The effect of Mitochondria in Regulation gene expression, Metabolism, Cell differentiationand Modulate synaptic transmission within the brain, as a Potential Target in Cancer and Autoimmunity Treatment and Prevention

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Abstract

Mitochondria are now recognized to perform multiple essential functions beyond energy production, impacting most areas of cell biology and medicine.

Mitochondria undergo function-defining dynamic shape changes, communicate with each other, regulate gene expression within the nucleus, modulate synaptic transmission within the brain, release molecules that contribute to oncogenic transformation and trigger inflammatory responses systemically, and influence the regulation of complex physiological systems.

The cell's capacity to maintain its mitochondria involves intra-mitochondrial processes, such as heme and protein turnover, and those involving entire organelles, such as fusion, fission, selective mitochondrial macroautophagy (mitophagy), and mitochondrial biogenesis.

Numerous studies have reported short-term and delayed T3 stimulation of mitochondrial oxygen consumption. Convincing data indicate that an early influence occurs through an extra-nuclear mechanism insensitive to inhibitors of protein synthesis.

Recent studies concerning the physiological importance of the direct mitochondrial T3 pathway involving p43 led to the conclusion that it is not only involved in the regulation of fuel metabolism, but also in the regulation of cell differentiation.

In this article, I discuss The Mitochondria; Delayed influence is probably induced at the nuclear level, Thyroid Hormone Influence on Mitochondrial Genome Expression, Thyroid Hormone Stimulates Mitochondriogenesis, Physiological Importance of the Direct Mitochondrial T3 Pathways and Induction of Mitochondrial Biogenesis by Hormones

Key Word: Mitochondria, Thyroid Hormone, T3 Pathways, Hormones, Cancer and Autoimmunity

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1. Introduction

The cell's mitochondrial mass is closely regulatedby complex intracellular and extracellular signaling pathways that respond to energy demand and is adjusted through the inducible process of mitochondrial biogenesis (1),(2),(3),(4). Mitochondrial biogenesis is defined as the set of molecular instructions by which cells replace or increase their mitochondria through the proliferation of pre-existing organelles(2),(5). It involves close cooperation between nuclear and mitochondrial genomes that wasoriginally characterized as part of the process of organelle expansion during mitosis, where the doubling of mitochondrial volume imparts each daughter cell with a roughly equivalent complement of mitochondria. This process is fundamental to growth and development, isregulated by specific hormonal or paracrine signals, and in adult tissues is induced in response to increased energy requirements, for instance, in cardiac and skeletal muscle during exercise training (6),(7). It is also induced by calorie restriction as well as loss of mitochondrial functional reserve due to damage to the organelles by a range of

pathologic events (3). To maintain its mitochondria and conserve aerobic energy reserve, the cell must integrate three processes near simultaneously: the identification of irreparably damaged mitochondria; their targeted elimination through selective mitochondrial autophagy (mitophagy); and their efficient replacement through mitochondrial biogenesis. If this cycle is compromised, the cell becomes susceptible not just to loss of energy regulation, but to calcium dysregulation, disruption of heme biosynthesis, oxidative damage from excessive generation of reactive oxygen species (ROS) by dysfunctional mitochondria and intrinsic apoptosis (8). Under most circumstances, mitochondria are the main endogenous producers of ROS in the cell but also constitute a major antioxidant defense. Both facets encompass central pro-survival functions involving antiapoptotic and anti-inflammatory pathways that limit tissue loss and hold fibrotic mechanisms in check. The antioxidant role is related both to inducible mitochondrial ROS-scavenging systems and to the fact that cytochrome c oxidase fullyreduces molecular O2 to water. The antiapoptotic effect derives from both the calcium storage function andwhereas counter-inflammatory mechanisms are related mainly to regulation of inflammasome assembly. Despite extensive work on the molecular regulation of mitochondrial turnover in health and disease, rational mitochondrial-based strategies are only now being formulated for conditions that involve mitochondrial dysfunction and have proven refractory to conventional therapeutics. The conditions that damage mitochondria entail a range of injuries including ischemia-reperfusion, systemic inflammatory states, cardiovascular disease, degenerative diseases of the musculoskeletal and central nervous systems, aging, and toxic injuries to solid organs such as the liver and kidney. Many of the signaling pathways that maintain energy homeostasis also support the resolution ofmitochondrial damage. In addition to ATP production, mitochondria coordinate numerous metabolic and anaplerotic reactions through the Krebs cycle and fatty acid metabolism (9). The capacity to regenerate mitochondria,however, is challenging because of the mitochondrial genome, as each organelle harbors multiple copies of the circular ;16.6-kb double-stranded DNA molecule (mitochondrialDNA, mtDNA) that encode for 13 electron transport chain proteins, 2 rRNA of the mitochondrialribosome, and 22 tRNA required for the translation of protein in the matrix (10). The genetic organization of mammalian mtDNA ishighly conserved (11). Genes arepresent on both DNA strands, designated by relativeweight per nucleotide as the heavy (H)- and light (L)-strands. The H-strand encodes two rRNAs, 12 mRNAs,and 14 tRNAs, whereas the L-strand encodes 1 mRNAand 8 tRNAs. The noncoding control regionor D-loop encompasses cis-acting regulatory elements the expression of antiapoptotic mitochondrial proteins,required for mtDNA transcription and replication (11). Polycistronic RNA generated by mtDNA transcription is processed into individual rRNAs, tRNAs, and mRNAs. Mitochondrial plasticity, however, is largely under nuclear control, and manynuclear-encoded mitochondrial proteins (NEMPs) are expressed in a tissue- or cell-specific manner that allows proteome modifications for specialized function (12). Mitochondria, of course, regulate intrinsic programmed cell death, aspects of innate immunity (13), and cellular responses to starvation, such as autophagosomal membrane genesis (14). Specific domains called mitochondria-associated membranes (15), form through interaction and communication with cytoskeleton and endoplasmic reticulum (ER), generating small vesicular carriers called mitochondrial-derived vesicles (MDVs) (16),that transport cargo to peroxisomes. Recently, a new aspect is the transport of mitochondrial proteins and lipids to other intracellular organelles, e.g., fusion with multivesicular bodies or the late endosome (17),(18). Interruption of mitochondrial assembly, turnover, or function without cell death contributes to a surprisingly wide range of pathologies, raising the need for highly targeted therapies (8),(19).

2. The Mitochondria

Mitochondria are intriguing subcellular organelles. With a bacterial evolutionary origin, they have become perhaps the ultimate symbiont, maintaining its own DNA while also deriving many important proteins from the nuclear DNA of the host cell. While they may maintain a modicum of independence from the host cell in some respects, they nevertheless lie at the heart of the life of almost all eukaryotic cells. The primary function of the mitochondrion is oxidative phosphorylation (ox-phos) and ATP supply, i.e. the function upon which all cellular activities depend (20). The mitochondria are the "energy powerhouse of the cell" generating approximately 90% of cellular energy and consuming about 98% of the total O2 we breathe (21). Multicellular organism have indeed high-energy requirements necessary to carry out complex function, such as muscle contraction, hormones and neurotransmitters synthesis and secretion, in addition to ba-sal cellular metabolism (biomolecules synthesis and transformation, maintenance of ionic gradients across membrane, cell division) (22).

3. Thyroid Hormone Influence on Mitochondrial Oxygen Consumption

3.1. Short-term influence

Several studies have reported that T3 injection in hypothyroid rats increases oxygen consumptionand oxidative phosphorylations measured in isolated liver mitochondria collected less than30 min after hormone administration (23),(24). Inaddition, this effect was not abrogated by proteinsynthesis inhibitors (24). *In vitro*experiments also demonstrated that adding T3 tothe incubation medium of isolated mitochondria from hypothyroid animals induced a similarinfluence within 2 min of the hormone being present (25),(26). Moreover, (27), reportedastimulation of the mitochondrial carrier adenine nucleotide translocase (ANT) displaying the same features. Rapidity, refractoriness to inhibitors of protein synthesis, and occurrence in the absence of nuclei ruled out the involvement of the T3 genomic pathway. Parallel to this, several studies have demonstrated that the mitochondrion is a major compartment of T3 accumulation in the cell (23),(28),(29),(30). These data led to the proposition that ANT was a major T3 target involved in the short-term influence of the hormone on the organelle. In agreement with this hypothesis, (31), reported that ANT is a high-affinity binding site for T3. However, despite the availability of the purified protein and related antibodies or expression vectors, this last result has not received any confirmation. In particular, as were others, we were unable to demonstrate significant T3 binding to purified ANT or to the protein in its mitochondrial context (32),(33). However, the possibility that T3 by itself could induce this early influence is still under debate.First, after inhibiting deiodinations by propylthiouracil, (34), reported that diiodothyronines(T2s), but not T3, induce this short-term mitochondrial influence. In addition, in agreementwith the detection of 3,5-T2-binding sites in the organelle (35),(36),(37), found that 3,5-T2 binds to a subunit of cytochrome-c-oxidase, leading to a conformational change of the enzyme and an activation of the respiratory chain. Next, as mentioned previously for T3, inhibitors of protein synthesis do not alter the influence of T2 on the organelle (38),(39), reported that 5_-deiodinase activity could be detected in mitochondria, thus suggesting that T3 to T2 conversion in the isolated organelle is not unlikely. Although controversial, this observation could explain the T3 influence recorded in this *in vitro* system. These data led to the

proposition that 3_,5-T2 is actually a mediator of the short-term thyroid hormone influence. However, in our opinion, the detection of specific T3-binding sites in mitochondria by three separate teams (40),(41),(42), does not allow us to exclude the possibility that T3 by itself is able to induce a part of the short-term hormonal influence. In particular, (43), found that a 28 kDa T3-binding protein was localized in the mitochondrial inner membrane. In agreement with this result, we have more recently identified a truncated form of the T3 nuclear receptor c-Erb A_1 displaying a similar molecular mass and the same localization in the organelle as Sterling's protein (p28) (33). According to (44), p28 is synthesized by alternative translational initiation at an internalAUG in the messenger encoding the full-length nuclear receptor. Now, we have evidencethat this T3-binding protein is actively imported in isolated mitochondria (F Casas, C Wrutniak-Cabello & G Cabello, unpublished observations). Although its exact function remains to be established, p28 could act as a receptor involved in the early mitochondrial T3 influence, taking into account its co-localization with components of the respiratory chain, uncoupling proteins (UCPs) or ANT.

3.2. Delayed influence is probably induced at the nuclear level

Studies were performed in order to identify the sites of action of T3 involved in delayed stimulation of oxygen consumption(45). In isolated mitochondria or in hepatocytes, they led to the conclusion that the proton leak across the inner membrane is an important target of thyroid hormone involved in its influence on oxygen consumption. In addition, studies performed in isolated mitochondria from hypothyroid rats suggested that reactions dissipating the protonmotive force like ATPase or ANT activity are also involved in this regulation, but these data were not confirmed in hyperthyroid mitochondria or in hepatocytes. The proton leak represents about 20% of the multifactorial control of mitochondrial respiration (46), and convergent data demonstrate that it is increased by thyroid hormone, according to several mechanisms. First, thyroid hormone increases the area of the inner membrane and alters its phospholipid composition(47),(48). leading to increased permeability to protons recorded 9–12 h after hormone administration(49). More recently, the discovery of a family of mitochondrial UCPs (50), provided another clue to explain this influence. In contrast to initialfindings indicating that UCP1 expression was restricted to brown adipose tissue, it appears that almost all tissues express at least one member of the UCP family (UCP2, 3 and brain mitochondrial carrier protein-1). Interestingly, it is now established that UCP1(51),(52),(53), (54), and UCP3(55),(56), gene expression is increased byT3. In addition,(57), reported theexistence of a substantial correlation between UCP3 mRNA levels, mitochondrial coupling and the thyroid state, thus suggesting that control of UCPs expression is involved in the T3 regulation of the proton leak. Another finding of these studies is that thyroid hormone-induced changes in the phospholipid composition of the inner membrane include stimulation of cardiolipin synthase activity due to a rise in the mitochondrial phosphatidylglycerol pool (58),(59), thus increasing the amounts of cardiolipin(60),(61). As cardiolipin stimulates severalmitochondrial carriers and enzymes activities(60),(61). This event couldcontribute to the delayed hormone influence onmitochondrial respiration. Besides the proton leak, the influence of thyroid hormone on the processes involved in dissipation of the protonmotive force previously mentioned is in agreement with the observation that subunit F1-ATPase of the mitochondrial complex synthesizing ATP (62), and ANT (63),(64), is encoded by genes whose

expression is regulated by T3. As ATPase and ANT activities contribute to the decrease in protonmotive force, these data suggest that direct or indirect induction of gene transcription is involved in delayed T3 influence. Delayed influence of thyroid hormone on mitochondrial oxygen consumption, involving alterations in phospholipid synthesis, appeared clearly to be mainly initiated at the nuclear level. It remains to be established what is the contribution of direct mechanisms involving the c-Erb A nuclear receptors, and of indirect ones mediated by the induction of transcription factors responding to T3, such as nuclear respiratory factor 1, whose RE has been identified in several nuclear respiratory genes (65).However, recent data discussed below have raised the possibility that a direct mitochondrial pathway could also be involved in this delayed T3 influence.

4. Thyroid Hormone Influence on Mitochondrial Genome Expression

Besides its influence on oxygen consumption, numerous reports have established the influence of thyroid hormone on mitochondrial genome expression. Thyroid hormone administration in hypothyroid rats induces a 2- to 8-fold increase in liver mitochondrial mRNA levels(66), and similar data have been reported in skeletal muscle with some tissue specificities(67). According to(66), this rise was accounted for by an elevated RNA synthesis. Two short c-Erb A_1 protein isoforms (p28 and p43) are synthesized by alternative translational initiation at internal AUG in the message encoding the full-length thyroid hormone receptor(44). Whereas p28 is detected in the mitochondrial inner membrane, p43 is localized in the matrix of the organelle where it stimulates mitochondrial genome transcription in the presence of T3(33),(68). TR, T3 nuclear receptor c-Erb A1 (47 kDa); 1, 109 and 442, number of nucleotides on the transcript (1=A of the first AUG); 1, 53, 120, 194 and 410, number of amino acids on the c-Erb A1 receptor. This conclusion is substantially supported by a recent observation indicating that T3 decreases mitochondrial mRNA half-life (69), thus ruling out the possibility that thyroid hormone could raise mitochondrial (mt) RNA levels by improving their stability.
This transcriptional influence has been explained by the finding that T3 increases mitochondrial transcription factor (mt-TFA) mRNA levels in rats(70). As mt-TFA acts in mitochondria to stimulate mt-DNA replication and expression(71), this result suggested that the T3 transcriptional influence was essentially elicited at nuclear level. However, studies using isolated mitochondria from hypothyroid or control rat liver led to the conclusion that this mechanism was not exclusive. First,(72), observed that *in vitro* addition of T3 stimulates mt-RNA polymerases in the absence of nuclear influence, with a latency period of less than 5 min. Secondly, (69), demonstrated that addition of minute amounts of the hormone to isolated mitochondria influenced mitochondrial transcription, and particularly the mRNA/rRNAratio, in relation to changes in the pattern of protein binding to the mitochondrial genome. These data demonstrated that thyroid hormone influence on mitochondrial transcription involves direct action on the organelle transcription machinery. In support of this result, we have previously identified, in the matrix of rat liver mitochondria, a second truncated form of the c-Erb A_1 nuclear receptor with a molecular mass of 43 kDa (p43) (33), synthesized by alternative translational initiation at another internal AUG in the messenger encoding the full-length nuclear receptor. This protein, which, like p28, is not detected in the nucleus (33), binds T3 with an affinity unsurprisingly similar to that reported for c-Erb A1 (68). Moreover, in contrast to p28, this protein harbours the DNA-binding domain of the T3 nuclear receptor. Interestingly, gel shift experiments established that p43 efficiently bound to four sequences of the mitochondrial genome previously identified (73),(68), sharing strong homologies with T3

REs described on nuclear genes. Last, *in organello*transcription experiments demonstrated that p43 strongly increases mitochondrial genome transcription, and, as a consequence, mitochondrial protein synthesis (68). In agreement with (72), this influence was detected as soon as the hormone had been present for 5 min. Complementary studies were performed in cultured cells. We found that p43 overexpression raises the level of mt-RNAs in a myoblast model in which mt-TFA is not a transcriptional T3 target(68). In addition, it stimulates cytochrome-c-oxidase activity and increases mitochondrial membrane potential assessed by rhodamine 123 uptake (33). According to the short latency period recorded in our experiments, we suggest that this mechanism is in particular involved in the influence of T3 on mitochondrial oxygen consumption culminating in some hours, by increasing mitochondrial protein synthesis and consequently the activity of the respiratory chain as experimentally demonstrated(33), (68). From a molecular point of view, we obtained indications that p43 monomer does not bind tomt-DNA(68);Which led us to search for dimerization partners of this receptor. Werecently found that p43 binds to one particular T3RE located in the mitochondrial D-loop by forming a complex with a 45 kDa truncated form of another member of the nuclear receptor superfamily, PPAR2 (peroxisome proliferator activated receptor), whose expression is induced by peroxisome proliferators (mt-PPAR)(74),(75). Although devoid of any mitochondrialactivity by itself, due to the absence of a ligand-binding domain(74), co-expression of mt-PPAR with p43 significantly enhanced the stimulation of mitochondrial activity induced by p43 alone (F Casas, CWrutniak-Cabello & G Cabello, unpublished observations). These results provide an interesting explanation of the thyromimetic influence of fibrates reported in several studies(76),(77). In addition, they also suggest that p43 binds to the three other mitochondrial T3RE sequences by forming homodimerical or heterodimerical complexes with unidentified partners. Taken together, our data raise the possibility that other members of the nuclear receptor superfamily could be imported into the organelle. This hypothesis is already wellsupported by our data demonstrating that a particular c-Erb Aisoform (0), expressed innon-mammalian species, is actively imported into mitochondria where it plays the same roleas p43(74), and by the finding that the glucocorticoid receptor is addressed intomitochondria(78). This possibility acutely raises the question of theprocess involved in the mitochondrial import of these receptors. We have not recorded putativemitochondrial localization signals in p43. However,we observed that deletion of the DNAbindingdomain abrogates p43 import (F Casas, C Wrutniak-Cabello & G Cabello, unpublishedobservations), thus emphasizing the importance of this well-conserved sequence among members of the nuclear receptor superfamily. In addition, studies of p28 import indicated that this receptor devoid of the DNA-binding domain is addressed into the organelle only in the presence of T3 (F Casas, C Wrutniak-Cabello & G Cabello, unpublished observations). This last observation suggests that conformational changes consequent to T3 binding allow unmasking of a sequence inducing mitochondrial import. Overall, it appears that, at least for c-ErbA mitochondrial proteins, translocation in the organelle involves two domains withconstitutive or T3-dependent activities. Besides their interest in endocrine regulation of mitochondrial activity, such studies could bring new original data concerning mitochondrial protein import. As nuclear receptors exert their activity by interacting with transcriptional cofactors, other interesting questions are raised. In particular, the occurrence in the organelle of coactivators or corepressors has to be questioned. Today, no evidence has been provided that histone acetylation and deacetylation are important processes for mitochondrial genome transcription, according to the organization of the circular mt-DNA molecule. Therefore, it is unlikely that coactivators with histone acetylase activity, or interacting with histones acetylases, could play an important role in the regulation of mitochondrial

transcription. Despite that, a search should be made for the presence of PPAR_ coactivator, a common c-Erb A and PPAR_ coactivator(79), interacting with steroid receptor coactivator histone acetylase(80), taking intoaccount its involvement in the regulation of mitochondrial biogenesis(81). However,a more systematic study of p43 interactions with known mitochondrial proteins, such asmt-TFA or mt-RNA polymerase, could bring interesting data. Although numerous questions remains unsolved, these studies, which include the characterization of a new mitochondrial T3 receptor, have clearly established the existence of a T3 extra-nuclear pathway. As we have detected p43 in all tested vertebrate species (human, rat, mouse, rabbit, chicken, *Xenopus*), we suggest that this well conserved pathway is of significant physiological importance. More generally, these results are of further interest; as a specific stimulation by p43 overexpression of the synthesis of enzyme subunits encoded by the mitochondrial genome is sufficient to induce stimulation of the organelle activity (33), we suggest that the expression of subunits encoded by nuclear genes is not rate-limiting. This observation is consistent with previous data indicating the occurrence of an unassembled cytochrome-c-oxidase subunit pool in the cytosol of rat liver(82). Similarly, in synchronous cultures of yeast, whereas nuclear-encoded cytochrome-c-oxidase subunits accumulate during the G1 and early S phases, they are integrated into the inner membrane in the late S phase only after the mitochondrially made subunits have accumulated (83), suggesting the latter could have rate-limiting importance for enzyme functioning. Moreover, it emphasizes the importance of the rapid regulation of mitochondrial transcription for organelle activity.

5. Thyroid Hormone Stimulates Mitochondriogenesis

Another well-established influence of thyroid hormone concerns the stimulation of mitochondriogenesis, considered as a long-term influence detected after a latency period much longer than 24 h (84). Mitochondriogenesis is the result of numerous events leading to membrane phospholipid synthesis and assembly, DNA replication and stimulation of the expression of the mitochondrial genome and of nuclear genes encoding mitochondrial proteins. This apparent complexity is probably the reason for the length of the T3 latency period.
It is likely that T3 regulation of mitochondriogenesis involves both nuclear and mitochondrial receptors. As previously discussed, *de novo* lipid synthesis and mobilization in membranes probably result from the general influence of the hormone on lipid turnover assumed to be elicited at the nuclear level. Moreover, T3 stimulation of mt-TFA expression(70), probably a major mechanism involved in mitochondriogenesis as this factor stimulates mitochondrial genome expression and replication. The expression of several nuclear genes encoding mitochondrial proteins is T3- regulated, as shown for F1ATPase, ANT, cytochrome c1, mt-TFA, UCPs and several sub-units of the respiratory chain (65). In addition, improvement in the mitochondrial import of nuclear-encoded proteins has been observed in cardiac muscle cells (85), in agreement with the study of (86), indicating that mt-heat shock protein 70 expression, a chaperone involved in import, is increased by thyroid hormone. However, the work of (87), reporting that expression of mitochondrial preproteintranslocase of outer membrane 70, a component of the organelle import apparatus encoded by a nuclear gene, is negatively regulated by T3 in several regions of the brain, points to the existence of differential regulation depending on the relevant tissue. Lastly, at the mitochondrial level, by activating p43 the hormone directly increases mitochondrial genome transcription and synthesis of the corresponding proteins (68). Therefore, it appears that mitochondriogenesis needs some coordination between nuclear and mitochondrial genome expression. Interestingly, the c-erb

Agene simultaneously encodes a nuclear and a mitochondrial T3 receptor, thus providing an efficient system to coordinate expression of a number of nuclear genes encoding mitochondrial proteins, and expression of the mitochondrial genome (68). This dual influence not only explains the major role of T3 in the regulation of mitochondriogenesis, but also underlines the complementarities between the nuclear and direct mitochondrial T3 pathways. As other members of the nuclear receptor superfamily have been characterized in the organelle (PPAR, glucocorticoid receptor), it is likely that they could also contribute to this coordination, thus ensuring fine regulation of mitochondriogenesis in response to physiological stimuli.

6. Physiological Importance of the Direct Mitochondrial T3 Pathways

In this review, it clearly appears that a direct T3 mitochondrial pathway does indeed exist, mediated by at least one receptor encoded by the c-erb A gene. As p43 is the first T3 receptor identified at the origin of an extra-nuclear action of thyroid hormone, this raises the question of the exact physiological importance of this new hormonal pathway. T3 influence at the mitochondrial level initially suggested that the pathway was essentially involved in the regulation of fuel metabolism and thermogenesis. This possibility is consistent with the observation that p43 overexpression induces stimulation of mitochondrial activity(33).
In addition, whereas high amounts of this receptor are present in mitochondria from brown adipose tissue implicated in non-shivering thermogenesis, p43 is not detected in brain organelles, a tissue considered as not responsible for the calorigenic influence of thyroid hormone(33),(74). These data argue in favour of an involvement of this pathway in T3 thermogenic effects. This possibility agrees well with the observation that body temperature is specifically altered by disruption of the c-erb A_ gene, encoding a nuclear and a mitochondrial receptor, whereas knock-out of the c-erb A_ gene only encoding nuclear T3 receptors is without influence (88),(89). However, the importance of mitochondrial activity in other important physiological processes is currently emerging. The organelle function in particular seems strongly implicated in the processes of development. First, mitochondria play a key role in the induction of apoptosis(90). In addition, severalstudies have established that inhibition of mitochondrialactivity, either by deleting mt-DNA(Rho0 cells) or by blocking translation in theorganelle, stops or decreases proliferation ofdifferent cell lines (91),(92),(93). Furthermore, the general activity of the organelle,not restricted to energy production, is implicated insuch regulation(94),(95). Lastly, mitochondrial protein synthesisinhibition is associated with the impairmentof differentiation in different cell types, such asmouse erythroleukaemia(96), andmastocytoma cells neurons(97), and human(98), avian(99), or murine myoblasts(100). In agreement with this set of data, mt-TFA gene knock-out in mice is associated with embryonic lethality(101). Despite these reports, it was not clear if these adverse influences were a non-specific consequence of impairment in cell viability due to insufficient ATP stores, or attested to the occurrence of an actual physiological regulation of cell proliferation and differentiation by the organelle activity. To clarify this point, we studied the influence of the direct mitochondrial T3 pathway on myoblast differentiation(102). First, T3 is a major regulator of myoblast differentiation (103), through mechanisms involving its c-Erb A nuclear receptors(104),(105). Secondly, themolecular events inducing terminal differentiationin this cell type are relatively well known, with amajor influence of myogenic factors acting as muscle-specific transcription factors (Myf 5, MyoD, myogenin and MRF4). Gene knock-out in mice provided evidence that Myf 5 and MyoD are more involved in the acquisition of the muscle phenotype, whereas

myogenin is involved in terminal differentiation by inducing myoblast fusion and expression of muscle-specific proteins. In addition, overexpression of only one of these transcription factors in cells other than myoblasts can induce expression of a myogenic phenotype. We first observed that p43 overexpression increases myoblast withdrawal from the cell cycle, an important step in myogenic differentiation, and stimulates their differentiation. In contrast, chloramphenicol, a drug inducing the opposite influence to p43 by reducing mitochondrial protein synthesis, inhibits myoblast withdrawal from the cell cycle and their differentiation. In this study(102), we obtained good evidence that changes in ATP production were not involved in this myogenic influence. More interestingly, we found that myogenin expression was increased by p43 overexpression and decreased by chloramphenicol, events elicited at transcriptional level, thus establishing the existence of an actual regulation of myoblast differentiation by mitochondrial activity. The signalling at the origin of the influence of the organelle on nuclear gene expression remains to be identified, but recent data already suggest that calcium signalling is probably involved(106),(107). We also observed that the ability of myogenic factors to induce terminal differentiation was under the control of mitochondrial activity. These data shed new light on the sharp increase in mitochondrial activity spontaneously occurring just before myoblast differentiation, already proposed as a possible mechanism involved in the commitment of these cells in the differentiation programme(108). As we have recently observed a similar regulation of preadipocyte differentiation (A Fraysse, C Wrutniak- Cabello, L Daury, A Rodier, F Casas, P Rochard, G Cabello & J Charrier, unpublished observations), this set of data demonstrates that, like the nuclear pathway, the direct mitochondrial T3 pathway is involved in the regulation of cell differentiation.

7. Induction of Mitochondrial Biogenesis by Hormones, Drugs, and Natural Products

A. Estrogens, Erythropoietin, and Thyroid Hormone Certain hormones modulate metabolism and mitochondrialfunction through the actions of the nuclearreceptor (NR) superfamily of proteins. Upon ligandbinding, these receptors enter the nucleus and bindhormone-responsive elements in the promoter regionsof target genes, including TFAM, TFB1M, and TFB2M (109). In various tissues, steroid (type I) and nonsteroid (type II) NRs influence mitochondrial biogenesis and OXPHOS components(110). Some NRs, such as the glucocorticoid receptor (GR), estrogen receptor, and thyroid receptor (TR) are also found in mitochondria where certain direct transcriptional effects can occur.

1. Estrogens. The loss of the main circulating estrogen 17b-estradiol (E2) due to either natural or surgical menopause leads to a prompt reduction in body metabolic rate. Other manifestations may include muscle weakness, fatigue, reduced exercise capacity, and weight gain. Some of these signs and symptoms are clearly associated with changes in aerobic energy metabolism. Molecular studies have shown a regulatory role for E2 in mitochondrial function involving ATP production, generation of membrane potential, mitochondrial biogenesis, and calcium regulation(111),(112). The mechanisms of these effects, especially in humans, are not well understood. Some evidence suggests that ERs localize to mitochondria and elicit their effects directly. ERais essential for most of the E2-mediated increase in electron transport chain (ETC) and antioxidant proteins(113),(114). On the other hand, ERbcan downregulate mRNA expression of nuclear-encoded subunits of the ETC complexes in vasculature(113). E2 may also influence mitochondrial function by altering mitochondrial ROS production

(115), by induction of antioxidant responses (116). E2 also activatesNRF1/2, Tfam, and PGC1a (117).Further research on E2 is warranted to understand these mitochondrial effects in greater detail. E2 also stimulates ERarelocation to mitochondria where it interacts with hydroxysteroid (17-b) dehydrogenase 10 (HSD10). HSD10 is involved in steroid metabolism and functions as a core subunit of the mitochondrial RNaseP complex responsible for cleavage of polycistronic mitochondrial transcripts. This interaction results in mitochondrial transcript processing and mature RNA that is available for translation. Conversely, HSD10 inactivates E2 to a weaker form, estrone, the significance of which requires further investigation(118). Impaired E2 signaling and subsequent mitochondrial dysfunction may also be involved in insulin resistance. Mitochondrial dysfunction is associated with reduced or partial FAO that can activate stress kinases that inhibit insulin signaling(119),(120). The expression of the adipokine, adiponectin, and its receptor, AR1, is induced by estrogen in conjunction with mitochondrial biogenesis(121), and adiponectin may improve insulin sensitivity. Estrogen replacement therapy to protect postmenopausal women from diabetes and other metabolic disorders and osteoporosis is offset by the increased cancer risk by E2 and ER agonists. Bazedoxifene with conjugated E2 is a combination of selective tissue E2 complexes and receptor modulator that provides tissue specific benefits of E2 in menopausal osteoporosis in women(122), and improves cardiovascular disease risk and metabolic syndrome with greater effects in endometrium and breast in animal models (123),(124). Although selective tissue E2 complexes are still in trials, newer, more innovative, efficient, and tissue-specific E2 receptor agonists are being investigated. An E2 conjugated preparation with glucagon-like peptide-1 is more active than either hormone alone in the reversal of obesity, hyperglycemia, and dyslipidemia in mice and prevents reproductive endocrine toxicity and oncogenicity(125). It is not yet clear which patients benefit and which agents would minimize the risks of E2-related therapy.

2. Erythropoietin. EPO regulates erythrocyte mass in response to hypoxia and anemia, but EPO activity is detectable in some non-erythroid cells that express functional EPO receptor (EpoR). Protective effects of EPO have been demonstrated in various nonerythroid tissues and experimental models of I/R injury and attributed to nonhematopoietic metabolic effects, inhibition of apoptosis, or to stimulation of angiogenesis (126). EPO stimulates cardiac mitochondrial proliferation through mitochondrial biogenesis mediated by NO and NRF-1 and PGC-1a(127). Clinically, EPO reverses cardiac remodeling, improves cardiac function, and enhances exercise tolerance and quality of life of a subset of heart patients by protective effects beyond the correction of anemia (128). These findings highlight the possibility that EPO-mediated protection may depend on modulatory effects on bioenergetics. EPO can stimulate proliferation of cultured myoblasts through binding to EpoR to expand the progenitor population during differentiation, and it may have a role in muscle repair (129),(130). EPO/EpoRsignaling also improves glucose tolerance and protects against dietary obesity in association with skeletal muscle adaptation (131),(132). The association of EPO treatment in mice with increased mitochondrial biogenesis and PGC-1a activation in myocytes raises the possibility that EPO may contribute to the balance between slow and fast-twitch fibers. Furthermore, recombinant protein increases OXPHOS in human skeletal skeletal muscle plasticity and muscle (133).The enhancement and recovery of cellular functions through stimulation of hemoglobin production and mitochondrial activity in nonhematopoietic cells by EPO-like drugs might be a testable therapeutic strategy for certain ischemic or mitochondrial diseases in carefully selected patient populations, although the procoagulant effects of EPO administration have raised a legitimate caution.

3. Thyroid Hormone. The ability of thyroid hormone (T3 and T4) and thyroid hormone receptors (TRs) to regulate oxygen uptake and energy utilization is related to the thyroid system's multiple effects on mitochondrial function. TH targets several regulatory pathways for gene expression that may contribute to mitochondrial biogenesis (134). TH binds to nuclear-localized TR belonging to a ligand-dependent transcription factor family that modulates nuclear gene expression via binding to a thyroid response or TRE motif.TH also directly affects mitochondria by binding a mitochondrial-localized TR. However, intermediate factors are also expressed (perhaps via TREs) that enter the nucleus and regulate other TH-target genes. PGC-1a and PGC-1b and NRF-1, NRF-2 have been postulated to serve as these intermediate factors. There is evidence of rapid PGC-1a induction by TH both at the mRNA and protein levels [mediated by a TRE in the gene promoter (135), but its impact on mitochondrial proliferation seems modest and the therapeutic opportunities limited.

8. Conclusion

More recently, a growing body of research has continued to uncover aspects of mitochondrial biology beyond energy production, including transcriptional remodeling with in the nucleus, mitochondrial dynamics and quality control, inter-mitochondrial communication, the inter-cellular transfer of mitochondria, mitochondrial regulation of inflammatory processes and immune function, mitochondrial regulation of brain functions, and modulation of systemic physiological processes across organ systems, among others discussed here. With the tools of molecular biology, and a growing recognition of bioenergetics aspects of modern chronic diseases, the rise of mitochondria in medicine appears likely to continue. With it should come further insights into disease pathogenesis, as well as new strategies to intervene on a number of medical conditions through targeted behavioral pharmacological, and other interventions rooted in the principles of mitochondrial bioenergetics. However, mitochondrial ROS production is substantially increased and mitochondrial antioxidants may be more useful than the induction of biogenesis, which could increase the number of ROS generating sites in the cell. On the other hand, the re-establishment of a healthy population of working mitochondria through mitochondrial biogenesis may actually ameliorate ROS production by both close regulation of mitochondrial ROS release and by the concurrent antioxidant response, for example the SIRT3-dependent PGC-1a-mediated antioxidant response. The natural molecular correspondence between mitochondrial biogenesis and mitophagy, for instance mediated by AMPK during an impending energy crisis, may provide opportunities for targeted protection against persistent mitochondrial dysfunction through overall QC mechanisms.Besides the well-established nuclear pathway involving the c-ErbA receptors, it appears that a recently identified direct mitochondrial pathway also plays a significant role by stimulating mitochondrial genome transcription with a very short latency period. Interestingly, both mechanisms could contribute to setting up efficient coordination in the induction of transcription of the mitochondrial genome and of nuclear genes encoding mitochondrial proteins needed for mitochondriogenesis. Moreover, it appears that by its short-term action, T3 and/or T2 could immediately adapt mitochondrial activity to abrupt changes in environmental conditions, whereas when acting through p43, T3 rapidly increases the efficiency of the mitochondrial apparatus to respond to these changes within minutes. In association with more delayed responses through the nuclear pathway leading to a stimulation of mitochondriogenesis, these mechanisms provide an efficient mitochondrial response to abrupt and/or prolonged changes in physiological

conditions. In addition, I would emphasize that thyroid hormone regulation of mitochondrial activity, simultaneously influencing ATP production and cell differentiation, an energy-expensive process, could be a major link between metabolism and development. All these considerations led us to the conviction that studies on mitochondrial T3 regulation will shed new light on major interactions between endocrinology, metabolism and development.

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