HAL
open science

Transcriptional control of mitochondrial biogenesis. The central role of PGC-1alpha.

Renée Ventura-Clapier, Anne Garnier, Vladimir Veksler

To cite this version:

Renée Ventura-Clapier, Anne Garnier, Vladimir Veksler. Transcriptional control of mitochondrial biogenesis. The central role of PGC-1alpha.: Transcriptional control of mitochondrial biogenesis. Cardiovascular Research, 2008, pp.CVR-2007-1636R2. inserm-00290124

HAL Id: inserm-00290124

https://inserm.hal.science/inserm-00290124

Submitted on 24 Jun 2008

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Spotlight issue on Signaling in Cardiac Metabolism:
Transcriptional control of mitochondrial biogenesis. The central role of PGC-1a.

VENTURA-CLAPIER Renée, GARNIER Anne, VEKSLER Vladimir

INSERM, U-769, F-92296 Châtenay-Malabry, France;

Univ Paris-Sud, IFR141, F-92296 Châtenay-Malabry, France;

Address for correspondence: Dr Renée Ventura-Clapier
U-769 INSERM
Faculté de Pharmacie, Université Paris-Sud
5 rue J-B Clément
92296 Châtenay-Malabry
France

Tel: (33-1) 46.83.57.62.
Fax: (33-1) 46.83.54.75.
E-mail: renee.ventura@u-psud.fr
Running title: **Transcriptional control of mitochondrial biogenesis.**
Word count: 7497

Abstract

Although the concept of energy starvation in the failing heart was proposed decades ago, still very little is known about the origin of energetic failure. Recent advances in molecular biology have started to elucidate the transcriptional events governing mitochondrial biogenesis. In particular a great step forwards was taken with the discovery that peroxisome proliferator-activated receptor gamma co-activator (PGC-1α) is the master regulator of mitochondrial biogenesis. The molecular mechanisms underlying the downregulation of PGC-1a and the consequent decrease in mitochondrial function in heart failure are, however, still poorly understood. Indeed, the main pathways involved in mitochondrial biogenesis are thought to be up- rather than down-regulated in pathological hypertrophy and heart failure. The current review summarizes recent advances in this field and is restricted to the heart when cardiac data is available.

I. MITOCHONDRIAL BIOGENESIS:

A. Definition

Mitochondrial biogenesis can be defined as the growth and division of pre-existing mitochondria. According to the well-accepted endosymbiotic theory, mitochondria are the direct descendants of an α-Proteobacteria endosymbiont that became established in a host cell. Due to their ancient bacterial origin, mitochondria have their own genome and a capacity for autoreplication. Mitochondrial proteins are encoded by the nuclear and the mitochondrial genomes. The double-strand circular mitochondrial DNA (mtDNA) is ~16.5 kb in vertebrates and contains 37 genes encoding 13 subunits of the electron transport chain (ETC) complexes I, III, IV and V, 22 transfer RNAs, and 2 ribosomal RNAs necessary for the translation. Correct mitochondrial biogenesis relies on the spatiotemporally coordinated synthesis and import of ˜ 1000 proteins encoded by the nuclear genome, of which some are assembled with proteins encoded by mitochondrial DNA within newly synthesized phospholipid membranes of the inner and outer mitochondrial membranes. In addition, mitochondrial DNA replication and mitochondrial fusion and fission mechanisms must also be coordinated (Figure 1). All of these processes have to be tightly regulated in order to meet the tissue requirements. Mitochondrial biogenesis is triggered by environmental stresses such as exercise, cold exposure, caloric restriction and oxidative stress, cell division and renewal, and differentiation. The biogenesis of mitochondria is accompanied by variations in mitochondrial size, number and mass. The discovery that

alterations in mitochondrial biogenesis contribute to cardiac pathologies such as the hypertrophied or failing heart have increased the interest of the scientific community in this process and its regulation.

B. Protein import

Because the majority of mitochondrial proteins are encoded in the nucleus, a mechanism for the targeting, import and correct assembly exists to ensure proper mitochondrial function and shape (for review see[1,2]). Following activation of the nuclear genome, mRNAs are translated in the cytosol to precursor proteins having signals for targeting to specific mitochondrial compartments. These proteins are escorted by molecular chaperones, unfolded and imported into mitochondria via the translocase of the outer membrane (TOM) complex. After transfer across the outer membrane, certain precursors are directed through the import machinery of the inner membrane (TIM) complex into the mitochondrial matrix in a membrane potential-dependent manner. Subsequently, these precursors are cleaved of their import sequences and are refolded by intramitochondrial proteins. A majority of mitochondrial protein precursors, however, do not contain typical N-terminal targeting signals but instead contain targeting information within their mature sequences. Other mechanisms ensure proper assembly and processing of the different subunits in the mitochondrial complexes of the respiratory chain at the inner membrane or in the matrix. These processes are an integral part of mitochondrial biogenesis.

C. Fusion and fission

Mitochondria in the cells of most tissues are tubular, and dynamic changes in morphology are driven by fission, fusion and translocation[3]. The ability to undergo fission/fusion enables mitochondria to divide and helps ensure proper organization of the mitochondrial network during biogenesis. The processes of fission/fusion are controlled by GTPases, most of which were identified in genetic screens in yeast (for recent reviews see[4,5]). Mitochondrial fission is driven by dynamin-related proteins (DRP1 and OPA1), while mitochondrial fusion is controlled by mitofusins (Mfn1 and 2). Mitofusins are highly expressed in heart and skeletal muscle, and their expression is induced during myogenesis and physical exercise[6,7]. In addition to the control of the mitochondrial network, Mfn2 also stimulates the mitochondrial oxidation of substrates, cell respiration and mitochondrial membrane potential, suggesting that this protein may play an important role in mitochondrial metabolism, and as a consequence, in energy balance[6]. OPA1, by contrast, is involved in the remodeling of cristae. Mfn and DRP1 expression increases in parallel with mitochondrial content and exercise capacity in human skeletal muscle[8], suggesting that fusion/fission processes are an integral part of mitochondrial biogenesis. However, these processes have received less attention in the heart up until now.

D. Cardiolipin biosynthesis

Increases in mitochondrial content/number involve the proliferation of mitochondrial membranes. Phospholipids are important structural and functional components of mitochondrial membranes[9], and are involved in the regulation of various processes including apoptosis, electron transport, and mitochondrial lipid and protein import. Cardiolipin is the main functional phospholipid of the mitochondrial inner membrane, representing 8-15% of the entire cardiac phospholipid mass, and is the only phospholipid that is both synthesized and localized exclusively within mitochondria. Cardiolipin plays a key role in the activity of several inner membrane proteins and in the binding of mitochondrial creatine kinase in the vicinity of translocase. De novo synthesis of cardiolipin starts with the conversion of phosphatidic acid to CDP-diacylglycerol and ends with the condensation of phosphatidylglycerol and CDP-diacylglycerol by cardiolipin synthase. A second mechanism of cardiolipin biosynthesis is through a deacylation-reacylation reaction catalyzed by phospholipases and acyltransferases, which are regarded as the principal enzymes involved in phospholipid remodeling in mammalian tissues[9].

II. TRANSCRIPTIONAL CONTROL OF MITOCHONDRIAL BIOGENESIS

Much progress in uncovering the transcriptional regulatory mechanisms involved in mitochondrial biogenesis has been made in the last ten years. Some of the major research will be presented here. Readers are referred to recent excellent reviews on the subject for more complete details[10-13].

A. mitochondrial transcription factor A

Transcription and replication of mitochondrial DNA is driven by the nuclear-encoded mitochondrial transcription factor A (Tfam), which binds to a common upstream enhancer of the promoter sites of the two mitochondrial DNA strands. Cardiac specific Tfam deletion results in decreased levels of mtDNA, impaired respiratory chain function, cardiac hypertrophy and progressive cardiomyopathy[14]. Additionally, two proteins that interact with the mammalian mitochondrial RNA polymerase and Tfam, TFB1M and TFB2M, can support promoter-specific mtDNA transcription[15]. Although usually complex and promoter-specific, certain DNA binding motifs are present in the promoters of several of genes encoding oxidative phosphorylation (OXPHOS) complex subunits and enzymes involved in mtDNA metabolism and are, therefore, able to participate in a coordinated response. These motifs include the OXBOX/REBOX motif, the Mt motif, Sp1, and nuclear respiratory factor (NRF) motifs (see[11] for original references).

B. Nuclear respiratory factors

The nuclear respiratory factors 1 and 2 have been linked to the transcriptional control of many mitochondrial genes whose list has expanded greatly in the last few years (see Table1 in[10]). Electrical stimulation of neonatal cardiomyocytes produces an increase in mitochondrial content that is preceded by enhanced expression of NRF1, indicating a role for this transcription factor in cardiac mitochondrial biogenesis[16]. The Tfam promoter contains recognition sites for NRF1 and/or NRF2, thus allowing coordination between mitochondrial and nuclear activation during mitochondrial biogenesis. However, a subset of genes does not appear to be regulated by NRFs. For example, fatty acid transport proteins and oxidation enzyme genes are mainly regulated by the peroxisome proliferator-activated receptor alpha PPARα (see below and[12] for recent review).

C. Peroxisome proliferator-activated receptor gamma co-activator

Since its discovery by Spiegelman and coworkers[17], peroxisome proliferator-activated receptor gamma co-activator (PGC-1α) has been the focus of much attention. PGC-1α lacks DNA-binding activity but interacts with and co-activates numerous transcription factors including NRFs on the promoter of mtTFA[17]. Mitochondrial biogenesis and respiration are stimulated by PGC-1α through powerful induction of NRF1 and NRF2 gene expression. PGC-1α is enriched in tissue with high oxidative activity like heart and brown adipose tissue and, to a lesser extent, skeletal muscle and kidney, and it is rapidly induced under conditions of increased energy demand such as cold, exercise, and fasting. Data are accumulating that show PGC-1α to be a master regulator of mitochondrial biogenesis in mammals. Ectopic expression of PGC-1α in myotubes strongly induces the expression of downstream transcription factors such as NRFs and Tfam[17]. Unlike NRFs or Tfam, however, PGC-1α levels correlate with cardiac and skeletal muscle oxidative capacity, suggesting that it plays a major role in setting mitochondrial content[18]. PGC-1α expression is greatly enhanced in the developing mouse heart immediately before the burst of mitochondrial biogenesis that precedes birth[19]. Constitutive cardiospecific PGC-1α overexpression in mice results in uncontrolled mitochondrial proliferation, leading to dilated cardiomyopathy[19]. During the neonatal stages, inducible cardiospecific overexpression of PGC-1α leads to a dramatic increase in mitochondrial number and size, concomitant with upregulation of genes associated with mitochondrial biogenesis[20]. In the adult, this leads to a more modest increase in mitochondrial number, but with perturbation of mitochondrial ultrastructure and development of cardiomyopathy[20]. Given the significant volume occupied by mitochondria in mouse cardiomyocyte (~45% in adult), and the extremely low cytosolic volume (around 4-7%), any increase in mitochondrial mass will automatically be at the expense of myofibrillar volume, thus compromising contractile function. Consequently, it is likely that a strict control of mitochondrial volume exists in the adult heart in order to keep constant the ratio of mitochondrial to myofibrillar volume. Two lines of PGC-1α-deficient mice have been independently generated, which differ slightly in their cardiac dysfunction[21,22]. However, somewhat surprisingly, both lines appear to have close to normal mitochondrial volume density in the heart[21,22] yet the expression of mitochondrial genes is blunted[22]. Chronic hemodynamic overload in these mice induces accelerated cardiac dysfunction accompanied by overt clinical signs of heart failure, indicating that decreased PGC-1α expression may

play a significant role in the development of heart failure[23]. However, the maintenance of the mitochondrial volume fraction suggests that additional mechanisms controlling mitochondrial biogenesis exist.

PGC-1α is the first-discovered member of a family of three related proteins that control major metabolic functions. Whereas the PGC-1-related coactivator (PRC) is expressed ubiquitously, PGC-1α and β are enriched in mitochondria-rich tissues such as cardiac and skeletal muscles. Overexpression studies suggest that PGC-1α and β exert specific bioenergetic effects, with PGC-1β preferentially inducing genes involved in the removal of reactive oxygen species[24]. Deficiency in PGC-1β in the heart results in a general defect in the expression of genes encoding components of the electron transport chain and in a reduced mitochondrial volume fraction, leading to a blunted response to dobutamine stimulation[25]. However, only PGC-1α seems to respond to metabolic challenges such as exercise, starvation or cold, suggesting that PGC-1β could play a role in constitutive mitochondrial biogenesis[26].

D. Additional targets of PGC-1α

In addition to NRFs, PGC-1α also interacts with and co-activates other transcription factors like PPARs, thyroid hormone, glucocorticoid, estrogen and estrogen-related ERRα and ? receptors (Figure 2). The two orphan nuclear receptors ERRα and ? target a common set of promoters involved in the uptake of energy substrates, production and transport of ATP across the mitochondrial membranes, and intracellular fuel sensing[27]. Ablation of ERRα induces signs of heart failure in mice subjected to left ventricular pressure overload, indicating that ERRα is required for the adaptive bioenergetic response[28]. By contrast, ERR? deficiency was recently shown to induce complex cardiac defects in embryos involving changes in the expression of genes involved in mitochondrial biogenesis, suggesting a possible role for ERR? in the postnatal transition to oxidative metabolism and fatty acid utilization[29].

The PPAR family of transcription factors plays a major role in the expression of proteins involved in extra and intramitochondrial fatty acid transport and oxidation (FAO). All PPARs are expressed in the myocardium, although PPARα and β/δ are the main cardiac isoforms. PPARα binds its obligate partner the retinoid-X-receptor (RXR), and the resulting heterodimer is involved in the regulation of enzymes, transporters and proteins of FAO[19]. The activity of the PPAR/RXR complex is modulated by the availability of ligands, the most relevant of which are long-chain fatty acids and their metabolites. FAO is increased in cardiomyocytes exposed to PPARα and PPARβ/δ ligands, but not PPARγ ligands, consistent with the PPAR isoform expression pattern in heart tissue[30]. PGC-1α cooperates with PPARα to regulate expression of mitochondrial FAO enzymes and transport proteins, thus enabling increases in FAO pathway activity to be coordinated with mitochondrial biogenesis[31]. PPARβ/δ plays also a prominent role in the regulation of cardiac lipid metabolism. Cardiomyocyte-restricted PPARβ/δ deletion perturbs myocardial FAO and leads to lipotoxic cardiomyopathy[32]. However, because PPARβ/δ null mice do not exhibit a fasting–induced phenotype, it was proposed that these isoforms probably serve to regulate basal metabolism whereas PPARα is involved in the response to physiological conditions that stimulate FA delivery[33]. Among the two PPAR? isoforms, PPAR?1 is predominantly expressed in the heart. Cardiomyocyte specific PPAR?1-KO mice develop cardiac hypertrophy with preserved systolic function and signs of heart failure that develop with aging, together with abnormal mitochondrial structure[34], suggesting that PPAR? could also play a role in mitochondrial biogenesis. However, it is not yet firmly established whether the mitochondrial defects observed in these studies result directly from deletion of PPARs or whether they are secondary effects of the cardiac phenotype.

Mitochondrial biogenesis thus involves an intricate, complicated network of transcription factors NRFs/PPARs/ERRs that activate target genes encoding enzymes of FAO, oxidative phosphorylation, and anti-oxidant defenses (Figure 2). PGC-1α, by co-activating and controlling the expression of this network, directly links external physiological stimuli to the regulation of mitochondrial biogenesis and function. Additionally, mitochondrial biogenesis involves fusion/fission and requires protein import and processing and cardiolipin biosynthesis. Whether the transcriptional regulation of these processes involves the same or similar transcription cascades is still largely

unknown, although in skeletal muscle, PGC-1α and mitochondrial content correlate strongly with expression of certain proteins involved in mitochondrial dynamics and protein processing[8].

III. SIGNALING PATHWAYS INVOLVED IN PGC-1a ACTIVITY

A large number of signaling pathways have been proposed to regulate PGC-1α (Figure 2).

A. Calcium- and second messenger-dependent regulation of PGC-1a expression

Increased contractile activity translates into a sustained increase in intracellular calcium concentration, which activates the calcium-dependent phosphatase calcineurin (CaN) and Ca^{2+}-calmodulin dependent kinase (CaMK)[35]. CaN controls the expression of PGC-1α in muscle, providing a calcium-signaling pathway whose stimulation results in increased mitochondrial content[36]. Loss of calcineurin in heart results in impaired mitochondrial electron transport associated with high levels of superoxide production[37]. Moreover, in early embryonic development, the dephosphorylation of nuclear factors of activated T cells (NFATs) by calcineurin is required for mitochondrial energy metabolism[38]. Transcriptional profiling studies demonstrated that CaN and CaMK activate distinct but overlapping metabolic gene regulatory programs[39]. CaN, but not CaMK, activates the mouse PPARα promoter, indicating that FAO genes are selectively activated by CaN. CaN-mediated PGC-1α promoter activation is dependent on myocyte enhancer factor-2 (MEF2) activity and the histone deacetylases (HDACs). Expression of a signal-resistant form of HDAC in mouse heart results in loss of mitochondria and changes in their morphology[40]. MEF2, which is stimulated by CaN signaling, binds to the PGC-1α promoter and activates it, predominantly when co-activated by itself[36]. Deletion of MEF2A in mice results in perturbation of mitochondrial structure and significant loss of mitochondria[41]. CaMK activation of PGC-1α expression requires the cAMP response element binding protein (CREB)[42]. Moreover, the transducer of regulated CREB binding protein (TORC) may enhance CREB-dependent PGC-1α transcription[43]. In the heart in response to both physiological and pathological hypertrophic stimuli, there is a strong positive correlation of CREB activation with PGC-1α expression and mitochondrial respiratory rate and protein content[44]. Interestingly, DrPp1 expression correlates with PGC-1α content and calcineurin activation in human skeletal muscle[8], and dephosphorylation of Drp1 by CaN induces its translocation to mitochondria thus triggering mitochondrial fission[45].

Activation of the p38 mitogen-activated-protein kinase (MAPK) pathway in skeletal muscle has been shown to promote PGC-1α expression. However, the cardiac mitochondria of transgenic mice overexpressing the p38MAPK upstream kinase MAPK-kinase-6 (MKK6) have lower oxidative respiration and decreased generation of reactive oxygen species[46], suggesting that p38MAPK is involved in the negative regulation of mitochondrial biogenesis.

Treatment of various cells with NO donors increases their mtDNA content, and this is sensitive to removal of NO by NO scavengers[47]. The effects of NO occur via increased expression of PGC-1α and its down-stream effectors, and depend on the second messenger cGMP by activation of particulate guanylyl cyclase. Tissues of eNOS-/- mice such as the brain, liver, muscle and heart have a slightly decreased content of some mitochondrial proteins[47]. However, oxidative capacity and mitochondrial enzymes are not altered in hearts of eNOS-/- mice, suggesting that eNOS is not involved in cardiac basal mitochondrial biogenesis[48]. However, eNOS may be necessary for the cardiac response to stress, since caloric restriction involves an eNOS-dependent increase in cardiac mitochondrial biogenesis[49].

B. Energy-dependent regulation of PGC-1a activity

It has been proposed that the phylogenetically-conserved AMP-dependent serine/threonine protein kinase (AMPK) plays a role in skeletal muscle-induced mitochondrial biogenesis. PGC-1α is induced by exercise and by chemical activation of AMPK in skeletal muscle (for review see[50]). Activation of AMPK and mitochondrial biogenesis in muscle in response to chronic energy deprivation is diminished in AMPKα2-kinase-dead mice, revealing the importance of AMPK in this response[51]. Indeed, cardiac mitochondrial respiration is altered in mice lacking the main catalytic subunit of cardiac and skeletal muscle AMPK (AMPKα2-/-) by a mechanism that involves decreased

cardiolipin biosynthesis[52], suggesting that AMPK is involved in cardiolipin biosynthesis. However, there are no changes in mitochondrial markers or PGC-1α expression in the hearts of these mice[52,53].

Sirtuins are highly conserved NAD^+-dependent deacetylases recently shown to control lifespan. Increased lifespan is associated with augmented mitochondrial oxidative phosphorylation and aerobic capacity. Resveratrol, a polyphenol that was shown to extend lifespan, increases aerobic capacity in mice and induces expression of genes that encode proteins involved in oxidative phosphorylation and mitochondrial biogenesis. These effects occur via a SIRT-1-dependent increase in PGC-1α expression in skeletal muscle and adipose tissue, although not in heart[54]. Interestingly, caloric restriction-induced mitochondrial biogenesis in heart is accompanied by increased SIRT1 expression in wild-type but not $eNOS^{-/-}$ mice[49]. These results again indicate that mitochondrial biogenesis is strictly-controlled in the heart.

C. Hormonal control of PGC-1a.

Thyroid hormones (TH) drastically alter the expression of nuclear- and mitochondria-encoded genes in several tissues. TH can control mammalian mitochondrial biogenesis through direct and indirect pathways. The direct pathway involves the binding of TH receptors (TR a and ß) on TRE recognition sites on nuclear-encoded mitochondrial genes, and activation of the mitochondrial genome via a truncated form of TRα called p43[55]. However, of the nuclear genes necessary for the biogenesis of mitochondria, only a few respond directly to thyroid hormone[11]. An indirect pathway involves the control of PGC-1a expression, and activation of its downstream transcription cascade[56]. However, the effects of TH on mitochondrial content in the adult heart are not clear. Indeed, one study found that TH treatment of rats increased cardiac oxygen consumption, mitochondrial bioenergetic capacity and expression of markers of mitochondrial biogenesis such as PGC-1α and its transcription cascade[57]. By contrast, other studies (including our own unpublished results) found no change in PGC-1α myocardial expression/activity with TH treatment[58]. Interestingly, an interaction betweenPGC-1α and thyroid hormone receptors has been reported[59]. Hypothyroidism induces a decrease in the maximal oxidative capacity and expression/activity of mitochondrial enzymes in cardiac muscle, which is independent of PGC-1α and its transcription cascade, suggesting that there exists a unique mode of regulating mitochondrial respiration by TH[60]. Additionally, thyroid hormones control cardiolipin biosynthesis and regulate the mitochondrial protein import machinery, thus providing another ways of regulating mitochondrial function[9,61,62].

D. Cyclin-dependent kinases

Cyclin-Dependent Kinases (CDKs) are involved in cell cycle and/or transcriptional control. Gene expression profiling studies demonstrated that, cyclinT/Cdk9, an RNA polymerase kinase involved in cardiac hypertrophy, suppresses the expression of many genes that encode mitochondrial proteins such as PGC-1α and its downstream effectors[63]. In addition, the Cdk7/cyclinH/ménage-à-trois-1 (MAT1) heterotrimer is activated in adult hearts by stress-dependent pathways for hypertrophic growth. Ablation of MAT1 causes suppression of genes involved in energy metabolism as well as the PGC-1α and β genes, indicating that a requirement exists for MAT1 in the operation of PGC-1 that control cardiac metabolism[64].

IV. POSTRANSLATIONAL CONTROL OF PGC-1a

In addition to their regulated expression by various metabolic stimuli, the family of PGC-1 co-activators is controlled by post-translational modifications. PGC-1α phosphorylation by p38MAPK, for example, is most likely involved in mediating the effects of cytokines[65,66]. An interesting observation made recently is that, in addition to increasing PGC-1α expression, AMPK can directly phosphorylate PGC-1α, this phosphorylation being required for the PGC-1α-dependent induction of the PGC-1α promoter[67]. Another important post-translational modification of PGC-1α is the deacetylation induced by the NAD^+-dependent SIRT1 deacetylase[68]. In skeletal muscle, SIRT1-induced deacetylation of PGC-1α is required for activation of mitochondrial fatty acid oxidation genes in response to fasting and low glucose[69]. In the heart, SIRT1 regulates aging and resistance to

oxidative stress[70]. PGC-1α activity is also potentiated by arginine methylation, which is catalysed by protein arginine methyltransferase-1 (PRMT1), another nuclear receptor coactivator. Mutation of three arginine residues in the C-terminal region of PGC-1α compromises the ability of PGC-1α to induce expression of endogenous target genes[71]. These forms of post-translational regulation of PGC-1α activity are additional mechanisms that link mitochondrial biogenesis with intracellular signaling pathways, thereby increasing the complex regulation of oxidative metabolism.

V. MITOCHONDRIAL BIOGENESIS AND CARDIOVASCULAR DISEASES

The energetic failure of the hypertrophied and failing heart has been extensively reviewed elsewhere (for example see[72-76]). Briefly, and as summarized in Figure 3, the energetic changes includes 1) an early switch in substrate utilization from fatty acids to glucose, 2) decreased oxidative capacity and energy production due to decreased mitochondrial biogenesis, 3) decreased energy transfer by the phosphotransfer kinases, 4) altered energy utilization and 5) decreased efficiency of energy consumption. The signaling and molecular origins of these defects are largely unknown.

A. Hypertophy and heart failure

1. Physiological hypertrophy and mitochondrial biogenesis

The adaptation of cardiac muscle to training involves cardiomyocyte remodeling and hypertrophy. Recent studies present evidence that exercise training increases expression of PGC-1α and its downstream cascade, at least during hypertrophic growth[44,77]. Whether or not exercise training is accompanied by a sustained increase in mitochondrial content independent of cardiac hypertrophy is not at all clear. In animal models, some studies showed that regular endurance exercise increases glycolysis and oxidative metabolism, whereas others demonstrated that adaptive responses result from increased muscle mass rather than changes in mitochondrial gene expression (see[78] for review). This could be related to the existence of an already “optimal” basal level of mitochondrial content in adult heart as a result of an optimized contractile protein/mitochondria ratio.

2. Pathological hypertrophy and heart failure

It is now widely accepted that FAO enzymes and other mitochondrial proteins are down-regulated in the failing heart[18,79]. The group of Kelly has done extensive work on the dynamic regulation of the cardiac PPAR/PGC-1a complex and its control of cardiac mitochondrial energy production following the onset of pathological cardiac hypertrophy. During pathological growth of the heart, downregulation of PPARα and PGC-1α causes decreased expression of FAO genes[80]. In our research on the origin of decreased cardiac muscle oxidative capacity in the pathogenesis of heart failure, we have shown that the decrease in mitochondrial function in both cardiac and skeletal muscle following pressure overload is linked to the down-regulation of PGC-1a and its downstream effectors, NRF2 and Tfam[18]. Similar findings have now been reported in a number of other models of heart failure, including the muscle LIM protein-null mouse[81], rats with myocardial infarction[82-85], spontaneously hypertensive rats and a mouse model of hypertrophic cardiomyopathy[44]. Recently, downregulation of the PPAR/PGC-1a complex and of its targets was reported in failing human hearts[86]. Interestingly, single polymorphisms in the PGC-1a gene have been identified which correlate with an increased risk of hypertrophic cardiomyopathy[87]. This suggests that the decreased expression of the PGC-1α/PPARα transcription cascade is the molecular basis for energy starvation of the failing myocardium.

3. Signaling pathways for downregulation of PGC-1a in HF

The molecular mechanisms underlying the loss of PGC-1a/PPAR in heart failure are poorly understood. Indeed, the main signaling pathways involved in mitochondrial biogenesis, such as MAPK, calcineurin, cAMP-dependent signaling and AMPK, are considered to be up- rather than down-regulated in pathological hypertrophy and heart failure[88,89].

Similarities between the changes in cardiac gene expression in pathological hypertrophy and hypothyroidism led to the hypothesis that a reduction in thyroid hormone plays a role in the development of metabolic and functional alterations in these conditions. Indeed, HF is accompanied

by low or subclinical blood levels of thyroid hormone, altered expression of thyroid receptors[90], and increased cellular degradation of thyroid hormones[91]. However, hypothyroidism induces a metabolic pattern that differs from heart failure, suggesting that HF-induced downregulation and deactivation of PGC-1a is not, in fact, due to cellular hypothyroidism[60]. Elevated Akt activity has been demonstrated in the failing heart[88], and overexpression of Akt has been shown to induce a threefold downregulation of PGC-1α gene expression[92]. The downregulation of mitochondrial transcription factors induced by postinfarction remodeling can be significantly attenuated by Na^+/H^+ exchanger-1 inhibition, and mitochondrial function is improved by changes in the regulation of Akt activity[85]. Chronic activation of Cdk9 in HF causes defective mitochondrial function, via loss of PGC-1a[63,93].

Studies to determine the role of calcineurin in cardiac hypertrophy and heart failure have produced contradictory results, showing either calcineurin activation or no change or a decrease in calcineurin activity[88,94]. Despite the importance of CREB for transcriptional activation of PGC-1α, treating cardiac cells in culture with catecholamine, which stimulates adenylate cyclase, leads to repression of PGC-1a and many of its target genes which can be reversed by ectopic expression of PGC-1α[23]. On the other hand, in spontaneously hypertensive rats, decreased CREB phosphorylation strongly correlates with expression of PGC-1α and mitochondrial protein content[44], indicating decreased rather than increased cAMP-dependent gene activation. At present nothing is known about the post-translational modification of PGC-1α in HF.

B. Diabetes, insulin resistance and obesity

Obesity and diabetes are complex metabolic syndromes in which cardiac disease is a significant cause of mortality. Recent studies have shown that mitochondrial function is altered in the hearts of diabetic animals. In type I diabetes there is a decrease in PGC-1 mRNA expression[95], whereas in the insulin-resistant heart mitochondrial biogenesis occurs driven by the PPARα/PGC-1α gene regulatory pathway[96]. In addition, cardiolipin depletion has been observed in diabetic myocardium using shotgun lipidomics, thus linking altered substrate utilization with mitochondrial dysfunction[97]. Mitochondrial damage and decreased mitochondrial density and mtDNA content in high-fat diet-induced obesity are closely associated with downregulation of PGC-1a and its downstream cascade[98]. Cardiac changes in this pathology also include defects in mitochondrial function, lipid oxidation and mitochondrial biogenesis leading to cardiac lipotoxicity, possibly involving eNOS-dependent NO production[99].

C. Ischemia

Evidence have been accumulating that protection against ischemic damage could be linked to mitochondrial biogenesis (see[100] for review). Preconditioning is an intervention that causes attenuation of ischemic damage. Following delayed preconditioning, mitochondria display increased tolerance to anoxia-reperfusion injury associated with increased biogenesis (induction of PGC-1a and NRF-1) and expression of mitochondrial proteins[101]. Other indirect evidence supports a mechanistic link between ischemic preconditioning and mitochondrial biogenesis. The preconditioning-mimetic diazoxide activates the mitochondrial biogenesis regulatory protein CREB[102]. Moreover, NO, a trigger of preconditioning, also directly activates the mitochondrial biogenesis program. Mitochondrial biogenesis also upregulates a broad spectrum of ROS detoxification systems[24], providing a mechanism by which the mitochondrial biogenesis program may additionally augment tolerance to cardiac ischemia.

VI. CONCLUSIONS.

Mitochondria are of the utmost importance for cardiac function. Forced activation of mitochondrial biogenesis in the adult heart results in heart failure, suggesting that there is an optimal mitochondrial volume. Mitochondrial biogenesis involves multiple processes that need to be tightly coordinated. It appears that the co-activator PGC-1α, the master regulator of mitochondrial biogenesis, plays a role in coordinating the growth of the mitochondrial compartment. Energy starvation and decreased expression/activity of the PGC-1α transcription cascade are hallmarks of cardiac dysfunction, which lead to impaired energy metabolism and which contribute to contractile failure. Many signaling pathways have been shown to be involved in mitochondrial biogenesis. Whether they directly control PGC-1α expression or whether impaired energy metabolism is a secondary

consequence of the complex overlap of energy metabolism with cardiac function remains to be determined. More work is needed in this growing area, but the PGC-1α axis could be envisioned as a new, exciting therapeutic target in metabolic disorders and heart failure.

VII. FUNDING.
RV-C is supported by "Centre National de la Recherche Scientifique".

VIII. ACKNOWKLEDGMENTS.
We thank Dr. R. Fischmeister for continuous support. We apologize for the many seminal contributions that have not been cited for lack of space. We thank James Wilding for carefully reading the manuscript and for revising the English and Dominique Fortin and other co-workers.

IX. CONFLICT OF INTEREST.
None declared

X. REFERENCES

[1] Baker MJ, Frazier AE, Gulbis JM, Ryan MT. Mitochondrial protein-import machinery: correlating structure with function. *Trends Cell Biol* 2007;**17**:456-464.
[2] Hood DA, Adhihetty PJ, Colavecchia M, Gordon JW, Irrcher I, Joseph AM *et al*. Mitochondrial biogenesis and the role of the protein import pathway. *Med Sci Sports Exerc* 2003;**35**:86-94.
[3] Bereiter-Hahn J. Behavior of mitochondria in the living cell. *Int Rev Cytol* 1990;**122**:1-63.
[4] Hoppins S, Lackner L, Nunnari J. The machines that divide and fuse mitochondria. *Annu Rev Biochem* 2007;**76**:751-780.
[5] Chan DC. Mitochondria: dynamic organelles in disease, aging, and development. *Cell* 2006;**125**:1241-1252.
[6] Bach D, Pich S, Soriano FX, Vega N, Baumgartner B, Oriola J *et al*. Mitofusin-2 determines mitochondrial network architecture and mitochondrial metabolism. A novel regulatory mechanism altered in obesity. *J Biol Chem* 2003;**278**:17190-17197.
[7] Soriano FX, Liesa M, Bach D, Chan DC, Palacin M, Zorzano A. Evidence for a mitochondrial regulatory pathway defined by peroxisome proliferator-activated receptor-gamma coactivator-1 alpha, estrogen-related receptor-alpha, and mitofusin-2. *Diabetes* 2006;**55**: 1783-1791.
[8] Garnier A, Fortin D, Zoll J, N'Guessan B, Mettauer B, Lampert E *et al*. Coordinated changes in mitochondrial function and biogenesis in healthy and diseased human skeletal muscle. *FASEB J* 2005;**19**:43-52.
[9] Hatch GM. Cell biology of cardiac mitochondrial phospholipids. *Biochem Cell Biol* 2004;**82**:99-112.
[10] Kelly DP, Scarpulla RC. Transcriptional regulatory circuits controlling mitochondrial biogenesis and function. *Genes Dev* 2004;**18**:357-368.
[11] Garesse R, Vallejo CG. Animal mitochondrial biogenesis and function: a regulatory cross-talk between two genomes. *Gene* 2001;**263**:1-16.
[12] Finck BN, Kelly DP. Peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) regulatory cascade in cardiac physiology and disease. *Circulation* 2007;**115**:2540-2548.
[13] Ryan MT, Hoogenraad NJ. Mitochondrial-nuclear communications. *Annu Rev Biochem* 2007;**76**:701-722.
[14] Hansson A, Hance N, Dufour E, Rantanen A, Hultenby K, Clayton DA *et al*. A switch in metabolism precedes increased mitochondrial biogenesis in respiratory chain-deficient mouse hearts. *Proc Natl Acad Sci USA* 2004;**101**:3136-3141.
[15] Falkenberg M, Gaspari M, Rantanen A, Trifunovic A, Larsson NG, Gustafsson CM. Mitochondrial transcription factors B1 and B2 activate transcription of human mtDNA. *Nat Genet* 2002;**31**:289-294.
[16] Xia Y, Buja LM, Scarpulla RC, McMillin JB. Electrical stimulation of neonatal cardiomyocytes results in the sequential activation of nuclear genes governing mitochondrial proliferation and differentiation. *Proc Natl Acad Sci USA* 1997;**94**:11399-11404.
[17] Wu ZD, Puigserver P, Andersson U, Zhang CY, Adelmant G, Mootha V *et al*. Mechanisms

controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell* 1999;**98**:115-124.

[18] Garnier A, Fortin D, Delomenie C, Momken I, Veksler V, Ventura-Clapier R. Depressed mitochondrial transcription factors and oxidative capacity in rat failing cardiac and skeletal muscles. *J Physiol* 2003;**551**:491-501.

[19] Lehman JJ, Barger PM, Kovacs A, Saffitz JE, Medeiros DM, Kelly DP. Peroxisome proliferator-activated receptor gamma coactivator-1 promotes cardiac mitochondrial biogenesis. *J Clin Invest* 2000;**106**:847-856.

[20] Russell LK, Mansfield CM, Lehman JJ, Kovacs A, Courtois M, Saffitz JE *et al*. Cardiac-specific induction of the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator-1alpha promotes mitochondrial biogenesis and reversible cardiomyopathy in a developmental stage-dependent manner. *Circ Res* 2004;**94**:525-533.

[21] Leone TC, Lehman JJ, Finck BN, Schaeffer PJ, Wende AR, Boudina S *et al*. PGC-1alpha deficiency causes multi-system energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis. *PLoS Biol* 2005;**3**:e101.

[22] Arany Z, He H, Lin J, Hoyer K, Handschin C, Toka O *et al*. Transcriptional coactivator PGC-1 alpha controls the energy state and contractile function of cardiac muscle. *Cell Metab* 2005;**1**:259-271.

[23] Arany Z, Novikov M, Chin S, Ma Y, Rosenzweig A, Spiegelman BM. Transverse aortic constriction leads to accelerated heart failure in mice lacking PPAR-gamma coactivator 1alpha. *Proc Natl Acad Sci USA* 2006;**103**:10086-10091.

[24] St-Pierre J, Lin J, Krauss S, Tarr PT, Yang R, Newgard CB *et al.* Bioenergetic analysis of peroxisome proliferator-activated receptor gamma coactivators 1alpha and 1beta (PGC-1alpha and PGC-1beta) in muscle cells. *J Biol Chem* 2003;**278**:26597-26603.

[25] Lelliott CJ, Medina-Gomez G, Petrovic N, Kis A, Feldmann HM, Bjursell M *et al.* Ablation of PGC-1beta results in defective mitochondrial activity, thermogenesis, hepatic function, and cardiac performance. *PLoS Biol* 2006;**4**:e369.

[26] Meirhaeghe A , Crowley V, Lenaghan C, Lelliott C, Green K, Stewart A *et al.* Characterization of the human, mouse and rat PGC1 beta (peroxisome-proliferator-activated receptor-gamma co-activator 1 beta) gene in vitro and in vivo. *Biochem J* 2003;**373**:155-165.

[27] Dufour CR, Wilson BJ, Huss JM, Kelly DP, Alaynick WA, Downes M *et al.* Genome-wide orchestration of cardiac functions by the orphan nuclear receptors ERRalpha and gamma. *Cell Metab* 2007;**5**:345-356.

[28] Huss JM, Imahashi K, Dufour CR, Weinheimer CJ, Courtois M, Kovacs A *et al.* The nuclear receptor ERRalpha is required for the bioenergetic and functional adaptation to cardiac pressure overload. *Cell Metab* 2007;**6**:25-37.

[29] Alaynick WA, Kondo RP, Xie W, He W, Dufour CR, Downes M *et al.* ERRgamma directs and maintains the transition to oxidative metabolism in the postnatal heart. *Cell Metab* 2007;**6**:13-24.

[30] Gilde AJ, van der Lee KA, Willemsen PH, Chinetti G, van der Leij FR, van der Vusse GJ *et al.* Peroxisome proliferator-activated receptor (PPAR) alpha and PPARbeta/delta, but not PPARgamma, modulate the expression of genes involved in cardiac lipid metabolism. *Circ Res* 2003;**92**:518-524.

[31] Vega RB, Huss JM, Kelly DP. The coactivator PGC-1 cooperates with peroxisome proliferator-activated receptor alpha in transcriptional control of nuclear genes encoding mitochondrial fatty acid oxidation enzymes. *Mol Cell Biol* 2000;**20**:1868-1876.

[32] Cheng L, Ding G, Qin Q, Huang Y, Lewis W, He N *et al.* Cardiomyocyte-restricted peroxisome proliferator-activated receptor-delta deletion perturbs myocardial fatty acid oxidation and leads to cardiomyopathy. *Nat Med* 2004;1245-1250.

[33] Huss JM, Kelly DP. Mitochondrial energy metabolism in heart failure: a question of balance. *J Clin Invest* 2005;**115**:547-555.

[34] Ding G, Fu M, Qin Q, Lewis W, Kim HW, Fukai T *et al.* Cardiac peroxisome proliferator-activated receptor gamma is essential in protecting cardiomyocytes from oxidative damage. *Cardiovasc Res* 2007;**76**:269-279.

[35] Heineke J, Molkentin JD. Regulation of cardiac hypertrophy by intracellular signalling

pathways. *Nat Rev Mol Cell Biol* 2006;**7**:589-600.
[36] Handschin C, Rhee J, Lin J, Tarr PT, Spiegelman BM. An autoregulatory loop controls peroxisome proliferator-activated receptor {gamma} coactivator 1{alpha} expression in muscle. *Proc Natl Acad Sci USA* 2003;**100**:7111-7116.
[37] Sayen MR, Gustafsson AB, Sussman MA, Molkentin JD, Gottlieb RA. Calcineurin transgenic mice have mitochondrial dysfunction and elevated superoxide production. *Am J Physiol Cell Physiol* 2003;**284**:C562-C570.
[38] Bushdid PB, Osinska H, Waclaw RR, Molkentin JD, Yutzey KE. NFATc3 and NFATc4 are required for cardiac development and mitochondrial function. *Circ Res* 2003;**92**:1305-1313.
[39] Schaeffer PJ, Wende AR, Magee CJ, Neilson JR, Leone TC, Chen F *et al.* Calcineurin and calcium/calmodulin-dependent protein kinase activate distinct metabolic gene regulatory programs in cardiac muscle. *J Biol Chem* 2004;**279**:39593-39603 .
[40] Czubryt MP, McAnally J, Fishman GI, Olson EN. Regulation of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1alpha) and mitochondrial function by MEF2 and HDAC5. *Proc Natl Acad Sci USA* 2003;**100**:1711-1716.
[41] Naya FJ, Black BL, Wu H, Bassel-Duby R, Richardson JA, Hill JA *et al.* Mitochondrial deficiency and cardiac sudden death in mice lacking the MEF2A transcription factor. *Nat Med* 2002;**8**:1303-1309.
[42] Akimoto T, Sorg BS, Yan Z. Real-time imaging of peroxisome proliferator-activated receptor-gamma coactivator-1alpha promoter activity in skeletal muscles of living mice. *Am J Physiol Cell Physiol* 2004;**287**:C790-C796.
[43] Wu Z, Huang X, Feng Y, Handschin C, Feng Y, Gullicksen PS *et al.* Transducer of regulated CREB-binding proteins (TORCs) induce PGC-1alpha transcription and mitochondrial biogenesis in muscle cells. *Proc Natl Acad Sci USA* 2006;**103**:14379-14384.
[44] Watson PA, Reusch JE, McCune SA, Leinwand LA, Luckey SW, Konhilas JP *et al.* Restoration of CREB function is linked to completion and stabilization of adaptive cardiac hypertrophy in response to exercise. *Am J Physiol Heart Circ Physiol* 2007;**293**:H246-H259.
[45] Cribbs JT, Strack S. Reversible phosphorylation of Drp1 by cyclic AMP-dependent protein kinase and calcineurin regulates mitochondrial fission and cell death. *EMBO Rep* 2007;**8**:939-944.
[46] Wall JA, Wei J, Ly M, Belmont P, Martindale JJ, Tran D *et al.* Alterations in oxidative phosphorylation complex proteins in the hearts of transgenic mice that overexpress the p38 MAP kinase activator, MAP kinase kinase 6. *Am J Physiol Heart Circ Physiol* 2006;**291**:H2462-H272.
[47] Nisoli E, Clementi E, Paolucci C, Cozzi V, Tonello C, Sciorati C *et al.* Mitochondrial biogenesis in mammals: the role of endogenous nitric oxide. *Science* 2003;**299**:896-899.
[48] Momken I, Fortin D, Serrurier B, Bigard X, Ventura-Clapier R, Veksler V. Endothelial nitric oxide synthase (NOS) deficiency affects energy metabolism pattern in murine oxidative skeletal muscle. *Biochem J* 2002;**368**:341-347.
[49] Nisoli E, Tonello C, Cardile A, Cozzi V, Bracale R, Tedesco L *et al.* Calorie restriction promotes mitochondrial biogenesis by inducing the expression of eNOS. *Science* 2005;**310**:314-317.
[50] Reznick RM, Shulman GI. The Role of AMP-Activated Protein Kinase in Mitochondrial Biogenesis. *J Physiol* 2006;**574**:33-39.
[51] Zong H, Ren JM, Young LH, Pypaert M, Mu J, Birnbaum MJ *et al.* AMP kinase is required for mitochondrial biogenesis in skeletal muscle in response to chronic energy deprivation. *Proc Natl Acad Sci U S A* 2002;**99**:15983-15987.
[52] Athea Y, Viollet B, Mateo P, Rousseau D, Novotova M, Garnier A *et al.* AMP-Activated Protein Kinase {alpha}2 Deficiency Affects Cardiac Cardiolipin Homeostasis and Mitochondrial Function. *Diabetes* 2007;**56**:786-794.
[53] Jorgensen SB , Treebak JT, Viollet B, Schjerling P, Vaulont S, Wojtaszewski JF *et al.* Role of AMPKalpha2 in basal, training-, and AICAR-induced GLUT4, hexokinase II, and mitochondrial protein expression in mouse muscle. *Am J Physiol Endocrinol Metab* 2007;**292**:E331-E339.
[54] Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F *et al.* Resveratrol

improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. *Cell* 2006;**127**:1109-1122.

[55] Wrutniak-Cabello C, Casas F, Cabello G. Thyroid hormone action in mitochondria. *J Mol Endocrinol* 2001;**26**:67-77.

[56] Weitzel JM, Radtke C, Seitz HJ. Two thyroid hormone-mediated gene expression patterns in vivo identified by cDNA expression arrays in rat. *Nucleic Acids Res* 2001;**29**:5148-5155.

[57] Goldenthal MJ, Weiss HR, Marin-Garcia J. Bioenergetic remodeling of heart mitochondria by thyroid hormone. *Mol Cell Biochem* 2004;**265**:97-106.

[58] Irrcher I, Adhihetty PJ, Sheehan T, Joseph AM, Hood DA. PPARgamma coactivator-1alpha expression during thyroid hormone- and contractile activity-induced mitochondrial adaptations. *Am J Physiol Cell Physiol* 2003;**284**:C1669-C1677.

[59] Puigserver P, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell* 1998;**92**:829-839.

[60] Athea Y, Garnier A, Fortin D, Bahi L, Veksler V, Ventura-Clapier R. Mitochondrial and energetic cardiac phenotype in hypothyroid rat. Relevance to heart failure. *Pflugers Arch* 2007;**455**:431-442.

[61] Colavecchia M, Christie LN, Kanwar YS, Hood DA. Functional consequences of thyroid hormone-induced changes in the mitochondrial protein import pathway. *Amer J Physiol Endocrinol Metab* 2003;**284**:E29-E35.

[62] Craig EE, Chesley A, Hood DA. Thyroid hormone modifies mitochondrial phenotype by increasing protein import without altering degradation. *Amer J Physiol Cell Physiol* 1998;**44**:C1508-C1515.

[63] Sano M, Wang SC, Shirai M, Scaglia F, Xie M, Sakai S *et al.* Activation of cardiac Cdk9 represses PGC-1 and confers a predisposition to heart failure. *EMBO J* 2004;**23**:3559-3569.

[64] Sano M, Izumi Y, Helenius K, Asakura M, Rossi DJ, Xie M *et al.* Menage-a-Trois 1 Is Critical for the Transcriptional Function of PPARgamma Coactivator 1. *Cell Metab* 2007;**5**:129-142.

[65] Knutti D, Kressler D, Kralli A . Regulation of the transcriptional coactivator PGC-1 via MAPK-sensitive interaction with a repressor. *Proc Natl Acad Sci USA* 2001;**98**:9713-9718.

[66] Puigserver P, Rhee J, Lin J, Wu Z, Yoon JC, Zhang CY *et al.* Cytokine stimulation of energy expenditure through p38 MAP kinase activation of PPARgamma coactivator-1. *Mol Cell* 2001;**8**:971-982.

[67] Jager S, Handschin C, St-Pierre J, Spiegelman BM. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1{alpha}. *Proc Natl Acad Sci U S A* 2007;**104**:12017-12022.

[68] Rodgers JT, Lerin C, Haas W, Gygi SP, Spiegelman BM, Puigserver P. Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1. *Nature* 2005;**434**:113-118.

[69] Gerhart-Hines Z, Rodgers JT, Bare O, Lerin C, Kim SH, Mostoslavsky R *et al.* Metabolic control of muscle mitochondrial function and fatty acid oxidation through SIRT1/PGC-1alpha. *EMBO J* 2007;**26**:1913-1923.

[70] Alcendor RR, Gao S, Zhai P, Zablocki D, Holle E, Yu X *et al.* Sirt1 regulates aging and resistance to oxidative stress in the heart. *Circ Res* 2007;**100**:1512-1521.

[71] Teyssier C, Ma H, Emter R, Kralli A, Stallcup MR. Activation of nuclear receptor coactivator PGC-1alpha by arginine methylation. *Genes Dev* 2005;**19**:1466-1473.

[72] van Bilsen M. "Energenetics" of heart failure. *Ann N Y Acad Sci* 2004;**1015**:238-249.

[73] Ventura-Clapier R, Garnier A, Veksler V. Energy metabolism in heart failure. *J Physiol* 2004;**555**:1-13.

[74] Taegtmeyer H , Wilson CR, Razeghi P, Sharma S. Metabolic energetics and genetics in the heart. *Ann N Y Acad Sci* 2005;**1047**:208-218.

[75] Ingwall JS, Weiss RG. Is the failing heart energy starved? On using chemical energy to support cardiac function. *Circ Res* 2004;**95**:135-145.

[76] Neubauer S. The failing heart--an engine out of fuel. *N Engl J Med* 2007;**356**:1140-1151.

[77] O'Neill BT, Kim J, Wende AR, Theobald HA, Tuinei J, Buchanan J *et al.* A conserved role for phosphatidylinositol 3-kinase but not Akt signaling in mitochondrial adaptations that

accompany physiological cardiac hypertrophy. *Cell Metab* 2007;**6**:294-306.
[78] Ventura-Clapier R, Mettauer B, Bigard X. Beneficial effects of endurance training on cardiac and skeletal muscle energy metabolism in heart failure. *Cardiovasc Res* 2007;**73**: 10-18.
[79] Sack MN, Rader TA, Park SH, Bastin J, McCune SA, Kelly DP. Fatty acid oxidation enzyme gene expression is downregulated in the failing heart. *Circulation* 1996;**94**:2837-2842.
[80] Lehman JJ, Kelly DP. Transcriptional activation of energy metabolic switches in the developing and hypertrophied heart. *Clin Exp Pharmacol Physiol* 2002;**29**:339-345.
[81] van den Bosch BJ, van den Burg CM, Schoonderwoerd K, Lindsey PJ, Scholte HR, de Coo RF *et al.* Regional absence of mitochondria causing energy depletion in the myocardium of muscle LIM protein knockout mice. *Cardiovasc Res* 2005;**65**:411-418.
[82] Zoll J, Monassier L, Garnier A, N'Guessan B, Doutreleau S, Mettauer B *et al.* ACE inhibition prevents myocardial infarction-induced skeletal muscle mitochondrial dysfunction. *J Appl Physiol* 2006;**101**:385-391.
[83] Kemi OJ, Hoydal MA, Haram PM, Garnier A, Fortin D, Ventura-Clapier R *et al.* Exercise training restores aerobic capacity and energy transfer systems in heart failure treated with losartan. *Cardiovasc Res* 2007;**76**:91-99.
[84] Sun CK, Chang LT, Sheu JJ, Wang CY, Youssef AA, Wu CJ *et al.* Losartan Preserves Integrity of Cardiac Gap Junctions and PGC-1 alpha Gene Expression and Prevents Cellular Apoptosis in Remote Area of Left Ventricular Myocardium Following Acute Myocardial Infarction. *Int Heart J* 2007;**48**:533-546.
[85] Javadov S, Huang C, Kirshenbaum L, Karmazyn M. NHE-1 inhibition improves impaired mitochondrial permeability transition and respiratory function during postinfarction remodelling in the rat. *J Mol Cell Cardiol* 2005;**38**:135-143.
[86] Sebastiani M, Giordano C, Nediani C, Travaglini C, Borchi E, Zani M *et al.* Induction of mitochondrial biogenesis is a maladaptive mechanism in mitochondrial cardiomyopathies. *J Am Coll Cardiol* 2007;**50**:1362-1369.
[87] Wang S, Fu C, Wang H, Shi Y, Xu X, Chen J *et al.* Polymorphisms of the peroxisome proliferator-activated receptor-gamma coactivator-1alpha gene are associated with hypertrophic cardiomyopathy and not with hypertension hypertrophy. *Clin Chem Lab Med* 2007;**45**:962-967.
[88] Haq S, Choukroun G, Lim H, Tymitz KM, del Monte F, Gwathmey J *et al.* Differential activation of signal transduction pathways in human hearts with hypertrophy versus advanced heart failure. *Circulation* 2001;**103**:670-677.
[89] Tian R, Musi N, D'Agostino J, Hirshman MF, Goodyear LJ. Increased adenosine monophosphate-activated protein kinase activity in rat hearts with pressure-overload hypertrophy. *Circulation* 2001;**104**:1664-1669.
[90] Kinugawa K, Yonekura K, Ribeiro RC, Eto Y, Aoyagi T, Baxter JD *et al.* Regulation of thyroid hormone receptor isoforms in physiological and pathological cardiac hypertrophy. *Circ Res* 2001;**89**:591-598.
[91] Wassen FW, Schiel AE, Kuiper GG, Kaptein E, Bakker O, Visser TJ *et al.* Induction of thyroid hormone-degrading deiodinase in cardiac hypertrophy and failure. *Endocrinol* 2002;**143**:2812-2815.
[92] Cook SA, Matsui T, Li L, Rosenzweig A. Transcriptional effects of chronic Akt activation in the heart. *J Biol Chem* 2002;**277**:22528-22533.
[93] Sano M, Schneider MD. Cyclin-dependent kinase-9: an RNAPII kinase at the nexus of cardiac growth and death cascades. *Circ Res* 2004;**95**:867-876.
[94] Bueno OF, van Rooij E, Molkentin JD, Doevendans PA, De Windt LJ. Calcineurin and hypertrophic heart disease: novel insights and remaining questions. *Cardiovasc Res* 2002;**53**:806-821.
[95] Chang LT, Sun CK, Wang CY, Youssef AA, Wu CJ, Chua S *et al.* Downregulation of peroxisme proliferator activated receptor gamma co-activator 1alpha in diabetic rats. *Int Heart J* 2006;**47**:901-910.
[96] Duncan JG, Fong JL, Medeiros DM, Finck BN, Kelly DP. Insulin-Resistant Heart Exhibits a Mitochondrial Biogenic Response Driven by the Peroxisome Proliferator-Activated Receptor-{alpha}/PGC-1{alpha} Gene Regulatory Pathway. *Circulation* 2007;**115**:909-917.

[97] Han X, Yang J, Cheng H, Yang K, Abendschein DR, Gross RW. Shotgun Lipidomics Identifies Cardiolipin Depletion in Diabetic Myocardium Linking Altered Substrate Utilization with Mitochondrial Dysfunction. *Biochemistry (Mosc)* 2005;**44**:16684-16694.

[98] Reznick RM, Zong H, Li J, Morino K, Moore IK, Yu HJ *et al.* Aging-Associated Reductions in AMP-Activated Protein Kinase Activity and Mitochondrial Biogenesis. *Cell Metab* 2007;**5**:151-156.

[99] Nisoli E, Clementi E, Carruba MO, Moncada S. Defective mitochondrial biogenesis: a hallmark of the high cardiovascular risk in the metabolic syndrome? *Circ Res* 2007;**100**:795-806.

[100] McLeod CJ, Pagel I, Sack MN. The mitochondrial biogenesis regulatory program in cardiac adaptation to ischemia-a putative target for therapeutic intervention. *Trends Cardiovasc Med* 2005;**15**:118-123.

[101] McLeod CJ, Jeyabalan AP, Minners JO, Clevenger R, Hoyt RF Jr, Sack MN. Delayed ischemic preconditioning activates nuclear-encoded electron-transfer-chain gene expression in parallel with enhanced postanoxic mitochondrial respiratory recovery. *Circulation* 2004;**110**:534-539.

[102] Eliseev RA, Vanwinkle B, Rosier RN, Gunter TE. Diazoxide-mediated preconditioning against apoptosis involves activation of cAMP-response element-binding protein (CREB) and NFkappaB. *J Biol Chem* 2004;**279**:46748-46754.

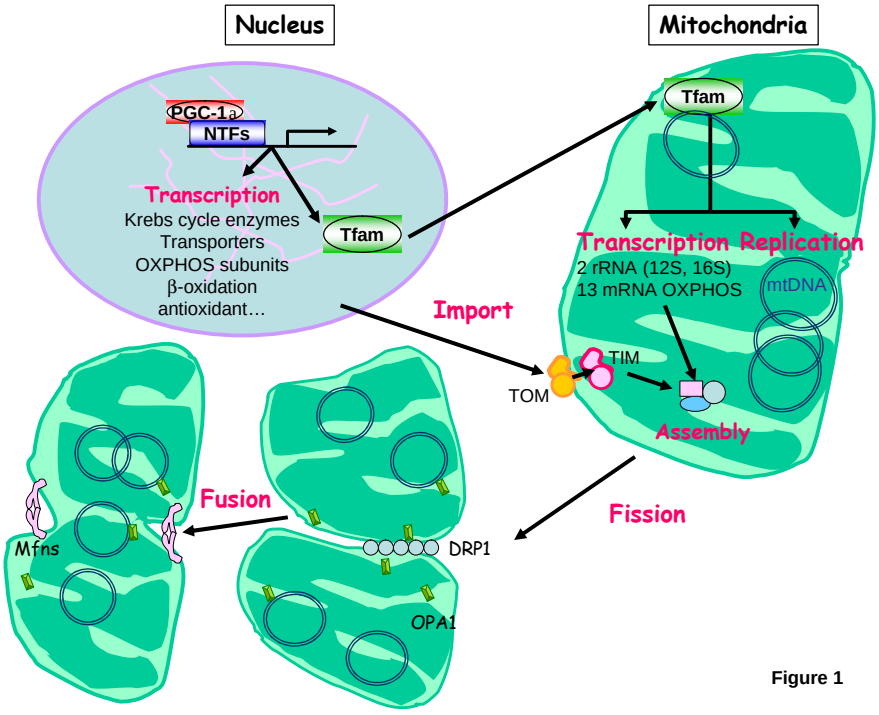

Figure 1: **Schematic representation of mitochondrial biogenesis.** peroxisome proliferator-activated receptor gamma co-activator (PGC-1α) activates nuclear transcription factors (NTFs) leading to transcription of nuclear- encoded proteins and of the mitochondrial transcription factor Tfam. Tfam activates transcription and replication of the mitochondrial genome. Nuclear-encoded proteins are imported into mitochondria through the outer- (TOM) or inner (TIM) membrane transport machinery. Nuclear- and mitochondria-encoded subunits of the respiratory chain are then assembled. Mitochondrial fission through the dynamin-related protein 1 (DRP1) for the outer membrane and OPA1 for the inner membrane of mitochondria allow mitochondrial division while mitofusins (Mfn) control mitochondrial fusion. Processes of fusion/fission lead to proper organization of the mitochondrial network. OXPHOS: oxidative phosphorylation.

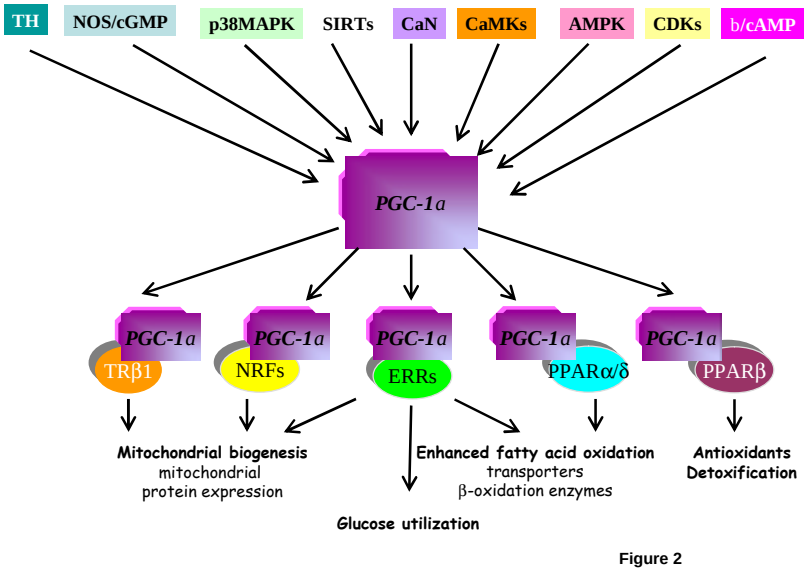

Figure 2: PGC1a **regulatory cascade.** Thyroid hormone (TH), nitric oxide synthase (NOS/cGMP), p38 mitogen-activated-protein-kinase (p38MAPK), sirtuines (SIRTs), calcineurin, calcium-calmodulin-activated kinases (CaMKs), adenosine-monophosphate-activated kinase (AMPK), cyclin-dependent kinases (CDKs), and β-adrenergic stimulation (β/cAMP) have been shown to regulate expression and/or activity of PGC-1α. PGC-1α then co-activates transcription factors such as nuclear respiratory factors (NRFs), estrogen-related-receptors (ERRs) and PPARs, known to regulate different aspects of energy metabolism including mitochondrial biogenesis, fatty acid oxidation and antioxidant

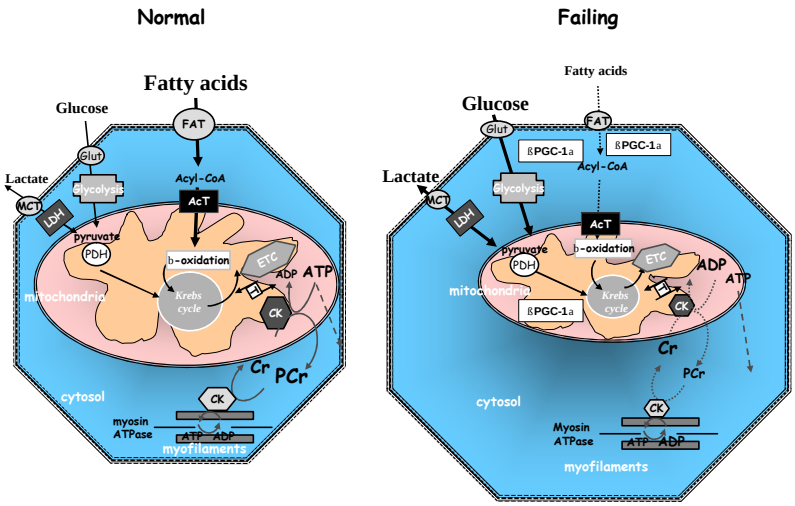

Figure 3. Cardiomyocyte energy metabolism. **A. Normal Cardiomyocyte.** Cardiomyocyte mainly uses fatty acids that enter the cell membrane through fatty acid transports (FAT) at the cell membrane and (CPT) at the mitochondrial membrane before being used by ß-oxidation and electron transport chain (ETC) to produce ATP. Glucose and lactate enter through their respective transporters (Glut and MCT) and are transformed into pyruvate by glycolysis and lactate dehydrogenase (LDH) respectively. Pyruvate enters the Krebs cycle to produce ATP. ATP is then converted into phosphocreatine by mitochondrial creatine kinase (CK). Phosphocreatine is used by localized CK close to ATPases to rephosphorylate ADP. **B. Failing cardiomyocyte**. In heart failure, fatty acid utilization is blunted, mitochondrial activity decreases and ATP synthesis is impaired. Moreover, decreased CK expression compromises energy transfer within the cardiomyocyte. The possible sites of action of PGC-1α are indicated.