REVIEW

Functional crosstalk of PGC-1 coactivators and inflammation in skeletal muscle pathophysiology

Petra S. Eisele · Christoph Handschin

Abstract Skeletal muscle is an organ involved in whole body movement and energy metabolism with the ability to dynamically adapt to different states of (dis-)use. At a molecular level, the peroxisome proliferator-activated receptor γ coactivators 1 (PGC-1s) are important mediators of oxidative metabolism in skeletal muscle and in other organs. Musculoskeletal disorders as well as obesity and its sequelae are associated with PGC-1 dysregulation in muscle with a concomitant local or systemic inflammatory reaction. In this review, we outline the function of PGC-1 coactivators in physiological and pathological conditions as well as the complex interplay of metabolic dysregulation and inflammation in obesity with special focus on skeletal muscle. We further put forward the hypothesis that, in this tissue, oxidative metabolism and inflammatory processes mutually antagonize each other. The nuclear factor κB (NF-κB) pathway thereby plays a key role in linking metabolic and inflammatory programs in muscle cells. We conclude this review with a perspective about the consequences of such a negative crosstalk on the immune system and the possibilities this opens for clinical applications.

Keywords Skeletal muscle · Metabolism · Metabolic disorders · Inflammation · PGC-1 · NF-κB · Macrophages

Introduction

Obesity has become a global epidemic, and a large number of deaths can be attributed to obesity-related disorders

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commonly known as the "metabolic syndrome." Understanding the molecular mechanisms underlying this syndrome is crucial to be able to develop appropriate treatment strategies and improve quality of life of patients. Skeletal muscle is important in glucose homeostasis as a large part of blood glucose is taken up into this tissue, stored as glycogen, or used as substrate. Skeletal muscle insulin resistance is thus detrimental as it disturbs whole body glucose metabolism. The development of insulin resistance is closely linked to inflammation, which has been studied extensively in white adipose tissue. Macrophages and other cells of the immune system interact with cells of the resident tissue to promote or restrain inflammatory reactions. This fosters or impedes the genesis of insulin resistance, respectively. In skeletal muscle, these processes and their interdependence have just started to be elucidated.

PGC-1 coactivators are transcriptional coregulators that facilitate expression of an oxidative metabolic program in energy-demanding organs including skeletal muscle, in particular, in adaptation to endurance training. Many skeletal muscle pathologies, for example, muscle wasting, are associated with PGC-1 repression and accompanied by inflammatory reactions in muscle tissue. PGC-1 downregulation has also been observed in skeletal muscle of diabetic patients that display higher levels of pro-inflammatory cytokines both in muscle and blood, a situation that is recapitulated in mice that lack PGC-1α. Inversely, exercise is known to promote anti-inflammatory effects and PGC-1 coactivators recently have been shown to have anti-inflammatory properties in vitro.

In the current review, we therefore examine the influence of inflammation on PGC-1 coactivators and vice versa focusing on skeletal muscle. We provide thorough background information on all the relevant areas including skeletal muscle physiology and pathology, PGC-1 coactivator regulation and function, and the molecular basis of inflammatory reactions. We then explore how oxidative metabolism and inflammatory

processes are linked providing evidence for a mutual, negative regulation. This antagonism has far-reaching consequences both for muscle and immune cells, positioning skeletal muscle at the crossroad of metabolic and inflammatory processes.

Skeletal muscle

Skeletal muscle structure and function

The human body contains different types of muscle, mainly skeletal muscle, cardiac muscle, and smooth muscle that all have the ability to contract. While cardiac and smooth muscle contraction is involuntary, skeletal muscle contraction can be controlled deliberately as it contributes fundamentally to locomotion and posture.

To fulfill these purposes, skeletal muscle is attached to the bone by tendons, enveloped by a layer of connective tissue (the epimysium) and organized in several functional units. The largest unit is the muscle bundle. Each skeletal muscle comprises several bundles, so-called fasciculi, which are confined by the perimysium, another layer of connective tissue. The second functional unit is the myofiber, a postmitotic, syncytial muscle cell, itself lined by connective tissue (the endomysium). Multiple myofibers run in parallel to form a bundle. Each myofiber contains numerous myofibrils, the smallest functional unit of skeletal muscle. Myofibrils are linear sequences of sarcomers, which are the fundamental contractile element of muscle cells. Under the microscope, these sarcomere repeats appear as distinct bands giving skeletal muscle its unique, striated pattern. At a molecular level, sarcomers are composed of the interdigitating myofilaments myosin and actin, which contract by sliding along each other and thereby shorten the muscle [1].

Skeletal muscles are innervated by motor neurons, which originate in the spinal cord. The synapse between motor neuron and muscle constitutes the neuromuscular junction. One motor neuron and all muscle fibers that are innervated by this neuron are called a motor unit. All fibers of a motor unit always contract in conjunction upon excitation of the innervating motor neuron. This excitation manifests in an action potential which leads to release of the neurotransmitter acetylcholine into the synaptic cleft at the neuromuscular junction. Postsynaptically, acetylcholine binds to its receptor, a ligand-gated ion-channel, and evokes an end plate potential by depolarization. This potential propagates along the fiber membrane (sarcolemma) which has deep invaginations (transverse tubules) harboring voltage-gated dihydropyridine receptors. These receptors in turn activate ryanodine receptors in the adjacent sarcoplasmic reticulum (SR) leading to a release of calcium from this compartment. Increased intracellular calcium concentrations finally initiate contraction. The close proximity of dihydropyridine receptors in the sarcolemma of

transverse tubules and ryanodine receptors in the SR enables excitation–contraction coupling [1].

Contraction requires the binding of myosin to actin filaments. In the basal state, the binding sites (active sites) are however masked by the troponin–tropomyosin complex, thus hindering interactions. Binding of calcium to troponin exposes the active sites and enables myosin heads to form cross-bridges which subsequently move, hence the sliding of the myofilaments against one another. The cross-bridges are released by binding of ATP allowing another cycle of contraction. Contraction ends when calcium is pumped back to the SR and no further actin-myosin interactions occur [1].

Metabolic characteristics of skeletal muscle

Myosin filaments in skeletal muscle contain six subunits, two heavy chains, and four light chains, whereby different types of myosin heavy chains (MHC) can be distinguished. They vary in their contractile characteristics and are prototypical for different types of muscle fibers, which are adapted to different kinds of contraction. Type I or slow fibers that contain MHC I contract with low maximal force but are highly resistant to fatigue while type II or fast fibers that contain MHC II fatigue rapidly but are able to produce a high maximal force. Type I fibers appear red due to a high level of vascularization while type II fibers appear white. The latter can be further subdivided into type IIa (moderately fast), type IIx (intermediate), and type IIb (very fast) fibers. According to their contraction properties, the various fiber types primarily rely on different metabolic pathways as energy source: While type I and IIa fibers are oxidative, type IIx and IIb fibers are glycolytic [1].

Glycolytic fibers mainly metabolize glucose, which is taken up into muscle cells by glucose transporters (GLUT), some of which translocate to the membrane upon higher energy demand. In the cytosol, glucose is then converted into pyruvate by glycolysis producing ATP via substrate-level phosphorylation. As glycolytic fibers contain few mitochondria, pyruvate is further transformed anaerobically into lactic acid, recovering the pool of NAD^+, an essential cofactor of glycolysis [2]. This process enables very fast supply of energy for intensive bursts of work, however only for limited periods of time. Type II muscle fibers are thus typical for strength athletes.

At the other end of the spectrum, oxidative fibers contain a high number of mitochondria, which are the main site of aerobic energy production. The mitochondrial matrix harbors enzymes of fatty acid β oxidation and the citric acid cycle while the mitochondrial inner membrane comprises the components of the electron transport chain. Fatty acids are the main energy substrate of oxidative fibers besides glucose. They are taken up into muscle cells by fatty acid translocase CD36, activated in the cytosol, and shuttled into mitochondria as acylcarnitines. Fatty acid β oxidation then generates acetyl-CoA that is fed into the citric acid cycle producing NADH,

which serves as electron donor of the electron transport chain (complex I-IV) with oxygen being the final acceptor. The energy liberated during the electron passage is stored as an electrochemical proton gradient across the inner mitochondrial membrane and ultimately dissipated by the ATP synthase that drives aerobic ATP production [2].

ATP fuels muscle contraction because it enables the release of myosin-actin interaction which is a prerequisite for the subsequent contraction cycle whereas ATP depletion results in muscle fatigue and the inability to sustain performance. In addition, ATP is required for various other processes that are important for muscle contraction, for example, ATP-driven re-uptake of calcium into the SR. The availability and utilization of energy substrates is therefore vital for continuous contraction. As oxidative metabolism in type I muscle fibers is well-adapted to prolonged periods of intermediate workloads, these fibers are characteristic for endurance athletes.

Obesity-related changes in skeletal muscle

Skeletal muscle is the main site of glucose disposal in the body and therefore contributes substantially to whole-body glucose homeostasis. In metabolic diseases, glucose homeostasis becomes dysregulated, resulting in hyperglycemia due to elevated levels of hepatic gluconeogenesis and diminished levels of glucose uptake into target tissues like skeletal muscle and fat. The deficit in glucose uptake stems from progressive insulin resistance of target tissues that precedes the exhaustion of insulin-producing pancreatic β cells in type 2 diabetes [3].

Overnutrition raises free fatty acid levels in the circulation. Target cells including myocytes are unable to deal with the constant oversupply of lipids as it exceeds their capacities to oxidize fatty acids in mitochondria or store them as triglycerides. Therefore, lipid metabolites like diacylglycerol and ceramides accumulate within the cell. These lipids activate serine kinases, for example, protein kinase C that may phosphorylate insulin receptor substrate 1 (IRS1) at inhibitory serine residues [3]. In healthy muscle, IRS1 is phosphorylated at tyrosine residues upon insulin binding to its receptor. This in turn initiates phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) and subsequent protein kinase B (PKB)/Akt activation, which finally phosphorylates GLUT4 leading to membrane translocation and glucose uptake into the cell. Inhibitory IRS1 serine phosphorylation in obesity blunts this signaling cascade as it prevents the required tyrosine phosphorylation events and therefore causes insulin resistance [3]. Indeed, intramyocellular lipid levels strongly correlate with insulin resistance. In non-diabetic subjects, insulin resistance initially may be compensated for by hyperinsulinemia in order to preserve normal glucose tolerance. Aggravated insulin resistance and β cell dysfunction then mark the transition to overt type 2 diabetes where glucose tolerance is lost.

Mitochondria produce reactive oxygen species (ROS) as byproducts of cellular respiration when oxygen is reduced prematurely. The excess of fatty acids in skeletal muscle of obese patients and the associated overload of mitochondria leads to higher rates of ROS generation. Together with an insufficient ROS detoxification, this creates an environment of permanent oxidative stress [4]. Apart from the direct damage that ROS inflict upon macromolecules like DNA, proteins, and lipids, oxidative stress also activates a number of cellular stress pathways including c-Jun N-terminal kinases (JNK) and p38/mitogen-activated protein kinases (MAPK) [4]. These serine kinases directly target IRS1 at inhibitory residues and thus bring about skeletal muscle insulin resistance. Furthermore, the nuclear factor κB (NF-κB) pathway is redox-sensitive. Activation of JNK, p38/MAPK, and NF-κB additionally induces transcription of inflammatory factors that substantially contribute to the development of insulin resistance. The exact role of inflammation in obesity and type 2 diabetes will be outlined below.

The endoplasmic reticulum (ER) is responsible for synthesis, correct folding, and secretion of proteins within the cell. It also plays an important role in calcium homeostasis, which is especially relevant in myocytes as calcium release from the SR initiates contraction. ER stress arises when this organelle is overburdened. Consequently, the unfolded protein response (UPR) acts as adaptive mechanism to resolve ER stress by reducing protein synthesis, increasing protein degradation and ER folding capacities through higher chaperone levels [5]. If chronically active, the UPR also induces NF-κB and JNK signaling, which both cause transcription of inflammatory factors and inhibitory IRS1 phosphorylation events leading to insulin resistance. ER stress may also heighten ROS levels, which again has a negative influence on insulin sensitivity.

The accumulation of lipid derivatives in skeletal muscle of obese patients leads to considerable ER stress, which is also evident in vitro when treating muscle cells with palmitate [6, 7]. Tunicamycin-induced, profound ER stress dampens insulin action in myocyte cultures by evoking JNK and mammalian target of rapamycin (mTOR)/S6 kinase-1 (S6K1) signaling, which both target IRS1 serine residues [6]. Whether the same pathways are active in muscle cells treated with palmitate is less clear, and the contribution of ER stress to the development of insulin resistance under these conditions remains controversial [7].

The PGC-1 family

Molecular characteristics of PGC-1 coactivators

Transcription is a tightly regulated process that involves the binding of transcription factors to response elements in the promoter region of target genes. Those transcription factors

subsequently attract chromatin remodeling enzymes and the RNA polymerase complex to the promoter in order to initiate transcription. Transcriptional activation is further fine-tuned by coregulators that either facilitate (coactivators) or hinder (corepressors) initiation.

The peroxisome proliferator-activated receptor (PPAR) γ coactivator 1 (PGC-1) family comprises three members, PGC-1α, PGC-1β, and PGC-1-related coactivator (PRC) that all act as transcription coactivators. Their common structure features an N-terminal activation domain (AD), one or several LXXLL or LLXXL motifs (where L is leucine and X is any amino acid) that represent the interface for nuclear receptor (NR) binding, a serine-rich or arginine-/serine-rich domain, and a C-terminal RNA recognition and splicing motif (Fig. 1). PGC-1α and PGC-1β also contain an inhibitory domain of about 200 amino acids adjacent to the AD. Two glutamine-rich domains are further characteristic for PGC-1β, while PRC has a unique proline-rich domain (Fig. 1).

The PGC-1 coactivators do not harbor a DNA binding domain but interact with specific transcription factors and NRs. PGC-1α was originally discovered as cofactor of PPARγ and thyroid hormone receptor (TR) [8]. Subsequent studies identified most NRs as PGC-1α binding partners, including PPARα, PPARβ/δ, liver X receptor (LXR), farnesoid X receptor (FXR), vitamin D receptor (VDR), constitutive androstane receptor (CAR), pregnane X receptor (PXR), estrogen receptor α (ERα), estrogen-related receptor α (ERRα) and ERRγ, glucocorticoid receptor (GR), hepatic nuclear factor 4 α (HNF4α), and retinoid X receptor (RXR) [9–20]. This interaction can be either constitutive or ligand-dependent, and indeed, human PGC-1α was identified in a screen for steroid-responsive genes [21]. PGC-1α is further able to coactivate a number of non-NR transcription factors like forkhead box protein O1 (Fox O1), FoxO3a, nuclear respiratory factor 1 (NRF1), myocyte-specific enhancer factor 2A (MEF2A), and MEF2C [22–26]. They bind PGC-1α via domains that are distinct from the LXXLL motifs.

PGC-1β interacts with the NRs PPARα, ERα, ERRα, and ERRγ; the transcription factors sterol regulatory element-binding protein 1a (SREBP1a) and SREBP1c; and FoxA2 [27–33]. Finally, PRC is able to potentiate ERRα- and NRF1-dependent transcription [34, 35].

Mechanistically, after binding to NRs or transcription factors, the PGC-1 coactivators act as recruitment platform for protein complexes that further boost transcription. The details of this assembly have been explored meticulously for PGC-1α: The AD interacts with the histone acetyltransferases (HATs) steroid receptor-1 (SRC-1) and cyclic AMP response element-binding protein (CREB) binding protein (CBP)/p300, which mediate decondensation of chromatin [36]. BRG-1-associated factor 60a (BAF60a) tethers the chromatin remodeling switch/sucrose nonfermentable (SWI/SNF) complex to a central stretch within the PGC-1α protein, while the C-terminal region binds the TR-associated protein (TRAP)/vitamin D receptor-interacting protein (DRIP) or Mediator complex that directly associates with the basal transcription machinery and thus contributes to preinitiation complex formation [37, 38].

The positive effect of PGC-1 coactivators on transcription can be abrogated by nuclear corepressors that compete for binding sites on NRs and thus displace the coactivators. Examples include small heterodimer partner (SHP), SHP interacting leucine zipper protein (SMILE), and dosage-sensitive sex reversal adrenal hypoplasia congenital critical region on X chromosome, gene 1 (DAX-1) [39–42]. Beyond the initiation of RNA polymerization, PGC-1α is also implicated in RNA processing via the RNA recognition and splicing domain at the C terminus [43].

Several isoforms of PGC-1 coactivators are currently known (Fig. 1). Alternative splicing gives rise to NT-PGC-1α (amino acids 1–270), and to PGC-1β-a and PGC-1β-b (differing in exon 11) while alternative promoter usage generates PGC-1β-1 (comprising exon 1a) and PGC-1β-2 (comprising exon 1a′ and exon 1b) [44, 45]. PGC-1α can also be transcribed from either the proximal or the alternative promoter (about 13 kb upstream) resulting in expression of PGC-1α-a/PGC-1α1 (proximal promoter, exon 1), PGC-1α-b/PGC-1α2 (exon 1b″), PGC-1α-c/PGC-1α3 (exon 1b′), and PGC-1α4 (exon 1b″), the last three all originating at the alternative promoter [46–48] (Fig. 1). In skeletal muscle, PGC-1α-b/PGC-1α2 and PGC-1α-c/PGC-1α3 are involved in adaptations to endurance exercise while PGC-1α4 mediates a hypertrophic response upon resistance training [47, 48].

Regulation of PGC-1α activity

As PGC-1 coactivators are potent inducers of transcription, their activity and expression levels are tightly controlled within the cell. Post-translational modifications (PTMs) and intracellular signaling events are by far best-studied for PGC-1α and will be outlined in the following sections.

Different transcription factors control the synthesis of PGC-1α mRNA: CREB is a potent inducer of PGC-1α expression in different tissues and binds to CRE in the promoter region of PGC-1α when phosphorylated by protein kinases [49]. In skeletal muscle, exercise-mediated calcium release activates calcium/calmodulin-dependent protein kinase type IV (CaMK IV), which targets CREB and thereby augments PGC-1α transcription [50].

MEF2C and MEF2D are able to bind to MEF2 sites in the PGC-1α promoter and elevate PGC-1α expression. Free, cytosolic calcium not only activates CaMK IV in skeletal muscle but also the phosphatase calcineurin A (CnA), which boost the activities of MEF2C and MEF2D. These transcription factors are bound and coactivated by PGC-1α at its own promoter constituting a positive, autoregulatory feed-forward
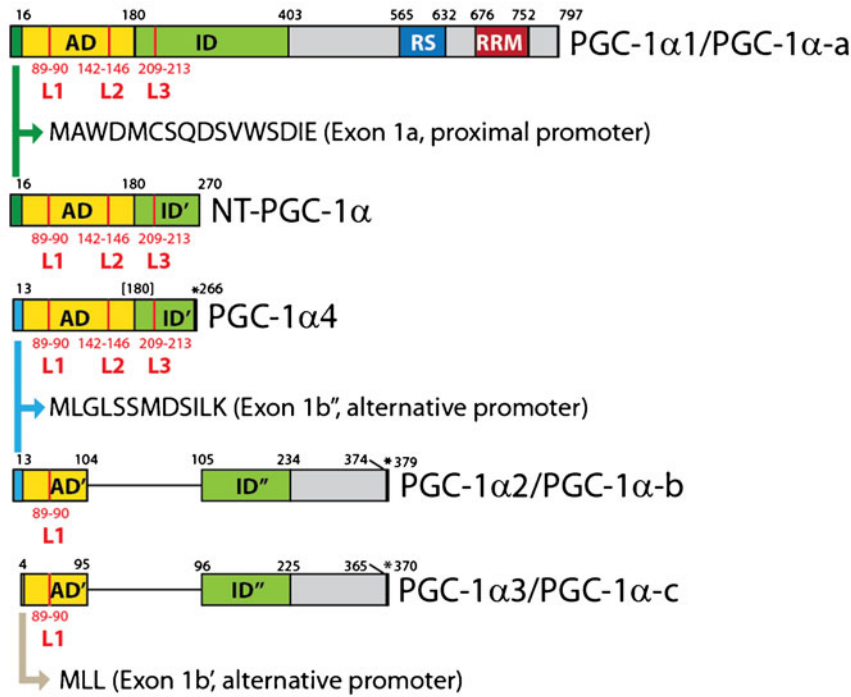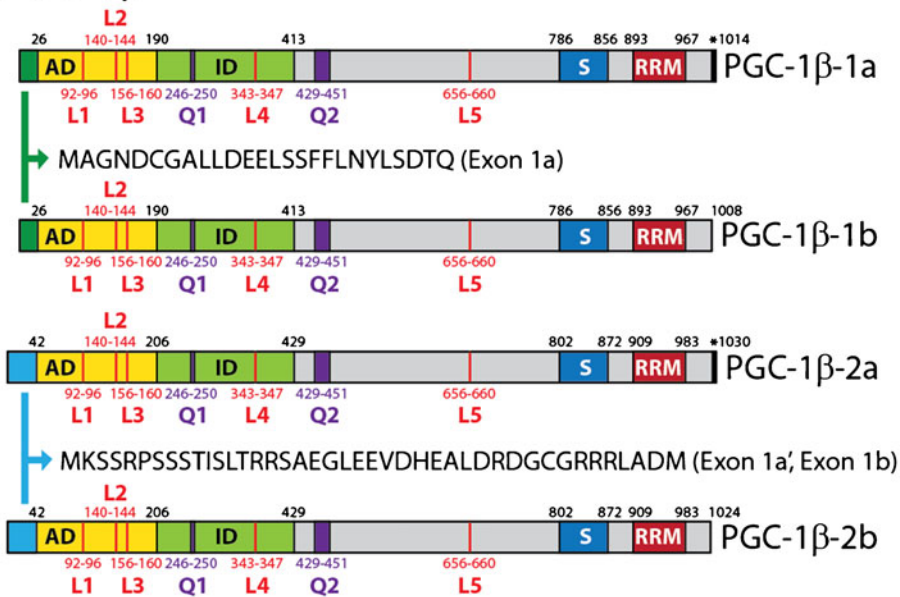
Fig. 1 Schematic representation of the murine PGC-1 family members and transcript variants. *AD*, activation domain; *ID*, inhibitory domain; *RS*, arginine-/serine-rich domain; *RRM*, RNA recognition and splicing motif; *S*, serine-rich domain; *P*, proline-rich domain; *L*, LXXLL or LLXXL motif; *Q*, glutamine-rich domain 1 and 2. *Numbers* indicate amino acid positions and refer to RefSeq transcripts; different N-terminal amino acid sequences corresponding to a different exon 1 and arising from alternative promoter usage are indicated in *green* and *blue*; an *asterisk* indicates additional C-terminal amino acids that are not shared by all splice variants [27, 29, 35, 44–48, 318]

loop [50]. Exercise also activates p38/MAPK, which participates in PGC-1α transcriptional regulation at two places: p38/MAPK phosphorylates both MEF2C/D and activating transcription factor 2 (ATF2), thereby facilitating their binding to the PGC-1α promoter and further boosting transcription [51, 52]. Direct PGC-1α phosphorylation will be discussed below.

As a sensor of low energy levels in the cell, AMP-activated protein kinase (AMPK) is also activated upon muscle contraction and promotes PGC-1α expression [53]. Another autoregulatory loop has been described for PPARβ/δ: PGC-1α heightens both PPARβ/δ and its own expression by coactivating this NR at the PGC-1α promoter [54]. PPARα and PPARγ are part of similar autoregulatory mechanisms in other organs, which therefore appear to be a common strategy in the induction of PGC-1α expression [54, 55].

Reciprocally, transcription of the PGC-1α gene can be inhibited by several factors. In hepatocytes, insulin-stimulated Akt targets FoxO1, which as a result dissociates from the PGC-1α promoter [56]. The recruitment of chromatin remodeling enzymes and transcription corepressors to the promoter also influences PGC-1α expression levels. Binding of histone deacetylases (HDACs) like HDAC5 to MEF2 compromises transcription as does the presence of SHP and nuclear corepressor 1 (NcoR1) [57–59]. A more general mechanism of repression is hypermethylation of non-CpG nucleotides in the PGC-1α promoter, which is caused by DNA methyltransferase 3B (DNMT3B) [60].

The second important aspect defining the transcriptional coactivator potential of PGC-1α is the modulation of PTMs that regulate protein stability and the binding affinity to transcription factors. A number of PTMs of PGC-1α have been reported, including phosphorylation, acetylation, methylation, GlcNAcylation, sumoylation, and ubiquitination.

Kinases target several serine and threonine residues within the PGC-1α protein. AMPK- and p38/MAPK-dependent phosphorylation stabilizes PGC-1α and decreases the interaction with the repressor p160 myb binding protein (p160 mbp) [53, 61, 62]. As both kinases also affect PGC-1α transcription, they have a dual effect involving an acute (phosphorylation) and a more sustained (expression) response. Similarly, PKA phosphorylates NT-PGC-1α, a short transcript variant of PGC-1α, and at the same time CREB, again constituting a dual, positive mode of action [63]. Akt and glycogen synthase kinase 3β (GSK3β) both mediate inhibitory PGC-1α phosphorylation events [64, 65]. Prior negative phosphorylation is also required for polyubiquitination of PGC-1α, which targets the protein for proteasomal degradation [66].

The acetylation status of PGC-1α further affects its activity. Acetyltransferase general control of amino acid synthesis 5 (GCN5) acetylates PGC-1α at multiple lysine residues, thus rendering it inactive due to relocalization to nuclear foci, while NAD$^+$-dependent protein deacetylase sirtuin 1 (Sirt1) removes these inhibitory acetyl residues [67–69]. As Sirt1

and AMPK are both sensors of cellular energy status, they act in concert to coordinately activate PGC-1α [70].

SUMOylation of PGC-1α does not change its subcellular localization or stability, but presumably facilitates interaction with receptor-interacting protein 140 (RIP140), a known repressor of PGC-1α [71, 72]. Finally, O-linked β-N-acetylglucosylation and arginine methylation of PGC-1α contribute to sustained transcription activity of this coactivator [73, 74].

The multitude of PTMs is a result of the complex signaling network that converges on PGC-1α. Uncovering mutual influences and resolving the chronology of events in different organs in greater detail remains to be done.

Role of PGC-1 coactivators in oxidative metabolism and skeletal muscle function

PGC-1α orthologs are present in all vertebrate species, with 95 % sequence homology between mouse and human, and a high degree of conservation in the AD and NR interaction domain [21, 75]. In *Drosophila*, the PGC-1 homologue spargel is essential for mitochondrial gene expression and spargel mutants display respiration defects [76]. This fundamental role of PGC-1 coactivators in cellular respiration is conserved across species, redundant between all three family members and important in all tissues that express PGC-1 coactivators. PGC-1α and PGC-1β are primarily enriched in organs with high oxidative capacity like skeletal muscle, heart, brown adipose tissue (BAT), kidney, and brain whereas PRC is found ubiquitously [8, 27, 35]. Hence, it appears that the coordination of oxidative metabolism is the central property of the PGC-1 family.

Mitochondrial biogenesis is necessary to meet higher energy demands in a cell. This complex process requires transcription of nuclear genes, import of the resulting proteins into mitochondria, transcription of mitochondrial DNA, and its replication. PGC-1 coactivators integrate these events in cooperation with nuclear transcription factors 1 (NRF-1), NRF-2 (also called GA-binding protein or GABP), and ERRα that induce nuclear-encoded mitochondrial genes like cytochrome C oxidase subunit 4 (COX IV), β-ATP synthase, and mitochondrial transcription factor A (Tfam) [24, 29, 34, 35, 77]. In turn, Tfam governs transcription and replication of mitochondrial DNA.

PGC-1α also induces NRF-1, NRF-2, and ERRα at the expression level [25, 78]. Further signal amplification occurs through NRF-2 and ERRα, which boost their own and each others' transcription respectively, to promote mitochondrial biogenesis in biological switches [79].

Surprisingly, however, mice with a global deletion of either PGC-1α or PGC-1β are viable, fertile, and do not show overtly deranged mitochondria [80–83]. Their ability to cope with different stress conditions (for example, exposure to

cold) is however grossly compromised. This indicates that PGC-1 coactivators are less required for basal mitochondrial function but are instrumental in orchestrating adaptations to environmental challenges.

Interestingly, the PGC-1 coactivators affect mitochondrial function in a specific manner. During electron transport, protons may leak over the inner mitochondrial membrane. Ectopic expression of PGC-1α in muscle cells promotes this leakage to a larger extend than PGC-1β, although their effect on respiration is comparable [84].

Mitochondrial biogenesis is accompanied by an increase in ROS production. To alleviate the resulting oxidative stress, PGC-1α and PGC-1β enhance the expression of ROS detoxifying enzymes like glutathione peroxidise 1 (GPx-1) and mitochondrial superoxide dismutase [Mn], (Sod2). Accordingly, PGC-1α acts neuroprotectively under oxidative stress conditions [85].

Higher rates of oxidative phosphorylation require elevated substrate supply. PGC-1α and PGC-1β augment fatty acid oxidation by coactivating ERRα and PPARα in a constitutive and a ligand-dependent manner, respectively, which propagates the expression of key enzymes of this process such as medium-chain specific acyl-CoA dehydrogenase (MCAD) [9, 17, 86]. In addition, PGC-1α fosters peroxisome biogenesis, an organelle that catabolizes very long- and branched-chain fatty acids [87]. In summary, PGC-1 coactivators drive a whole program of oxidative metabolism to provide sufficient amounts of energy to the cell.

In skeletal muscle, PGC-1α is abundant and particularly enriched in slow twitch, oxidative muscle fibers that contain a large number of mitochondria. Forced expression of PGC-1α converts white muscles with mainly fast fibers into red muscles with properties of slow-twitch type I and IIa fibers while PGC-1β provokes a fiber type switch to type IIx fibers [88, 89]. In agreement with its role in oxidative myofiber determination, PGC-1α is transiently induced in skeletal muscle after a single bout of endurance exercise and chronically elevated in endurance trained muscle both in rodents and humans [90–92].

Many, if not all, major adaptations of skeletal muscle in response to endurance training are mediated by PGC-1α, which therefore represents an important point of convergence in the exercise-triggered signaling network. The formation of a larger proportion of oxidative fibers requires mitochondrial biogenesis, fatty acid uptake (e.g., by CD36), and oxidation (e.g., by MCAD) in the myocyte to ensure adequate substrate supply. All of these processes are coordinately regulated by PGC-1α [93, 94]. PGC-1α also augments GLUT4 expression in vitro and in vivo yielding higher glucose uptake into muscle cells [26, 94]. Pyruvate dehydrogenase kinase 4 (PDK4) is induced concomitantly to promote fatty acid oxidation at the expense of glucose metabolism [95]. Excess glucose that cannot be diverted into glycolysis is consequently stored in the form of glycogen and funneled into the pentose phosphate pathway [94, 96, 97]. The resulting elevation of NADPH and the PGC-1α-mediated activation of fatty acid synthase boost de novo lipogenesis and thus increased storage of intramyocellular lipids that serve as energy substrate. Thereby PGC-1α coordinates anabolic and catabolic metabolic pathways in skeletal muscle [98].

Elevated ROS are a byproduct of higher mitochondrial activity in contracting skeletal muscle. As ROS reinforce PGC-1α expression, which contributes to ROS detoxification by raising enzymes like Sod2 (see above), this negative feedback loop protects myocytes effectively from oxidative stress [99, 100].

Apart from metabolic fluxes within the cell, PGC-1α also tightly links muscle and nerve by regulating neuromuscular junction genes and promoting acetylcholine receptors clustering at the motor end plate [101]. In addition, PGC-1α triggers a remodeling of calcium handling in muscle cells towards a slow fiber-type phenotype [102]. Finally, PGC-1α further affects angiogenesis by potently inducing vascular endothelial growth factor expression to maintain nutrient and oxygen supply to muscles during sustained contractions [103, 104].

In combination, all of these PGC-1α-mediated changes functionally translate into a higher endurance capacity as observed in PGC-1α skeletal muscle-transgenic mice whereas skeletal muscle-specific deletion of PGC-1α decreases performance [96, 105].

The regulation and function of PGC-1β is much less clear. For example, PGC-β is not uniformly influenced by exercise. Nevertheless, when overexpressed in skeletal muscle, genes involved in oxidative phosphorylation and fatty acid oxidation are also upregulated by PGC-1β resulting structurally in a higher mitochondrial density and functionally in a better endurance performance [89]. Inversely, skeletal muscle-specific PGC-1β deletion causes lower endurance capacity [106]. A combined deficiency of PGC-1α and PGC-1β in a global PGC-1α and a muscle-specific PGC-1β knockout background aggravates this phenotype displaying a very severe exercise deficit, strongly reduced oxidative capacity, and mitochondrial structure and function derangements. However, fiber type determination is only slightly changed in these mice [106]. Similar to PGC-1α, PGC-1β was also shown to enhance angiogenesis [107]. It therefore appears that PGC-1α and PGC-1β share some properties in skeletal muscle and can potentially compensate for one another in some cases. The role as "exercise factor" is however unique to PGC-1α, and such a clear physiological function has not been assigned to PGC-1β so far.

Aside from the regulation of endurance adaptations, PGC-1α is a target of the myogenic regulatory factor MyoD in terminal muscle differentiation and plays a role in regulating circadian clocks in muscle [108, 109]. Interestingly, MyoD itself is under the control of circadian transcription activators

and their disruption perturbs muscle function as well as PGC-1α and PGC-1β expression [110]. Further studies are needed to investigate the mutual dependencies of PGC-1 coactivators, MyoD, and clock genes to define their contribution to skeletal muscle physiology.

Other organ-specific functions of PGC-1 coactivators

In addition to the regulation of oxidative metabolism, PGC-1 coactivators also execute an array of tissue-specific functions. In the liver, PGC-1α is markedly upregulated in response to fasting and controls several important starvation pathways including gluconeogenesis and ketogenesis [18, 22, 49]. PGC-1α further governs hepatic heme, bile acid, selenoprotein P, and homocystein biosynthesis [111–114]. PGC-1β by contrast is central to lipid metabolism in the liver by inducing lipogenesis and the secretion of triglycerides/VLDL into plasma [31, 33].

Cardiac PGC-1α is augmented both in development when, perinatally, fatty acids replace glucose as main source of energy, and in adult animals upon fasting. Lack of either PGC-1α or PGC-1β promotes heart failure under stress conditions while a PGC-1β cardiac deficiency combined with a global PGC-1α gene ablation is lethal shortly after birth as those hearts are unable to mature [115–118]. Inversely, cardiac PGC-1α overexpression causes disturbances in the sarcomere structure leading to dilated cardiomyopathy [119]. PGC-1 coactivator levels are thus only protective within a certain window of expression.

PGC-1α was originally discovered as thermogenic regulator in BAT induced by cold exposure [8]. BAT produces heat by uncoupled respiration whereas white adipose tissue (WAT) mainly stores energy in form of lipid droplets. Both PGC-1α and PGC-1β are critical for adequate BAT function and participate in brown fat lineage determination [118, 120, 121]. Induction of PGC-1α in WAT thus results in "browning" while PGC-1α suppression favors a white adipocyte phenotype [122–125]. Accordingly, mice with an adipose tissue-specific deletion of PGC-1α on high fat diet develop insulin resistance as the excess energy cannot be sufficiently dissipated [126].

In pancreas, both PGC-1α and PGC-1β are involved in glucose-stimulated insulin secretion from β cells; their contribution is however controversial as suppression and induction of insulin release have been reported [32, 127, 128].

Both coactivators control mitochondrial density in nerve cells [129]. Neuroprotection through PGC-1α was shown in the contexts of oxidative stress and amyotrophic lateral sclerosis whereas neurodegeneration is associated with a loss of PGC-1α in various disorders including Huntington's and Alzheimer's disease [85, 130–132]. Consistently, global and brain-specific deletion models of PGC-1α exhibit striatal degenerative lesions and increased susceptibility for other neurodegenerative events [80, 133].

PGC-1α also plays a role in light damage-induced retinal regeneration and function and in chondrogenesis [134, 135]. PGC-1β is further implicated in osteoclast activation and PRC has a non-redundant function in proliferative growth [136, 137].

PGC-1 coactivators in skeletal muscle pathology

Skeletal muscle exhibits considerable plasticity and adapts to different training regiments as well as disuse. While endurance exercise induces PGC-1α as described above, different experimental or pathological muscle wasting conditions like denervation-induced atrophy, statin treatment, diabetes, uremia, and cancer cachexia reduce PGC-1α and/or PGC-1β levels [138–141]. Accordingly, ectopic expression of PGC-1α or PGC-1β counteracts the atrophic state by suppressing atrogenes in vitro and in vivo [140–142]. PGC-1 coactivators are thus able to preserve muscle structure and function under unfavorable circumstances. This observation extends to sarcopenia (progressive muscle loss with age) as old mice with transgenic PGC-1α expression in skeletal muscle show a higher degree of muscle integrity, improved mitochondrial function, and better exercise performance than age-matched wild-type animals [100].

Several inherited disorders affect skeletal muscle function. Duchenne muscular dystrophy (DMD) is caused by a mutation in dystrophin. Mutated dystrophin fails to link the cytoskeleton to the extracellular matrix leading to muscle degeneration and premature death. Mitochondrial myopathies stem from mutations in mitochondrial DNA. Skeletal muscle-specific overexpression of PGC-1α is able to antagonize symptoms of both disorders in respective mouse models [101, 143]. PGC-1α therefore dampens fiber damage and preserves muscle function in those contexts. A non-genetic approach deploying endurance training also raised PGC-1α levels and protected mice with mitochondrial myopathy [144].

The etiology of Huntington's disease (HD) involves loss of muscle mass which coincides with a reduction of PGC-1α expression in rodents and humans. This wasting phenotype could be improved by artificially increasing PGC-1α levels in skeletal muscle [145].

Genetic and acquired obesity are strongly correlated with the development of insulin resistance and diminish both PGC-1α and PGC-1β levels in rodent skeletal muscle [146]. In human diabetic patients, a coordinate suppression of genes involved in oxidative phosphorylation has been observed concomitant with a reduction of PGC-1α and PGC-1β in some, but not all studies [147–149]. This suggests that dysregulated PGC-1 coactivator levels may account for disturbed energy metabolism in skeletal muscle contributing to the development of insulin resistance. Inversely, a moderate PGC-1α increase in skeletal muscle improves insulin sensitivity through the selective elevation of fatty acid oxidation in subsarcolemmal, but not intermyofibrillar mitochondria [150].

The relationship between PGC-1 coactivators and insulin resistance is however more complex as two independent mouse strains lacking PGC-1α are less susceptible to diet-induced obesity possibly owing to hyperactivity, which is likely a consequence of striatal brain lesions [80, 81]. Skeletal muscle-specific deletion models still display higher peripheral insulin sensitivity; however, they do become glucose-intolerant on a high fat diet. This puzzling phenotype is the result of muscle-islet crosstalk whereby muscle-derived IL-6 and possibly other factors might impair insulin secretion from pancreas leading to a deficit in glucose clearance from blood but at the same time to high insulin sensitivity in the periphery [151].

Surprisingly, muscle-specific PGC-1α overexpressing animals develop insulin resistance at an accelerated pace on high fat diet compared with wild-type mice presumably due to excess lipid storage within muscle cells [152]. Interestingly, the same model is however protected from sarcopenia and preserves insulin signaling and sensitivity until old age [100]. In a twin study, PGC-1α and PGC-1β emerged as factors declining with age which might contribute to an increased risk of diabetes in this phase of life [153]. Dropping PGC-1α levels are associated with the common Gly482Ser variant, but an unequivocal mechanistic link of this polymorphism to diabetes could not be established as the serine containing variant seems fully functional [154–156]. A polymorphism within the PGC-1α promoter however clearly contributes to diabetes in Koreans and Austrians [157, 158].

PGC-1β protects mice from genetic and acquired obesity, but without effect on whole-body glucose metabolism or skeletal muscle insulin sensitivity [29, 82, 159]. Loss of function however promotes hepatic insulin resistance because of lipid accumulation in the liver [82, 159]. Yet, genetic linkage studies failed to prove a clear association of the Ala203Pro variant with obesity or diabetes [160, 161].

A PGC-1α/PGC-1β double-deficient model based on global PGC-1α and muscle-specific PGC-1β gene ablation surprisingly is unaffected in terms of glucose or insulin tolerance on different diets. Importantly, however, the global PGC-1α deletion background confounds interpretation of these findings due to its complex brain phenotype [106].

Pharmacological treatment of mice with resveratrol protects them from diet-induced obesity and insulin resistance as Sirt1-dependent PGC-1α activation stimulates oxidative metabolism in skeletal muscle [162, 163]. Furthermore, the insulin-sensitizing properties of thiazolidinediones are at least partially ascribed to an induction of PGC-1α and the concomitant restoration of mitochondrial bioenergetics in muscle, e.g., in db/db mice [164].

Targeting PGC-1 coactivators in skeletal muscle to fight musculoskeletal and metabolic diseases and especially increase insulin sensitivity is therefore a worthwhile venture. There is however a therapeutic window for these beneficial effects as excessive PGC-1 coactivator levels may act counterproductive [165]. Dysregulation of these coactivators in other organs further complicate treatment as, for example, in liver and pancreas of diabetic patients, PGC-1α levels are increased which contributes to pathology in these tissues [165]. Finding potent and specific PGC-1α and PGC-1β activators and inhibitors is thus of prime interest.

Inflammation

Major molecular pathways in inflammation

Inflammation is the protective response of the body to harmful insults like pathogens and wounding aiming at defense and repair to secure the organism's integrity. The immune system has evolved to govern these inflammatory reactions and comprises two branches, innate and adaptive immunity, respectively. The innate immune system is able to react rapidly and initiate an inflammatory reaction within minutes. The adaptive immune system operates secondarily and thus delayed, but is highly specific. Immune cells communicate with injured or infected cells and other immune cells via small, soluble peptides, so-called cytokines, which may elicit, potentiate, or dampen inflammation and thus fundamentally influence its progression. Potent pro-inflammatory cytokines include the tumor necrosis factor α (TNFα), interleukin 1β (IL-1β), IL-6, and macrophage inflammatory protein 1α (MIP-1α) while IL-4, IL-10, IL-13, and IL-1 receptor antagonist (IL-1Ra) act primarily as anti-inflammatory cytokines [166].

To transmit their signals, cytokines bind to cytokine receptors. These are grouped into different families according to their structure. Type I and type II cytokine receptors are multimeric transmembrane receptors that signal via the janus kinase (JAK)–signal transducers and activators of transcription (STAT) pathway while chemokine receptors are G protein-coupled receptors (GPCRs) with seven transmembrane domains that signal through G proteins. Members of the TNF receptor (TNFR) family oligomerize upon ligand binding. They are associated with adaptor proteins that may activate inflammatory or apoptotic pathways via TNFR-associated factors (TRAFs) and the caspase cascade, respectively. The transforming growth factor β (TGFβ) receptor family has three members that connect to SMAD proteins. Finally, some cytokine receptors belong to the immunoglobulin (Ig) superfamily.

Pathogens contain conserved structures, so-called pathogen-associated molecular patterns (PAMPs) that can be recognized by the host's immune system to initiate inflammation. PAMPs bind to Toll-like receptors (TLRs), which are expressed on the surface of immune and most other cells. So far, 12 mammalian TLRs with different binding specificities have been identified, e.g., TLR4 detecting lipopolysaccharide

(LPS). TLRs signal through adaptor proteins like myeloid differentiation primary response gene 88 (Myd88) that further activate IL-1R-asscoiated kinases (IRAKs) and TRAFs finally leading to inflammation [167].

While STATs and SMAD proteins are able to translocate to the nucleus and modulate transcription of inflammatory genes directly, GPCR signaling typically leads to the production of second messengers. TRAF activation downstream of TNFRs and TLRs causes activation of the NF-κB pathway [167]. This pathway is central to inflammatory reactions and has been shown to be involved in a large number of diseases. NF-κB activating signals converge at the inhibitor of κB (IκB) kinase (IKK) complex which comprises three subunits, IKKα, IKKβ (both catalytic), and IKKγ/NF-κB essential modulator (NEMO, regulatory). Canonical NF-κB signaling involves activation of IKK, which subsequently phosphorylates IκB preexisting in a cytosolic complex with NF-κB. Phosphorylation-induced polyubiquitination targets IκB for proteasomal degradation, consequently releasing NF-κB that then translocates to the nucleus where it binds to κB sites and thus promotes transcription of inflammatory genes [168].

NF-κB binds DNA as homo- or heterodimer, and five different NF-κB family members are known: RelA/p65, RelB, c-Rel, p100/p52, and p105/p50 that all share an N-terminal Rel homology domain (RHD). P65, RelB, and c-Rel additionally contain a transactivation domain (TAD) which facilitates transcription whereas p50 and p52 homodimers act repressive as they lack this domain. The most common and best studied NF-κB dimer is p65/p50 [168].

Several ankyrin repeat domains are characteristic for the IκB family. The typical members IκBα, IκBβ, and IκBε sequester NF-κB dimers in the cytosol. They are degraded at different rates upon stimulation and also possess specific re-synthesis kinetics [169]. As NF-κB target genes, the IκBs initiate a negative feedback loop to terminate NF-κB signaling [170]. The atypical IκB family members IκBγ, B cell lymphoma 3 (Bcl3), and IκBζ bind to NF-κB dimers in the nucleus and modulate their transcription activation potential at this level [168]. The precursor proteins p100 and p105 can also be classified as IκBs with ankyrin repeat domains despite constitutive processing to p52 and p50 even in the basal state. P100 and p105 may also dimerize with other NF-κB subunits, e.g., RelB and c-Rel, respectively, retaining this complex in the cytosol in unstimulated cells. Stimulus-dependent processing of p100 and p105 to p52 and p50 then yields active NF-κB dimers [168].

The canonical pathway described above involves the heterotrimeric IKK complex, IKKβ-dependent phosphorylation of IκBα, and subsequent release of p65/p50 [168, 171]. While IKKα is dispensable for canonical signaling, it is required for noncanonical NF-κB activation [172]. The noncanonical pathway is initiated by IKKα dimers that phosphorylate p100 upon stimulation. As p100 preexists in a complex

with RelB, processing to p52 generates the RelB/p52 dimer, which is able to induce a subset of NF-κB target genes [173]. Noncanonical NF-κB activation has been described, for example, downstream of CD40, lymphotoxin β receptor (LTβR), and B cell activating factor receptor (BAFFR) [174–176].

PTMs of NF-κB subunits also influence inflammatory signals, and p65 has been studied extensively in this regard. Inducible phosphorylation, acetylation, ubiquitylation, prolyl isomerisation, poly(ADP-ribosyl)ation, monomethylation, and S-nitrosylation have been reported so far. Their presence affects the subcellular localization, the stability of DNA binding, and the affinity to coactivator and corepressor complexes which determine the NF-κB transcription activation potential [168].

Besides the NF-κB pathway, activator protein 1 (AP-1) signaling plays an important role in inflammatory reactions. The induction of MAPK cascades, e.g., downstream of TNFR and TLRs, leads to activation of AP-1, which, similar to NF-κB, is a homo- or heterodimeric transcription factor. The subunits belong to the Jun, Fos, or activating transcription factor (ATF) families of basic-region leucine-zipper (B-ZIP) proteins that bind DNA at specific sequences and thus induce transcription of inflammatory target genes. A well-studied example is the activation of JNK, which in turn translocates to the nucleus where it phosphorylates c-jun, thereby promoting AP-1's transcription activation potential [177, 178].

Finally, interferon regulatory factors (IRFs) mediate the induction of interferons and are as such critical in the response to viral infections [179].

The many players within the NF-κB and AP-1 pathway illustrate the complexity and redundancy of inflammatory signaling. This complexity is necessary to allow the body to mount a highly specific immune response to different kinds of injury and infection in order to protect the body at all times. The nature of inflammation is transient, and therefore termination of immune responses is as important as initiation. If inflammatory reactions do not resolve and become chronic, they in fact turn detrimental and harmful to the body. Chronic inflammation also accompanies many pathologies including type 2 diabetes and cardiovascular diseases.

Inhibition of inflammation may occur at several levels. Changes in gene expression of the pro-inflammatory transcription factors themselves and/or their upstream regulators affect inflammatory promoters. Examples are the resynthesis of IκB proteins that retain NF-κB in the cytosol and thus block transcription, and the induction of repressive p50 or p52 homodimers that compete for κB sites in the nucleus [168].

PTMs also interfere with inflammatory signaling. Suppressor of cytokine signaling 1 (SOCS1), for example, is able to ubiquitinate p65, and its overexpression inhibits IL-1β-dependent NF-κB activation [180]. Then, A20-deficient mice develop severe inflammation because the dual ubiquitin-editing enzyme A20 targets important signaling molecules

like RIP1 and TRAF6 for degradation, thereby confining inflammatory processes [181, 182]. As phosphorylation events are important during the activation of most inflammatory pathways, changes in kinase and phosphatase activity influence pro-inflammatory gene expression. Again, the NF-κB pathway provides excellent examples: IKKβ-deficient MEFs can neither phosphorylate IκBα nor p65 while IKKα-deficient MEFs normally degrade IκBα but are still unable to phosphorylate p65, which blunts transcription from NF-κB-inducible promoters [183]. Inversely, mice lacking Wip1, the only known p65-specific serine phosphatase, display increased NF-κB target gene expression alongside higher p65 phosphorylation levels [184].

Transrepression by NRs has emerged as a potent mechanism to confine inflammation. Accordingly, PPARα activation reduces expression of IL-6, cyclooxygenase 2 (COX2), vascular cell adhesion molecule 1 (VCAM1), and other inflammatory factors in different cell types whereas PPARα deletion renders mice hypersensitive to LPS [185–187]. PPARγ ligands and glucocorticoids, activators of the GR, likewise exhibit strong anti-inflammatory effects [188–191]. In contrast to transactivation that requires direct NR-DNA binding, transrepression may occur indirectly without direct contact to DNA.

Several molecular mechanisms of transrepression were established so far. DNA–binding-dependent or DNA–binding-independent induction of IκBα as shown for PPARα terminates NF-κB target gene expression [192–194]. Moreover, competition for a limiting pool of coactivators like CBP results in mutual antagonism between inflammatory and NR pathways [195, 196]. NRs may also disrupt the coactivator complex at inflammatory transcription factors by binding either to the transcription factor, thus preventing coactivator binding (e.g., GR on p65) or to the coactivator thus hindering its recruitment [197]. Additional cofactors like nuclear TR-interacting protein 6 may favor GR binding, which in turn promotes transrepression, while secondary recruitment of corepressors like glutamate receptor-interacting protein or CoREST propagate this state [198–200]. PPARγ and LXR can further inhibit corepressor clearance from NF-κB by preventing proteasomal degradation of NcoR1 in a ligand- and SUMOylation-dependent manner [201, 202]. SUMOylation is also implicated in LXR-mediated transrepression of STAT1 downstream of interferon signaling [203]. Furthermore, PPARα interacts with both c-jun and p65 to repress AP-1- and NF-κB-driven gene expression, respectively [204]. As a consequence of this direct interaction, NR and inflammatory signaling pathways reciprocally interfere with each other constituting a negative cross-talk. Finally, GR may also constrain both transcription initiation and elongation by blocking RNA polymerase II hyperphosphorylation and chromatin remodeling by tethering HDACs to promoters of inflammatory genes [205–208].

Obesity and inflammation

Overweight and obesity do not only increase the risk for metabolic complications like insulin resistance but also foster a sterile, low-grade inflammation. This is evidenced by high plasma levels of circulating pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-12, and TNFα), chemokines (monocyte chemoattractant protein (MCP) 1/CCL2, RANTES/CCL5, MIP-1), acute phase proteins (C-reactive protein, serum amyloid A, ferritin), adipokines associated with insulin resistance (retinol binding protein 4 and resistin), and procoagulative and hypertensive factors (plasminogen activator inhibitor 1 and angiotensinogen) in obese patients [209]. Inversely, negative acute phase proteins (transcortin and transferrin) and adipokines associated with insulin sensitivity (adiponectin, visfatin, omentin, and vaspin) are lowered in plasma of those subjects [209].

As expansion of adipose depots is the prime effect of obesity, an inflammatory reaction in WAT is the major source of elevated circulating pro-inflammatory factors [210]. WAT inflammation thereby involves both adipocytes and different immune cells that reside within WAT. Activation of the NF-κB and AP-1 pathways in adipocytes is a critical event in this process as it leads to expression and secretion of pro-inflammatory cytokines but also to adipocyte insulin resistance because IKK and JNK are able to phosphorylate IRS1 at inhibitory serine residues [211]. Consequently, JNK deletion ameliorates insulin resistance and improves insulin receptor signaling in obese animals [212].

To date, it is unknown which primary stimulus sets off the inflammatory reaction, but a number of aberrantly active cellular processes in WAT of obese subjects were shown to contribute. The presence of pro-inflammatory cytokines promotes IKK and JNK activation and indeed treatment of adipocytes with TNFα inhibits IRS1 action. In contrast, animals with disrupted TNFα signaling are protected from obesity-induced insulin resistance [211, 213]. High levels of free fatty acids that prevail in obesity are able to induce pro-inflammatory TLR signaling, and consequently, TLR4 deletion rescues animals from obesity-induced insulin-resistance [214]. Furthermore, ROS levels are aberrantly high in accumulated fat, producing oxidative stress and, as a result, NF-κB/AP-1 signaling [215]. If the capacity of adipocytes to store fat is exceeded, ER stress arises and free fatty acids leak into the cytoplasm where they in turn activate JNK [216]. The expansion of adipocytes might also outbalance angiogenesis, which leads to tissue hypoxia and the induction of hypoxia-inducible factor 1α (HIF-1α) that itself promotes pro-inflammatory cytokine expression [217]. In combination, ER stress and hypoxia exacerbate adipocyte necrosis. The dying cells then nucleate the formation of crown-like structures (areas of necrotic cells surrounded by macrophages), which are absent in lean animals [218].

Adipose tissue macrophages (ATMs) are plastic cells that may polarize towards an anti-inflammatory M2 or a pro-inflammatory M1 state. The two phenotypes are characterized by the distinct sets of cytokines that they express. Hence, the highly inflammatory TNFα, IL-1β, and IL-6 are secreted by M1 macrophages while M2 macrophages produce anti-inflammatory factors like IL-10. In WAT of lean animals, M2 macrophages are more prominent than M1 macrophages. Their polarization is driven by adipocyte-derived IL-13, IL-4, and adiponectin as well as the prevalence of unsaturated free fatty acids leading to PPAR activation [219–221]. Accordingly, myeloid ablation of PPARγ or PPARβ/δ impairs M2 skewing and fosters inflammation and insulin resistance [219, 222]. M2 macrophages exhibit an oxidative metabolic profile, and PGC-1β is essential in initiating M2 polarization [223].

In contrast, M1 macrophages are highly enriched in WAT of obese animals where they amplify and sustain tissue inflammation [224, 225]. The altered cytokine/adipokine profile in fat, high levels of saturated free fatty acids, and the emergence of crown-like structures promote the phenotypic switch from M2 to M1 macrophages [226]. M1 macrophages also express MCP-1, which attracts monocytes that migrate from the circulation into WAT where they differentiate into M1 macrophages further perpetuating inflammation. Adipose tissue-specific overexpressing of MCP-1 thus renders animals insulin-resistant, while deletion of the MCP-1 receptor CCR2 prevents M1 macrophage accumulation and maintains insulin sensitivity under high fat feeding [227–229]. Similarly, myeloid deletion of TLR4, JNK, or IKKβ interferes with M1 macrophage polarization and consequently rescues insulin sensitivity on a high fat diet without differences in body weight gain [230–232].

Besides ATMs, other immune cells contribute to both anti-inflammatory, insulin-sensitive and the pro-inflammatory, insulin-resistant states. Eosinophils, CD4+ regulatory T, and Th2 cells all reside in WAT of lean animals where they preserve M2 macrophage activation and insulin sensitivity while the T cell balance in obese animals tips towards Th1 cells that secret IFNγ, hence skewing macrophages towards the M1 phenotype [233–236]. This polarization is further advanced by pro-inflammatory neutrophils, CD8+ effector T cells, and B cells that all have been detected in WAT in the early stages of obesity [237–239]. Therefore, depletion of immune cells types associated with M1 polarization or induction of M2-sustaining immune cells ameliorates insulin resistance [233, 234, 239, 240].

In other organs, inflammatory reactions during the course of obesity have received less attention. The liver plays a major role in glucose metabolism due to hepatic gluconeogenesis. M1 polarization of Kuppfer cells (liver macrophages) is now thought to contribute to hepatic inflammation, insulin resistance, and steatosis. Recently, pancreatic β cell failure has also been linked to islet inflammation and M1 macrophage accumulation [241]. It therefore appears that inflammation with M1 macrophage polarization could be a general mechanism underlying organ dysfunction in obesity.

The situation in skeletal muscle is somewhat less clear. Intramuscular fat depots form in obese animals and attract inflammatory macrophages, however to a much smaller extent compared to *bona fide* adipose tissue [224]. These macrophages exert a negative influence on muscle insulin sensitivity as shown in obese animals with myeloid deletion of either JNK or IKKβ [231, 232]. In these models, inhibition of M1 macrophage activation preserved muscle insulin sensitivity [231, 232]. The same effect was observed after depletion of Cd11c+ cells that correspond to the main M1 macrophage subset in muscle [242]. Inversely, even lean animals with myeloid deletion of PPARγ developed muscle insulin resistance, which deteriorated in the obese state due to impaired M2 macrophage polarization [243]. In contrast, myeloid deletion of PPARβ/δ or TLR4 did not entail any effect on muscle insulin sensitivity [219, 230].

These observations imply that skeletal muscle insulin resistance is at least partially regulated by mechanisms that are different from WAT. Investigating these common and distinct processes in skeletal muscle warrants further studies. The caveat of myeloid deletion approaches is however that all macrophages in the body are polarized towards one or the other phenotype. Distinguishing between purely skeletal muscle-specific cross-talk of macrophages and myocytes versus whole body effects on the muscle, e.g., through generally lower circulating cytokine levels, remains a difficult endeavor. Future experiments will have to discern the exact role of M1 and M2 macrophages in skeletal muscle under conditions of obesity.

Inflammatory pathways in skeletal muscle

Adult skeletal muscle contains substantial amounts of different NF-κB family members; their role in muscle physiology is however not fully resolved. It is unclear whether NF-κB is a pro-myogenic or an anti-myogenic factor during muscle differentiation as relevant data are conflicting, but suppression of myogenesis by means of inhibiting MyoD, myogenin, and myofibrillar gene expression has been linked to canonical NF-κB signaling [244–252]. In contrast, noncanonical NF-κB signaling that involves IKKα and RelB does not affect myogenesis but drives an oxidative muscle fiber switch by targeting PGC-1β, which stimulates mitochondrial biogenesis [253]. Exercise-dependent NF-κB activation has also been reported in skeletal muscle and potentially induces ROS defense, regeneration of damaged fibers, and adaptations in fuel metabolism [254–256].

In muscle pathology, inflammatory reactions accompany a number of disorders like cachexia, muscular dystrophy,

atrophy, and inflammatory myopathies [257]. NF-κB activation in these contexts is a well-established disease mechanism that contributes significantly to deterioration of muscle function. This also is evident in mice with skeletal muscle-specific overexpression of IKKβ, which causes severe muscle wasting while muscle-specific deletion of this kinase improves strength and counteracts denervation-induced atrophy and fiber type changes [258, 259]. Moreover, the latter model, similar to a p65 deletion model, regenerates faster from injury as inflammation is substantially inhibited in both mouse lines [252, 259].

Regeneration of skeletal muscle requires the activation of satellite cells (muscle stem cells), their fusion to damaged fibers, or the formation of new fibers depending on the degree of injury. Satellite cell proliferation is stimulated by IL-6 while IL-4 promotes myoblast fusion [260, 261]. Satellite cells also attract and interact with monocytes/macrophages to foster muscle growth [262]. Therefore, macrophages are also engaged in the different stages of regeneration: M1 macrophages (CD68+/CD163−) readily remove cellular debris by phagocytosis directly after injury and contribute to satellite cell activation while M2 macrophages (CD68−/CD163+) invade the tissue later [263]. They promote satellite cell differentiation and muscle growth in later regenerative stages to restore muscle function [264]. The M1/M2 macrophage switch is presumably initiated by muscle-derived IL-4 [261]. In dystrophic muscle, M1 macrophage activation and concomitant M2 macrophage repression, e.g., by IFNγ exacerbates muscle wasting in DMD while, conversely, symptoms are alleviated by IL-10, which activates M2 and represses M1 macrophages [265, 266].

PGC-1 coactivators and inflammation in skeletal muscle

Anti-inflammatory effect of exercise

Skeletal muscle has been recognized as an endocrine organ that releases myokines (muscle-derived cytokines) like IL-6, IL-8, and IL-15 during contraction [267]. These myokines presumably mediate beneficial effects of exercise both on the muscle itself and on distant organs. IL-6 has received most of the attention and the majority of studies deal with this myokine. The induction of IL-6 after exercise was speculated to be under the control of nuclear factor of activated T cells (NFAT) and/or p38/MAPK as opposed to NF-κB during inflammatory reactions [268]. While elevated IL-6 levels are also associated with chronic inflammation, the contraction-induced rise of IL-6 is transient and thus not detrimental. Accordingly, IL-6 infusion increases insulin-stimulated glucose disposal in humans whereas deletion of IL-6 in mice results in mature-onset diabetes [269, 270]. Importantly, IL-6 receptor expression is augmented concomitantly to IL-6 post

exercise. This heightens "IL-6 sensitivity" while reciprocally, under conditions of chronic inflammation, "IL-6 sensitivity" might be lost (analogous to insulin resistance with high levels of insulin) [271].

Diseases that are associated with a systemic, low-grade inflammation may be antagonized by physical activity, e.g., diabetes, sarcopenia, and neurodegeneration [272–275]. Muscle-derived IL-6 preludes expression of the anti-inflammatory cytokines IL-1Ra and IL-10 in blood while inhibiting pro-inflammatory TNFα production [276, 277]. This skews the immune reaction towards a type 2 response.

Following contraction, plasma levels of immunomodulatory hormones like epinephrine, cortisol, growth hormone, and prolactin are all high and suppress inflammatory reactions [272]. On monocytes, exercises reduce TLR1, TLR2, and TLR4 expression and function, alongside a decrease in major histocompatibility complex II and costimulatory molecules rendering these cells less inflammatory [278]. Potentiation of these effects after very strenuous training leads to temporary immunodepression as observed in high-performance athletes [272].

Mutual influence of inflammatory factors and PGC-1s

Inflammatory stimuli affect endogenous PGC-1 coactivator levels in different organs whereby LPS-induced sepsis is the most extensively studied model in this regard. In heart, kidney, and liver, PGC-1α, ERRα, and MCAD mRNA was markedly reduced 16 h after LPS injection [279]. Furthermore, in cardiac tissue, inflammation-dependent PGC-1α repression was further confirmed in vitro and in vivo, which could be rescued by inhibiting the NF-κB pathway [280–282]. Sepsis-associated acute kidney injury is associated with swollen, dysfunctional mitochondria and reduced PGC-1α levels that correlate with renal impairment [283]. This phenotype can be recapitulated by treatment of tubular cells with TNFα and reversed by excess PGC-1α while lack of this coactivator results in persistent kidney injury after endotoxemia [283]. In contrast, one study reported an opposite regulation of PGC-1α and PGC-1β in liver of septic mice, as both coactivators were induced in a TLR2-dependent manner [284].

In skeletal muscle, the regulation of PGC-1 coactivators by inflammatory stimuli is ambiguous. An early study found that LPS, TNFα, and IL-1β augment PGC-1α expression, resulting in increased oxidative phosphorylation while, more recently, sepsis was shown to lower PGC-1α and PGC-1β in skeletal muscle of rats [61, 285]. In support of these data, PGC-1α and PGC-1β are also reduced in diaphragm after LPS administration with concomitant decrease in fatty acid oxidation [286]. A more careful examination of the time-course revealed that intraperitoneal injection of LPS induced PGC-1α in skeletal muscle after 2 h, but decreased its expression after 24 h, suggesting a short-term upregulation but a

long-term downregulation [287]. This model is also well in line with the induction of PGC-1α after exercise in the transient presence of myokines that return to basal levels quickly as opposed to the chronic, low-grade inflammation observed in metabolic disorders with dampened PGC-1 coactivator levels in skeletal muscle. A repression of PGC-1α and PGC-1β upon chronic TNFα or IL-1β exposure was also observed in C2C12 myotubes [288]. Importantly, inflammatory stimulation with the activation of classical NF-κB signaling clearly impaired the oxidative phenotype in this system [288]. Cell culture studies with palmitate further back the abovementioned, dual regulation as long-term treatment repressed, while short-term treatment increased PGC-1α expression [289]. However, one study also associated long-term palmitate administration with an increase in PGC-1α in vascular smooth muscle cells [290].

A pathological condition frequently associated with muscle wasting and low oxidative capacity is chronic obstructive pulmonary disease (COPD). COPD patients also exhibit high TNFα levels in skeletal muscle alongside decreased PGC-1α expression [291]. This repression can be replicated in vitro by chronically treating the C2C12 muscle cell line with TNFα. The subsequent inhibition of oxidative phosphorylation is dependent on NF-κB [291, 292]. Similarly, TNFα is augmented in mice exposed to cigarette smoke while PGC-1α levels in skeletal muscle of these animals are diminished [292]. The impairment in expression of PGC-1α and some of its target genes is more pronounced in oxidative muscles [292]. Of note, plasma TNFα levels in COPD patients negatively correlate with PPARα expression in skeletal muscle [293]. Overall, these data imply that chronic inflammatory stimulation and especially NF-κB signaling lead to a suppression of PGC-1 coactivator levels.

An inverse, body mass index-independent correlation between PGC-1α and IL-6 as well as TNFα expression is also present in skeletal muscle of diabetic patients [151]. In accordance, mouse models that lack PGC-1α in skeletal muscle or only express it heterozygously display higher IL-6 levels in muscle and blood [151]. Complete lack of muscle PGC-1α further promotes the expression of pro-inflammatory markers like TNFα and CD68 in skeletal muscle [151]. After exercise that increases PGC-1α levels in wild-type mice, excessive TNFα expression in muscle and blood can be observed in this model [105]. Therefore, low PGC-1α levels in skeletal muscle are associated with inflammatory processes in muscle and the appearance of circulating pro-inflammatory cytokines.

A causal relationship between PGC-1 coactivators and inflammation has recently been established. PGC-1α and PGC-1β were shown to diminish the increase in pro-inflammatory cytokine expression elicited by TNFα, TLR agonists, and saturated free fatty acids in C2C12 muscle cells [294]. In human aortic smooth muscle and endothelial cells, PGC-1α likewise decreased TNFα-induced VCAM-1 and MCP-1 expression [295]. Mechanistically, the PGC-1 coactivators target the NF-κB pathway and for example dampen expression of luciferase from an NF-κB-driven reporter in vitro and in vivo [142, 294]. More precisely, the PGC-1s lower phosphorylation of p65 in C2C12 cells and muscle-specific PGC-1α transgenic mice [100, 294]. One study however found elevated p65 phosphorylation levels in this model and no difference between wild-type and transgenic mice concerning muscle IL-6 and TNFα expression after short-term, intraperitoneal LPS injection [296]. In vitro, transrepression by PPARα is a second mechanism that contributes to the repression of pro-inflammatory cytokines in skeletal muscle cells [294].

Together, these results suggest that PGC-1 coactivators and inflammatory processes in skeletal muscle are linked in a reciprocal manner (Fig. 2). Therefore, high PGC-1 expression not only determines an oxidative metabolic state but also favors an anti-inflammatory environment (Fig. 2a). Inversely, pro-inflammatory cytokines suppress PGC-1 coactivators leading to a more glycolytic metabolism in a highly inflammatory environment (Fig. 2b). The NF-κB pathways appears to be a nodal point in this mutual repressive action as NF-κB signaling strongly induces pro-inflammatory genes and at the same time suppresses PGC-1 coactivator expression. Conversely, at least canonical NF-κB signaling can be restrained by PGC-1 coactivators constituting an interdependent, negative, molecular regulation of oxidative metabolism and inflammation in muscle cells (Fig. 2).

In macrophages, this antagonism has previously been described during alternative activation which is associated with a decrease in the expression of pro-inflammatory markers and requires PGC-1β induction [223]. These M2 macrophages show signs of an oxidative metabolic program as opposed to M1 macrophages that rely mainly on glycolysis as energy-producing pathway. PGC-1β expression in macrophages furthermore drives the generation of mitochondrial ROS, which are vital in pathogen clearance [297]. The role of PGC-1α in macrophages is not well understood, but it likely participates in M2-like polarization as hypothesized for macrophages in epidydimal adipose tissue while it is downregulated after LPS exposure which leads to M1 macrophage polarization [298, 299]. PGC-1α inhibition in this case enables ROS production as many ROS-detoxifying enzymes are among PGC-1α target genes [299].

M1 and M2 macrophage-polarizing signals are mutually exclusive and thus preclude the opposite activation state. The anti-inflammatory cytokines IL-4, IL-10, and Il-13, for example, suppress M1 macrophage activation because they disturb NF-κB signaling and STAT1 activation by inducing inhibitory p50 dimers and STAT3/STAT6 [300, 301]. STAT6 is an important molecular determinant of M2 macrophage activation that cooperates with Krüppel-like factor 4 (KLF4) to induce anti-inflammatory M2 and inhibit pro-inflammatory M1
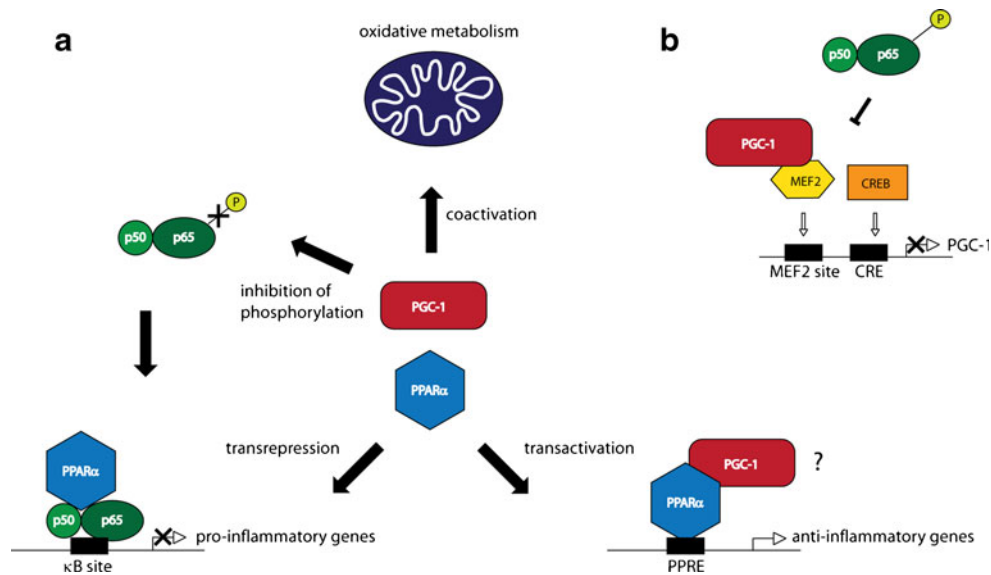
Fig. 2 Molecular mechanisms of the mutual antagonism between oxidative metabolism and inflammation in skeletal muscle. **a** PGC-1 coactivators negatively regulate inflammation. PGC-1 coactivators are at the crossroad of cellular respiration and inflammation as PGC-1α and PGC-1β coactivate a set of nuclear receptors and transcription factors to induce genes involved in oxidative metabolism. At the same time, PGC-1 coactivators interfere with inflammatory signaling at different levels. PGC-1α and PGC-1β inhibit phosphorylation of the NF-κB subunit p65 and thus restrain NF-κB signaling resulting in diminished expression of pro-inflammatory cytokines. Both coactivators also induce PPARα. This nuclear receptor acts as transrepressive on the promoters of pro-inflammatory genes equally limiting their expression. Inversely, expression of some anti-inflammatory genes has been shown to depend on PPARα. Whether PGC-1α and/or PGC-1β play a direct role in coactivating PPARα on the promoters of those genes is not known. Taken together, PGC-1 coactivators lower pro-inflammatory but induce anti-inflammatory genes, contributing to a less inflamed environment. **b** Classical NF-κB signaling inhibits PGC-1 expression. Inflammatory stimuli like NF-κB activation reduce expression levels of both PGC-1α and PGC-1β in various contexts. Expression of PGC-1α is driven by CREB and MEF2, the latter being coactivated by PGC-1α in a positive autoregulatory loop. NF-κB might constrain binding of those transcription factors to the PGC-1α promoter; the exact mechanism of this inhibition is however not known. Decreased PGC-1 coactivator expression in turn results in a decline of oxidative metabolism. *PGC-1*, peroxisome proliferator-activated receptor γ coactivator 1; *PPARα*, peroxisome proliferator-activated receptor α; *PPRE*, PPAR response element; *MEF2*, myocyte enhancer factor 2; *CREB*, cAMP response element binding protein; *CRE*, cAMP response element

genes [302]. Similarly, KLF2 also impairs NF-κB activation [303]. PPARγ and PPARβ/δ are required for M2 macrophage polarization. They induce both a more oxidative metabolic program within these immune cells and simultaneously transrepress pro-inflammatory promoters, which renders these nuclear receptors central players in the dichotomy between M1 and M2 macrophages reflecting the antagonism between oxidative metabolism and inflammatory gene expression [219, 222, 304]. If this adverse regulation that we propose to take place in macrophages and muscle cells also plays a role in other tissues remains to be determined. For example, canonical NF-κB signaling has previously been associated with positive regulation of mitochondrial biogenesis in embryonic fibroblasts and cancer cells [305, 306].

Transcription factors implicated in mitochondrial biogenesis are also potent inducers of the anti-inflammatory cytokines IL-10 and IL-1Ra in both macrophages and but also liver cells reinforcing opposite roles for oxidative metabolism and inflammation respectively [307]. IL-1Ra and IL-15α induction in primary hepatocytes after fasting, exercise, glucagon, or cAMP exposure which coincides with PGC-1α expression in these cells further confirms the association [308]. Elevation of

IL-1Ra and IL-15α is thereby dependent on PPARα [308]. PPARα thus seems to play a dual role in mediating the anti-inflammatory effect of oxidative metabolism: While this nuclear receptor acts transrepressive on the induction of NF-κB-dependent, pro-inflammatory genes, it also promotes the expression of anti-inflammatory cytokines, at least in hepatocytes. Both activities in concert then shift the balance between pro- and anti-inflammatory gene expressions. Similarly, conjugated linoleic acid ameliorates colitis in a model of inflammatory bowel disease by targeting PPARγ [309]. The treated mice show higher PGC-1α levels while NF-κB activation and TNFα expression are decreased [309].

A direct negative effect of any of the PGC-1 coactivators on pro-inflammatory gene expression is somewhat unlikely, as they have been described unequivocally as transcription coactivators that recruit factors which facilitate transcription at the promoter. In contrast, no corepressor activity for the PGC-1s is known so far. Besides PPARα-dependent transactivation and transrepression, direct interaction of PGC-1α or PGC-1β with NF-κB family members has been reported in various cell types. In bone marrow stromal cells, constitutive binding of PGC-1α to p65 and p50 was decreased in the presence of

PPARγ ligands leading to the hypothesis that PGC-1α is a shared coactivator that NF-κB and PPARγ compete for [310]. In hepatocytes, free fatty acids induce a p50–PGC-1α interaction and binding of this complex to the IL-10 promoter however with uncertain results concerning the role of PGC-1α in regard to coactivator or corepressor activity at this site [311]. In cardiomyocytes, binding of PGC-1α to p65 that increased upon TNFα exposure was detected [312]. The authors propose that p65 inhibits PGC-1α activity leading to a drop in PDK4 and subsequently higher glucose oxidation rates [312]. This would fit the model of NF-κB-dependent blockade of oxidative metabolism; some ambiguities concerning the exact mechanism however remain to be uncovered. In skeletal muscle cells, no direct interaction of p65 or any other NF-κB family member and PGC-1α or PGC-1β has been found.

PGC-1α may also interfere with upstream NF-κB signaling. An induction of IκBα has been observed in quadriceps of whole body PGC-1α transgenic mice in vivo but not in vitro while Bcl3 interacts with PGC-1α synergistically to coactivate ERRα and PPARα in cardiomyocytes [313, 314]. The reciprocity of oxidative metabolism and inflammatory signaling may thus extend beyond the antithetic roles of PGC-1 and NF-κB at the transcription activation level and could involve mechanisms like cofactor competition and up-regulation of phosphatases. The molecular details of such processes however remain to be investigated in future studies.

Functionally, it is clear that inflammation in WAT substantially contributes to the development of insulin resistance

under conditions of overfeeding with detrimental crosstalk between immune and fat cells (see above). Cues that this mechanism might also be in place in skeletal muscle derive from myeloid deletion studies where silencing of the pro-inflammatory genes JNK1, or IKKβ, in the hematopoietic compartment or depletion of Cd11c⁺ cells increased insulin-stimulated glucose disposal (which correlates to muscle insulin sensitivity) under high fat diet feeding conditions whereas hematopoietic PPARγ deletion had the opposite effect [231, 232, 242, 243]. M1 macrophage polarization thus seems to be associated with muscle insulin resistance while M2 polarization is linked to muscle insulin sensitivity. Accordingly, an accumulation of M1 macrophages in obese rodents and humans has been described, and pro-inflammatory macrophage markers within skeletal muscle correlate with poor glycemic control in diabetic patients whereas anti-inflammatory markers correlate with improved parameters in this setting [315, 316]. The model proposed here therefore implies that, in the insulin-sensitive state, M2 macrophages are the predominant phenotype in skeletal muscle (Fig. 3). Endurance training, which increases PGC-1α in the muscle cells, leads to the release of myokines that further mediate the anti-inflammatory effects of exercise, e.g., downregulation of certain TLRs on monocytes. In the ensuing anti-inflammatory environment, macrophages would remain polarized in an alternative activation state and retroact on myocytes through the release of anti-inflammatory factors that favor the maintenance of insulin sensitivity (Fig. 3). Indeed, a single bout of exercise has recently been shown to increase insulin
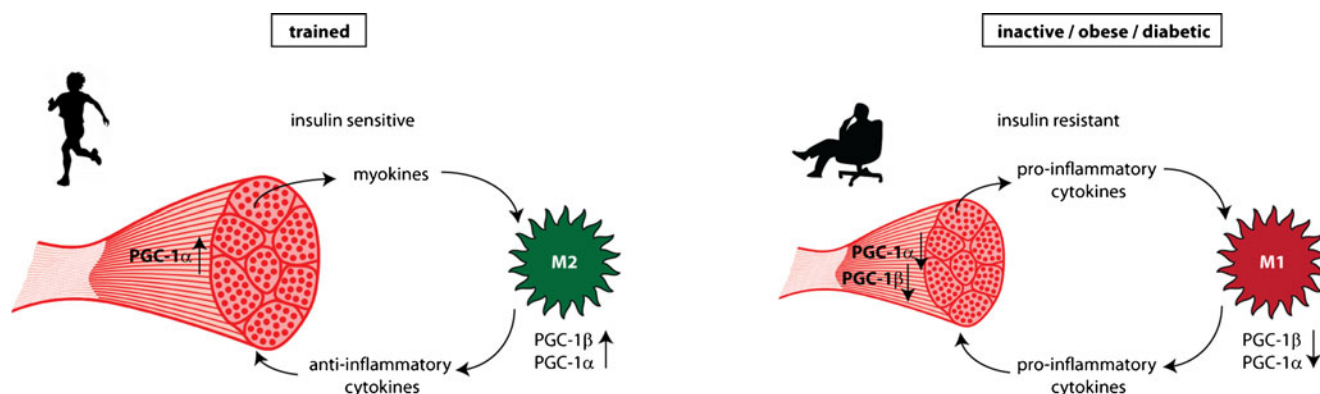

Fig. 3 Potential crosstalk of skeletal muscle and the immune system. In the trained state, skeletal muscle is insulin-sensitive, and PGC-1α levels are chronically increased. Muscle contraction leads to the release of myokines, which mediate many of the beneficial effect of exercise both locally and systemically. Analogous to the events in fat tissue of lean animals and humans, exposure of muscle-resident macrophages to these myokines could polarize them towards an anti-inflammatory M2 phenotype. These M2 macrophages in turn further secrete anti-inflammatory factors that help to maintain skeletal muscle in an insulin sensitive state. On the other side of the spectrum, PGC-1α and PGC-1β are chronically lowered in skeletal muscle of inactive/obese/diabetic animals or patients. The release of pro-inflammatory factors from this insulin resistant muscle tissue presumably drives polarization of muscle-resident macrophages

towards a pro-inflammatory M1 phenotype. M1 macrophages themselves release more pro-inflammatory cytokines, which negatively act back onto the muscle contributing to deterioration of muscle contractile and metabolic function. In macrophages, PGC-1β has been shown to be required for M2 macrophage activation and PGC-1α seems to be involved in this process at least in some contexts while production of reactive oxygen species typical for M1 macrophage activation is only possible in the absence of PGC-1α. A comprehensive understanding of the regulation of both coactivators in different macrophage activation states is however still missing. *PGC-1*, peroxisome proliferator-activated receptor γ coactivator 1; *M1*, classically activated, pro-inflammatory macrophage; *M2*, alternatively activated, anti-inflammatory or regulatory macrophage

sensitivity in murine skeletal muscle and entail a concomitant accumulation of M2 macrophages [317]. If the balance between muscle cells and M2 macrophages is lost, e.g., in the etiology of diabetes, a vicious cycle would commence ultimately resulting in insulin resistance in an inflamed environment. This involves a switch to M1 macrophages, the secretion of pro-inflammatory cytokines by both classically activated macrophages and muscle cells, worsening insulin sensitivity on one hand and promoting inflammation on the other hand concomitant with a decrease in muscle oxidative capacity and PGC-1 coactivator levels (Fig. 3). The antagonism between oxidative metabolism and inflammatory signaling would thus not only provide an attractive explanation for the different states of muscle cells in healthy and obese subjects but is further extended to the macrophage phenotypes. High PGC-1α levels in skeletal muscle and high PGC-1β levels in M2 macrophages would hereby correspond to the trained state while downregulation of PGC-1 coactivators in both skeletal muscle and macrophages would translate into an insulin-resistant, pro-inflammatory environment in inactive, obese patients (Fig. 3). Detailed evidence for such a myocyte–macrophage crosstalk remains to be provided.

In muscle diseases, such a model would also be feasible because ectopic expression of PGC-1α ameliorated fiber integrity and function, for example in DMD, sarcopenia, a mitochondrial myopathy and denervation-induced fiber atrophy [100, 101, 140, 143]. Reducing the inflammatory reaction in these conditions likely explains at least a part of the beneficial PGC-1α effect as other strategies to counteract inflammation have proven useful e.g. in DMD [101, 265, 266]. Conversely, endurance training that fosters PGC-1α expression protects against fiber damage, muscle inflammation and soreness.

Taken together, muscle cells take active part in immune reactions and are thus able to influence immune cells, e.g., in their activation state. The complex interplay between those cell types is only incompletely understood to date, and further studies are needed to elucidate the molecular mechanisms underlying this crosstalk. The antagonism between PGC-1 coactivators and inflammatory processes should thereby receive special attention as an imbalance is associated with metabolic and musculoskeletal diseases.

Conclusion

Metabolism and inflammation used to be considered as two completely independent processes in the body. In the past decade, it has become clear that both are tightly linked at multiple levels, which is particularly evident in cases where homeostasis is lost like nutritional overload. The dysregulation of metabolism is associated with an inflammatory reaction in different organs that significantly contributes to the development of insulin resistance while in the opposite, healthy state, an anti-inflammatory environment prevails. We have focused here on this interaction in skeletal muscle, which is both metabolically and immunologically active. One of the nodal points in this context seems the crosstalk of oxidative metabolism through the PGC-1 coactivators and NF-κB signaling that mutually suppress each other. It will be of prime interest to define this relationship in greater detail in the future and take pathological muscle conditions into account. This would pave the way for treatment strategies aimed not only at bringing back metabolic balance but also at halting inflammation to improve muscle structure and function.

Although no specific activators of PGC-1α or PGC-1β are available at the moment, exercise induces PGC-1α in skeletal muscle and training has been shown to counteract diseases with sterile inflammation like diabetes and neurodegeneration. Exercise capacity is furthermore a strong predictor of all-cause mortality while a sedentary lifestyle is a major risk factor for chronic diseases. Developing training regimes that optimally target an induction of oxidative metabolism and concomitantly block inflammation is a promising route to take as this would improve both the metabolic and the immune dysfunction very likely without major side effects.

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