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Case Report

Dynamic Organization of Il-6 Signaling During Exercise: A Three-Level Framework

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Abstract

Interleukin-6 (IL-6), secreted by skeletal muscle during exercise, is considered an important myokine involved in interorgan metabolic communication. Despite a substantial body of experimental evidence, its physiological role remains a subject of debate. On the one hand, exogenous IL-6 reproduces several metabolic effects of exercise; on the other hand, the persistence of these effects following genetic or pharmacological blockade of IL-6 indicates that it is not an obligatory mediator of adaptation. This highlights the need for a new interpretation of its physiological role.

In this review, the actions of IL-6 are considered as a three-level regulatory system comprising cytokine production, receptor signaling, and clearance. The key integrative parameter is IL-6 signal exposure — the cumulative effect of the cytokine on target cells over time, determined by the interaction of these three regulatory levels. IL-6 production exhibits a biphasic organization, including rapid vesicular release and transcription-dependent synthesis; signaling is determined by the balance between classical and trans-signaling pathways, whereas clearance is mediated by hepatic uptake and receptor-mediated internalization. The proposed approach provides a framework for interpreting discrepancies among experimental findings and defines directions for future research, including quantitative assessment of the contribution of each of the three regulatory levels to IL-6 signal exposure.

Introduction

Interleukin-6 (IL-6) is one of the most extensively studied signaling molecules involved in the regulation of the systemic response to exercise. According to classical concepts, IL-6 is considered a pro-inflammatory cytokine; however, during exercise, it exhibits predominantly metabolic and anti-inflammatory effects, acting as a myokine involved in the regulation of interorgan metabolic interactions and energy metabolism [1–6].

An important feature of IL-6 during exercise is its pronounced dynamic variability. Unlike most myokines, IL-6 is characterized by a high amplitude and rapid rate of change in concentration: its circulating levels can increase several-fold in response to exercise, with the magnitude of this increase depending on exercise intensity and duration. In addition, IL-6 participates in interorgan communication involving skeletal muscle, adipose tissue, the liver, and the immune system [3,6,7].

However, despite the substantial amount of accumulated data, a considerable gap remains between experimental observations and their systemic interpretation. In particular, the mechanisms regulating IL-6 secretion, the dependence of its dynamics on exercise parameters, and its contribution to the development of metabolic adaptations remain insufficiently understood. This limits the ability to unambiguously interpret the physiological role of IL-6

during exercise.

The available evidence suggests the existence of a multilevel regulatory system involving rapid IL-6 release mechanisms, transcription-dependent synthesis, specific features of receptor signaling, and cytokine clearance pathways. Therefore, IL-6 may be considered not as an obligatory mediator of metabolic adaptation, but rather as a context-dependent modulator that enhances and coordinates the activity of other signaling systems.

The aim of this review is to analyze the dynamic organization of the IL-6 signal during exercise and to develop a conceptual framework integrating three interconnected levels of its regulation: production, receptor signaling, and clearance.

Within this framework, IL-6 signal exposure is proposed as an integrative parameter reflecting the duration and intensity of cytokine action on target cells (Fig.1). This approach allows a shift from the analysis of static IL-6 concentrations toward the assessment of its integrated signaling impact and provides an analytical framework for interpreting experimental data.

Methods

This study is a narrative review addressing the three-level regulatory system of interleukin-6 (IL-6) action during physical exercise, including skeletal muscle cytokine production, receptor-mediated signaling, and cytokine clearance. To ensure comprehensiveness and transparency, a literature search was conducted in PubMed, Scopus, and Web of Science databases covering the period from January 1996 to May 2025.

The search strategy included the following keywords: “interleukin-6”, “IL-6”, “myokine”, “skeletal muscle”, “exercise”, “cytokine production”, “receptor signaling”, “trans-signaling”, “ADAM17”, “sgp130”, “sIL-6R”, “cytokine clearance”, “metabolic adaptation”, and “inter-organ crosstalk”.

Inclusion criteria were: (1) original experimental studies addressing mechanisms of IL-6 production in skeletal muscle in response to physical exercise; (2) studies describing the molecular basis of classical and

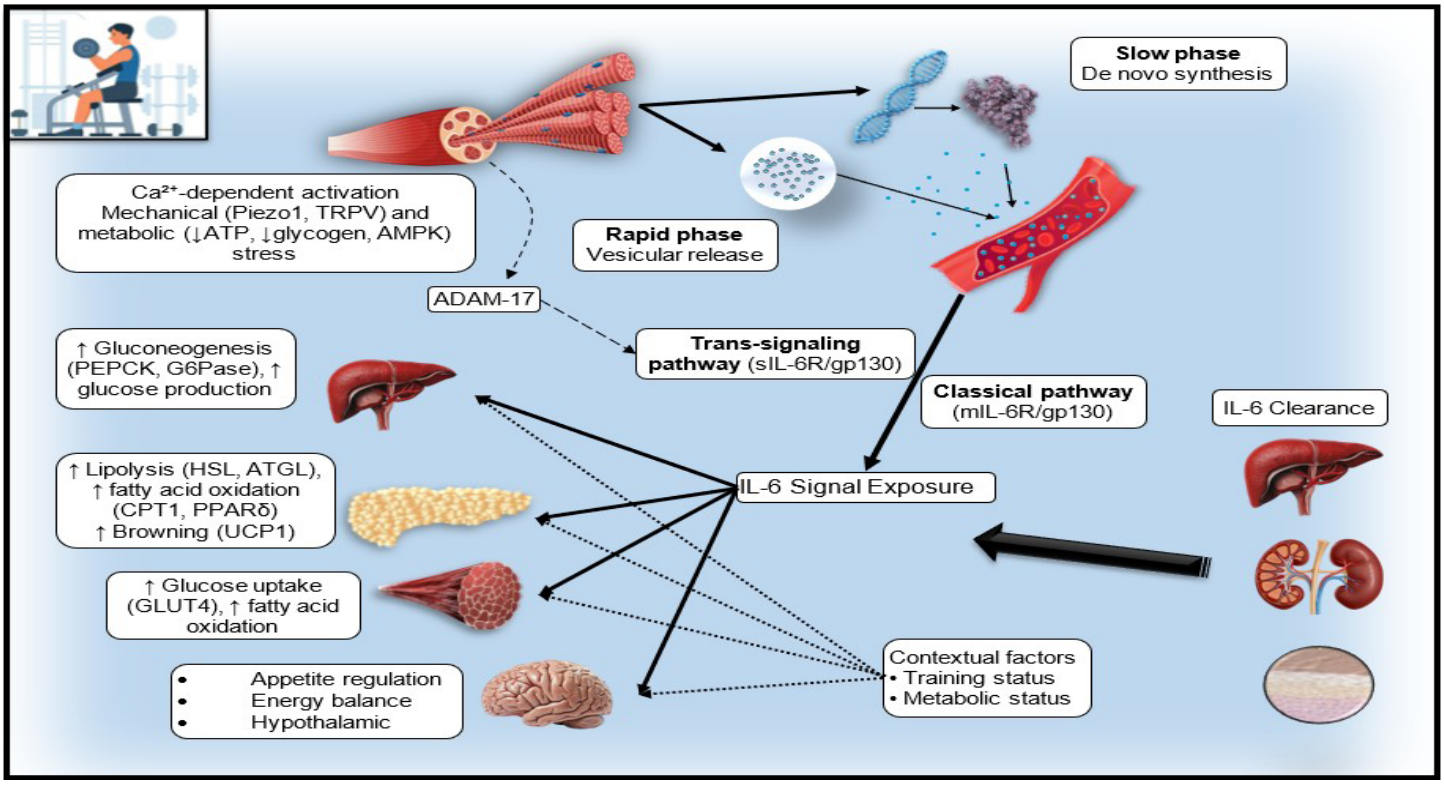

Figure 1: *Three-level regulatory system of IL-6 action during physical exercise*

Notes*: IL-6 — interleukin-6; mIL-6R — membrane-bound IL-6 receptor; sIL-6R — soluble IL-6 receptor; gp130 — glycoprotein 130; sgp130 — soluble form of gp130; ADAM17 — A Disintegrin and Metalloproteinase 17; GLUT4 — Glucose Transporter Type 4; HSL — Hormone-Sensitive Lipase; UCP1 — Uncoupling Protein 1.*

IL-6 production by skeletal muscle, receptor-mediated signaling, and cytokine clearance constitute three interconnected levels regulating IL-6 action during physical exercise. Their interaction determines IL-6 signal exposure — the integrated time-dependent effect of the cytokine on target cells. IL-6 signal exposure defines the potential contribution of the cytokine to the regulation of metabolic processes in skeletal muscle, liver, and adipose tissue and depends on contextual factors, including exercise intensity and duration, training status, and metabolic state of the organism.

trans-signaling pathways of IL-6; (3) investigations of IL-6 clearance and the role of soluble receptors (sIL-6R, sgp130) in limiting its bioavailability; (4) publications analyzing systemic metabolic and immunoregulatory effects of IL-6 during physical exercise; and (5) reviews summarizing the role of IL-6 as a myokine in inter-organ communication.

Results

IL-6 production by skeletal muscle during physical exercise

The first level of regulation of IL-6 biological action—skeletal muscle cytokine production—determines the amount and temporal dynamics with which IL-6 is released into the circulation in response to physical exercise (Fig.1). The role of IL-6 as a myokine during exercise is one of the most actively studied topics in contemporary physiology. Despite a substantial body of accumulated evidence, there is no unified understanding of the mechanisms regulating its production in skeletal muscle during physical activity. IL-6 regulation during exercise can be considered as a two-level process, comprising:

- Slow mechanisms associated with transcription and protein synthesis;
- Rapid mechanisms of secretion from intracellular stores.

These levels differ in their temporal dynamics, molecular mechanisms, and physiological roles, and are considered separately below.

Slow mechanisms: transcription and synthesis

A key role in IL-6 production is played by calcium-binding proteins such as calmodulin and calcineurin, inhibition of which leads to reduced IL-6 secretion. Classical studies by Pedersen and Febbraio (2012) demonstrated that increased cytosolic calcium activates calcineurin, thereby promoting mRNA expression and IL-6 production [7]. Experimentally, this is supported by findings that ionomycin (a calcium ionophore) dose-dependently increases IL-6 mRNA expression, whereas the calcineurin inhibitor cyclosporin A markedly suppresses this effect [8,9].

At the molecular level, calcium-dependent activation of IL-6 expression via calcineurin can be described as being mediated through the transcription factor MEF-2. Elevated intracellular Ca^{2+} activates calcineurin, which, through dephosphorylation of MEF-2, promotes transcriptional activation of the IL-6 gene [7,10].

Additional context-dependent mechanisms of IL-6 gene regulation have been described in the literature, although with more limited experimental validation under physiological exercise conditions. These include hypoxia-induced regulation involving HIF-1α. HIF-1α can translocate to the nucleus and interact with promoter regions of the IL-6 gene, thereby stimulating its transcription [11]. However, this mechanism has primarily been characterized in vitro and under conditions of pronounced hypoxia, and is likely to play a secondary role in exercise physiology.

Another line of research concerns metabolically dependent regulation associated with glycogen depletion in working muscle. According to classical concepts, depletion of glycogen stores is associated with altered cellular energy status and activation of stress-responsive signaling pathways, including p38 MAPK [12,13].

However, this pathway lacks specificity with respect to IL-6 regulation. Overall, it likely reflects a generalized cellular response to energy deficiency rather than a direct mechanism for initiating IL-6 secretion. Accordingly, the causal relationship between glycogen levels and IL-6 production remains controversial.

It should be noted that transcriptional mechanisms are constrained by a temporal delay required for mRNA and protein synthesis and cannot fully account for the rapid increase in circulating IL-6 observed at the onset of exercise. This suggests the existence of an independent mechanism involving the release of a pre-existing intracellular protein pool, which is addressed in the following section.

Rapid mechanisms: Secretion from intracellular vesicles

In contrast to transcription-dependent processes, the rapid increase in IL-6 concentration at the onset of muscle activity cannot be fully explained by de novo synthesis. This has led to the proposal of a vesicular model, in which a preformed intracellular pool of IL-6 is available for rapid release upon muscle contraction.

This hypothesis was supported by the study of H.P. Lauritzen et al. (2013) [14], which used live-cell imaging approaches to identify IL-6-positive vesicles in muscle fibers. The authors showed that the number of these vesicles decreases significantly during electrically induced contractions, even in the absence of AMPKα2, indicating the existence of an AMPK-independent, contraction-dependent exocytotic mechanism.

A potential trigger for this exocytosis may involve mechanosensitive ion channels (Piezo1, TRPV), which generate localized Ca^{2+} signals coupled to vesicle release [15,16]. Supporting this, M. Sciancalepore et al. (2022) demonstrated that pharmacological activation of Piezo1 stimulates IL-6 release from cultured myotubes [15]. However, this mechanism remains hypothetical under physiological exercise conditions in humans.

Energy stress associated with muscle contraction may further modulate IL-6 release from intracellular vesicles. Under such conditions, AMP-activated protein kinase

(AMPK), a key cellular energy sensor, is activated. AMPK is thought to coordinate metabolic responses during exercise and may modulate signaling pathways involved in IL-6 production [17,18]. However, the specific molecular links between AMPK activation and IL-6 exocytosis remain insufficiently characterized.

Neurohumoral factors may also contribute to the regulation of IL-6 secretion from intracellular stores. Circulating adrenaline, acting via β_2-adrenergic receptors on muscle fibers, activates the adenylyl cyclase cascade and increases intracellular cAMP levels. Infusion of β-agonists induces a dose-dependent increase in circulating IL-6 even at rest [19,20], indicating that this pathway is independent of contractile activity per se. This mechanism is not muscle-specific; its most likely physiological role is to "prime" the secretory response at the onset of exercise and to amplify IL-6 release during systemic stress conditions.

Lactate has also been proposed as a potential co-activator of rapid IL-6 secretion; however, its mechanism of action remains complex and partially hypothetical. Hojman et al. (2019) demonstrated that lactate administration (in combination with hyaluronidase) in mice can induce rapid IL-6 release from intracellular vesicles [21]. The proposed mechanism involves pH-dependent activation of proteases (including MMP2/9), which may contribute to vesicular trafficking remodeling. However, under physiological exercise conditions in humans, the degree of local acidosis is likely insufficient to fully activate this cascade, suggesting that this pathway acts as a context-dependent enhancer of IL-6 secretion rather than a primary mechanism.

Thus, IL-6 production by skeletal muscle during physical exercise operates as a biphasic regulatory system. The slow phase involves transcriptional mechanisms associated with calcium signaling, cellular energy status, and hypoxia-related pathways, and supports sustained cytokine production during prolonged exercise. The rapid phase is mediated by the release of a preformed intracellular IL-6 pool in response to muscle contraction.

IL-6 signaling: Classical and trans-signaling pathways

The second level of regulation determines which specific biological response is elicited in target cells at a given circulating concentration of IL-6 (Fig.1). Following secretion by skeletal muscle fibers, the interaction of IL-6 with receptors on target cells represents a key step in the execution of its biological effects. Two major mechanisms of IL-6 signal transduction are recognized: the classical pathway mediated by the membrane-bound IL-6 receptor (mIL-6R), and trans-signaling mediated by the soluble form of the receptor (sIL-6R).

Classical signaling pathway (mIL-6R/gp130)

In the classical signaling pathway, signal transduction is initiated by the binding of IL-6 to the membrane-bound α-receptor (mIL-6R, also known as gp80 or CD126). The expression pattern of mIL-6R is restricted: the receptor is predominantly expressed on hepatocytes and specific immune cell populations, whereas its expression is substantially lower in adipose tissue and skeletal muscle [1-4]. The resulting IL-6/mIL-6R complex recruits and induces dimerization of the co-receptor gp130 [22,23]. Only in this configuration is the intracellular Janus kinase (JAK) cascade activated, followed by signaling through the STAT3 (signal transducer and activator of transcription 3) pathway. This mechanism is canonical and the best-characterized IL-6 signaling route.

The tissue-specific distribution of mIL-6R determines the physiological profile of the classical response: during physical exercise, it is predominantly associated with metabolic and anti-inflammatory effects [24]. Classical signaling is considered the primary mechanism underlying the physiological actions of IL-6 during muscle activity, whereas trans-signaling is more commonly linked to chronic inflammatory and metabolic disorders [25]. The balance between these pathways is likely dynamic and dependent on both the magnitude and duration of the IL-6 signal.

Trans-signaling (sIL-6R/ADAM17)

The second mode of IL-6 signaling—trans-signaling—is mediated by the soluble form of the receptor (sIL-6R). sIL-6R can be generated via alternative mRNA splicing of IL-6R, producing a truncated receptor lacking the transmembrane domain that is subsequently secreted into plasma. However, this mechanism accounts for only a minor fraction (<1%) of circulating sIL-6R [26].

The major source of sIL-6R in humans is proteolytic shedding of membrane-bound IL-6R mediated by the metalloprotease ADAM17 (A Disintegrin and Metalloproteinase 17), also known as TNF-α converting enzyme (TACE) [27,28]. ADAM17 is a transmembrane metalloprotease with more than 80 known substrates, including cytokines (e.g., TNF-α), receptors (IL-6R, TNFR), and adhesion molecules [28-30]. Although ADAM10 has also been implicated in IL-6R shedding, particularly under basal conditions or specific stimuli, ADAM17 represents the primary inducible "sheddase" for IL-6R in humans [29,31].

ADAM17 activity is regulated by multiple mechanisms, many of which are directly induced by muscle contraction. These include increases in intracellular Ca^{2+} concentration, activation of protein kinase C (PKC), and activation of stress-responsive kinases such as p38 MAPK [32,33]. Notably, these same pathways are also involved in the regulation of IL-6 secretion in skeletal muscle fibers.

These data suggest an important consideration: IL-6 production and soluble receptor generation represent parallel regulatory processes that are temporally coordinated by common upstream activators rather than being directly causally linked. Such parallel regulation allows muscle contraction to be viewed as a unified trigger that simultaneously generates both the signal (IL-6) and the conditions for its propagation (sIL-6R). As a result, a coordinated system may emerge in which local cytokine production is accompanied by parallel modulation of the mechanisms controlling its dissemination, including changes in the conditions that enable IL-6 trans-signaling.

Traditionally, the switch between classical and trans-signaling is viewed as a binary process; however, accumulating evidence supports a continuum-based organization [31,34,35]. Within this framework, ADAM17 should not be considered a simple "switch," but rather a quantitative regulator determining sIL-6R levels and thus the extent of trans-signaling. Because ADAM17 activation is kinetically coupled to exercise-related signaling pathways (Ca^{2+}, PKC, p38 MAPK), the relative contribution of each signaling mode may vary depending on exercise intensity and duration.

Kinetic regulation of IL-6 availability

Despite high circulating concentrations of soluble IL-6 receptor (sIL-6R; 25–75 ng/mL), which substantially exceed IL-6 levels itself (1–5 pg/mL at rest and up to 10–20 pg/mL during exercise), a significant fraction of IL-6 remains biologically active in circulation [1,36]. Theoretically, such an excess of receptor molecules would be expected to result in near-complete sequestration of IL-6 in IL-6/sIL-6R complexes.

However, experimental data indicate that a substantial proportion of IL-6 circulates in a free form, suggesting incomplete complex formation even under apparent receptor excess. One possible explanation lies in the kinetic constraints of the system. A key factor is the relatively low affinity of IL-6 for sIL-6R (Kd ~22 nM), which is substantially higher than previously assumed values [37]. Baran et al. (2018) demonstrated that even under IL-6 concentrations typical of inflammatory conditions, more than 95% of IL-6 molecules remain unbound [37]. Experimental evidence from Leggate et al. (2010) further shows that exercise-induced increases in IL-6 are not accompanied by proportional increases in IL-6/sIL-6R complexes, indicating kinetic limitations in complex formation under physiological conditions [26].

It can therefore be suggested that this low binding affinity, together with the short half-life of IL-6 (3–5 min), constitutes an important regulatory mechanism limiting spontaneous formation of IL-6/sIL-6R complexes. Under physiological conditions, this favors classical signaling, whereas trans-signaling becomes more prominent only under conditions of substantially elevated IL-6 concentrations. Thus, the biological availability of IL-6 is determined not only by the absolute concentrations of the cytokine and its receptors, but also by the kinetics of their interactions, making temporal signal exposure an important determinant of its physiological effects.

Beyond kinetic constraints, IL-6 signaling is further regulated by specialized intracellular and extracellular control mechanisms.

Regulation and restriction of IL-6 signaling

IL-6 signaling, particularly trans-signaling, requires tight regulation to prevent excessive cellular activation. Two key inhibitory systems are involved: the intracellular suppressor of cytokine signaling 3 (SOCS3) and the soluble gp130 (sgp130) protein. Together, these mechanisms limit excessive activation of gp130-dependent pathways.

SOCS3 binds components of the JAK/STAT cascade and inhibits their activity, thereby limiting the duration of IL-6 signaling. SOCS3 knockout mice exhibit prolonged gp130-dependent signaling, whereas complete SOCS3 deficiency results in embryonic lethality [38].

In contrast, extracellular regulation of IL-6 signaling is mediated by soluble gp130 (sgp130), which acts as a key systemic inhibitor of trans-signaling. sgp130 circulates in blood and interstitial fluids, where it selectively binds the IL-6/sIL-6R complex without affecting classical IL-6 signaling [39].

Binding of sgp130 to the IL-6/sIL-6R complex results in the formation of an inactive trimeric complex incapable of interacting with membrane-bound gp130 on target cells. In this way, sgp130 restricts the spread of IL-6 trans-signaling and prevents excessive cellular activation [39,40].

Disruption of this balance, characterized by relative sgp130 deficiency or excessive sIL-6R production, has been associated with chronic inflammatory conditions. Thus, IL-6 signaling is regulated by two complementary mechanisms: intracellular inhibition via SOCS3 and extracellular buffering via sgp130.

Overall, IL-6 represents a kinetically constrained signaling network in which cytokine bioavailability is determined not only by equilibrium concentrations of soluble receptors, but also by production rate, local interaction dynamics, and receptor signaling architecture. Under these conditions, classical and trans-signaling pathways mediate distinct biological effects, predominantly associated with metabolic and inflammatory responses, respectively. In addition, signal termination is reinforced by clearance mechanisms that

determine cytokine half-life and the duration of signaling responses.

IL-6 Clearance

The third level of regulation — clearance — determines the duration of IL-6 action and, consequently, the temporal window during which its signaling effects are realized (Fug.1). Physical exercise is accompanied by a pronounced but transient increase in circulating interleukin-6 (IL-6), driven primarily by skeletal muscle production. Despite a substantial elevation during exercise, IL-6 levels rapidly return to baseline after cessation of activity, indicating highly efficient clearance mechanisms. IL-6 clearance represents a multi-level process involving uptake and subsequent intracellular degradation. These levels differ in kinetics and relative contribution to the overall elimination profile.

The primary and best-characterized pathway of IL-6 elimination is receptor-mediated uptake followed by lysosomal degradation in target and immune cells. The saturability of this receptor-dependent mechanism is considered a key determinant of IL-6 clearance kinetics.

Organ clearance (liver and kidneys)

The liver plays a major role in the initial clearance of IL-6, accounting for the largest fraction of its rapid removal from the systemic circulation. Arteriovenous measurements demonstrate that IL-6 concentrations in the hepatic vein are lower than in arterial blood, indicating extraction during hepatic passage. This process is thought to be primarily mediated by receptor-dependent uptake of IL-6 by hepatocytes at their surface [41,42].

Further evidence for receptor-mediated uptake is provided by M.A. Febbraio et al. (2003) [41], who showed that labeled cytokine administered intravenously predominantly localizes to the surface of hepatic parenchymal cells. This indicates the presence of specific receptor-mediated mechanisms for IL-6 uptake by hepatocytes and highlights the liver not only as a target organ but also as a key regulator of systemic IL-6 availability [42].

The classical experiment by O. Sonne et al. (1990), using radiolabeled IL-6, further supports this view [43]. Importantly, administration of excess unlabeled IL-6 reduces hepatic uptake and abolishes the rapid clearance phase, indicating a saturable receptor-dependent process rather than passive diffusion or nonspecific binding. In the later phase of clearance, the label redistributes from the liver to peripheral tissues, including the skin, which likely reflects transport and excretion of IL-6 degradation products [44]. The physiological significance of this phase remains unclear.

Thus, the liver serves as a central organ of IL-6 clearance, with hepatocytes playing a leading role in receptor-mediated removal from circulation. Kupffer cells and sinusoidal endothelium, which possess high endocytic activity, may further contribute to cytokine uptake [45,46], enhancing the overall hepatic capacity for circulating cytokine elimination.

In addition to the liver, other organs participate in systemic IL-6 clearance, although their contribution is secondary and less well quantified. The kidneys may provide an additional pathway for IL-6 elimination [47]. However, direct receptor-mediated uptake mechanisms in the kidney remain insufficiently characterized. Based on general principles of protein handling, glomerular filtration followed by proximal tubular reabsorption and lysosomal degradation may represent the most likely renal pathway of IL-6 processing.

Cellular uptake and receptor-mediated internalization

In addition to organ-level clearance, an additional regulatory layer exists at the level of receptor-mediated IL-6 uptake by individual cells. Since internalization of the IL-6/IL-6R/gp130 complex is an essential step in signal transduction, it can be assumed that IL-6 bound to its receptor is also targeted for lysosomal degradation together with gp130. This assumption is consistent with early work by L. Graeve et al. (1996), showing that IL-6/sIL-6R complexes are internalized by gp130-expressing cells, and that most internalized sIL-6R is degraded in lysosomes [48].

According to C.M. Flynn et al. (2021) [49], IL-6R and gp130 receptors are constitutively internalized in a ligand-independent manner. This process depends on dynamin and clathrin and is regulated by specific motifs within the cytoplasmic domains of both receptors. Therefore, receptor complex endocytosis may function not only as a mechanism of signal initiation but also as an additional pathway for cytokine clearance from the extracellular space. It likely plays a more prominent role in regulating local signaling effects, whereas systemic reduction of IL-6 concentration is primarily determined by organ-level clearance.

Collectively, these findings indicate that IL-6 clearance is not merely a passive elimination process but a regulated system functionally integrated with receptor signaling and biological activity.

Systemic Effects of IL-6

The mechanisms described above — IL-6 production, classical and trans-signaling, and clearance — collectively determine the tissue-specific nature of IL-6 action at the organismal level. Within this framework, IL-6 can be regarded as an integrative signal that coordinates redistribution of energy substrates and modulation of immune responses. Its effects are predominantly modulatory and are manifested as changes in the amplitude and duration of metabolic and

immune processes depending on the physiological context (Fig.1). These effects are mediated via activation of gp130-dependent intracellular cascades, including JAK/STAT3-dependent regulation of metabolic and immune gene expression in key target organs such as the liver, skeletal muscle, and adipose tissue.

Autocrine effects in skeletal muscle

The best-characterized IL-6 action is its autocrine effect associated with increased glucose uptake in skeletal muscle cells. AMPK is considered one of the key mediators of IL-6-induced enhancement of GLUT4 translocation via phosphorylation of TBC1D4 (AS160), although contributions of alternative pathways (PI3K-independent and CaMKII-dependent mechanisms) are also discussed in the literature. However, in this context AMPK acts not as a regulator of secretory processes, but as an effector of metabolic adaptation, reflecting its functional versatility. This leads to the accumulation of Rab proteins in their active GTP-bound state, which in turn promotes mobilization of GLUT4-containing vesicles, their trafficking along the cytoskeleton, and subsequent fusion with the plasma membrane [50,51].

Molecular studies are consistent with findings from human experiments. It has been shown that IL-6 infusion in healthy volunteers under hyperinsulinemic–euglycemic clamp conditions increases glucose disposal. This demonstrates the ability of IL-6 to enhance insulin-stimulated glucose uptake in humans [6,52]. However, current evidence indicates that the regulation of GLUT4 trafficking by IL-6 is a complex, multicomponent process. In addition to the AMPK-dependent pathway, alternative signaling mechanisms may also be involved. The contribution of each pathway appears to depend on the physiological context, including the intensity and duration of exercise, as well as the metabolic state of the organism [53,54].

It should be noted that such experiments often employ pharmacological concentrations of IL-6 that may substantially exceed physiological levels observed during exercise, which limits direct extrapolation to exercise conditions.

Metabolic effects in the liver

IL-6 exerts effects on hepatic metabolism primarily via the classical mIL-6R/gp130/JAK/STAT3 signaling pathway, stimulating transcription of key gluconeogenic enzymes, including PEPCK and G6Pase [52,55]. Administration of recombinant IL-6 at rest reproduces this effect, indicating relative independence from concomitant hormonal signals associated with physical exercise.

IL-6 may also play an important role in the development of stress-induced hyperglycemia by promoting the redistribution of energy substrates toward insulin-independent tissues, including the brain and working skeletal muscles [56]. At the same time, IL-6 can transiently reduce insulin sensitivity in adipose tissue and inactive muscle, thereby limiting glucose uptake in these tissues.

Beyond its direct effects on hepatocytes, IL-6 indirectly influences hepatic glucose production via stimulation of glucagon secretion from pancreatic α-cells and activation of the hypothalamic–pituitary–adrenal axis, leading to increased cortisol levels and enhanced gluconeogenesis and lipolysis [57,58].

The systemic coordinating role of IL-6 is not limited to the liver. Exercise-induced IL-6 released from contracting muscles can cross the blood–brain barrier and act on hypothalamic centers regulating energy balance, thereby modulating expression of neuropeptides that control appetite and energy expenditure [58,59]. These findings support the concept of IL-6 as a component of a “muscle–brain axis,” through which peripheral metabolic signals are integrated into central homeostatic regulation [60].

Thus, systemic effects of IL-6 arise from a combination of direct tissue-specific responses and indirect endocrine circuits operating across different temporal scales.

Lipid mobilization in adipose tissue

In parallel with its effects on hepatic metabolism, IL-6 acts on adipose tissue to promote mobilization of energy substrates. IL-6 stimulates key lipolytic enzymes — hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) — catalyzing triglyceride breakdown into free fatty acids (FFAs) and glycerol [61]. In addition to the direct action of IL-6, lipolysis is enhanced by β-adrenergic receptor activation induced by catecholamines [61,62]. Released FFAs enter the circulation and serve as an important energy substrate for working muscle, particularly during prolonged exercise [63].

It should be noted that exercise-induced IL-6 may contribute to the induction of browning of white adipose tissue. This process is associated with increased expression of uncoupling protein 1 (UCP1) and enhanced mitochondrial biogenesis, leading to increased thermogenesis and energy expenditure [54,64]. However, the role of IL-6 in this process remains controversial: some studies support IL-6-dependent induction of UCP1 [64,65], whereas others attribute a dominant role to other myokines, including irisin and meteorin-like protein, as well as fibroblast growth factor 21 (FGF21), whose levels increase during exercise and promote expression of oxidative metabolism-related genes [66].

In addition to lipid mobilization from adipose tissue,

IL-6 also influences fatty acid utilization in skeletal muscle by enhancing coordination between uptake and mitochondrial oxidation via upregulation of carnitine palmitoyltransferase 1 (CPT1), a key enzyme of β-oxidation [67,68]. A potential contribution of the PPARδ signaling pathway, which regulates expression of genes involved in lipid oxidation, has also been proposed [69].

Issues in data interpretation

Despite a substantial body of evidence describing molecular mechanisms of IL-6 action, its physiological role in metabolic regulation during exercise remains controversial. Experimental studies using different models (IL-6 knockout animals, pharmacological IL-6 receptor blockade in humans, and recombinant IL-6 administration) yield inconsistent results and do not allow a definitive conclusion regarding its role in the regulation of glucose and lipid metabolism [54,70].

First, studies in IL-6 knockout animals show that the absence of circulating IL-6 does not impair glycemic maintenance or reduce lipolysis during acute exercise. These effects may instead be maintained by compensatory mechanisms, including activation of the sympathoadrenal system and glucagon secretion [71].

Studies in IL-6 receptor knockout (IL-6R-KO) models show that disruption of IL-6 signaling does not affect diet-induced obesity, insulin sensitivity, or glycemic control. Moreover, exercise-induced metabolic benefits are preserved in IL-6R-deficient mice to a similar extent as in wild-type animals. In parallel, mice with enhanced trans-signaling (sIL-6R overexpression) also show no significant metabolic differences [72].

Second, IL-6 receptor blockade in humans using tocilizumab does not alter blood glucose or free fatty acid concentrations during a 3-hour cycle ergometer exercise test. However, a reduction in fat oxidation measured by indirect calorimetry has been observed, suggesting a more specific role of IL-6 in fatty acid utilization rather than mobilization [73].

Third, administration of recombinant IL-6 reproduces metabolic effects under resting conditions. However, during exercise, when catecholamines and other counter-regulatory hormones are already activated, the additional contribution of IL-6 may be limited. [74,75].

An additional factor is training status. Ellingsgaard et al. (2008) demonstrated that IL-6 blockade reduces hepatic glucose production in untrained individuals but has no significant effect in trained athletes, suggesting the development of adaptive mechanisms with regular physical activity, possibly involving alternative signaling pathways or other myokines [57].

Thus, the available evidence suggests that IL-6 is not an obligatory mediator of metabolic adaptation to exercise but rather functions as a context-dependent integrator that enhances the coordination and efficiency of interorgan metabolism under conditions of energetic stress.

Discussion

The findings discussed above suggest an interpretative challenge: although exogenous IL-6 is capable of reproducing key metabolic effects of exercise, these effects are largely preserved under genetic or pharmacological blockade of IL-6 signaling. This precludes interpreting IL-6 as a linear and essential mediator and necessitates an alternative analytical framework.

Within the proposed system, the key parameter is not the instantaneous concentration of IL-6, but its integrated signaling impact, reflecting the cumulative effect on target cells over time. This is determined not only by IL-6 levels, but also by its duration in circulation, clearance rate, and the state of receptor availability, including the ratio of membrane-bound to soluble receptors. Thus, the biological effect of IL-6 depends on the temporal structure of the signal and the tissue context in which it is interpreted.

It should be emphasized that this parameter has no direct standard experimental equivalent and is used as a conceptual construct describing the dependence of physiological responses on the temporal dynamics of IL-6 rather than on its instantaneous levels alone.

The proposed framework remains hypothetical and requires quantitative validation; however, it shifts the discussion of IL-6 from a question of its “importance” to an analysis of the conditions determining the nature and outcome of its action, thereby establishing a testable research agenda.

Conclusion

Thus, the available data support the view that the physiological role of IL-6 involves context-dependent modulation of the interorgan metabolic response, with the direction and magnitude of its effects being associated with the balance between rapid and slow phases of secretion, the relative contribution of classical and trans-signaling pathways, and the characteristics of cytokine clearance. This organization defines IL-6 as a dynamic and flexible signal rather than a single determining mediator of metabolic adaptations. Its role likely lies not in independently initiating metabolic adaptations, but rather in their context-dependent modulation and coordination with other regulatory systems. Further validation requires quantitative assessment of the contribution of each of the three regulatory levels under different exercise conditions

in humans, taking into account metabolic status.

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