the percentage in blood tests can indicate whether the body has symptoms such as decreased immunity. Studies have shown that the content of Neutrophils in the circulation significantly increases after intense exercise. For instance, after weight training, the number of Neutrophils significantly increases one hour later, and remains at a high level two hours later [2]. Combined with exercise intensity, low or moderate intensity exercise can increase Neutrophils.

2.3 Phagocytes

Through experiments on mice, it was found that the content of phagocytes would increase under different durations and intensities of movement, and their phagocytic function would be enhanced, thereby improving the immune system [3][4]. Phagocytes produce IL-6, which plays a significant part in the immune system.

2.4 IL-6

Interleukin-6, also known as interleukin-6 (IL-6). It can promote T cell development, stimulate cytotoxic T cell responses, induce B cell proliferation and differentiation, and produce antibodies. It can be secreted by skeletal muscle during exercise.

2.5 IL-15

IL-15 can combine with IL-5 receptor to activate JAK/STAT, MAPK and other signaling pathways, promote the proliferation and differentiation of T cells and NK cells, and regulate the secretion of B cells antibody, which expands the network effect of cytokines in immune regulation.

2.6 ICOS

ICOS is regarded as a key protein for the function of T cells that can significantly enhance Finally, we introduce the well-known model theory and combine it with the cellular and molecular level to explain the bidirectional regulatory mechanism of movement on immunity. a variety of T cell responses to heterologous antigens. It is a significant in promoting the proliferation of T cells, secretion of lymphokines and also cell-to-cell's upregulation molecules and can promote the efficient secretion of B cell antibodies. Wu Mingfang's experiment showed that the expression of ICOS molecule increased after long-term moderate to upper intensity exercise [5].

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2.7 MAPK Signaling Pathway

The MAPK pathway is normally activated by sequential phosphorylation of MEK kinase, leading to ERK. MAPK/ERKsignaling pathway is involved in the proliferation and differentiation of hematopoietic cells. During cerebral ischemia/reperfusion, epidermal growth factor receptor (EGFR) is transactivated, thereby stimulating the Raf/MAPK/ERK signaling cascade to protect cells or enhance cell damage [6][7].

2.8 PI3K-Akt Pathway

The PI3K-Akt pathway acts a key part in the survival, metabolism and growth of cell. The PI3K-Akt signaling pathway is one of the major intracellular signal transduction pathways that regulate numerous cellular activities in the body. PI3K kinase converts phosphatidylinositol-4, 5-diphosphate (PIP2) to phosphatidylinositol-3,4, 5-triphosphate (PIP3), resulting in the recruitment of Akt to the plasma membrane and subsequent activation, thereby regulating cell survival, metabolism, and growth. In the tumor microenvironment, oncogene PI3K/AKT signaling mediates metabolic switching in cancer cells and immune cells. Thus, the activation of the PI3K-Akt pathway can restrain apoptosis, thereby promoting cell survival [6][7][8].

3. Negative Regulation-Molecular Mechanisms of Exercise-Induced Immunosuppression

3.1 Endocrine and Exercise-Induced Immunosuppression

Long-duration exercise will lead to inhibition of formation of anti-inflammatory cytokines, suppressing the cytotoxicity of natural killer cells and reducing NK cells' number. Activation of hypothalamo-pituitary adrenal (HPA) axis and secretion of hormones such as cortisol is significant in this process. Hormonal level which shows plasma also increases after exercising. Including cortisol, adrenaline. Arduous exercise can lead cortisol and epinephrine to result in the decline of type 1 T cells which provide primary protection against virus [9]. Exercise has a strong physiological stimulating effect on HPA axis [10].

3.1.1 Hypothalamo-pituitary Adrenal Axis

During exercise, the stimulation of HPA axis is achieved by mainly three pathways. First, Neuronal homeostatic signals. For example, chemoreceptor stimuli. Second, Circulating metabolic signals. Third, Pro-inflammatory mediators, such as IL-6 and TNF-a. A human study of circulating brachial blood sample demonstrates that hypophysiotropic corticotropin-releasing hormone (CRH) -dominated secretion promotes anterior pituitary adrenocorticotropic hormone (ACTH) release. Consequently, elevating immunosuppressive cortisol [10].

3.1.2 Cortisol

Cortisol is a type of hormone secreted by the adrenal glands. It is in the category of glucocorticoids in humans, which are a type of steroid hormones. Glucocorticoids have anti-inflammatory function which can affect most of the immune cells. They are known as immunomodulators. Glucocorticoids can control migration and apoptosis of dentritic cells, preventing them from maturation. By inhibiting cell adhesion molecules, the neutrophils' migrations are suppressed by glucocorticoids. B cells' antibody production is also inhibited by activation of glucocorticoids [11].

3.1.3 The Cellular Mechanism of Cortisol Inhibiting Immunity

By disrupting the NF-κB signaling pathway, glucocorticoids inhibit diverse pro-inflammatory cytokines. For example, TNF-α, IL-1β, and IL-6.

Pro-inflammatory cytokines are a class of small-molecule proteins secreted by immune cells such as macrophages and T cells, or non-immune cells. Their main function is to promote the inflammatory response. They do this by activating immune cells, increasing vascular permeability, inducing fever, and promoting tissue repair, helping the body to eliminate pathogens or cope with damage. Common pro-inflammatory cytokines include tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), etc.

The NF-κB signaling pathway is an important transcriptional regulatory pathway widely present in eukaryotic cells. This mechanism is primarily involved in regulating various biological processes such as inflammatory responses, immune reactions, cell survival, and programmed cell death. proliferation and differentiation. This pathway is centered around the NF-κB transcription factor family and, by receiving extracellular stimuli such as pathogens, cytokines, stress signals, activates the expression of downstream genes, especially pro-inflammatory factors.

This effect is achieved through the upregulation of IκBα mediated by the glucocorticoid receptor (GR) - IκBα sequesters NF-κB in the cytoplasm and directly interferes with the DNA binding activity of NF-κB.

IκBα (Inhibitor of κB alpha) is a key inhibitory protein in the NF-κB signaling mechanism. Its function is to bind to NF-κB in the cytoplasm. They are able to prevent NF-κB's entrance into the nucleus and leading to the expression of target genes.

Corticosteroids can bind to the glucocorticoid receptor (GR) effortlessly by diffusion of molecule through cell surface membrane. After binding to the glucocorticoid receptor (GR), the shape of receptor is changed. This process triggers the dissociation of molecular chaperones, which unmasks the nuclear localization signal on the glucocorticoid receptor (GR). Consequently, the activated GR–corticosteroid complex is rapidly translocated into the nucleus and binds to specific DNA sequences known as glucocorticoid response elements (GREs) within gene promoter regions. Following binding, two GR molecules form a homodimer that interacts with the GRE, ultimately modulating gene transcription.

Corticosteroids might control gene expression in multiple methods. After entering cell, corticosteroids attach to GR, which then translocates to the nucleus. The GR homodimer binds to the GRE in the steroid-sensitive gene promoter area, and the steroid-responsive gene codes for anti-inflammatory proteins [12]. The regulations of gene expressions by corticosteroid are shown in figure 1.

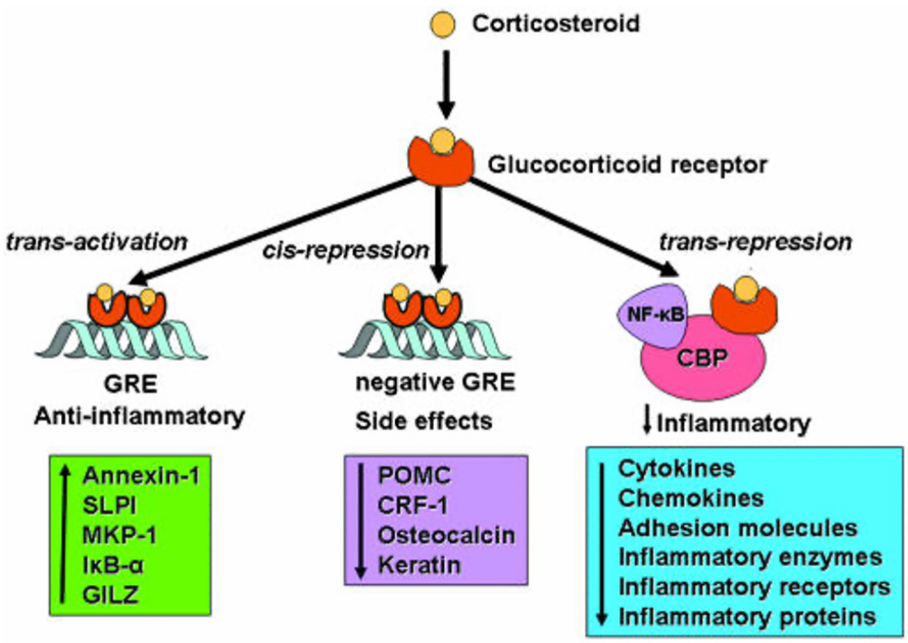

Fig. 1 GR/GRE binding mediates anti-inflammatory gene upregulation, pro-inflammatory gene suppression, and adverse effects [12]

It is worth noting that, other than directly inhibiting the formation of pro-inflammatory factors, glucocorticoids also exert immunosuppressive effects by regulating key microRNA molecules. Studies have confirmed that GCs can significantly regulate lower expression level of microRNA-21 (miR-21) in mouse and human T cells. Overexpression of miR-21 by human can significantly counteract the inhibitory effect of GCs. From the perspective of target gene regulation, the main function of miR-21 is to specifically inhibit the translation of the tumor suppressor protein PDCD4 (Programmed Cell Death Protein 4). Interestingly, study has demonstrated that PDCD4 promotes activation in T cells. Consequently, the miR-21 inhibition induced by GCs directly led to the accumulation of PDCD4 protein levels. Subsequently, through the PDCD4-mediated signaling pathway, it cooperatively suppressed the immune response of T cells [13]. This mechanism reveals a new pathway by which GCs finely control T cell functions. Expanding our understanding of GCs' immunosuppressive mechanism.

4. J Model Theory

To sum up, the most obvious manifestation of the relationship between exercise and immunity is the J-model theory proposed by Nieman [14]. At the molecular level, regular moderate-intensity exercise builds a strong immune defense system through multiple pathways, like the previous pathways that mentioned, including the MAPK pathway and the PI3K-Akt pathway.

However, prolonged and intense vigorous exercise or excessive training may push the body onto the descending branch on the right side of the J-shaped curve. At this point, intense physiological stress leads to persistently elevated stress hormones, for example, cortisol, the massive secretion of pro-inflammatory factors such as excessive IL-6, TNF-α, may trigger a local or systemic inflammatory response like a 'cytokine storm', accompanied by a

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decline in mucosal immune barrier function and impaired functions of key immune cells. Additionally, energy depletion, tissue micro-injuries, and oxidative stress accumulation jointly form a brief 'immune suppression window period', increasing susceptibility to pathogens.
Therefore, a profound understanding of the complex molecular network regulating immunity by exercise and its dynamic balance within the J-shaped curve framework not only reveals the exquisite regulatory mechanism of life activities, but also has crucial theoretical and practical significance for guiding individuals to formulate scientific and individualized exercise prescriptions, maximizing the immunological benefits of exercise for health, and avoiding potential immune risks brought by excessive exercise. Figure 2 demonstrates the relationship between URTI risks and intensity of exercise.

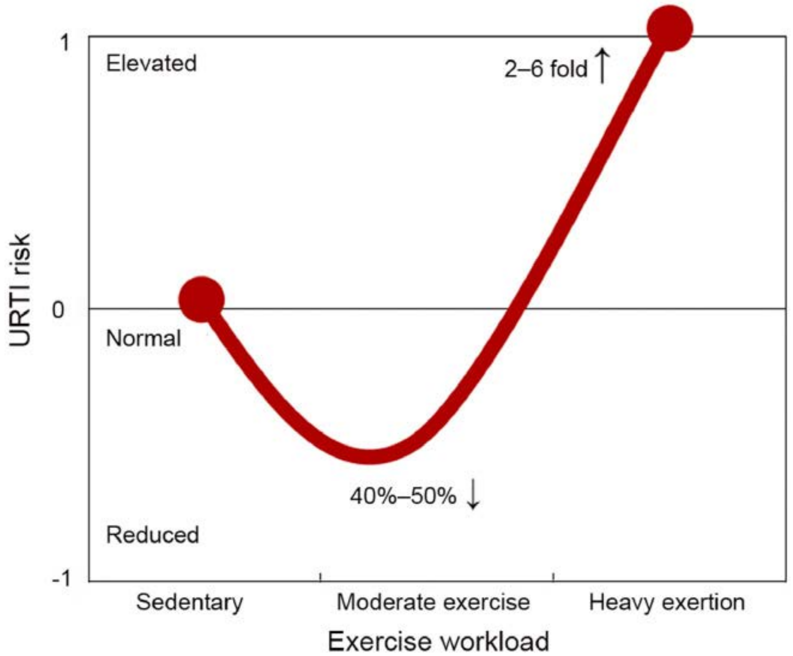

Fig. 2 J model of relationship between sport workload and disease incidence rate [6]

5. Conclusion

At present, the clear relationship between exercise and the immune system is still not established. For instance, what specific amount of exercise, the maximum oxygen uptake, lactate concentration, and heart rate range are needed to promote or inhibit the immune system. Moreover, based on the numerous existing blood test reports after athletes' training, the same maximum oxygen uptake intensity exercise may increase some immune molecules but simultaneously reduce the content of some other immune molecules. Therefore, whether exercise promotes or inhibits the immune system still requires continued doubt. Most of the experimental subjects are athletes or elite amateur sportspeople, so the effects of exercise on ordinary people cannot be fully referenced by the current experimental data and conclusions. The athlete's body is a precise biological machine that supplements different types of supplements and legal drugs, and all its actions are aimed at improving performance during competitions. Moreover, the exercise volume of athletes is almost at the physical limit level, and long-term such high-intensity exercise will inevitably lead to changes in the expression of related proteins, such as hemoglobin. However, most ordinary people exercise merely for health, to prevent excessive obesity, diabetes and other unhealthy diseases. For this reason, future research should focus more on the physiological conditions of ordinary people and clarify the relationship between exercise and the immune system.

Authors Contribution
All the authors contributed equally and their names were listed in alphabetical order.

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