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PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-γ COACTIVATOR-1α IN MUSCLE LINKS METABOLISM TO INFLAMMATION

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INVITED REVIEW

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-γ COACTIVATOR-1α IN MUSCLE LINKS METABOLISM TO INFLAMMATION

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SUMMARY

1. In higher eukaryotes, metabolism and immunity are tightly coupled. However, whereas in evolutionary terms a compromised immune response due to undernourishment has been the predominant problem, the inflammatory response to obesity and other lifestyle-associated diseases has increased in relevance in Western societies in the past 100 years.

2. Traditionally, fat tissue has been considered as the major source of pro-inflammatory secreted factors in these pathologies. However, in recent years the contribution of other tissues to disease-causing chronic inflammation has been increasingly appreciated.

3. Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) is one of the key regulatory factors in active skeletal muscle. Aberrant expression of PGC-1α in inactive muscle fibres could be linked to a sedentary lifestyle, persistent systemic inflammation and a higher risk for many chronic diseases. Accordingly, modulation of PGC-1α activity in skeletal muscle may have a broad range of therapeutic effects. Here, recent advances in the understanding of the role of muscle PGC-1α in health and disease are reviewed.

Key words: exercise, inflammation, metabolism, muscle, peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α).

INTRODUCTION

Multicellular organisms depend on the ability to store energy for times of famine and to fight infections.[1,2] The immune response is very energy demanding and therefore inflammatory processes strongly inhibit anabolic processes, such as those controlled by insulin signalling. For example, fever boosts energy consumption by 7–13% for each 1°C increase in body temperature and sepsis can increase energy consumption by 30–60%.[3] Conversely, an undernourished state is immunosuppressive, as observed in malnourished or starving individuals with an increased susceptibility to infectious diseases. Accordingly, the molecular systems regulating metabolic processes and immune response have coevolved and mutually regulate each other.[4] In lower organisms like the common fruit fly *Drosophila melanogaster*, metabolic and

immune processes are even associated with one organ, the fat body, whereas in higher organisms, a deeper specialization of tissues has occurred. Nevertheless, even in humans, metabolic organs are often closely linked with immune cells or have intrinsic immunomodulatory functions. For example, in the liver, hepatocytes are located adjacent to Kupffer cells and macrophages are in close contact with adipocytes in fat.[1,2,4]

In the past 100 years, physical activity and food intake patterns have changed markedly in Western countries. Concomitant with this shift in energy metabolism, the incidence rates for obesity, Type 2 diabetes, cardiovascular disease, hypertension and other lifestyle-associated pathologies have reached epidemic proportions.[5,6] Thus, in contrast with the previous 250 000 years, when *Homo sapiens* mainly struggled with a lack of food, we now pay the price for an abundance of energy-rich food and the decreased importance of physical activity in daily life. Like malnutrition, overnutrition is linked to pathological changes in immune function, but in a diametrically opposite way. In contrast with the immunosuppression in undernourished individuals, the imbalance between energy intake and dissipation triggered by overnutrition leads to a persistent, low-grade inflammatory state and an increased susceptibility to chronic diseases.[2,4] Importantly, this chronic inflammation is different from the classic immune response to an infectious agent and has thus been referred to as meta- or para-inflammation.[2,4] However, the same organs at the intersection of metabolism and immune function are involved in precipitating all these different inflammatory responses.[7]

ADIPOSE TISSUE IS A MAJOR DRIVER OF INFLAMMATION IN OBESITY

Excess energy is mostly stored in adipose tissue, where adipocytes become enlarged, ultimately resulting in obesity. In addition to energy storage, fat is an important endocrine organ and, accordingly, secretes a number of hormones that regulate systemic energy homeostasis and appetite.[8–10] In an obese individual, adipocytes are also a major source of pro-inflammatory cytokines and other detrimental factors.[10,11] Hotamisligil *et al.* described the production and secretion of tumour necrosis factor (TNF)-α by fat tissue in 1993 and thereby provided the first link between obesity, inflammation and insulin resistance.[12] In the meantime, numerous other adipose-derived pro-inflammatory proteins, members of the 'adipokine' family, have been identified.[11,13] Once released, many of these hormones promote insulin resistance in other peripheral tissues. Thus, an inflammatory response from adipose tissue and, to a lesser extent, from the liver triggers early disease-causing events in obesity.

SKELETAL MUSCLE AS AN ENDOCRINE ORGAN

Although increased production of TNF-α in the skeletal muscle of obese patients was reported in 1996,[14] skeletal muscle as a significant contributor to chronic inflammation in metabolic diseases has been neglected for years. This is surprising because skeletal muscle makes up approximately 40% of bodyweight and is the largest storage site for glucose in the form of glycogen. Moreover, in a healthy organism, muscle tissue is very sensitive to insulin and the developing insulin resistance of this tissue contributes significantly to the aetiology of Type 2 diabetes.[15,16] Finally, a sedentary lifestyle is a strong and independent risk factor for many chronic diseases, including those that are associated with persistent, systemic inflammation.[17] For example, lack of adequate physical activity is linked to Type 2 diabetes, obesity, cardiovascular diseases, certain cancers, neurodegeneration, musculoskeletal disorders and other pathologies, thereby increasing morbidity and mortality and reducing quality of life, as well as overall life expectancy.[17] In contrast, exercise, even in the absence of significant weight loss, is an excellent preventative and therapeutic intervention for many chronic disorders.[18] For example, changes in lifestyle that consist of diet and exercise rival, or even exceed, currently prescribed drugs in terms of therapeutic efficacy against Type 2 diabetes.[19]

In recent years, factors produced and secreted by the contracting muscle fibres have been found and termed 'myokines', analogous to the adipokines that are released from fat.[20,21] Interestingly, many myokines have a complex expression pattern and exert either beneficial or detrimental effects depending on the cellular context.[20,22,23] For example, short-lived pulses of interleukin (IL)-6, IL-8 and IL-15 are elicited by moderate bouts of exercise and could mediate some of the systemic effects of physical activity (Fig. 1).[24,25] In contrast, persistent elevation of IL-6 is strongly associated with obesity and Type 2 diabetes.[4] Thus, depending on the secretion pattern and the cellular context, IL-6 may mediate pro- or anti-inflammatory effects.[23] Very high-intensity exercise paradigms are accompanied by increases in a specific set of cytokines that includes IL-6 and the unequivocally pro-inflammatory TNF-α.[20,26] In that context, these myokines most likely contribute to the immunocompromised and inflammatory state that is observed after extreme physical activity.[26]

REGULATION OF MUSCLE FIBRE PLASTICITY BY PEROXISOME PROLIFERATOR-ACTIVATED

RECEPTOR-γ COACTIVATOR-1α

Exercise triggers major phenotypic adaptations in skeletal muscle. This biological programme is predominantly regulated by changes in gene transcription.[27] Importantly, molecular changes in myofibres differ between the acute adaptations to individual bouts of exercise and those observed in a chronically trained muscle. However, in both cases, similar signalling pathways are responsible for initiating the adaptations. Motor neuron activation of muscle fibres results in an elevation of intracellular calcium levels.[28–30] Increased energy metabolism, and hence ATP consumption, shifts the ATP to AMP ratio and thereby activates AMP-dependent protein kinase (AMPK).[31,32] At the same time, an altered NAD^+ to NADH ratio alters the activity of the silencing information regulator (SIRT) 2 orthologue SIRT1.[33–35] The cellular stress associated with fibre contraction leads to an increased activity of the p38 mitogen-activated protein kinase (MAPK) and the production of nitric oxide (NO).[36,37] Hormonal changes elicited by the fight-or-flight reaction to physical activity include elevated levels of β-adrenoceptor agonists, some of which bind to β_2-adrenoreceptors on the surface of muscle fibres.[27,38–40] Finally, exercise-induced synaptic remodelling of the neuromuscular junction (NMJ) are initiated and maintained by motor neuron-released paracrine factors that act on muscle.[41–43] Importantly, all these signalling pathways converge on the peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), resulting in either transcriptional induction, changes in protein activity or both (Fig. 2).[44,45] In turn, by binding to a diverse set of transcription factors, PGC-1α regulates many, if not all, of the adaptations of the muscle fibre to endurance exercise.[44,45] First and foremost, PGC-1α increases mitochondrial biogenesis and function.[46] Accordingly, fatty acid β-oxidation, oxidative phosphorylation and ATP production are augmented.[47–49] Then, the set of myofibrillar genes prototypical for the slow-twitch, high-endurance Type I and IIa muscle fibres is induced by PGC-1α.[50] Furthermore, expression of the ubiquitine ligases that promote protein degradation and fibre atrophy in an inactive muscle is reduced.[51] Finally, the transcriptional rate of genes encoding post-synaptic NMJ proteins is altered in synaptic nuclei.[41] Accordingly, ectopic expression of PGC-1α in skeletal muscle is sufficient to promote a fibre type shift towards a higher proportion of oxidative muscle fibres and thereby evoke a trained phenotype in the mouse model.[50,52] By inducing the biological programme for exercise, elevation of PGC-1α even prevents disuse-induced fibre atrophy,[51] blunts the detrimental side-effects of statin drugs in muscle[53] and ameliorates Duchenne muscular dystrophy[41] and a form of a mitochondrial myopathy[54] in respective animal models.

PATHOLOGICAL CONSEQUENCES OF PGC-1α DYSREGULATION IN MUSCLE

In humans, a tight correlation between the relative levels of physical activity and PGC-1α has been observed.[55] Expression of PGC-1α is transiently elevated after each bout of endurance exercise, similar to the expression pattern described for IL-6. However, a causal link between the expression patterns of PGC-1α and IL-6 is unclear. In a chronically trained muscle, basal levels of PGC-1α are higher than those observed in an untrained individual,[55] yet a superimposed pulsative regulation of PGC-1α expression following each exercise bout is maintained.[56] In contrast, aberrantly low PGC-1α levels are found in the muscle of sedentary individuals and Type 2 diabetic patients, at least in some populations.[57,58] It is unknown how much this dysregulation contributes to the aetiology and pathology of this disease. However, a significant contribution of PGC-1α to glucose homeostasis is implied by the results from muscle-specific knockout mouse models. Mirroring the data from PGC-1α muscle transgenic mice,[50] PGC-1α muscle-specific knockout animals exhibit a higher number of glycolytic Type IIx and IIb fibres concomitant with a reduction in mitochondrial gene expression and oxidative capacity.[59,60] As a consequence, these mice are hypoactive and restricted in their ability to exercise.[59,60] Moreover, whole -ody glucose and insulin homeostases are abnormally regulated.[60] These findings confirm the important role for PGC-1α in the metabolic and myofibrillar plasticity of muscle fibres. Surprisingly, PGC-1α muscle-specific knockout animals reveal signs of muscle damage, as indicated by an increase in plasma creatine kinase levels and the number of perforated fibres in histological stainings.[59] Whereas this fibre damage is limited in sedentary animals, the myopathy is exacerbated by physical activity.[59] Thus, physiological levels of PGC-1α seem essential for normal muscle fibre integrity.

INCREASED INFLAMMATION COULD LINK PGC-1α TO MUSCLE FIBRE DAMAGE

It is unclear how fibre damage is triggered in muscle-specific PGC-1α knockout animals. Similarly, the molecular mechanisms that underlie the therapeutic effects of PGC-1α in different muscle diseases are unknown, although several candidate mechanisms have been suggested.[61] Intriguingly, pro-inflammatory markers are elevated in mice with an ablated PGC-1α gene in muscle.[59,60] In addition to the local inflammatory reaction in skeletal muscle, PGC-1α muscle-specific knockout animals exhibit higher levels of circulating TNF-α and IL-6.[59,60] Inflammation contributes to fibre damage and muscle wasting in a variety of different muscle diseases.[62–64] Whether the inflammation in PGC-1α muscle-specific

knockout mice is a cause or the consequence of fibre damage has not been elucidated. For example, PGC-1α may directly modulate inflammatory gene expression, for example by altering reactive oxygen species in muscle, or the inflammation could be secondary to fibre damage and the subsequent removal of the debris. However, the elevation of circulating pro-inflammatory factors and hence the systemic inflammatory state seem sufficient to link dysregulated muscle function to pathologies in other organs, such as the deficient insulin secretion from pancreatic β-cells in these animals.[60]

CONCLUSIONS

Chronic systemic inflammation is associated with an increased risk for many diseases. In addition, exercise has health benefits on the whole body, not just skeletal muscle. Thus, intrinsic adaptations in muscle fibres and the consequent distal signalling, most likely by hormonal or neuronal pathways, must mediate the cross-talk between active muscles and other organs. Reduction of PGC-1α levels and the subsequent systemic elevation of pro-inflammatory cytokines may be the elusive link between a sedentary lifestyle and the increased risk for chronic diseases (Fig. 1).[61] Accordingly, a pharmacological modulation of PGC-1α in muscle may have therapeutic benefits beyond that tissue. Unfortunately, despite various efforts, compounds that robustly alter PGC-1α gene expression in skeletal muscle and not other tissues, thus avoiding potential detrimental side-effects, and that can be used safely and chronically in patients remain elusive.[65,66] Thus, as long as the inherent limitations of targeting a coactivator protein have not been overcome, a healthy lifestyle remains the best remedy against chronic diseases.

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Fig. 1 Myokine production and the inflammatory state in skeletal muscle. Myokines secreted by an active muscle may contribute to the systemic beneficial effects of exercise. Reduced muscle activity is associated with impaired peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) expression. A number of pro-inflammatory cytokines are elevated in individuals with inadequate physical activity. This persistent, low-grade inflammation could subsequently increase the risk for a number of chronic diseases. In contrast, extreme performance and the accompanying fibre damage result in a state of temporary immunosuppression. IL, interleukin; TNF-α, tumour necrosis factor-α.

Fig. 2 Regulation and function of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) in skeletal muscle fibres. All major signalling pathways that are activated in an active muscle fibre converge on the PGC-1α promoter, the protein or both. In turn, PGC-1α initiates the adaptations of muscle to physical activity by regulating metabolic, myofibrillar and neuromuscular junction-specific genes. MAPK, mitogen-activated protein kinase; AMPK, AMP-activated protein kinase; SIRT1, silencing information regulator 1, Erk, extracellular signal-regulated kinase; Jnk, c-Jun N-terminal kinase; NO, nitric oxide; OXPHOS, oxidative phosphorylation.

Fig. 1

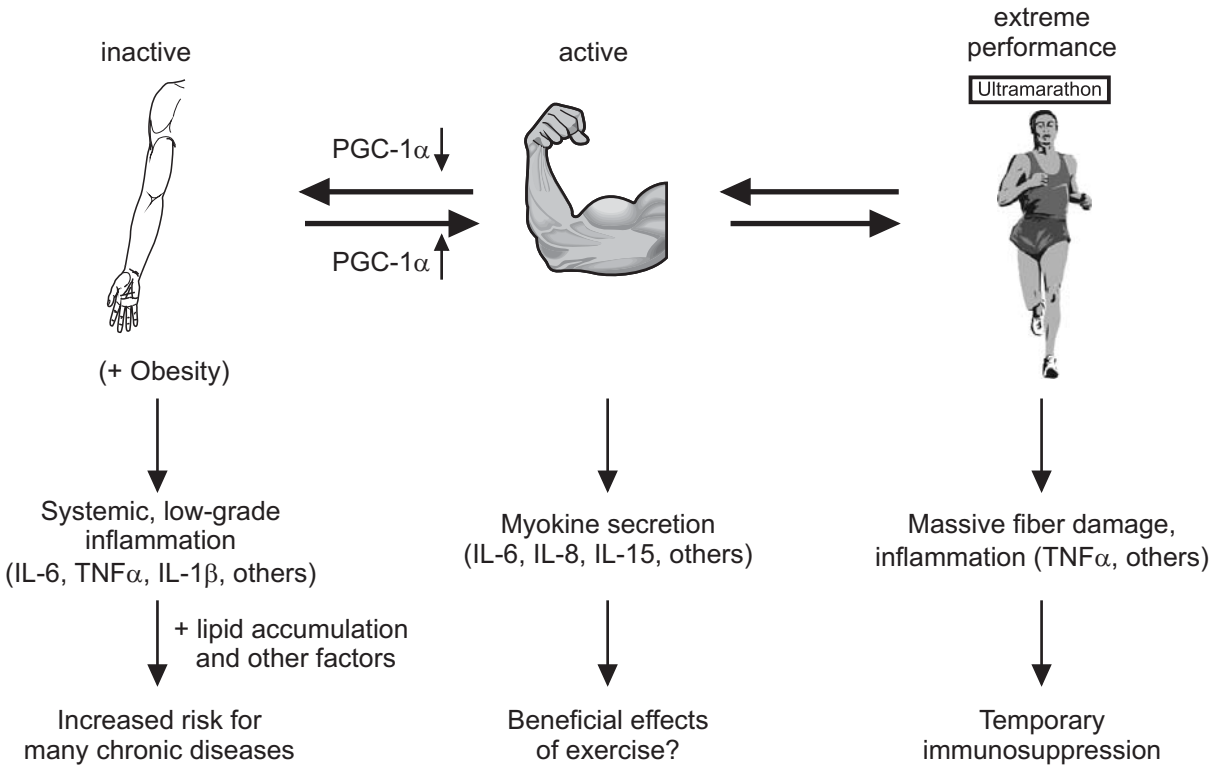
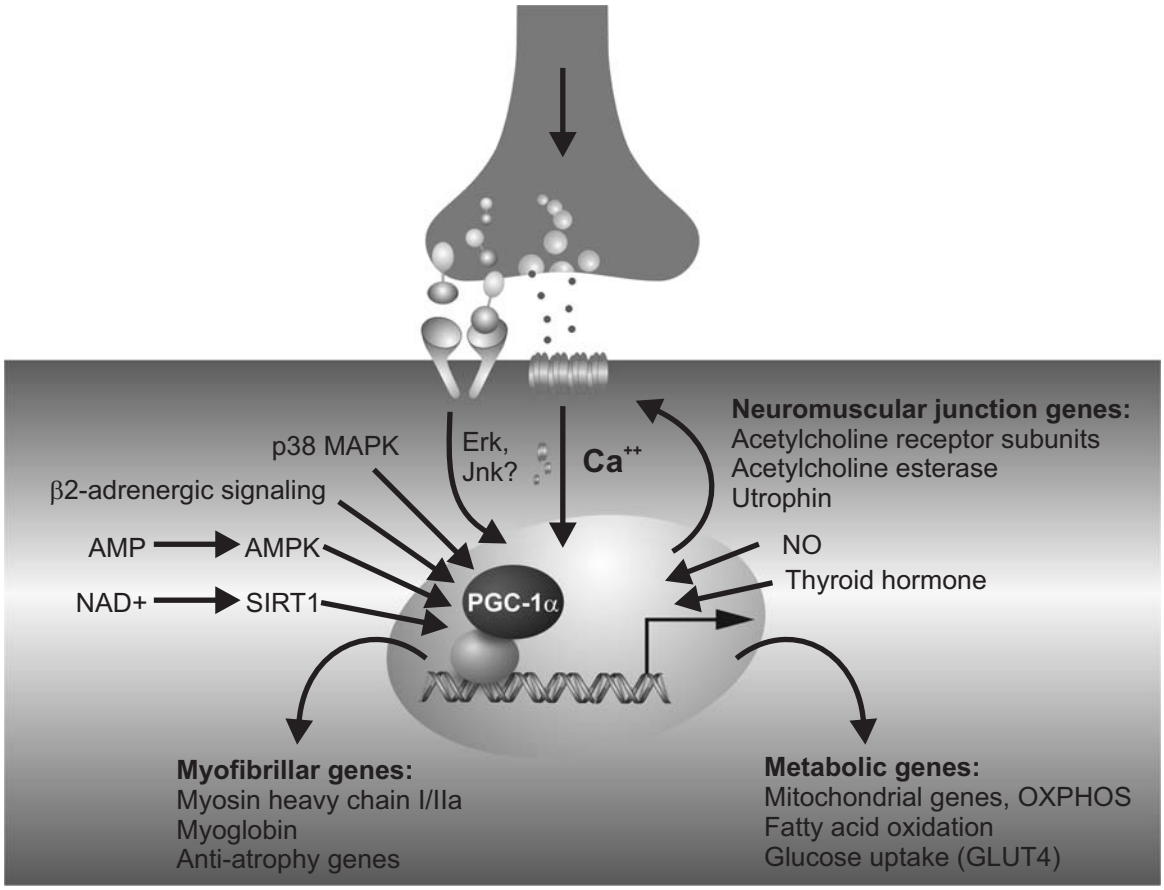

inactive
active
extreme performance
Ultramarathon
PGC-1α
PGC-1α
(+ Obesity)
Systemic, low-grade inflammation (IL-6, TNFα, IL-1β, others)
+ lipid accumulation and other factors
Increased risk for many chronic diseases
Myokine secretion (IL-6, IL-8, IL-15, others)
Beneficial effects of exercise?
Massive fiber damage, inflammation (TNFα, others)
Temporary immunosuppression

Fig. 2


p38 MAPK
Erk,
Jnk?
Ca++
β2-adrenergic signaling
AMP
AMPK
NAD+
SIRT1
PGC-1α
Neuromuscular junction genes:
Acetylcholine receptor subunits
Acetylcholine esterase
Utrophin
NO
Thyroid hormone
Myofibrillar genes:
Myosin heavy chain I/IIa
Myoglobin
Anti-atrophy genes
Metabolic genes:
Mitochondrial genes, OXPHOS
Fatty acid oxidation
Glucose uptake (GLUT4)