

# Transcriptional control of energy homeostasis through the PGC1 coactivators

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*Abstract.* The PGC1 transcriptional coactivators are major regulators of several crucial aspects of energy metabolism. PGC1 $\alpha$  controls many aspects of oxidative metabolism, including mitochondrial biogenesis and respiration through the coactivation of many nuclear receptors, and factors outside the nuclear receptor family. ERR $\alpha$ , NRF1 and NRF2 are key targets of the PGC1s in mitochondrial biogenesis. We have recently addressed the question of the role of PGC1 coactivators in the metabolism of reactive oxygen species (ROS). We now show that PGC1 $\alpha$  and  $\beta$  are induced when cells are given an oxidative stressor, H<sub>2</sub>O<sub>2</sub>. In fact, experiments with RNAi for the PGC1s show that the ability of ROS to induce a ROS scavenging programme depends entirely on the PGC1s. This includes genes encoding mitochondrial proteins like SOD2, but also includes cytoplasmic proteins like catalase and GPX1. Cells lacking PGC1 $\alpha$  are hypersensitive to death from oxidative stress caused by H<sub>2</sub>O<sub>2</sub> or paraquat. Mice deficient in PGC1 $\alpha$  get excessive neurodegeneration when given kainic acid-induced seizures or MPTP, which causes Parkinsonism. These data show that the PGC1s are important protective molecules against ROS generation and damage. The implications of this for diabetes and neurodegenerative diseases will be discussed.

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Oxidative metabolism is crucial for most living systems, and the majority of oxidative metabolism in eukaryotic cells occurs in the mitochondria. Mitochondria generate ATP through the function of the electron transport system, whereby the passage of high energy electrons down this chain is coupled to the extrusion of protons across the inner membrane of the mitochondria. This proton gradient can be dissipated by passage through complex V of the electron transport chain, which couples this proton movement to the phosphorylation of ADP to ATP.

Recent data have implicated mitochondrial dysfunction in a large number of important human diseases, including neurodegeneration, heart failure and

diabetes. The skeletal muscle of humans with type 2 diabetes, glucose intolerance or a family history of diabetes all have a reduced expression of multiple genes of the mitochondrial oxidative phosphorylation (OXPHOS) system, and their dominant regulators, the peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) coactivator 1 (PGC1) coactivators (Mootha et al 2003, Patti et al 2003). In this paper, I review recent data related to the role of PGC1s, especially PGC1 $\alpha$ , in energy metabolism related to diabetes and neurodegeneration.

PGC1 $\alpha$  was discovered as a binding partner and coactivator of PPAR $\gamma$  in brown fat (Puigserver et al 1998). It is induced in this tissue by exposure of animals to cold, a condition which activates the thermogenic function of brown fat tissue. Functional studies in our group and others showed that PGC1 $\alpha$  increased mitochondrial OXPHOS gene expression and the expression of UCP1 when expressed in white fat cells in culture or *in vivo* (Puigserver et al 1998, Tiraby et al 2003). Detailed analysis of the effects of PGC1 $\alpha$  on mitochondria indicated that it could increase the expression of a wide variety of mitochondrial genes, whether encoded in the nuclear or mitochondrial genomes (Wu et al 1999). This ability to activate a broad mitochondrial programme results, in large measure, from the ability of PGC1 $\alpha$  to coactivate ERR $\alpha$ , NRF1 and NRF2 (Handschin et al 2003, Wu et al 1999, Mootha et al 2004, Schreiber et al 2004).

The ability of PGC1 $\alpha$ , and its closest homologue PGC1 $\beta$ , to induce respiration in muscle cells was examined (St. Pierre et al 2003). Both coactivators increase respiration greatly, as they induce mitochondrial biogenesis. However, PGC1 $\alpha$  increases the fraction of uncoupled respiration compared to controls, whereas PGC1 $\beta$ -induced respiration has the same relative proportions of coupled and uncoupled respiration as cells expressing a GFP control.

Regarding the role of PGC1 $\alpha$  in skeletal muscle, the gene sets activated are not restricted to mitochondria. Transgenic expression of PGC1 $\alpha$  stimulates a broad programme of fibre-type switching from type IIb fibres to type IIa and type I. These oxidative fibres include more mitochondria but also include myosin heavy chain (MHC) type IIa, I and myoglobin. These data are likely to be highly relevant from a physiological perspective because PGC1 $\alpha$  is expressed at highest levels in soleus muscle, which is very rich in type I fibres (Lin et al 2002) and is induced in rodents and humans by exercise (reviewed in Handschin & Spiegelman 2006).

### **PGC1s and disease**

Our recent studies have focused on the potential role of PGC1 $\alpha$  in the context of tissue degeneration and wasting, especially skeletal muscle and the brain.

Since PGC1 $\alpha$  mediates many of the effects of motor nerves on skeletal muscle relating to mitochondria and fibre-type switching, we have asked whether PGC1 $\alpha$  might mediate a key function of motor nerve activity: the suppression of muscle

atrophy. Indeed, if skeletal muscle is denervated, skeletal muscle loses mass coincident with shrinkage in the diameter of muscle fibres. This is also seen in rodents and humans if limbs suffer disuse. This loss of muscle mass is a catabolic process and is associated with induction of a set of genes termed 'atrogenes' that include E-3 ubiquitin ligases such as atrogin and MURF (Lecker et al 2004).

We were able to show that dissection of the sciatic nerve causes a loss of muscle fibre diameter of 50% within 12 days in control mice. However, transgenic expression of PGC1 $\alpha$  causes an almost complete suppression of muscle atrophy, as well as a significant reduction of the induction of the set of atrogenes (Sandri et al 2006). This suppression of the atrogenes by PGC1 $\alpha$  is likely to derive, at least in part, from a suppression of FOXO3 action by PGC1 $\alpha$ .

Many forms of neurodegeneration have been associated with mitochondrial dysfunction and increased oxidative damage (Lin & Beal 2006). Given that mice mutated in PGC1 $\alpha$  have a severe neurodegeneration in the striatum (Lin et al 2004), we recently studied the role of PGC1 coactivators and the metabolism of reactive oxygen species (ROS). PGC1 $\alpha$  and PGC1 $\beta$  mRNA are co-induced in cells treated with H<sub>2</sub>O<sub>2</sub> with the gene sets of protection from ROS, including SOD1 and SOD2, catalase, GPX1, UCP1 and UCP3. Studies with RNAi directed against PGC1 $\alpha$  show that this coactivator is required to get full expression of the antioxidant programme (St. Pierre et al 2006). Similar results were obtained with cells mutated in PGC1 $\alpha$ . The induction of PGC1 $\alpha$  by an oxidative stressor was stimulated, at least in part, by the increased binding of phosphorylated CREB to the PGC1 $\alpha$  promoter.

The neuroprotective and anti-ROS effects of endogenous PGC1 $\alpha$  could be illustrated by treating the PGC1 $\alpha$  knockout mice with agents that induce oxidative stress and neurodegeneration. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and kainic acid induced much more degeneration in the dopaminergic centres of the substantia nigra, and hippocampus, respectively. These degenerative processes were associated with greater levels of stable markers of oxidative damage, such as nitrotyrosylation of proteins and 8-OXO-guanine in DNA.

Gain of function studies in cultured cells show that elevation of PGC1 $\alpha$  levels above those of wild-type nerve cells give an increased resistance to death by the oxidative stressors H<sub>2</sub>O<sub>2</sub> and paraquat.

Future studies will involve finding known drugs or chemical compounds that can elevate PGC1 $\alpha$  in many tissues, especially brain and skeletal muscle. These will then be tested in models of neurodegeneration, muscle wasting and muscle dystrophies, and type 2 diabetes.

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## DISCUSSION

*Attie:* I'm interested in the islet results in PGC1 $\alpha$  mutant mice. You said that there is defective insulin secretion. Which secretagogues is this in response to?

*Spiegelman:* Glucose at this point. These are reproducible data, but we haven't broadened this work out yet.

*Attie:* When you isolate the islets do they all look the same?

*Spiegelman:* I gather they all look abnormal.

*Attie:* What is the insulin content of those islets?

*Spiegelman:* I believe this is reduced. They are big and lousy, with reduced insulin content.

*Bernlohr:* Could you say a bit about peroxisomal formation in the muscle knockout?

*Spiegelman:* I don't know anything about it.

*Bernlohr:* You could argue that it may mount some compensatory response to increased peroxisomal oxidation. Is PGC1 $\alpha$  involved in the transcription of peroxisomal components?

*Spiegelman:* That is a good question, because it generates ROS. I haven't done this. Perhaps the peroxisomes are trying to make up for the mitochondrial deficiency, and this is then turning into a ROS generating machine.

*Bernlohr:* I don't know whether those regulatory circuits are coupled or potentially uncoupled and overlapping.

*Sbi:* The knockout mice have brain dysfunction. How about their islet function?

*Spiegelman:* It looks quite normal.

*Sbi:* What is your explanation for this? I would expect a defect in islet function, since islet  $\beta$  cells share many common features with the brain and mitochondrial oxidative phosphorylation plays an important role in regulating glucose-stimulated insulin secretion, i.e. the second phase insulin secretion. Here you have a muscle-specific knockout showing a different phenotype to that of the whole body knockout. It would be interesting to investigate the phenotypes of islet-specific knockout mice.

*Spiegelman:* We are seeing several phenomena like this. The total knockout has some things going on systemically that the muscle knockout doesn't. The total knockout has constitutive activation of AMP kinase in the muscle. The muscle-specific knockout does not. There is something about the combination of hyperactivity with bad mitochondria. We get this tremendous activation of AMP kinase in muscle, but the muscle-specific knockouts are slightly hypo-active, with somewhat reduced respiration and no activation of AMP kinase. I think the muscle-specific knockout is really the naked PGC1 phenotype as far as muscle goes. The total knockout is fascinating but there are so many things going on in this animal it is very hard to work it all out. When we do tissue-specific knockouts we almost always see something different from the total knockout.

*Sbi:* What happens to the body weight in the muscle-specific knockout mice?

*Spiegelman:* It tends to be slightly low. There is almost a sense of cachexia. The data I showed you are exciting, but even the muscle-specific knockout is complicated. Personally, I am very interested in the heterozygotes, where we see glucose intolerance. In the total muscle knockout there is fibre-type switching and several things going on. This isn't what human patients with glucose intolerance have, and there is still a lot going on in those mice. The heterozygotes have no fibre type

switching, mild deficiency in mitochondrial biology, and we still see some glucose intolerance. This is the model I like for the human disease.

*Kim:* What about the PGC1 function and ROS in several different tissues? On the basis of your data it seems that ROS plays a role in inducing PGC1, but PGC1 has several different functions from tissue to tissue. Do you think that PGC1 has a role in ROS scavenging in every tissue?

*Spiegelman:* In the total knockout of PGC1, there is partial deficiency of the anti-ROS enzymes in all tissues that we have examined. It is not really a muscle or brain specific thing. In general SOD1, SOD2, GPX and catalases all tend to be expressed at 60–80% of what they would be in wild-type, a bit like the mitochondrial genes. And at least as far as we have looked, their inducibility is lost. More than the outright deficiency of the anti-ROS, the bad effect of PGC1 $\alpha$  loss is the loss of responsiveness of these enzymes to ROS. These are adaptive systems in mammals.

*Glass:* I have a question relating to a theme that will come up later in the meeting: that of the relationship between inflammation and insulin resistance. What are your thoughts on the impact of inflammation on the function of PGC1 $\alpha$  and its peers? We think of inflammatory stimuli affecting the phosphorylation of IRS1, and how this could have an impact on downstream insulin signalling, but it would also appear that inflammation could affect the function of PGC1. What are your thoughts on this?

*Spiegelman:* That's a very good point. In fact, we see inflammatory changes with deficiency in PGC1. In the total knockout all the inflammatory markers are up in muscle. In fact, we even wonder whether the weird islets in the knockout might be because TNF, IL1 and IL6 are going up. I don't know whether this happens in the heterozygote yet.

*Glass:* That is putting inflammation downstream of PGC1. I wasn't even thinking of this: I was considering inflammation affecting PGC1 function.

*Spiegelman:* We keep seeing these cycles with ROS both upstream and downstream. Some of the transcription factors are both upstream and downstream. Everything we see in this system looks like a cycle: almost everything downstream is also upstream. I know you have been doing some work with PGC1s and inflammation as well.

*Glass:* Yes. In the macrophage, if we remove PGC1 and look at gene expression, many inflammatory mediators are up-regulated. This would be consistent with what you are finding.

*Spiegelman:* A simple model that we could tie together would be to say that in the muscle-specific knockout there is something inflammatory going on. Something is getting to the  $\beta$  cell—inflammation, or lipotoxicity or some combination thereof. It would be exciting if the PGC1 defect in muscle can play out and affect the biology of the islets. Of course, in the diabetes field there are those who concen-

trate on insulin resistance and those who focus on islets. There hasn't been that much tying things together. It would be great if PGC1 in the mitochondrial pathway in muscle really does have a way to talk to the islets. Diabetes has to involve defects in both.

*O'Rabilly:* The strongest data from those papers (Patti et al 2001, Mootha et al 2003) were Mary Elizabeth Patti's in which they specifically chose insulin-resistant individuals. I'd like to press you a bit on this link between PGC1 deficiency, mitochondrial function and insulin resistance. There seems to be an idea that it is not quite as linear a pathway as some have thought. There are also a couple of critical papers that don't tend to be quoted. Firstly, humans with inherited mitochondrial diabetes develop severe  $\beta$  cell dysfunction but their insulin sensitivity in muscle is very well preserved (Maassen et al 2004). Secondly there is a body of evidence emerging from transgenic mice suggesting that primary disorders of mitochondrial oxidative phosphorylation in skeletal muscle do not result in muscle or whole body insulin resistance (see Wredenberg et al 2006).

*Spiegelman:* But I have to say that what for you and many people in the field is a mitochondrial/insulin resistance hypothesis, we call the PGC1 hypothesis. It could just be that the PGC1s have so many different functions, the mitochondrial deficiency was really a surrogate.

*O'Rabilly:* Out there in the broad community there is a very simple linear view.

*Spiegelman:* I don't assume that the defects we are seeing are due to the deficiency in mitochondria. They could be. We are not against that idea, but we know that there is a lot more going on. Inflammatory markers are going up. Lipid oxidation is going to be affected. It is a linked pathway, and deconvoluting these things is not trivial. But I don't assume that it is the mitochondria.

*Hotamisligil:* A little bit of hydrogen peroxide is needed to signal to most of the tyrosine kinase receptors. Could this be the reason why that if you regulate the production of ROS robustly, you might compromise what you would otherwise see in insulin action?

*Spiegelman:* It is possible: this system has tone, but it doesn't have to be set at zero ROS. Clearly, having too much ROS is bad, but as you say there are papers showing the beneficial effects of certain ROS. The tone in this homeostatic system isn't zero or infinity, but it should be set at some appropriate level.

*Sbi:* It is generally believed that an increase in mitochondrial activity will generate ROS. In your case you have PGC1 doing the opposite.

*Spiegelman:* This is a common misconception, and I am glad you asked this. It is not true that all mitochondrial activity increases ROS. I know people say it, but it isn't true. What is true is that most ROS come from mitochondria. But there are separate variables that tell a mitochondrion to make more or less ROS. Probably the single biggest variable is membrane potential. If it gets too high mitochondria

will generate ROS. The real-life variable that usually controls this is ATP turnover and the rate of its utilization. When there is a mismatch between mitochondrial electron transport, and ATP production and utilization, this then sets up a situation for ROS generation.

*Sbi:* In your cell line or cell based assay, have you ever measured ATP production in response to PGC1 overexpression or down-regulation?

*Spiegelman:* Yes, many times. Cells that are deficient in PGC1 $\alpha$  can't defend their ATP levels well at all.

*Sbi:* Do you understand the overall picture of your knockout? I didn't see any data on food intake or metabolic rates.

*Spiegelman:* The knockout mice eat normally but are lean because of increased energy expenditure. The muscle-specific knockout eats a little less and is a bit smaller and leaner, but basically it has a tendency towards lower metabolic rates. The total knockout has a tendency towards higher metabolic rates in large part because they have this Huntington-like thing going on and they move more.

*Hotamisligil:* So is that physical activity chorea?

*Spiegelman:* In the Huntington field they do a clasping test. Pick a mouse up by the tail and the Huntington mice will do clasping. Our mice do this. They are hyper-responsive and jumpy. People in our lab don't need to genotype the mice because they are so obvious.

*Attie:* One metabolite that has dramatic effects on insulin sensitivity, food intake and  $\beta$  cell function that is often overlooked is  $\beta$ -hydroxybutyrate. I would predict that your mice have a defect in ketone body oxidation. I noticed that your GTP was near normal on the chow diet, but abnormal in the high fat diet. Have you measured ketones?

*Spiegelman:* That is a good point. I don't know. We are always looking for plausible hypotheses. Lately we've been more interested in the inflammatory idea, but what you say needs consideration.

*P Li:* Do you see this neural degeneracy in the striatum in other cell types?

*Spiegelman:* In the total knockout there are three tissues that are morphologically abnormal. The brain (striatum in particular), brown fat (it looks like bad brown fat with a deficient thermogenic programme) and there is a tendency towards hepatic steatosis. Dan Kelly sees out-and-out hepatic steatosis in his knockout; we have seen a trend towards this. But morphologically the mice look quite good. They seem to be living fairly normal lives.

*Muoio:* When you showed data indicating an interplay between  $\beta$  cell function and PGC1 $\alpha$  expression in muscle, the first candidate mediator that came to mind was IL6, which is known to be robustly up-regulated in muscles that are experiencing energy stress (Pedersen et al 2004).

*Spiegelman:* Is it known to have effects on islets?

*Muoio:* *In vitro* experiments have shown quite convincingly that IL6 and other cytokines can impair  $\beta$  cell function (Zhao et al 2006, Hohmeier et al 2003). In

skeletal muscle, IL6 expression and secretion is induced by exercise. There are several reports suggesting that IL6 functions as a ‘myokine’ that communicates changes in muscle energy status, and in turn regulates metabolic programmes such as lipolysis and gluconeogenesis in adipose tissue and liver, respectively (Pedersen et al 2004).

You commented that ablation of PGC1 $\alpha$  in muscle does not lower mitochondrial number, but have you considered or examined changes in mitochondrial properties? Do you have any evidence that energy metabolism is altered in the knockout animals?

*Spiegelman:* We have taken cells in culture and done this analysis carefully. They are struggling to maintain their ATP homeostasis. *In vivo* we have looked in the heart by NMR, but not in skeletal muscle. We published a paper in 2005 in which we looked at the heart in a Langendorf preparation hanging in an NMR magnet (Arany et al 2005). We showed an inability to defend ATP in real time.

*Muoio:* What is the impact on ATP-generating pathways such as glycolysis, glucose oxidation and  $\beta$  oxidation?

*Spiegelman:* In culture, glycolysis is way up. We have submitted a paper on ATP homeostasis and the cells are trying to raise glycolysis. The near normal ATP homeostasis at basal levels is at the expense of highly elevated glycolysis.

*Hotamisligil:* Endoplasmic reticulum (ER) is also a major source for ROS. Some even propose that it might be as important as mitochondria. The two might be physically and functionally connected organelles. There is physiological ROS production, for example, during disulfide bond formation and breakdown. It could become pathological when the ER is under stress. With the neural degeneration phenotype, the muscle phenotype and the total knockout phenotype I can’t help but think there might be signs of ER stress.

*Spiegelman:* This is a subject I don’t know a great deal about. The idea strikes me as reasonable: let’s take a look at it.

*Zhang:* Have you looked at the glucose-stimulated insulin secretion from islets in the skeletal muscle-specific knockout?

*Spiegelman:* Yes. It is deficient. I am not sure we’ll see this in the heterozygotes, though.

*Kadowaki:* Reduced PGC1 expression in human skeletal muscle in type 2 diabetes may be both genetically and environmentally determined. Can you comment on the impact of lifestyle factors such as high fat diet and sedentary lifestyle on the expression of PGC1 $\alpha$ ?

*Spiegelman:* That is a good question. The first time I presented work on PGC1 $\alpha$  in muscle, someone asked what would happen if we elevated it. My response was that the experiment has already been done: exercise. It is known that exercise benefits this condition. In terms of environmental factors, there are now a lot of papers on exercise and the PGC1 coactivators in humans and animals. In all cases, exercise elevates the expression of PGC1 $\alpha$ . The simple-minded idea is that physical

movement and activity is probably a dominant player. There are papers showing that high fat diet suppresses PGC1 expression in skeletal muscle. I do believe that these are major mediators of the sedentary versus active lifestyle consequences.

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