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The biology of PGC-1 α and its therapeutic potential

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1 **The biology of PGC-1 α and its therapeutic potential**

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1 **Abstract**

2 In eukaryotes, cellular and systemic metabolism is primarily controlled by
3 mitochondrial activity. The peroxisome proliferator-activated receptor γ
4 coactivator 1 α (PGC-1 α) is a major regulator of mitochondrial biogenesis and
5 function. Furthermore, PGC-1 α controls many of the phenotypic adaptations of
6 oxidative tissues to external and internal perturbations. In contrast, dysregulated
7 metabolic plasticity is involved in the etiology of numerous diseases. Accordingly,
8 modulation of PGC-1 α levels and activity has recently been proposed as a
9 therapeutic option for several pathologies. However, pharmacological
10 interventions aimed at PGC-1 α have to overcome inherent limitations of targeting
11 a coactivator protein. This review focuses on the recent breakthroughs in the
12 identification of physiological and pathophysiological contexts involving PGC-1 α .
13 In addition, perspectives regarding the therapeutic importance of PGC-1 α -
14 controlled cellular and systemic metabolism are outlined.

15

1 **Introduction**

2

3 Transcriptional changes in gene expression underlie the coordinated regulation
4 of biological programs. These changes are initiated and maintained by the
5 binding of regulatory protein complexes to DNA elements in the enhancer and
6 promoter regions of target genes. Traditionally, DNA-binding transcription factors
7 were thought to be the main regulators of gene expression. However, in recent
8 years, the importance of transcriptional coregulators in the coordination of the
9 expression of genetic programs has been appreciated [1, 2]. The family of
10 peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1) genes
11 illustrates how coactivators respond to environmental cues and subsequently
12 regulate biological processes in a tissue-specific and highly coordinated manner
13 [3-5]. All three members of this small gene family, PGC-1 α , PGC-1 β and PGC-
14 related coactivator (PRC) are strong promoters of mitochondrial biogenesis and
15 oxidative metabolism [6-8]. In contrast to PRC that is ubiquitously expressed,
16 PGC-1 α and PGC-1 β are primarily found in oxidative tissues, including brain,
17 heart, kidney, muscle, liver, brown adipose tissue (BAT) and pancreas. In these
18 organs, PGC-1 α and PGC-1 β have overlapping as well as clearly distinct
19 functions [9]. Moreover, these two coactivators are differently regulated in
20 development and in response to nutritional and other challenges [8, 10].
21 However, whereas our understanding of the physiological role of PGC-1 β
22 remains rudimentary, significant progress in the study of PGC-1 α has been made
23 since its discovery more than a decade ago [11]. This review aims at

1 summarizing recent findings and at highlighting the potential therapeutic
2 applications of PGC-1 α .

3

4 **PGC-1 α regulates tissue-specific gene expression in health and disease**

5

6 The PGC-1 α protein is very versatile and coactivates many transcription factors
7 [3-5]. Binding to different partners enables PGC-1 α to regulate distinct biological
8 programs. For example, a combination of coactivation events among PGC-1 α ,
9 the hepatic nuclear factor 4 α (HNF4 α) and the forkhead transcription factor
10 Foxo1 determines the rate of fasting-induced hepatic gluconeogenesis [12, 13].
11 In skeletal muscle, myofibrillar genes are controlled by PGC-1 α -mediated
12 coactivation of myocyte enhancer factor 2 (MEF2) proteins [14]. In most tissues,
13 abnormal regulation of PGC-1 α expression and protein activity results in
14 pathological consequences. Furthermore, single nucleotide polymorphisms
15 (SNP) of *PPARGC1A*, the PGC-1 α gene, have been associated with a diverse
16 set of human diseases (<http://www.geneticassociationdb.nih.gov>). PGC-1 α SNPs
17 are found throughout the protein coding region as well as in the promoter, introns
18 and the 3' untranslated region (3' UTR). The functional consequences of the
19 SNPs are not clearly understood and disease-association of individual SNPs
20 seems highly population- and context-dependent.

21

22 **Adipose tissue**

23

1 In BAT, PGC-1 α expression is regulated by cold exposure and β -adrenoreceptor
2 agonists [11]. Subsequently, PGC-1 α coactivates PPAR γ and the thyroid
3 hormone receptor (TR) on the uncoupling protein 1 (UCP-1), type 2 deiodinase
4 (DIO2) and other BAT-specific gene promoters [11]. BAT vs. white adipose tissue
5 (WAT) selectivity of gene expression is controlled by the distinct assembly of
6 PGC-1 α / PR(PRDM1-BF1-RIZ1 homologous)-domain-containing protein (Prdm16)
7 / C-terminal binding protein-1 (CtBP1) protein complexes in these two tissues
8 [15]. PGC-1 α function is essential for BAT-mediated adaptive thermogenesis *in*
9 *vitro* and *in vivo* [9, 16, 17]. Thus, when exposed to cold, PGC-1 α knockout mice
10 rapidly become hypothermic and die after prolonged exposure [16, 17].

11

12 Levels of PGC-1 α in WAT are much lower than those in BAT and the
13 physiological role of PGC-1 α in this tissue is unclear [11]. PGC-1 α expression is
14 further reduced in the subcutaneous fat of morbidly obese and of insulin resistant
15 patients, respectively [18, 19]. In contrast, thiazolidinedione treatment and
16 hyperleptinemia elevate PGC-1 α transcription in WAT; this induction mediates
17 some of the beneficial effects of this class of anti-diabetic drugs and of leptin,
18 respectively [20, 21]. Ectopic expression of PGC-1 α in a WAT context results in
19 the induction of BAT-specific genes such as UCP-1 and an increase in
20 mitochondrial activity [11, 22].

21

22 *Therapeutic potential:* Augmenting the function of the remaining BAT in adult
23 humans or pushing WAT towards BAT-specific gene expression by elevating

1 PGC-1 α could tilt energy balance towards expenditure and thereby reduce
2 obesity (Fig. 1). Proof-of-concept for a therapeutic effect of augmented BAT
3 content is provided by chronic β 3-adrenoreceptor stimulation resulting in a lean
4 and healthy phenotype in animal models [23]. However, it remains to be tested
5 whether the limited capacity of PGC-1 α to increase BAT gene expression in WAT
6 is sufficient or if other factors such as Prdm16 are required to achieve a
7 therapeutic effect [24].

8

9 **Liver**

10

11 The first peak of PGC-1 α gene expression is observed in the liver at birth [10]. In
12 the adult, fasting and glucagon are the main drivers of hepatic PGC-1 α
13 transcription [12, 25]. PGC-1 α regulates most of the metabolic changes that
14 occur during the transition of a fed to a fasted liver, including gluconeogenesis,
15 fatty acid β -oxidation, ketogenesis and heme biosynthesis [12, 13, 26, 27].
16 Studies with knockout animals and adenovirally delivered shRNA constructs
17 revealed a blunted hepatic fasting response in the absence of adequate levels of
18 PGC-1 α [17, 27, 28]. Accordingly, these mice develop a fasting hypoglycemia
19 and hepatic steatosis [17, 28].

20

21 *Therapeutic potential:* An increase in PGC-1 α levels in the liver might obviously
22 alleviate hypoglycemia and hepatic steatosis. However, in contrast to the
23 induction sought after in most other tissues, a repression of PGC-1 α activity

1 holds more promise for therapy in the liver. First, hepatic PGC-1 α expression is
2 elevated in mouse models for type 1 and type 2 diabetes and probably
3 contributes to the unchecked glucose production and hyperglycemia in diabetes
4 [12]. Normalization of PGC-1 α levels might thus help to control hepatic
5 gluconeogenesis in these patients. Individuals with acute hepatic porphyrias,
6 diseases caused by mutations in the heme biosynthetic pathway, often suffer
7 from fasting-induced acute attacks that can be alleviated by glucose and heme
8 administration [29]. PGC-1 α has been identified as one of the main culprits in the
9 precipitation of acute porphyric attacks in fasting [27]. These attacks might be
10 prevented by pharmacological interventions that thwart the induction or activity of
11 PGC-1 α [29, 30]. Furthermore, PGC-1 α regulates the genes encoding
12 homocysteine synthesis enzymes in the fasted liver [31]. High plasma
13 homocysteine is an independent risk factor for the development of cardiovascular
14 diseases. Accordingly, inhibition of PGC-1 α could result in a drop of plasma
15 homocysteine levels and thereby a reduction of the risk for cardiovascular
16 diseases [31]. Finally, the hepatitis B virus (HBV) uses the transcriptional
17 machinery that regulates the hepatic fasting response for amplification [32].
18 Accordingly, HBV gene expression and life cycle, and thus the viral-host
19 interaction, are under the control of PGC-1 α [32]. Repression of PGC-1 α activity
20 might present a new anti-viral therapy for hepatitis B and help to restrict the viral
21 load in this disease.

22

23 **Brain**

1

2 In the developing brain, PGC-1 α transcription peaks two weeks postnatally in
3 many regions, a period of significant metabolic changes, mitochondrial
4 biogenesis and synaptic remodeling [33]. The highest PGC-1 α concentrations
5 are found in γ -aminobutyric acid (GABA)-positive neurons in the cortex,
6 hippocampus and cerebellum [33]. One of the existing global PGC-1 α knockout
7 line exhibits increased anxiety [17], whereas a second model shows a profound
8 hyperactivity [16]. Other behavioral changes include hind limb claspings, dystonic
9 posturing, an exaggerated startle response and stimulus-induced myoclonus
10 [16]. Besides the behavioral abnormalities, spongiform-like vacuolization events
11 are observed in the dorsolateral striatum [16], the vicinity of pyramidal neurons
12 [17], and more sporadically, in other regions of the brain of PGC-1 α knockout
13 mice [16]. Furthermore, the substantia nigra and the CA1 neurons of the
14 hippocampus are more susceptible to degenerative events triggered by the
15 reactive oxygen species (ROS)-generating 1-methyl-4-phenyl-1,2,3,6-
16 tetrahydropyridine (MPTP) and kainic acid, respectively, in these animals [34].
17 These findings suggest an important involvement of PGC-1 α in neuronal
18 maintenance and function.

19

20 *Therapeutic potential:* Mitochondrial dysfunction and oxidative stress are
21 associated with many neurodegenerative disorders, including Parkinson's,
22 Alzheimer's, Huntington's, Friedreich's ataxia and amyotrophic lateral disorder
23 (ALS) [35, 36]. PGC-1 α coordinately regulates the entire mitochondrial program

1 concomitant with an increase in the ROS detoxification system [34]. Reduced
2 PGC-1 α expression in Huntington's patients, the association of PGC-1 α SNPs
3 with the age of onset of Huntington's [37] and the Huntington's-like phenotype in
4 PGC-1 α knockout suggest that PGC-1 α is crucial for the maintenance of proper
5 striatal function [16, 38, 39]. A normalization of PGC-1 α expression in the
6 striatum of Huntington's patients might thus constitute a promising therapeutic
7 option [40-42]. In addition, the wide-spread neuronal lesions and the
8 susceptibility to chemically-induced neurodegeneration in different regions of the
9 brain of PGC-1 α knockout animals imply that PGC-1 α has a broader role in
10 neuroprotection beyond that related to Huntington's disease [16, 34].

11

12 **Skeletal muscle**

13

14 In the contracting muscle fiber, the main signaling pathways converge on PGC-
15 1 α to increase expression levels and the activity of this coactivator [3, 43, 44].
16 For example, p38 mitogen-activated protein kinase (p38 MAPK) and AMP-
17 dependent kinase (AMPK) are rapidly activated in exercise and subsequently
18 phosphorylate the PGC-1 α protein. In addition, PGC-1 α transcription is regulated
19 by the motor neuron-induced rise in intracellular calcium, AMPK, β 2-
20 adrenoreceptor signaling, nitric oxide and thyroid hormone [5]. As a
21 consequence, PGC-1 α levels in skeletal muscle are elevated following bouts of
22 endurance exercise. PGC-1 α is primarily found in type I and IIa slow-twitch, high
23 endurance muscle fibers and regulates the adaptations to exercise [14]. In fact,

1 ectopic expression of PGC-1 α in skeletal muscle is sufficient to promote a fiber-
2 type switching towards oxidative muscle fibers and bestow a trained phenotype
3 onto mice [14, 45].

4
5 Abnormally low PGC-1 α levels have been described in skeletal muscle of type 2
6 diabetic patients and physically inactive individuals [46, 47]. Mice with reduced or
7 ablated PGC-1 α gene expression suffer from a decreased exercise capacity,
8 abnormal systemic glucose and insulin homeostases, systemic inflammation and
9 activity-dependent fiber damage [48, 49]. Paradoxically, transgenic mice with
10 elevated PGC-1 α levels in muscle are prone to develop peripheral insulin
11 resistance on a high fat-containing diet [50].

12
13 *Therapeutic potential:* Many diseases are associated with inactive skeletal
14 muscle [51]. In animal models, transgenic elevation of PGC-1 α in muscle blunts
15 inactivity-induced fiber atrophy [52], reduces muscle wasting triggered by the
16 statin class of drugs [53], ameliorates Duchenne muscular dystrophy [54] and a
17 specific form of mitochondrial myopathy [55]. Since PGC-1 α promotes an
18 exercised phenotype in muscle, the therapeutic potential of PGC-1 α against
19 diseases that are associated with dysregulated muscle function is extremely
20 broad.

21
22 PGC-1 α controls the transcription of several genes encoding oxidative
23 phosphorylation (OXPHOS) genes that are dysregulated in muscle of type 2

1 diabetic patients [46, 47]. The specific disruption of the interaction between PGC-
2 1α and the estrogen-related receptor α (ERR α) using an inverse agonist in
3 muscle cells in culture promotes a change in gene expression similar to that
4 observed in muscle of diabetic patients [56]. Activation of the PGC- 1α /ERR α axis
5 could thus be a novel therapeutic approach against insulin resistance and type 2
6 diabetes [57]. However, the data from gain- and loss-of-function animal models of
7 PGC- 1α in muscle imply a complicated relationship between the expression of
8 this coactivator and systemic glucose and insulin levels that has yet to be
9 clarified [49, 50].

10

11 **Heart**

12

13 In the heart, PGC- 1α transcription is induced at birth and correlates with
14 metabolic maturation and remodeling [58]. As in other tissues, cardiac PGC- 1α
15 strongly promotes mitochondrial function and fatty acid β -oxidation [59]. In
16 several mouse models for heart disease accompanied with a substrate switch
17 from fatty acid to glucose utilization, expression of PGC- 1α is reduced [60]. At
18 baseline, heart function of PGC- 1α knockout mice appears normal [17, 61].
19 However, the cardiac reserve under stress conditions is impaired in mice with an
20 ablated PGC- 1α gene [61] and accordingly, these mice have a diminished
21 cardiac capacity in exercise [17]. In addition, prolonged pressure overload by
22 transverse aortic constriction precipitates ventricular dysfunction and clinical
23 signs of heart failure in PGC- 1α knockout animals [62]. Interestingly, ectopic

1 expression of PGC-1 α in the heart at superphysiological levels also results in
2 cardiomyopathy and heart failure in mice [58].

3

4 *Therapeutic potential:* Moderate elevation or normalization of PGC-1 α expression
5 in the failing heart might be sufficient to switch substrate usage from glucose
6 back to fatty acids and restore adequate energy production [62]. Thereby, PGC-
7 1 α could be cardioprotective against certain insults [60]. In contrast, insulin-
8 resistant hearts rely heavily on fatty acid oxidation and there, PGC-1 α levels are
9 elevated [63]. It is unclear if upregulation of cardiac PGC-1 α in insulin resistance
10 is an adaptive or a maladaptive process. In the former case, a reduction of PGC-
11 1 α expression should be the therapeutic goal. However, if the increase of PGC-
12 1 α is an adaptive process to cope with the excess amount of fatty acids, a further
13 elevation might be therapeutically beneficial [3, 60].

14

15 **Pancreas**

16

17 In obese mice, insulin resistant animal models and in a partial pancreatectomy as
18 a model for β cell decompensation, the transcriptional rate of the PGC-1 α gene in
19 the pancreas is increased over the normally low basal levels [64]. In pancreatic
20 islets, PGC-1 α prevents membrane polarization and induces glucose-6-
21 phosphatase and thereby reduces insulin secretion [64]. Notably, a second study
22 of PGC-1 α in human pancreatic islets resulted in opposite findings [65]. A
23 common PGC-1 α SNP was associated with reduced PGC-1 α expression and

1 insulin secretion in islets of tissue donors [65]. In addition, silencing of PGC-1 α
2 gene expression in isolated human islets likewise led to impaired insulin
3 secretion [65].

4
5 *Therapeutic potential:* At the moment, the diametrically opposed results of these
6 two studies are difficult to accommodate. Until these issues are resolved, it is
7 unclear whether a suppression or an induction of PGC-1 α activity in pancreatic
8 islets is the more promising avenue to restore insulin secretion in type 1 and type
9 2 diabetes.

10 11 **Bone and cartilage**

12
13 Parathyroid hormone-induced cAMP signaling is a major pathway in osteoclast
14 activation [66]. PGC-1 α is a primary target gene of this signaling cascade and
15 synergistically with Nurr1, a cAMP-induced orphan nuclear receptor, increases
16 the transcription of osteopontin and osteocalcin, two key genes in bone formation
17 [66]. Given the significant role of ERR α , one of the strongest interaction partners
18 of PGC-1 α , in osteoblasts and osteoclasts [67] and the coactivation of the
19 vitamin D receptor by PGC-1 α [68], an important function for PGC-1 α in
20 osteogenesis seems likely. These findings are intriguing in regard to a report
21 showing a role of PGC-1 α in chondrogenesis [69] suggesting an even broader
22 implication for PGC-1 α in the developing skeleton.

23

1 *Therapeutic options:* An activation of PGC-1 α might be useful in osteoporosis or
2 other disease associated with reduced bone density and morphology [66].
3 Similarly, PGC-1 α could be a promising target for molecular engineering of
4 cartilage in the clinical setting, e.g., osteoarthritis and other chondrodystrophies
5 [69].

6

7 **Problems, pitfalls and opportunities**

8

9 As a transcriptional coactivator, PGC-1 α lacks functional DNA- and ligand-
10 binding domains and therefore is not amenable to direct pharmacological
11 intervention. Strategies to alter the availability of PGC-1 α thus have to aim at
12 transcriptional regulation of the gene, modifications of the protein or the
13 interaction with binding partners. Modulation of PGC-1 α transcription is
14 hampered by the tight regulation of cellular metabolism. Accordingly, despite
15 different screening efforts [70, 71], clinically interesting compounds that
16 persistently induce PGC-1 α transcription are elusive. Optimally, such drugs
17 would act in a tissue-specific manner to circumvent unwanted side-effects by
18 elevating PGC-1 α in non-target tissues. For example, an elevation of PGC-1a in
19 WAT by thiazolidinedione drugs has been reported [20]; however, it is unclear
20 whether this induction is direct, secondary to other events or even sufficient to
21 contribute to the therapeutic effect of this class of drugs.

22

1 Posttranslational modifications of the PGC-1 α protein alter the half-life and the
2 specificity towards binding partners (Fig. 2). For example, PGC-1 α is
3 phosphorylated by AMPK at two different sites [44]. Metformin, a clinically used
4 anti-diabetic drug mediates at least some of its therapeutic effect through
5 activation of AMPK. Furthermore, deacetylation of 13 lysine residues on PGC-1 α
6 by the mammalian silencing information regulator 2-ortholog SIRT1 increases
7 PGC-1 α activity and thereby targets gene expression in muscle and liver [72, 73].
8 Resveratrol and other, more specific SIRT1 activators are promising drugs
9 against aging and aging-related diseases acting partially through PGC-1 α [74].
10 Other known modifications of PGC-1 α include phosphorylations by p38 MAPK
11 [75, 76] and Akt2/protein kinase B [77], methylation by protein arginine
12 methyltransferase 1 (PRMT1) [78], ubiquitination [79] and O-linked β -N-
13 acetylglucosamination [80]. Proteins with such enzymatic activities are attractive
14 drug targets for which specific activators and inhibitors can be designed.
15 Following the posttranslational modifications that modify the specificity of PGC-
16 1 α , the transcription of selective groups of target genes is altered (Fig. 2). Thus,
17 pharmacological manipulation of these enzymes upstream of PGC-1 α might
18 result in a fine-tuned modulation of PGC-1 α activity in a tissue- and target gene-
19 specific manner [5].

20

21 PGC-1 α regulates biological programs by interacting with different transcriptional
22 complexes. For instance, the strong potentiation of the transcriptional activity of
23 ERR α by PGC-1 α is responsible for mitochondrial OXPHOS gene expression in

1 muscle and other tissues and a specific disruption of this interaction selectively
2 reduces the expression of these, but not other PGC-1 α target genes [56]. The
3 use of partial agonists for ligand-binding transcription factors that modulate the
4 binding of individual coactivators [81] or of compounds that selectively disrupt or
5 enhance protein-protein interactions [56] could thus be another approach for a
6 specific modulation of PGC-1 α activity. Furthermore, pharmacological
7 interventions targeting the assembly of the PGC-1 α -containing transcriptional
8 complex that includes the p160 myb-binding protein [82], histone acetyl-
9 transferase enzymes (HAT) [83], members of the TRAP/DRIP/mediator complex
10 [84] and other proteins [85] are alternative strategies with therapeutic potential.

11

12 Finally, indiscriminate changes in the level of PGC-1 α in either direction are most
13 likely equally detrimental (Fig. 3). For example, cardiomyopathy and heart failure
14 develop with sub- and superphysiological levels of PGC-1 α [58, 62]. In skeletal
15 muscle, an increased exercise capacity was observed in a mouse line with
16 moderate transgenic expression of PGC-1 α [14]. However, the roughly ten-fold
17 increase in PGC-1 α transcript levels in these animals might already be excessive
18 for normal insulin sensitivity [50]. In contrast, an even more modest elevation of
19 PGC-1 α as demonstrated in an *in vivo* transfection experiment clearly increased
20 insulin sensitivity in skeletal muscle [86]. Higher expressing mouse lines suffer
21 from displacement of the contractile apparatus by excess mitochondria, weight
22 loss, fiber atrophy and muscle wasting [14, 87], reminiscent of the fiber damage
23 of muscle-specific knockout animals [48, 49]. Modulation of PGC-1 α thus has to

1 aim at either a moderate alteration or a normalization of PGC-1 α activity within a
2 therapeutically beneficial window that might be tissue- and context-dependent.

3

4 **Perspectives**

5

6 The transcriptional coactivator PGC-1 α plays a key role in maintaining cellular
7 metabolism. Dysregulation of gene expression and gene polymorphisms of PGC-
8 1 α have accordingly been found in a wide variety of different pathological
9 contexts. Furthermore, therapeutic efficacy of PGC-1 α modulation has been
10 demonstrated in animal models for different diseases. Thus, pharmacological
11 regulation of PGC-1 α expression and activity might be a promising novel
12 approach for the prevention and therapy of a number of pathologies despite the
13 inherent difficulties of targeting a coactivator. On the other hand, coactivators
14 exhibit some features that could be exploited for clinical use. By coordinating
15 different steps in biological programs through the integration of the activity of
16 many transcription factors, coactivators have kinetic advantages in controlling
17 biological programs over transcription factor-mediated regulation [1].
18 Furthermore, combinatorial combinations of posttranslational modifications of
19 coregulators exponentially increase the degree of specification of these proteins
20 [2, 5]. Thus, a selective targeting of PGC-1 α could potentially result in a fine-
21 tuned and highly specific response, which is unattainable by modulation of
22 transcription factors. Finally, modulation of PGC-1 α in one tissue might trigger
23 distal effects in other organs. For example, observations from muscle-specific

1 loss-of-function mouse lines suggest that PGC-1 α links muscle function to
2 systemic inflammation and ultimately, the risk of developing many chronic
3 diseases [48, 49, 51]. If these findings are substantiated, then modulation of
4 PGC-1 α might have a much broader therapeutic applicability [51]. Obviously, big
5 gaps of knowledge about the function of PGC-1 α , and even more about PGC-1 β
6 and PRC exist. Hopefully, a more comprehensive understanding of the
7 therapeutic potential of the PGC-1 family of coactivators will emerge from future
8 studies addressing mechanistic and physiological aspects of these intriguing
9 proteins.

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2

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13

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4

1 **Figure Legends**

2

3 **Fig. 1. Therapeutic potential of PGC-1 α .** For a number of tissues, different
4 functions of PGC-1 α have been described. A modulation of PGC-1 α expression
5 and activity could have therapeutic implications in the diseases listed for each of
6 these organs. Abbreviations: BAT, brown adipose tissue; CVD, cardiovascular
7 diseases.

8

9 **Fig. 2. Posttranslational modifications alter the specificity of PGC-1 α .** The
10 specificity of PGC-1 α to interact with its binding partners is altered by
11 posttranslational modifications of the PGC-1 α protein. For example,
12 phosphorylation of PGC-1 α by the AMP-dependent kinase (AMPK) primarily
13 affects PGC-1 α target genes that are involved in cellular metabolism. Selective
14 activation of neuromuscular junction (NMJ) genes in synaptic nuclei of the
15 muscle fiber is achieved by different phosphorylations of PGC-1 α through motor
16 neuron-derived signals. Abbreviations: OXPHOS, oxidative phosphorylation.

17

18 **Fig. 3. Clinical modulation of PGC-1 α has to occur in a therapeutically**
19 **beneficial window.** Super- and subphysiological expression of PGC-1 α cause
20 detrimental effects as described for heart and skeletal muscle. A pharmacological
21 modulation should thus aim at a moderate increase or a normalization of
22 pathologically dysregulated PGC-1 α . The therapeutic window might differ
23 between tissues and contexts.

Fig. 1

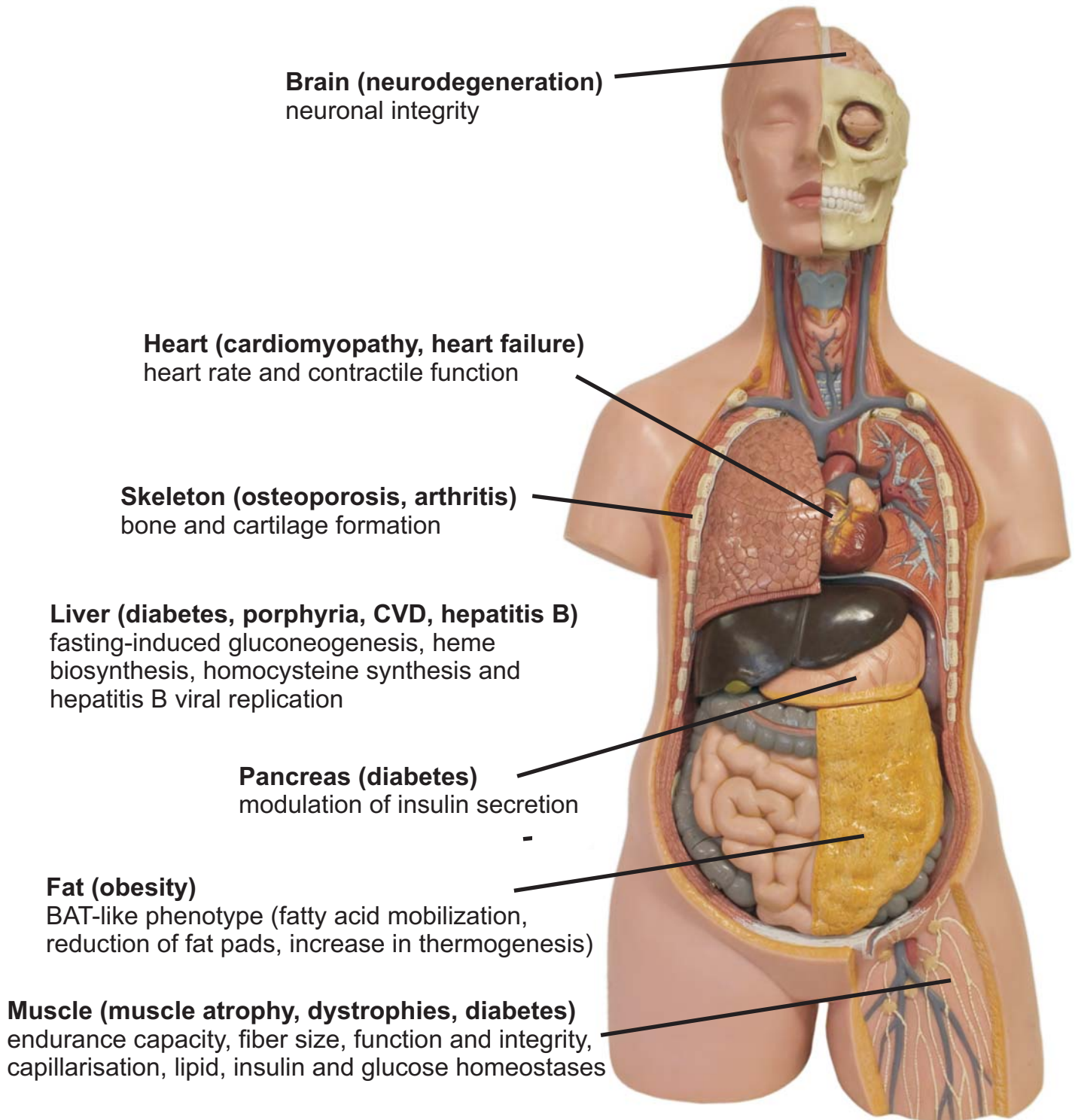


Fig. 2

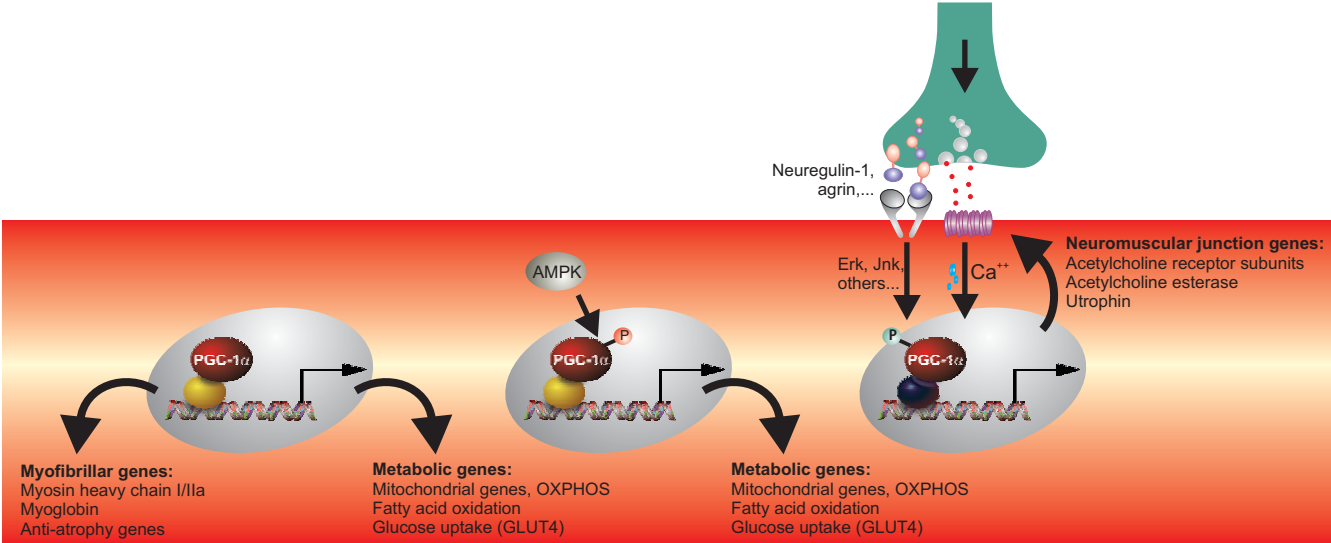


Fig. 3

