Health, 2026, 18(8), 766-772
https://www.scirp.org/journal/health
ISSN Online: 1949-5005
ISSN Print: 1949-4998

Myokines, the Growing Basis for "Exercise Is Medicine"

Hans-Christian Heitkamp

Faculty of Natural Sciences, Institute for Sportmedicine, University of Paderborn, Paderborn, Germany
Email: hansh@mail.upb.de

How to cite this paper: Heitkamp, H.C. (2026) Myokines, the Growing Basis for "Exercise Is Medicine". *Health*, **18**, 766-772.
https://doi.org/10.4236/health.2026.188047

Received: June 2, 2026
Accepted: August 15, 2026
Published: August 18, 2026

Abstract

Background: Myokines are set free during physical activity from the working muscles. The investigated autocrine, paracrine and endocrine effects support the immune system, lipid and carbohydrate metabolism, brain function, and vascular health. **Methods:** This review summarizes the current evidence on the myokines Interleukin-6 (IL-6), Irisin, and brain-derived neurotrophic factor (BDNF). In addition, the literature was reviewed to identify further health benefits associated with physical activity. Two aspects of muscular activity were examined: the acute effects of a single bout of exercise and the effects of endurance training interventions on basal myokine concentrations. **Results:** A single bout of exercise leads to a rise in IL-6, Irisin and BDNF, varying with intensity and duration. Training results in lowering the basal concentration of Irisin and IL-6 and in elevating BDNF. Most research focused on healthy volunteers. Few results obtained in obesity, type 2 diabetes mellitus in neurologic and oncologic patients were reported according to the rising evidence. **Conclusion:** The presented research points towards preventive and rehabilitative applications of myokines in the future. More investigations are needed to specify the kind of exercise, intensity and duration for general prevention and for personalized therapy in rehabilitation.

Keywords

Muscles, Physical Activity, Prevention, Rehabilitation, Training

1. Background

Myokines belong to a group of peptides and other signaling molecules named exerkines. Exerkines are released from various organs during physical exercise. Since the first description in 2003, the number of identified myokines has increased rapidly to more than 600 [1] [2]. They play a central role in maintaining energy homeostasis during exercise, facilitate communication between muscles and the brain, liver, pancreas, adipose tissue, and bone, and exert beneficial effects on the endothelium [1]. According to estimates, only approximately 5% have been characterized in detail, and this paper focuses on the most investigated ones. Myokines comprise interleukins and other peptide signaling molecules that exert autocrine, paracrine, and endocrine functions [2] [3]. They are released during muscular contraction, whereas a lack of exercise leads to a deficit. As the expression of myokine receptors varies across tissues and can be up- or downregulated depending on physiological conditions [2], their biological actions are highly context-dependent. This means changes in concentration in serum or plasma should be interpreted to a limited extent. Nevertheless, reliable investigations are available for some myokines.

This narrative review summarizes current knowledge on the preventive and rehabilitative potential of myokines, with particular emphasis on the changes in concentrations after an acute bout of exercise and adaptations in basal concentrations induced by training.

IL-6 is considered an important, long-established marker of both acute and chronic inflammation. Its role as a muscle-derived signaling molecule was first identified through experiments demonstrating the transfer of a circulating factor from exercising animals to resting animals [2]. Released from contracting muscles, it exerts predominantly anti-inflammatory effects by suppressing the production of tumor necrosis factor α (TNF-α). In addition, IL-6 enhances insulin sensitivity [4] and interacts with carbohydrate metabolism with sensor properties for intramuscular glycogen reserves [5]. During long-term exercise with low initial glycogen reserves, a 100-fold increase was documented with increased glucose release from the liver and an insulin-like effect [6].

In human intervention studies, IL-6 also activates lipid metabolism with lipolysis and increased fat oxidation [1] [5]. Beyond its metabolic functions, infusions with recombinant IL-6 result in delayed gastric emptying [1]. The different cellular and metabolic actions are summarized in **Figure 1**.

Irisin, first analyzed in 2012, is characterized by a functional conversion of white adipose tissue into brown-like adipose tissue, a process referred to as "browning" [7]. This leads to thermogenesis and enhances lipid metabolism without physical activity, referred to as shivering-free heat production [8]. Besides regulating lipid metabolism, Irisin contributes to glucose homeostasis and promotes glucose uptake into the muscles [7]. Anti-inflammatory properties were documented; although evidence regarding its role in cancer remains inconsistent, Irisin appears to exert protective effects in most tumor types, with the possible exception of hepatocellular carcinoma [9]. In autocrine function, it activates satellite cells, builds muscle, and contributes to bone health [7] (**Figure 1**).

Irisin crosses the blood-brain barrier, enters the cerebrospinal fluid, and leads to the release of the brain-derived neurotrophic factor (BDNF) in the brain [1] [10]. BDNF improves memory, cognitive function, and neural plasticity [2] [9]. The myokine cathepsin B has likewise been shown to mediate the exercise-induced upregulation of BDNF in the brain [7] [10]. As a myokine, BDNF is also expressed in the muscles and leads to satellite cell activation and optimizes fat and carbohydrate metabolism [1]. Whether muscle-derived BDNF is released into the systemic circulation remains a matter of ongoing debate. Consequently, its biological effects are currently thought to be predominantly autocrine and paracrine rather than endocrine [4].

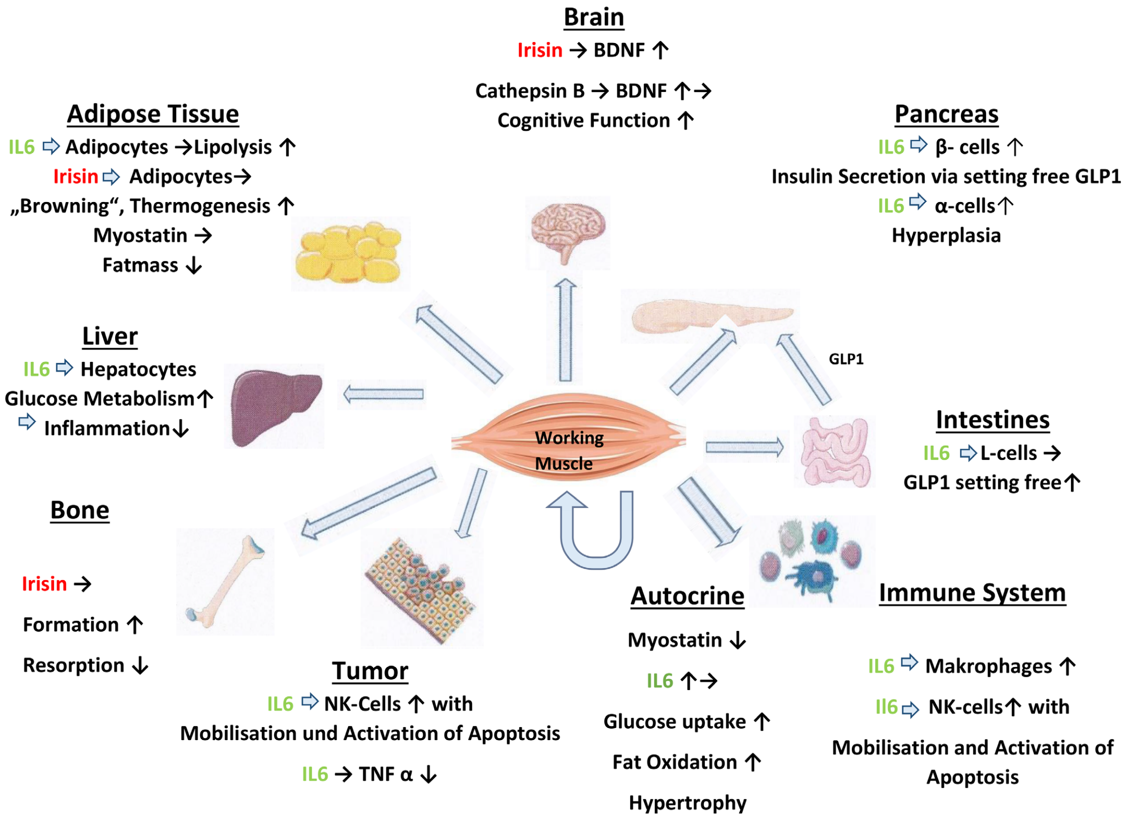

Figure 1. Postulated effects of myokines on organs, cells and metabolism. Arrows to the side indicate the direction of myokine influence. Perpendicular arrows upwards characterize a rise and downwards a slowing by the myokine influence. For clarification, IL-6 is marked green and Irisin red. IL-6: Interleukin 6; GLP1: Glucagon-like peptide 1; BDNF: Brain derived neurotrophic factor; TNF-*α*: Tumor necrosis factor α; NK cells: Natural killer cells (Modified and updated according to [3]).

Many types of muscular exercise exist, basically endurance and resistance exercise. From a preventive perspective, it is important to understand how myokine concentrations respond to a single bout of exercise of different modality, intensity and duration. Equally important is the duration of the change in baseline.

A second focus addresses the persistent change in baseline concentration induced by regular exercise training. As with the acute response to exercise, the influence of exercise modality, intensity, and duration on these long-term adaptations requires further investigation.

2. Myokine Response to a Single Bout of Exercise

Given the functions of myokines outlined above, understanding their response to acute exercise is of importance. Both the magnitude and duration of changes in circulating myokine concentrations are influenced by the type, intensity, and duration of the exercise performed.

IL-6 may increase by up to 85% following a single resistance training session, when large muscle groups are recruited or exercise is performed at high intensity. The response is more pronounced in trained individuals [4] [11] [12]. Prolonged endurance exercise, such as a single bout of activity like running a marathon, leads to an increase in IL-6 and a decrease in TNF-α, peaking after 1 - 2 hours and returning to baseline after 24 hours. The increase is less pronounced in trained individuals [2].

High-intensity endurance exercise such as cycling may lead to a 1.5-fold increase in BDNF [12]. According to several studies, trained individuals show a significant increase in BDNF after a single bout of exercise [12], while according to another study, it remains unchanged [2]. A review found a clear rise after one bout of high-intensity interval training (HIIT), but none after aerobic exercise [13]. Evidence regarding the acute BDNF response in older adults remains limited [13].

Irisin concentration generally increases only moderately immediately after a session of high-intensity interval training (HIIT), but rises exponentially with increasing duration of exercise during endurance exercise, remaining significant for up to 60 minutes [1] [14]. A study in adults older than 70 years demonstrated a clear increase in Irisin after intensive resistance exercise, after intensive endurance and after low-intensity endurance exercise comparable to those observed in younger adults [15]. The response to exercise is similar in trained and untrained individuals and is generally greater following aerobic than anaerobic exercise [16]. Depending on the exercise protocol, circulating Irisin concentrations return to baseline within 3-24 hours [14].

All increases in myokine concentrations are transient and influenced, at least in part, by training status. Consequently, long-term adaptations in basal myokine concentrations following regular exercise training are of particular interest.

3. Influence of Training

Of special interest for prevention and rehabilitation are the responses of myokines to training interventions such as resistance training, moderate endurance training and high intensity interval training (HIIT).

Both HIIT and endurance training, lead to a reduction in IL-6 [2], as more muscles are activated [4] and in myostatin after 8 weeks of resistance training [12]. BDNF increases following regular exercise training by an average of 50% in men and women, with a simultaneous increase in hippocampal volume [2] [12]. According to a recent review, it increases most effectively after resistance training [4]. Resistance training in older adults leads to an increase in BDNF and to a decrease in IL-6 and TNF-α, the results being clearer in extended investigations (over 20 weeks), more often per week and at intensities higher than 70% 1RM [17]. HIIT seems to be superior to resistance training [13].

Training of any kind appears to reduce the resting concentration of pro-inflammatory cytokines IL-6 and TNF-α [1] [2] [10]. Basal Irisin concentrations decline most effectively by HIIT, less so by resistance or aerobic endurance training [15]. These adaptations are thought to reflect the central role of Irisin in regulating metabolic responses to muscular activity rather than a diminished physiological function [8]. Inconsistent findings reported for Irisin are likely attributable to differences in study design, exercise modality, training intensity, and intervention duration [16].

Few reports exist on therapeutic exercise interventions, mainly in obesity, type 2 diabetes mellitus and some neurological diseases [1] [2] [10] [13] [17]-[19]. The exercise-induced release of IL-6 and Irisin contributes to reduction in visceral adipose tissue and suppression of TNF-α [1] [2] [11]. Most type 2 diabetes patients display low-grade inflammation. Therapeutic endurance training may lead to reduced inflammation status [2]. In oncology, accumulating evidence suggests that exercise may contribute to secondary prevention and improve rehabilitation outcomes [9].

Cognitive function is supported in type 2 diabetic patients when performing HIIT [18]. Comparing multimodal exercise, endurance exercise, mind-body exercise and resistance exercise training in type 2 diabetic patients, resistance exercise had no effect, while multimodal exercise was superior in studies lasting longer than three months, while mind-body exercise and endurance appeared to be more effective after short-term training [18].

Opposite to HIIT, aerobic training in patients suffering from depression induces an increase in BDNF and IL-6, correlating with an improvement of symptoms [19].

Limitations of the presented studies consist of small numbers and predominantly male and middle-aged participants, different types of exercise protocols and intervention duration, as well as different blood sampling procedures [3] [12] [14]. The small number of studies in chronic diseases so far limits training recommendations.

Future studies should adopt standardized training protocols with intervention periods of at least 12 weeks, incorporate a follow-up assessment to determine the duration of the baseline changes, and use standardized methods for blood sampling and analysis. Such improvements are essential for establishing evidence-based exercise recommendations. Randomized controlled studies in chronic disease would establish a firm base for rehabilitative training.

Looking ahead, therapeutic applications with recombinantly produced myokines are conceivable in the future, as already shown for IL-6 [1]. General and individualized sport therapy, especially in oncology during and after treatment, shows well-documented approaches for effective measures [1] [2] [18].

In conclusion, current evidence indicates that myokines form an important mechanistic link between physical activity and health, providing a biological basis for preventive and rehabilitative interventions. Beneficial persistent changes in myokine concentration and cross-talk with other organs appear to be most pronounced after long or high muscular activity. Although considerable progress has been made in elucidating the physiological functions of individual myokines, further research is needed before their therapeutic potential can be translated into routine clinical practice.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Bay, M.L. and Pedersen, B.K. (2020) Muscle-Organ Crosstalk: Focus on Immunometabolism. *Frontiers in Physiology*, **11**, Article ID: 567881. https://doi.org/10.3389/fphys.2020.567881

[2] Chow, L.S., Gerszten, R.E., Taylor, J.M., Pedersen, B.K., van Praag, H., Trappe, S., *et al.* (2022) Exerkines in Health, Resilience and Disease. *Nature Reviews Endocrinology*, **18**, 273-289. https://doi.org/10.1038/s41574-022-00641-2

[3] Heitkamp, H.C. (2023) Paracrine and Endocrine Function of Muscles. *MMW-Fortschritte der Medizin*, **165**, 13-19. https://doi.org/10.1007/s15006-023-2493-z

[4] Zunner, B.E.M., Wachsmuth, N.B., Eckstein, M.L., Scherl, L., Schierbauer, J.R., Haupt, S., *et al.* (2022) Myokines and Resistance Training: A Narrative Review. *International Journal of Molecular Sciences*, **23**, Article No. 3501. https://doi.org/10.3390/ijms23073501

[5] Kistner, T.M., Pedersen, B.K. and Lieberman, D.E. (2022) Interleukin 6 as an Energy Allocator in Muscle Tissue. *Nature Metabolism*, **4**, 170-179. https://doi.org/10.1038/s42255-022-00538-4

[6] Joisten, N., Kummerhoff, F., Koliamitra, C., Schenk, A., Walzik, D., Hardt, L., *et al.* (2020) Exercise and the Kynurenine Pathway: Current State of Knowledge and Results from a Randomized Cross-Over Study Comparing Acute Effects of Endurance and Resistance Training. *Exercise Immunology Review*, **26**, 24-42.

[7] Waseem, R., Shamsi, A., Mohammad, T., Hassan, M.I., Kazim, S.N., Chaudhary, A.A., *et al.* (2022) FNDC5/Irisin: Physiology and Pathophysiology. *Molecules*, **27**, Article No. 1118. https://doi.org/10.3390/molecules27031118

[8] Ma, C., Ding, H., Deng, Y., Liu, H., Xiong, X. and Yang, Y. (2021) Irisin: A New Code Uncover the Relationship of Skeletal Muscle and Cardiovascular Health during Exercise. *Frontiers in Physiology*, **12**, Article ID: 620608. https://doi.org/10.3389/fphys.2021.620608

[9] Mo, L., Zeng, X., Liu, Y., Zhang, J., Liu, L., Zhang, Y., *et al.* (2025) Irisin's Dual Role in Malignant Tumors and Its Potential as a Biomarker and Therapeutic Target. *Drug Design, Development and Therapy*, **19**, 7185-7205. https://doi.org/10.2147/dddt.s532658

[10] Pedersen, B.K. (2019) Physical Activity and Muscle-Brain Crosstalk. *Nature Reviews Endocrinology*, **15**, 383-392. https://doi.org/10.1038/s41574-019-0174-x

[11] Ringleb, M., Javelle, F., Haunhorst, S., Bloch, W., Fennen, L., Baumgart, S., *et al.* (2024) Beyond Muscles: Investigating Immunoregulatory Myokines in Acute Resistance Exercise—A Systematic Review and Meta-Analysis. *The FASEB Journal*, **38**, e23596. https://doi.org/10.1096/fj.202301619r

[12] Domin, R., Dadej, D., Pytka, M., Zybek-Kocik, A., Ruchała, M. and Guzik, P. (2021)

Effect of Various Exercise Regimens on Selected Exercise-Induced Cytokines in Healthy People. *International Journal of Environmental Research and Public Health*, **18**, Article No. 1261. https://doi.org/10.3390/ijerph18031261

[13] Jost, Z., Rozynkowska, A., Głąb, M., Sitkiewicz, A., Goiko, M., Laskowski, R., *et al.* (2026) Acute and Chronic Effects of High-Intensity Interval Training on Selected Exerkine Secretion in Health, Disease, and Aging: A Systematic Review. *Frontiers in Physiology*, **16**, Article ID: 1733269. https://doi.org/10.3389/fphys.2025.1733269

[14] Bettariga, F., Taaffe, D.R., Galvão, D.A., Lopez, P., Bishop, C., Markarian, A.M., *et al.* (2024) Exercise Training Mode Effects on Myokine Expression in Healthy Adults: A Systematic Review with Meta-analysis. *Journal of Sport and Health Science*, **13**, 764-779. https://doi.org/10.1016/j.jshs.2024.04.005

[15] Newman, J.E., King, I., Flemming, N., Broadhouse, K.M., Buhmann, R., Rose, G.L., *et al.* (2025) The Acute Response of Irisin to Resistance and Endurance Exercise at Both Lower and Higher Intensities in Healthy Older Adults. *Experimental Gerontology*, **209**, Article ID: 112850. https://doi.org/10.1016/j.exger.2025.112850

[16] Kazeminasab, F., Sadeghi, E. and Afshari-Safavi, A. (2022) Comparative Impact of Various Exercises on Circulating Irisin in Healthy Subjects: A Systematic Review and Network Meta-Analysis. *Oxidative Medicine and Cellular Longevity*, **2022**, Article ID: 8235809. https://doi.org/10.1155/2022/8235809

[17] Qipo, O., Gajauskaitė, G., Vints, W.A.J., Levin, O., Masiulis, N. and Bautmans, I. (2026) Dose-Response Relationship of Resistance Training and the Effects on Circulating Biomarkers of Inflammation or Neuroplasticity in Older Adults: A Systematic Review and Meta-Analysis. *Ageing Research Reviews*, **113**, Article ID: 102917. https://doi.org/10.1016/j.arr.2025.102917

[18] Gao, M., Sun, Z., Mao, D., Shang, Q. and Tian, X. (2026) The Effect of Different Exercise Interventions on Global Cognitive Function in Patients with Type 2 Diabetes: A Systematic Review and Network Meta-Analysis. *BMC Public Health*, **26**, Article No. 559. https://doi.org/10.1186/s12889-026-26256-0

[19] da Cunha, L.L., Feter, N., Alt, R. and Rombaldi, A.J. (2023) Effects of Exercise Training on Inflammatory, Neurotrophic and Immunological Markers and Neurotransmitters in People with Depression: A Systematic Review and Meta-Analysis. *Journal of Affective Disorders*, **326**, 73-82. https://doi.org/10.1016/j.jad.2023.01.086