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Short title: Regulation of skeletal muscle plasticity by PGC-1α / Regulation der Skelettmuskelzellplastizität durch PGC-1α

Keywords: skeletal muscle; exercise; metabolism; inflammation; PGC-1α / Skelettmuskel; Training; Metabolismus; Entzündung; PGC-1α

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Abstract

A sedentary lifestyle is a strong and independent risk factor for many chronic diseases. In most cases, inadequate levels of physical activity are linked to a persistent, sterile inflammation, both locally in various organs as well as systemically. Inversely, exercise is an efficient intervention for the prevention and treatment of various pathologies. Despite this obvious importance, the molecular mechanisms that underlie exercise-induced health benefits remain largely unclear. In recent years, the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) has emerged as a regulatory nexus of muscle adaptation to endurance exercise. Muscle PGC-1α not only promotes an oxidative, slow-twitch muscle fiber type, but also modulates the phenotype of non-muscle cells. For example, activation of epithelial cells contributes to PGC-1α-controlled muscle vascularization. Similarly, a muscle PGC-1α-dependent signaling results in a remodeling of the active zone of motor neurons at the neuromuscular junction. Intriguingly, PGC-1α also reduces pro-inflammatory gene expression in muscle and most likely other cell types. Thus, a bidirectional negative regulation of PGC-1α and the nuclear factor κB (NF-κB) might provide the molecular basis for the mutual antagonism between oxidative metabolism and inflammation in muscle. In this review, we summarize the regulation and function of these transcriptional regulators with a particular focus on exercise and inflammation in skeletal muscle.

Ein inaktiver Lebensstil ist ein starker und unabhängiger Risikofaktor für die Entstehung einer Reihe von chronischen Krankheiten. In vielen Fällen ist ungenügende Bewegung mit erhöhten Entzündungsmarkern verbunden, sowohl in einzelnen Organen wie auch systemisch im ganzen Körper. Umgekehrt entfaltet körperliche Aktivität und Training in der Prävention und Behandlung von verschiedenen Krankheiten eine grosse Wirkung. Trotz dieser klinisch relevanten Beobachtung sind die molekularen Vorgänge, die den therapeutischen Effekt von Training auslösen und kontrollieren, noch weitgehend unbekannt. In den letzten Jahren hat sich das Koaktivatorprotein PGC-1α (peroxisome proliferator-activated receptor γ coactivator 1α) als ein zentraler Regulator in der Anpassung des Skelettmuskels an Ausdauertraining herausgestellt. Neben der Förderung von oxidativen, langsam kontrahierenden Muskelfasern löst PGC-1α auch Änderungen in anderen Zelltypen aus. So wird zum Beispiel durch eine Aktivierung von Epithelzellen die Bildung von Blutgefässen im Muskel durch PGC-1α induziert. Weiter hat PGC-1α im Muskel einen Einfluss auf Motorneuronen, wenigstens lokal im Bereich der neuromuskulären Synapse. Interessanterweise kontrolliert PGC-1α im Muskel und wahrscheinlich auch in anderen Zelltypen anti-entzündliche Reaktionen. Eine gegenseitige funktionelle Unterdrückung der Aktivitäten von PGC-1α und NF-κB (nuclear factor κB) könnte so die molekulare Schnittstelle darstellen, die die reziproke Regulation von Metabolismus und Entzündung im Muskel bestimmt. In diesem Übersichtsartikel fassen wir die wichtigsten molekularen Aspekte dieser Regulation zusammen und stellen diese in den grösseren Zusammenhang von Training und Entzündung im Skelettmuskel.

Introduction

Obesity, hypertension, cardiac diseases and other chronic pathologies have reached epidemic proportions in Western societies and are rising world-wide (20). A first line of treatment for most chronic diseases includes lifestyle-based interventions such a smoking cessation, decreased salt intake, a balanced diet and exercise. Surprisingly, despite the potent effect of physical activity on the prevention and treatment of many of these pathologies that in some cases rivals that of prescribed drugs, our knowledge of the molecular mechanisms that underlie the beneficial adaptations induced by exercise or pathological events in skeletal muscle remains rudimentary.

The etiologies of most chronic diseases closely correlate with a persistent, low-grade, sterile inflammation (19). Importantly, besides a systemic elevation of pro-inflammatory cytokine levels, increased immune cell infiltration and activation is observed in various organs (24). Macrophage activation in white adipose tissue and thereby increased secretion of pro-inflammatory cytokines and similar events in other peripheral organs such as liver and skeletal muscle contribute to the development of peripheral insulin resistance and other disorders (24). Thus, reversing inflammatory processes by exercise might reduce the pathological consequences of chronic diseases (10).

The molecular systems that are responsible for regulating metabolism and inflammation have co-evolved and strongly influence each other in a negative manner (21). For example, in skeletal muscle, induction of a pro-inflammatory program by the nuclear factor κB (NF-κB), a master regulator of inflammatory gene transcription, results in a repression of oxidative capacity while at the same time promoting fiber atrophy and muscle wasting, at least when activated in a prolonged manner (8). A mechanistic understanding of the mutual regulation between muscle metabolism and inflammation is therefore of eminent importance for the development of novel pharmacological approaches for many chronic diseases.

Inflammation of muscle tissue in health and disease

Inflammatory processes are important for physiological muscle function, in particular for adaptation to exercise. Bouts of contraction are linked to fiber damage, which initiate a highly orchestrated activation of different cell types instrumental for normal repair and regeneration post-exercise (4). In regular muscle regeneration, resident granulocytes and leukocytes are rapidly activated in muscle beds with contraction-mediated fiber damage. These cells sense fiber damage and release chemokines to activate and attract additional immune cells (4,8). Moreover, the production and secretion of tumor necrosis factor α (TNFα), interleukin 6 (IL-6) and related cytokines establish a pro-inflammatory milieu. Subsequently, infiltrating macrophages complement the action of tissue-resident cells, and a classical, M1-type macrophage activation in this pro-inflammatory environment promotes debris removal. Later, the macrophage activation pattern shifts from the M1- to a M2-type in conjunction with the production of anti-inflammatory cytokines such as IL-10 and IL-4, indicating a transition from the clean-up to the repair and regeneration phase (31). In addition, activation of fibro/adipogenic progenitors (FAPs), pericytes, mesangioblasts, fibroblasts and epithelial cells contribute to muscle regeneration. Most importantly however, asymmetric proliferation and

differentiation of satellite cells, the resident, lineage-committed muscle stem cells, triggered by various signals is instrumental for fiber repair and de novo fiber generation (5).

Besides the importance of orchestrated inflammation in muscle regeneration and exercise adaptation, unchecked inflammatory reactions are associated with a number of skeletal muscle-related pathologies, most directly in inflammatory myopathies or cachexia (23). Then, inflammation is a major contributor to the pathology in various muscular dystrophies, including Duchenne muscular dystrophy, which are characterized by a sustained pro-inflammatory environment and dramatically increased fibrosis (23). Finally, a persistent, sterile inflammation in muscle accompanies a number of chronic diseases, such as type 2 diabetes (25). The exact steps leading to peripheral insulin resistance are still incompletely understood. In muscle, activation of the toll-like receptors 4 (TLR4) by excessively elevated levels of circulating fatty acids however initiates a signaling cascade involving NF-κB-mediated expression and secretion of TNFα, IL-1β and other pro-inflammatory cytokines and chemokines (11).

The peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) in skeletal muscle

Adaptation of skeletal muscle to physical activity is a complex biological program that entails a massive change in the transcription rates of numerous genes. The peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) has emerged as a potential regulatory nexus in the plastic changes of muscle fibers upon endurance exercise (27) (Fig. 1). PGC-1α integrates various signaling pathways that are activated in a contracting muscle fiber and result in increased transcription of the PPARGC1A gene (which encodes PGC-1α) and posttranslational modifications of the PGC-1α protein (15,28). As a transcriptional co-activator, PGC-1α subsequently interacts with numerous transcription factors in a temporally controlled manner to regulate a complex transcriptional program (3). In skeletal muscle, PGC-1α-controlled target gene expression collectively results in an endurance-trained muscle phenotype. Accordingly, transgenic overexpression of PGC-1α in mice leads to a contractile and metabolic shift towards oxidative, slow-twitch, high endurance muscle fibers (22). Importantly, activation of PGC-1α in skeletal muscle not only promotes most adaptations of muscle to endurance training, but also initiates changes in epithelial cells and hence tissue vascularization (1), the neuromuscular junction (2) and other non-muscle cell types (28).

Inversely, reduced muscle PGC-1α levels have been associated with increased insulin resistance in human patients, at least in certain populations (19). Likewise, skeletal muscle-specific ablation of the PPARGC1A gene results in abnormal glucose and insulin homeostases in mice (17). Moreover, these mice exhibit a switch towards glycolytic muscle fibers, impaired endurance capacity and activity-dependent fiber damage (16). Hence, in many aspects, muscle-specific PGC-1α knockout animals resemble pathological inactivity in humans (13). Elevation of PGC-1α in muscle improves various muscle diseases, for example Duchenne muscular dystrophy (18) or sarcopenia (32), and, at least in combination with physical activity, ameliorates systemic glucose homeostasis (29). Therefore, pharmacological targeting of proteins up- and downstream of PGC-1α is one of the main strategy in the design of so-called “exercise mimetics”, small molecules that should elicit exercise-like effects in skeletal muscle (7). However, the feasibility of obtaining true exercise mimetics is still hotly debated (6).

An anti-inflammatory action of exercise and PGC-1α

Physical activity is an efficient intervention to reduce the pathological, chronic, persistent inflammation observed in many patients (12) even though exercise and inflammation are linked in a complex manner (10) (Fig. 2). For example, extreme performance results in a massive inflammation and an ensuing temporary immune suppression (14). Surprisingly, even moderate training results in elevated levels of several cytokines and cytokine-like proteins (26,28). These signaling molecules that can act in an auto-, para- and/or endocrine manner, have been termed myokines (26,28), analogous to adipokines produces in adipose tissue. Intriguingly, the growing number of identified myokines includes factors that traditionally have been described as pro-inflammatory cytokines, e.g. the prototypical myokine IL-6. Thus, persistently elevated IL-6 levels have been associated with obesity and insulin resistance, but when released as a myokine, IL-6 mediates a number of beneficial effects (26). It is conceivable that these diametrically opposite effects are due to the very different secretion pattern of IL-6 in these two contexts, co-release of other factors or fundamental differences in IL-6 sensitivity in physiological compared to pathophysiological settings. However, the exact mechanisms are still unclear. In any case, the increase in plasma levels of immunomodulatory factors such as cortisol, growth hormone, epinephrine and others post-exercise favor an anti-inflammatory environment (12).

Based on its role as central regulator of exercise adaptation, it is not surprising that PGC-1α controls the expression of at least several myokines in the trained muscle fiber, e.g. irisin, meteorin-like, secreted phosphoprotein 1 (SPP1) or β-aminoisobutyric acid (BAIBA, a non-peptide myokine) (28). Meteorin-like and SPP1 induce changes in target tissues by activating eosinophils and macrophages, respectively. Thus, at least part of the exercise effect on inflammation is mediated by PGC-1α-controlled cellular cross-talk. In addition, PGC-1α also has a strong inhibitory role on pro-inflammatory gene expression in muscle, at least in part mediated by inhibition of activating phosphorylation events on the p65 subunit of the NF-κB transcription factor (9). Inversely, inflammation in most cases reduces the levels of PGC-1α in muscle, e.g. in the case of sepsis-induced muscle atrophy (8). Moreover, this inhibition is at least in part dependent on NF-κB, implying a mutually negative regulation of these two factors (8). Accordingly, the expression of TNFα and IL-6 in muscle both negatively correlate with PGC-1α levels in normal, glucose-intolerant and diabetic individuals (17). Therefore, the reciprocal regulation of PGC-1α and NF-κB conceivably is the molecular hinge in skeletal muscle that determines the balance between an anti-inflammatory, oxidative, trained environment in health and the pro-inflammatory, atrophic, insulin resistant conditions in disease (Fig. 3).

Summary

Inflammation, muscle metabolism and function are intrinsically linked and determine the health status of this organ, in many cases even systemic well-being. The complex interplay between these systems is underlined by shared mediators, in particular pro-inflammatory cytokines that in different

contexts also can act as beneficial myokines mediating systemic exercise effects. On the molecular level, the co-activator PGC-1α and the transcription factor NF-κB seem central in balancing physiological and pathophysiological states. Even though pharmacological activators of PGC-1α that can be applied in a chronic and safe manner remain elusive (30), a better understanding of the mutual regulation between these two factors will hopefully lead to the identification of novel therapeutic targets and thereby new prevention and treatment modalities not only for many skeletal muscle disorders, but also a number of other chronic diseases. In the meantime, exercise remains the most efficient manner to safely increase muscle PGC-1α and reduce the risk for such pathologies.

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Figure Legends

Fig. 1. Regulation and function of PGC-1α in skeletal muscle. Fiber contraction in endurance exercise training results in increased transcription of the PPARGC1A gene and post-translational modifications of the PGC-1α protein. Moreover, PGC-1α regulates its own transcriptional rate in a positive, autoregulatory loop. Subsequently, PGC-1α is recruited to target gene promoters by binding to nuclear receptors such as the estrogen-related receptor α (ERRα), transcription factors like the nuclear respiratory factor 1 (NRF1) and other non-nuclear receptor transcription factors (TFs). Collectively, various transcriptional programs are thereby activated both in muscle fibers as well as in non-muscle cells such as the epithelium or the neuromuscular junction (NMJ) ultimately resulting in an endurance-trained muscle phenotype.

Fig. 2. Complex regulation of inflammation by muscle activity. Inadequate levels of physical activity are linked to a local and systemic persistent, sterile inflammation and production of pro-inflammatory cytokines as well as a strongly elevated risk for many chronic diseases. Moderate levels of training result in the release of myokines and a tightly regulated local inflammation important for controlled fiber repair and regeneration culminating in exercise adaptation. Extreme performance exercise massively elevates fiber damage and inflammation, often accompanied by a temporary immunosuppression.

Fig. 3. PGC-1α and NF-κB are a molecular interface that controls metabolism and inflammation in muscle. A mutually negative regulation of PGC-1α and NF-κB in physiological and pathophysiological contexts determines the relative degree of metabolism and inflammation in skeletal muscle.

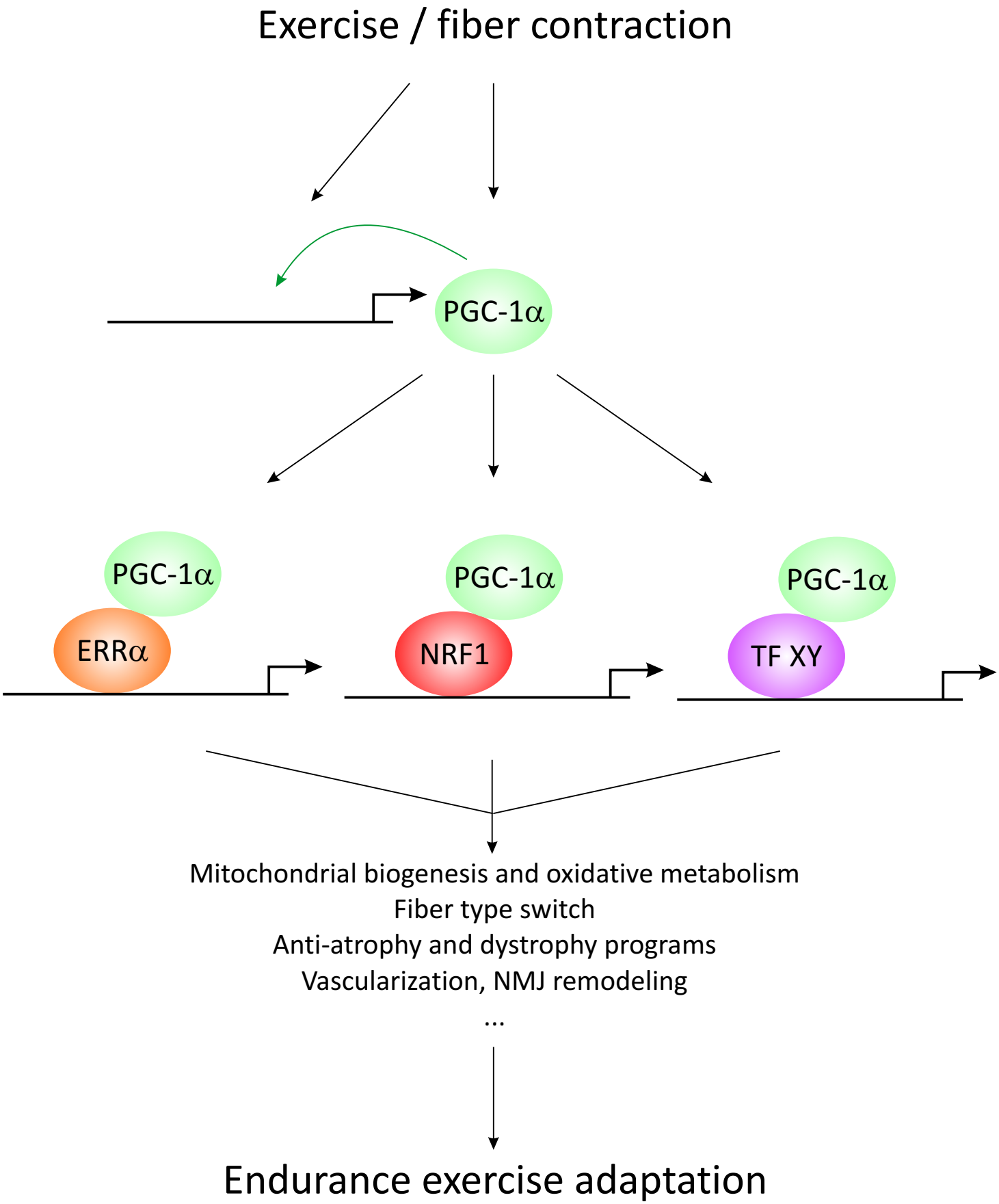
Exercise / fiber contraction
PGC-1α
PGC-1α
ERRα
PGC-1α
NRF1
PGC-1α
TF XY
Mitochondrial biogenesis and oxidative metabolism
Fiber type switch
Anti-atrophy and dystrophy programs
Vascularization, NMJ remodeling
...
Endurance exercise adaptation

Fig. 1

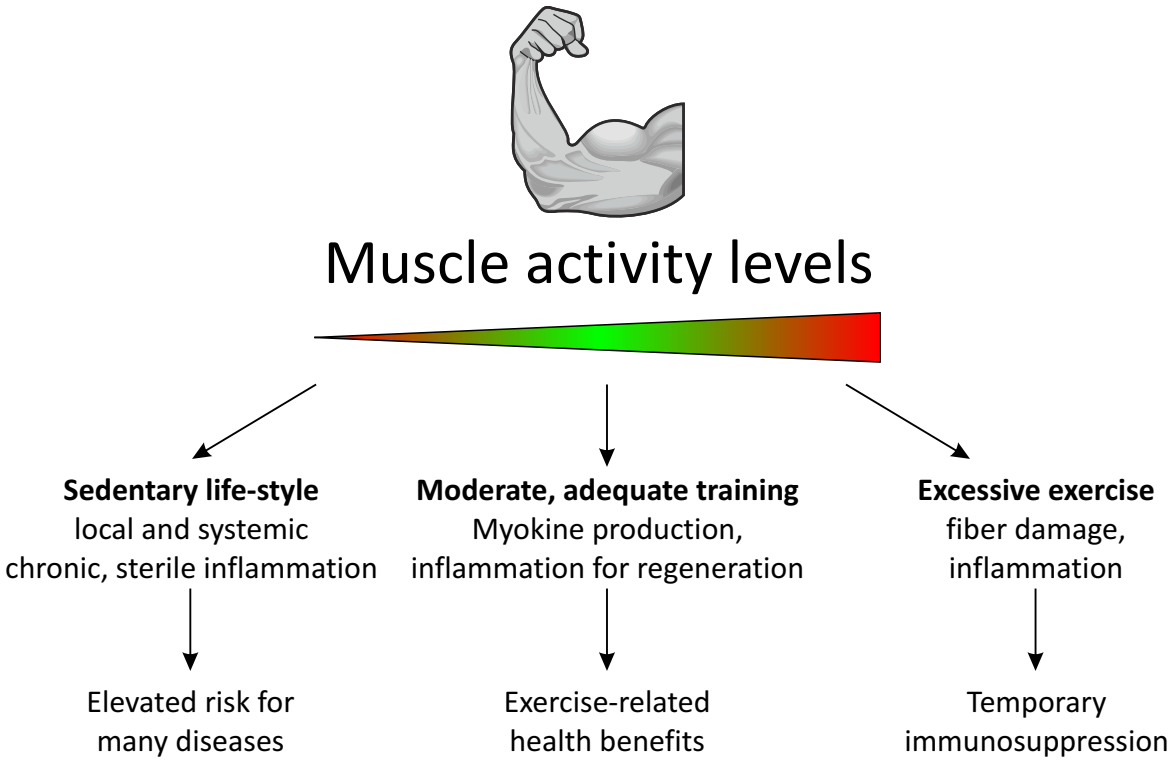
Muscle activity levels
Sedentary life-style
local and systemic
chronic, sterile inflammation
Moderate, adequate training
Myokine production,
inflammation for regeneration
Excessive exercise
fiber damage,
inflammation
Elevated risk for
many diseases
Exercise-related
health benefits
Temporary
immunosuppression

Fig. 2

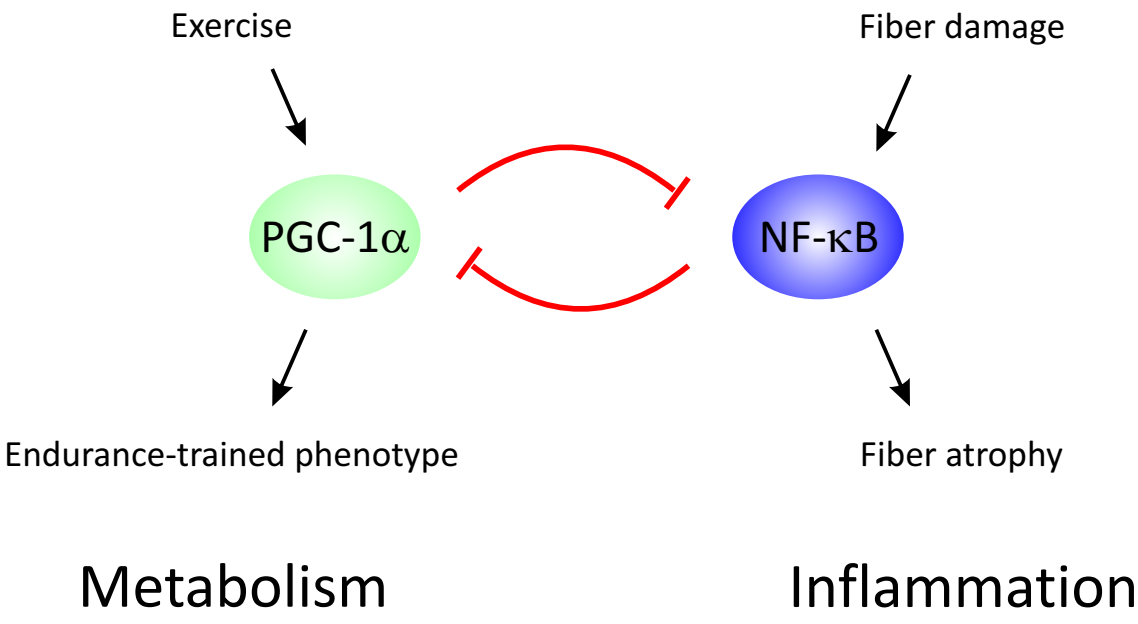
Exercise
Fiber damage
PGC-1α
NF-κB
Endurance-trained phenotype
Fiber atrophy
Metabolism
Inflammation

Fig. 3