Myokines relevance in exercise adaptations. A world still to be discovered

La importancia de las miokinas en las adaptaciones al ejercicio físico. Un mundo todavía por descubrir

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Nowadays, the beneficial effects of regular exercise are well-known, in fact, its effectiveness has been proved in at least 26 different pathologies[1]. However, little is known regarding the biomolecular and neuroendocrine mechanisms responsible for these effects.

In this regard, exercise has shown to trigger a cross-talk communication network that produces the activation and inhibition of different processes in several cell types facilitating, at least partially, the dissemination of the positive effects caused by exercise. The presence of this communication network can be observed in Catoire *et al.*[2] study, where 21 male adults (44-56 yr) performed 1h of cycling at 50% W_{max} with one leg, while the other leg remained in resting state. Muscle biopsies were taken from vastus lateralis of both legs before and after the exercise session revealing significant changes not only in the genetic expression of the exercised leg (938 genes) but also in the non-exercise leg (516 genes). The fact that some of these post-exercise genetic alterations were similar in the exercised and non-exercise legs, especially those changes related to the peroxisome proliferator-activated receptors (PPAR), reinforced the existence and relevance of circulating factors able to connect different tissues regulating the metabolic adaptations to exercise[2].

In humans, skeletal muscle has a critical role in the communication network established by these circulating factors among organs and tissues in response to exercise[3-5]. Skeletal muscle has a great adaptation ability that allows answering to any metabolic requirement stimulated by any previous locomotor stress. In fact, the locomotor stress caused or, in other words, the exercise dose performed dictates the adaptations that this tissue. Accomplishes in this context, a group of biomolecules called myokines have shown to promote a muscle-to-organ cross-talk communication[3,6].

Although the study of myokines is still a novel research topic, the existence of *exercise factors* with endocrine effects was proposed decades ago. In 1961, in an editorial from the journal Diabetes, Goldstein[7] speculated about the presence of what he called *'humoral factors'* or *'exercise factors'* released from the exercised muscles with the ability to mediate in glycaemia control, independently of insulin effects. Despite Goldstein's hypothesis[7] was not entirely correct, since glycaemia is not controlled by a single factor, the potential role of skeletal muscle as an endocrine tissue capable of producing and releasing exercise factors that regulate the metabolic adaptations to exercise remained untested. This idea persisted in latent state until last decade when Pedersen *et al.*[3] restarted the search for exercise factors focused on interleukin(IL)-6. The later confirmation of IL-6 as an exercise factor allowed to reinforce the idea of skeletal muscle as an endocrine tissue[3,6,8,9], as well as to delineate the term myokine to encompass all cytokines and peptides that are expressed, produced or released from skeletal muscle in response to repeated contractions exerting endocrine, paracrine or autocrine effects in other tissues and organs[3,6].

In the years after the elegant work performed by Pedersen *et al.*[3,6,8,9] several other myokines were discovered and categorized. The main muscle-to-organ cross-talk communication and functions that some of these myokines perform in response to exercise are presented below.

Glucose metabolism:

- *Muscle – Muscle.* IL-6 and IL-15 stimulate glucose uptake and oxidation via GLUT4 upregulation and translocation. Moreover, IL-13 has been related to glycogen production and oxidation, while fibroblast growth factor 21 (FGF-21) improves insulin sensitivity.
- *Muscle – Liver.* FGF-21 and IL-6 promote gluconeogenesis in the liver, while IL-6 and IL-15 regulate glucose production.

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- *Muscle – Pancreas.* IL-6 stimulates beta cells proliferation and preservation, while the chemokine (C-X3-C motif) ligand 1 (CX3CL1) has revealed to promote protective effects on pancreatic islets. Also, apelin activates insulin production in this organ.

  Lipid metabolism:
- *Muscle – Muscle.* Brain-derived neurotrophic factor (BDNF), IL-6 and IL-15 seem to increase lipolysis, while the alpha receptor of IL-15 (IL-15Rα) mediates in the energy substrate utilization by the mitochondria.
- *Muscle – Adipose tissue.* Irisin, apelin and IL-15 increase lipolysis, while irisin and IL-15 have anti-adipogenic effects. Besides, irisin and FGF-21 promote the browning of white adipocytes, and Nicotinamide N-methyltransferase (NNMT) facilitates fatty acid mobilization under low energy circumstances.
- *Muscle – Liver.* FGF-21 reduces the accumulation and increases the oxidation of fatty acid on this organ. Similar to adipose tissue, NNMT mobilizes fatty acid when energy availability is low.

  Bone metabolism:
- *Muscle – Bone.* The osteogenesis is stimulated by an increased osteoblasts activity promoted by irisin and IL-15Rα, as well as for a periosteum activation caused by leukemia inhibitory factor (LIF).

  Anabolic/catabolic balance:
- *Muscle – Muscle.* IL-6 and decorin have been associated with different hypertrophy pathways. Similarly, follistatin-related protein 1 (FSTL1) promotes the increase and maintenance of skeletal muscle mass by antagonizing myostatin effects. Lastly, IL-15 and IL-15Rα have anti-atrophic effects, especially in the presence of immune or metabolic diseases.

  Circulatory system:
- *Muscle – Endothelium.* Angiopoietin-like 4 (ANGPTL4), IL-8, IL-15 and FSTL1 activate angiogenesis in response to exercise, also facilitating endothelium preservation processes.

  Immune system:
- *Muscle – Immune cells.* IL-6, CX3CL1, chitinase-3-like protein 1 (CHI3L1) and, probably, FSTL1 and IL-15 promote anti-inflammatory effect when they are acutely produced in response to exercise. Although it has been suggested that these myokines mediate the metabolism of immune cells, mainly in lymphocytes B and T, the muscle-to-immune cells cross-talk communication remained to be elucidated.

In addition to the myokines mentioned above, there are ~3000 uncategorized myokines[10,11]. This reveals the vast potential of these biomolecules to establish a complex communication network which might be essential to facilitate the metabolic adaptations to exercise. Thus, the practical applications of the communication network formed by the myokines should not be limited to sports performance, as it is also relevant in some immune and metabolic pathologies. Nevertheless, most of the myokines have not been adequately characterized as a consequence of the tedious and complicated process required to complete this task, which is briefly described below[5]. Initially, the skeletal muscle origin of the target myokine needs to be confirmed via transcriptomic and proteomic; however, it should be taken into account that the genetic (mRNA) and protein expressions of myokines could not match, and that it remains unknown the stimuli that cause the expression of most myokines and the time-point in which these molecules are produced on this tissue. Subsequently, after skeletal muscle confirmation as the released tissue of the target myokine into the circulation, the post-exercise circulating expression should be analysed through the artery-venous difference. Finally, when skeletal muscle expression, production and release of a myokine have been characterized, the next step should be to determine those functions that the target myokine can exert in the different cell types able to uptake it from the circulation. In this regard, animal studies are indispensable to understand how the inhibition of a myokine can affect cell metabolism, although, human studies are also needed to support the functions of each myokine discovered in animal studies.

Unfortunately, in some cases, this process has not been followed and thus myokines research has reported some limitations. For instance, the identification of some myokines has been carried out only in non-exercise muscle tissue; consequently, the possibility of false negatives and the existence of undiscovered exercise factor cannot be avoided. Moreover, there are scarce of studies performed in human which support the existence and functions of some myokines described from *in vivo* and *ex vivo* studies in animals. Besides, in humans, some studies have reported a limited increase in skeletal muscle and circulating expression of some myokines in response to exercise; however, despite potential detection issues (e.g. time-point selection or antibodies efficacy), even low increased of these exercise factors might have an endocrine or auto-paracrine effect in response to exercise. Adding a higher level of complexity, some cytokines and peptides have reported exerting a dual function, sometimes antagonistic, depending on the tissue and stimuli that promote their expression. An example of that idea is IL-15[12] which stimulates pro-inflammatory effects when it is produced by T cells and remains chronically elevated in blood; while, in contrast, this cytokine promotes beneficial effect in several tissues when is released acutely and temporally by skeletal muscle in response to exercise.

Summarizing, myokines are capable of establishing a muscle-to-organ cross-talk communication network that facilitates exercise adaptations. Myokines are a hot topic that brings different research disciplines together given their unlimited implication in sports performance but especially as molecular targets in the prevention and treatment of some immune and metabolic diseases. Therefore, although myokines will possibly be a recurrent topic in the future, myokines' world is still to be discovered and given its potential repercussion to health and performance, rigorous studies are required to puzzle out the real implication of the communication network established by the myokines in the metabolic adaptations to exercise.

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