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ENERGETICS, EPIGENETICS, MITOCHONDRIAL GENETICS

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Abstract

The epigenome has been hypothesized to provide the interface between the environment and the nuclear DNA (nDNA) genes. Key factors in the environment are the availability of calories and demands on the organism's energetic capacity. Energy is funneled through glycolysis and mitochondrial oxidative phosphorylation (OXPHOS), the cellular bioenergetic systems. Since there are thousands of bioenergetic genes dispersed across the chromosomes and mitochondrial DNA (mtDNA), both *cis* and *trans* regulation of the nDNA genes is required. The bioenergetic systems convert environmental calories into ATP, acetyl-Coenzyme A (acetyl-CoA), S-adenosyl-methionine (SAM), and reduced NAD^+. When calories are abundant, ATP and acetyl-CoA phosphorylate and acetylate chromatin, opening the nDNA for transcription and replication. When calories are limiting, chromatin phosphorylation and acetylation are lost and gene expression is suppressed. DNA methylaton via SAM can also be modulated by mitochondrial function. Phosphorylation and acetylation are also pivotal to regulating cellular signal transduction pathways. Therefore, bioenergetics provides the interface between the environment and the epigenome. Consistent with this conclusion, the clinical phenotypes of bioenergetic diseases are strikingly similar to those observed in epigenetic diseases (Angelman, Rett, Fragile X Syndromes, the laminopathies, cancer, etc.), and an increasing number of epigenetic diseases are being associated with mitochondrial dysfunction. This bioenergetic-epigenomic hypothesis has broad implications for the etiology, pathophysiology, and treatment of a wide range of common diseases.

1. INTRODUCTION

"The modern definition of epigenetics is information heritable during cell division other than the DNA sequence itself" (Feinberg, 2007). Hence, epigenetics is thought to provide a flexible interface between the organism and its environment. Until now, the DNA sequences of interest to biology and medicine have been in the chromosomal DNA, which is transmitted during meiotic and mitotic cell division according to the rules of Gregor Mendel. However, most common metabolic and degenerative diseases and multiple cancers are familial, but are not classically Mendelian in their transmission. Therefore, such "complex diseases" have been attributed to epigenetic changes in response to the environmental change (Feinberg, 2007, 2008).

However, deficiency in energy metabolism has also emerged as an alternative explanation for the etiology of complex diseases over the past 21 years. The primary limiting factor for growth and reproduction of all biological systems is energy and the first reports that

mitochondrial DNA (mtDNA) mutations can cause disease (Goto et al., 1990; Holt et al., 1988; Holt et al., 1990; Shoffner et al., 1990; Wallace et al., 2007; Wallace et al., 1988a; Wallace et al., 1988b) have been followed by reports that a broad spectrum of metabolic and degenerative diseases can have a mitochondrial etiology (Wallace et al., 2007). Moreover, environmentally adaptive mtDNA variants have been associated with predisposition to virtually the entire range of common "complex" diseases (Wallace, 2008).

However, similar symptoms imply a common pathophysiology. Therefore, epigenetic and mitochondrial genetic diseases must be interrelated through their impinging on a common function.

To understand nuclear-mitochondrial interactions, we must consider the early stages in the endosymbiontic event that created the eukaryotic cell about 2 billion years ago (Lane, 2002, 2005; Wallace, 2007). In the beginning, the proto-nucleus-cytosol was limited by energy. This limitation was alleviated by its symbiosis with an oxidative α-protobacterion, the proto-mitochondrion. Therefore, growth and replication of the nucleus became limited by mitochondrial energy production and thus calorie availability. This necessitated the regulation of nuclear replication and gene expression by calorie availability mediated by mitochondrial energetics. This was achieved by coupling modulation of nDNA chromatin structure and function by modification via high energy intermediates: phosphorylation by ATP, acetylation by acetyl-Coenzyme A (Ac-CoA), deacetylation by nicotinamide adenine dinucleotide (NAD^+), and methylation by S-adenosyl-methionine (SAM).

Conversely, the nucleus had to develop mechanisms for modulating mitochondrial growth and replication. This was additionally complicated by the successive transfer of genes from the proto-mitochondrial DNA to the nDNA, with the cytosolic translation products being directionally imported back into the mitochondrion (Wallace, 2007). This process proceeded over a billion years with the result that the nDNA-encoded genes of the mitochondrial genome are now dispersed throughout the chromosomes (Wallace, 2007). Therefore, new mechanisms had to evolve to permit the coordinate expression of the mitochondrial genes based on nuclear requirements for energy for growth and reproduction. As a result, this became one of the early driving forces for the evolution of interchromosomal coordinate transcriptional regulation.

Over the subsequent 1.2 billion years, the nucleus-cytosol became increasingly specialized in specifying structure while the mitochondrion became entirely dedicated to energy production. Ultimately, this subcellular specialization became sufficiently refined and efficient that it permitted the advent of multicellularity and thus plants and animals (Wallace, 2007). Still, all subsequent tissue development, species radiation, and environmental adaptation were rooted in this fundamental energetic-epigenetic cooperation.

2. MITOCHONDRIAL BIOENERGETICS

Complex structures can only be maintained by the continual flux of energy. Life, therefore, is the interaction between structure, energy, and information, with information required for both structure and energetics (Wallace, 2007).

2.1. Mitochondrial Energetics: OXPHOS

Energetics in animals is based on the availability of reducing equivalents, consumed as carbohydrates and fats. Glucose is cleaved into pyruvate via glycolysis, and the pyruvate enters the mitochondrion via pyruvate dehydrogenase (PDH) resulting in acetyl CoA, $NADH + H^+$, and CO_2. The acetyl CoA then enters the Tricarboxylic Acid (TCA) Cycle which strips the hydrogens from the hydrocarbons generating $NADH + H^+$. Fatty acids are

oxidized within the mitochondrion by β oxidation to generate acetyl CoA, NADH + H^+, and $FADH_2$, the latter contained in the electron transfer factor (ETF). Two electrons (reducing equivalents from hydrogen) are transferred from NADH + H^+ to the OXPHOS complex NADH dehydrogenase (complex I) or from $FADH_2$ containing enzymes such as the ETF dehydrogenase or succinate dehydrogenase (SDH, complex II) to reduce ubiquinone (coenzyme Q_{10}, CoQ) to ubiquinol $CoQH_2$. The electrons from $CoQH_2$ are transferred successively to complex III (bc_1 complex), cytochrome *c*, complex IV (cytochrome *c* oxidase, COX), and finally to oxygen (½ O_2) to give H_2O.

The energy that is released as the electrons flow down the ETC is used to pump protons out across the mitochondrial inner membrane through complexes I, III, and IV creating a proton electrochemical gradient ($\Delta P = \Delta\Psi + \Delta\mu^{H+}$). The potential energy stored in ΔP is used for multiple purposes: to import proteins and Ca^{++} into the mitochondrion, to generate heat, and to synthesize ATP within the mitochondrial matrix. The energy to convert ADP + Pi to ATP comes from the flow of protons through the ATP synthetase (complex V) back into the matrix. Matrix ATP is then exchanged for cytosolic ADP by the inner membrane adenine nucleotide translocators (ANTs) (Wallace, 2007).

The efficiency by which dietary reducing equivalents are converted to ATP by OXPHOS is known as the coupling efficiency. This is determined by the efficiency by which protons are pumped out of the matrix by complexes I, III, and IV and the efficiency by which proton flux through complex V is converted to ATP. The uncoupler drug 2,4-dinitrophenol (DNP) and the nDNA-encoded uncoupler proteins 1, 2, and 3 (Ucp1, 2, and 3) render the mitochondrial inner membrane leaky for protons, by-passing complex V and dissipating the energy as heat (Wallace, 2007).

2.2. OXPHOS Complexes and the mtDNA

OXPHOS complexes are assembled from proteins encoded in both the nDNA and the mtDNA. Complex I is composed of 45 polypeptides, seven (ND1, 2, 3, 4, 4L, 5, and 6) encoded by the mtDNA; complex II from four nDNA polypeptides; complex III from 11 polypeptides, one (cytochrome *b*, cyt *b*) encoded by the mtDNA; complex IV form 13 polypeptides, three (COI, II, III) from the mtDNA; and complex V from about 16 polypeptides, two (ATP6 & 8) from the mtDNA. The mtDNA also encodes the 22 tRNAs and 12S and 16S rRNAs for translation of the 13 mtDNA polypeptides. Of the five complexes, only complexes I, III, IV, and V transport protons, and these are the same complexes for which key polypeptides are retained on the mtDNA. Therefore, it follows that the complex I, III, IV, and V electron and proton transfer proteins have been retained on the maternally-inherited and non-recombining mtDNA to avoid mixing OXPHOS complex proteins which could be incompatible and affect the coupling efficiency (Wallace, 2007).

Each mammalian cell contains hundreds of mitochondria and thousands of mtDNAs. When a mutation arises in a mtDNA, it creates a mixed population of normal and mutant mtDNAs, a state known as heteroplasmy. When a heteroplasmic cell divides, the two types of mtDNAs are randomly distributed into the daughter cells, resulting in genetic drift toward either pure mutant or wild type. Over time this replicative segregation results in segregation of the mutant mtDNAs into pure mutant or normal populations, termed homoplasmic cells (Wallace, 2007). As the percentage of mutant mtDNAs increases, mitochondrial energetic function decreases. When energy output is insufficient for normal tissue function, a threshold is crossed, symptoms appear, and apoptosis or necrosis may be initiated and clinical symptoms ensue (Wallace, 2005b; Wallace et al., 2007).

2.3. Reactive Oxygen Species (ROS)

As a by-product of OXPHOS, mitochondria generate much of the endogenous ROS of the cell. Under normal physiological conditions, ROS production is highly regulated, at least in part controlled by complex I (Evans et al., 2000; Hansen et al., 2006; Jones, 2006a; Kelley and Parsons, 2001; McCord, 2000). However, when the ETC becomes highly reduced, the excess electrons can be passed directly to O_2 to generate superoxide anion ($O_2^{\cdot -}$). The $O_2^{\cdot -}$ generated by complex I is released into the mitochondrial matrix where it is converted to hydrogen peroxide (H_2O_2) by the matrix manganese superoxide dismutase, MnSOD (*Sod2* gene). Superoxide generated from complex III is released into the mitochondrial intermembrane space where it is converted to H_2O_2 by Cu/ZnSOD (*Sod1*) which is positioned in the mitochondrial intermembrane space and cytosolic. Mitochondrial H_2O_2 can diffuse into the nucleus-cytosol. If H_2O_2 encounters a reduced transition metal or is mixed with $O_2^{\cdot -}$, the H_2O_2 can be further reduced to hydroxyl radical ($OH^{\cdot}$), the most potent oxidizing agent of the ROS (Figure 1). ROS can damage cellular proteins, lipids, and nucleic acids. Hence, excessive mitochondrial ROS production can exceed the antioxidant defenses of the cell, and the cumulative damage can ultimately destroy the cell.

2.4. The Mitochondrial Permeability Transition Pore (mtPTP)

The mitochondria evolved a self-destruct system, the mtPTP. The mtPTP is activated when the biochemical health of the mitochondria and cell decline, specifically when mitochondrial energy production declines, ROS generation increases, and excessive Ca^{++} is released into the cytosol and taken up by the mitochondrion. When the mtPTP is activated, it opens a channel in the mitochondrial inner membrane, short circuits ΔP, and initiates programmed cell death (apoptosis) (Wallace, 2005c).

2.5. Mitochondrial Dynamics

The mitochondria within a mammalian cell are in constant motion and undergoing repeated rounds of fission and fusion. Mitochondrial fusion and fission not only merges the mitochondrial inner and outer membranes but also mixes mitochondria matrices and redistributes the mtDNAs. The mammalian mitochondrial fusion machinery involves three major proteins: mitofusin 1 (Mfn1), 2 (Mfn2), and the Optic Atrophy-1 Protein (Opa1) (Chen et al., 2005; Chen et al., 2003a; Cipolat et al., 2004), while the mitochondrial fission machinery involves dynamin-related protein 1 (Drp1), Fis1, and Mff (Gandre-Babbe and van der Bliek, 2008; James et al., 2003; Smirnova et al., 2001; Yoon et al., 2003).

3. THE ENERGETIC EVOLUTION OF THE EPIGENOME

Prior to the advent of free oxygen in the biosphere, substrate-level phosphorylation was the primary mechanism for generating ATP in non-photosynthetic organisms. After the generation of free oxygen by photosystem II the redox range of biology was greatly expanded and OXPHOS became the most efficient system for generating ATP from the reducing equivalents present in organic molecules (Lane, 2002, 2005; Wallace, 2007).

3.1. The Energetic Evolution of the Epigenome

In the proto-nucleus-cytosol cell, ATP, from glycolysis, would have provided the high energy intermediate linking calories to cellular growth and replication. Consequently, phosphorylation-dephosphorylation must have been the first post-translational modification evoked for regulating DNA-protein interactions. When substrates were plentiful, ATP concentrations would increase, leading to increased phosphorylation of DNA-bound proteins. The resulting negative charge added to the protein by the phosphate group would then increase repulsion of the proteins from the DNA negatively charged sugar-phosphate backbone, opening chromatin for DNA transcription and replication. Phosphorylation also

was used to modulate enzyme activities, signal transduction pathways, and the transcriptional apparatus in relation to energy availability.

As atmospheric oxygen became a dominant terminal electron acceptor, OXPHOS became the major source of ATP in non-photosynthetic eukaryotic cells. This cemented the symbiosis between the oxidative proto-mitochondrion and the proto-nucleus-cytosol. As a result acetyl-CoA became the metabolic intermediate that linked glycolytic pyruvate and fatty acid catabolism with the mitochondrial TCA cycle and OXPHOS and the concentration of acetyl-CoA became the cytosolic correlate for caloric availability.

Therefore, acetyl-CoA must have been the next energetic substrate to be used to couple cellular energetics with nuclear gene expression and cellular proliferation. Acetylation of lysines on DNA binding proteins neutralizes their positive charge, reducing protein affinity for DNA. As a result, when carbohydrates and or fats were abundant, protein acetylation increased; DNA binding proteins became acetylated and detached; and transcription, replication, and cell proliferation were stimulated. When carbohydrates and fats were limited (fasting-starvation), acetyl-CoA levels decreased; acetylation decreased; chromatin became condensed; and cellular gene expression, replication and proliferation were suppressed. In mammalian cells the carbon for acetyl-CoA destined for histone acetylation is derived from glucose through the mitochondrial TCA cycle via citrate. Glucose atoms transverse glycolysis to pyruvate and the pyruvate enters the mitochondrion where it is converted to acetyl-CoA via pyruvate dehydrogenase. The mitochondrial acetyl-CoA is condensed with oxaloacetate by citrate synthetase to generate citrate and the citrate is exported from the mitochondrion into the cytosol and nucleus by mitochondrion inner membrane citrate carrier. Cytosolic and nuclear citrate can then be converted to acetyl-CoA via ATP-citrate lyase, an enzyme found in both the nucleus and the cytosol. The nuclear acetyl-CoA is then preferentially used for histone acetylation. In the absence of glucose and the presence of supraphysiological levels of acetate, the mammalian cytosolic acetyl-CoA synthetase (AceCS1) can also generate acetyl-CoA. This can diffuse into the nucleus for use in histone acetylation (Rathmell and Newgard, 2009; Wellen et al., 2009). The facultative anaerobe, *Saccaromyces* cerevisiae, lacks ATP-citrate lyase. Therefore, it generates acetyl-CoA for histone acetylation via cytosolic and nuclear acetyl-CoA synthetases (Asc2p and Asc1p) (Takahashi et al., 2006), which might reflect its unique metabolism. The importance of acetylation as an energy surrogate is also extended to the regulation of transcription factors, enzymes, and signal transduction pathways. However, the kinetics of acetylation of histones versus other substrates differs (Rathmell and Newgard, 2009; Wellen et al., 2009).

Reduced energy supplies (fasting) would not only reduce acetyl-CoA levels but also reduce available reducing equivalents, resulting in the oxidation of NADH to NAD^+. Since NAD^+ but not NADH is a substrate for the class III histone deacetylases, the Sirtuins, starvation would activate the Sirtuins to deacetylate the DNA-binding proteins. This would increase the positive charge of the chromatin proteins, causing chromatin condensation, and suppressing transcription, replication, growth, and proliferation.

The third macromolecular modification system for modulating nuclear gene expression and replication in response to energy availability and nutrient supply is methylation by S-adenosyl-L-methionine (SAM). Methylation can increase macromolecular interactions through increased van der Waals forces. Therefore, methylation is more versatile than phosphorylation or acetylation for chromatin regulation.

SAM is produced in the cytosol by the reaction L-methionine + ATP to give SAM + Pi + PPi. Ths, SAM links energy production to the methylation of lysines and arginines in proteins and cytosines in DNA. The production of methionine from homocysteine is also

regulated by mitochondrial metabolism. The single carbon metabolisms of the mitochondrion and cytosol are linked through the exchange of serine and glycine, which are interconvert within the two compartments through methylene-tetrahydrofolate via the mitochondrial and cytosolic serine hydroxymethyltransferases. The mitochondrial bifunctional enzyme converts methylene-tetrahydrofolate to formyl-tetrahydrofolate, thus diverting mitochondrial one carbon units from serine production to format, which is used in purine biosynthesis. Mitochondrial bifunctional enzyme is expressed in embryonic but not differentiated cells. When mitochondrial bifunctional enzyme is not expressed, mitochondrial serine production increases and the serine is exported to the cytosol. In the cytosol, the single carbon units of serine are transferred through methylene-tetrahydrofolate and methyl-tetrahydrofolate to convert homocystine to methionine, which can then be converted to SAM. The synthesis of serine within the mitochondrion requires NAD^+. When OXPHOS is inhibited, the mitochondrial NADH/NAD^+ ratio increases, thus inhibiting the mitochondrial production of methylene-tetrahydrofolate and thus serine. This reduces methionine and SAM production (Naviaux, 2008).

All of these macromolecular modification systems were in place prior to the advent of multicellularity 800 million years ago (Wallace, 1982, 2007). Multicellularity and terminal differentiation created two types of cell, the mortal somatic cells and the immortal germ and pluripotent stem cells. Since immortal cells predated mortal cells, it follows that immortal germ and stem cells should still utilize phosphorylation and acetylation to link energy availability with cell growth and reproduction and that stem cells should have the most open chromatin (Wen et al., 2009). However, to form tissues, the terminally differentiated cells must stop replicating. Hence, large blocks of chromatin must be shut down (Wen et al., 2009). Moreover, new genes were needed to block the cell cycle when activated by acetylation of the surrounding cellular chromatin. The p21 gene is one current example, being up-regulated when its promoter is acetylated and functioning to block replication (Glozak and Seto, 2007; Xiao et al., 2000). Cells which circumvented such replication blockades would then need to be destroyed before they could disrupt the tissue structure. This led to the development of mtPTP and pro-apoptotic proteins like Bax, which are also induced by histone acetylation at their promoters (Glozak and Seto, 2007). Additional layers of control were added once cellular proliferation became disconnected from energetics and increasingly complex structures were formed (Figure 2).

3.2. Energetic Regulation of the Epigenome

The nDNA of the modern eukaryotic cell is packaged in nucleosomes encompassing 146 to 147 base pairs of DNA wrapped around a complex of two copies each of histones H2A, H2B, H3, and H4. In yeast, these histones and the C-terminal domain of RNA Polymerase II (POLII) can be phosphorylated by kinases using ATP. Changes in histone serine/threonine phosphorylation in yeast are linked to changes in the extracellular environment. A change in carbon source results in the phosphorylation of serine 10 in H3 (H3-S10Pi), which is linked to acetylation of lysine 14 in H3 (H3-K14Ac). This stimulates transcription. ATP-driven phosphorylation of the POLII C-terminal domain also modulates transcription and phosphorylation of serine 10 in H2B (H2-S10Pi) is associated with stress and cell death (Fuchs et al., 2009).

3.2.1. Energetic Regulation at the Chromatin Level—Acetylation of histones is catalyzed by histone acetyltransferases (HATs) which catalyze the reaction of acetyl-CoA with the ε-amino group of lysines in histones. There are four classes of HATs known in eukaryotic cells, Gcn5/PCAF, MYST, p300/CBP, and Rtt109. All have structurally similar acetyl-CoA binding sites (Marmorstein and Trievel, 2009; Smith and Denu, 2009). The p300/CBP HAT complex was first characterized as an activator of cAMP responsive genes.

Elevated cAMP activates protein kinase A to phosphorylate CREB at serine 133. Phospho-CREB recruits CBP to cAMP response elements (CREs) in the DNA, and CBP uses its intrinsic HAT activity to open the chromatin for transcription (Tini et al., 2002).

Histone deacetylases (HDACs) fall into four classes. Three classes have similar deacetylase mechanisms involving Zn^{2+} and include class I (HDAC1–3 & 8), class II (HDAC 4–7 & 9–10), and class IV (HDAC 11). The class III Sirtuin HDACs catalyze deacetylation by the reaction of acetyl-lysine + NAD^+ → lysine + nicotinamide + 2'-O-acetyl-ADP ribose (OAADPr) (Smith and Denu, 2009).

Methylation of chromatin, with the methyl group donated by SAM, can occur on either lysines or arginines. Lysine methylation is catalyzed by histone lysine methyltransferases and can result in mono-, di-, or tri-methylation. There are two histone lysine methyltransferase classes: the SET domain family and the DOT1 family. The SET domain class methylates both nucleosomal and free histones while the DOT1 class only methylates nucleosomal histones (Smith and Denu, 2009). Histone demethylation involves two classes of reactions. The first class includes lysine-specific demethylase 1 (LSD1) and is specific for mono- and dimethylated histones. LSD1 employs FAD to oxidize the -N-CH_3 bond, which is then cleaved by water to generate formaldehyde. The resulting $FADH_2$ is reoxidized by O_2 to generate H_2O_2. The second class is the Jumonj family of histone demethylases. These demethylate trimethyl-lysines in a reaction using O_2 and 2-oxoglutarate as co-reactants generate succinate and CO_2 and release formaldehyde (Marmorstein and Trievel, 2009; Smith and Denu, 2009).

Arginine methylation is catalyzed by protein arginine methyltransferases (PRMT) in which the methyl group for SAM is transferred to the arginine guanidinium side chain There are two classes of PRMTs: PRMT1 first generates monomethylarginine and then asymmetric N, N' dimethylarginine while PRMT2 initially generates monomethylarginine but then generates symmetric N,N' dimethylarginine. JMJD6, a homologue of he JHDM family of lysine demethylases, provides an arginine demethylase (Smith and Denu, 2009). A number of additional chromatin modifications are also known including ubiquitination; sumoylation; and protein arginine deiminase, which hydrolyzes the guanidinium side chain to generate citrulline and ammonia (Marmorstein and Trievel, 2009; Smith and Denu, 2009)

The distribution of histone modifications has been hypothesized to provide a "histone code" of gene expression (Fuchs et al., 2009; Strahl and Allis, 2000). In yeast, the 5' coding regions of active genes have an increased density of H2A-K7Ac, H3-K9Ac, H3-K14Ac, H3-K18Ac, H4-K5Ac, and H4-K12Ac while the 3' coding regions of active genes are enriched for H2B-K16Ac, H4-K8Ac, and H4-K16Ac (Wyrick and Parra, 2009). Furthermore, H3-K4me is associated with active transcription, H3-K4me3 is prevalent near promoters, and H3-K4me1 is more abundant in coding regions (Fuchs et al., 2009). In mammalian cells, active chromatin histones H3, H4, and H2A are acetylated including H3-K9Ac and histones H3 and H4 are methylated including H3-K4me, H3-K4me2 and H3-K4me3, the later found at the 5' end of transcribed regions; H3-K36me3 found at the 3' end of transcribed regions; plus H3-K9me, H3-K27me, and H4-K20me. By contrast, in inactive chromatin histones are hypoacetylated and H3 is methylated to generate H3-K9me3, H3-K27me3, and H3-K79me3. Methylated H3-K9 specifically interacts with Heterochromatin Protein 1 (HP1). H4-K16Ac and H4-K20me have also been noted in cancer cell chromatin (Glozak and Seto, 2007; Schneider and Grosschedl, 2007).

Beyond local histone modifications, the nuclear genome is organized into structural and functional chromosomal territories (Schneider and Grosschedl, 2007). In general, gene-rich chromosomes such as human chromosome 19 are located toward the interior of the nucleus

while gene-poor chromosomes like 18 are located toward the periphery of the nucleus (Cremer et al., 2003). The functional genes within the nuclear interior are organized into "transcriptional factories" in which widely scattered genes can be colocalized into the same focus of active transcription. This permits positive and negative transcriptional regulatory factors bound to particular cis DNA elements to influence the expression of genes dispersed on the same of different chromosomes (Cai et al., 2006; Fraser and Bickmore, 2007; Gondor and Ohlsson, 2006; Schneider and Grosschedl, 2007; Zhao et al., 2006).

The chromatin in the central nucleus is generally gene-rich regions, more diffuse, and associated with increased gene expression (ridges). The chromatin toward the nuclear periphery is gene-poor, more compact, and has reduced gene expression (antiridges) (Goetze et al., 2007). Transcribed regions of the chromatin can form loops which can either interact with genes within the loop (Cai et al., 2006; Gondor and Ohlsson, 2006) or between chromatin loops on the same or different chromosomes (Schneider and Grosschedl, 2007; Zhao et al., 2006). In the case of the *IL3, 4, 5* gene cluster on mouse chromosome 11, activation of T helper 2 cells results in the 200 kb region becoming folded into a series of small loops through the induction and binding of the special AT-rich sequence binding protein 1 (SATB1). SABT1 binds to the base of each loop and is accompanied by the acetylation of H3-K9 and H3-K14; the binding of the regulatory factors GATA3, STAT6, c-maf, and Brg1; and the recruitment of RNA polymerase II (Cai et al., 2006). Therefore, the regional clustering of related transcriptional units plus the development of transcriptional factories between chromosomes can provide the capacity for the transcription regulation of the widely dispersed nDNA genes of the mitochondrial genome.

Transcriptionally inactive regions of the genome can be bound in large organized chromatin K9 modifications (LOCKs) blocks. These regions can range in size up to 4.9 Mb and have been identified by the immunoprecipitation of chromatin enriched for H3-K9Me2 or H3-K27me3. They are commonly demarcated by CCCTC-binding factor (CTCF) insulator sites, and are envisioned to represent relatively inactive chromatin regions associated with the periphery of the nuclear envelope. In undifferentiated mouse ES cells only about 4% of the chromatin is in LOCKs, but in differentiated ES cells this increases to 31%. In brain 10% of the chromatin is in LOCKs while in liver 46% is in LOCKs. In the human chromosome 15q11-13 imprinted region associated with Angelman and Prader-Willi syndromes, placental chromatin contains two Mb LOCKs, one encompassing the *SNRPN* gene associated with Pader-Willi and the other encompassing the *GABRB3* gene, the Angelman syndrome *UBE3A* gene lying between the two LOCKs (Wen et al., 2009). Regions of the chromatin ranging in size from 0.1 to 10 Mb have also been found to be preferentially associated with nuclear lamina, specifically lamin B1, located on the inside of the nuclear envelope. These lamina-associated domains (LADs) are generally low gene expression domains and are flanked by CTCF binding sites, CpG islands, and promoters oriented away from the LADs (Guelen et al., 2008). Approximately 82% of LOCKs correspond to LADs (Wen et al., 2009).

3.2.2. Energetic Regulation at the Signal Transduction Level—The post-translational modification of a wide spectrum of metabolic and regulatory proteins by phosphorylation and acetylation unifies the energetic regulation of chromatin with the physiological state of the cell. Phosphorylation modulates the activity of a significant portion of the cellular proteins. The great majority of receptors for environmental signals transmit these signals via tyrosine or serine-threonine phosphorylation. Most of the intermediate steps in signal transduction pathways are also mediated by kinases and phosphatases (Alberts et al., 2002).

3.2.2.1. Global Energetic Regulation of Metabolism: A more global regulation of metabolism by energy availability can be mediated by the conversion of ATP to cAMP by adenylylcyclase. cAMP is linked to cellular energetics throughout the kingdoms of life. Classic examples include modulation of the lactose operon in *E.* coli; providing the chemical gradient along which *Dictyostelium discoidum* amoebe migrate during starvation to form the fruiting body (Alberts et al., 2002); regulation of mitochondrial OXPHOS, ROS, and longevity in *Drosophila* (Tong et al., 2007); the modulation of peroxisome-proliferator-activated receptor γ-coactivator-1α (PGC-1α) transcription (Daitoku et al., 2003); and phosphorylation of complex I and IV proteins in mammalian cells (Bellomo et al., 2006; Chen et al., 2004; Lee et al., 2005; Papa et al., 2002; Technikova-Dobrova et al., 2001).

Acetylation-deacetylation of regulatory and metabolic proteins is also ubiquitous. The p53 protein can be acetylated by p300/CBP at six lysines and by PCAK at another lysine. Acetylation at lysine 382 by p300/CBP increases its activity, while the deacetylation of lysine by Sirt1 reduces its activity. Acetylation of transcriptional co-repressor PLZF by p300 at five lysines within the Zn-finger domain increases its DNA binding and enhances its suppression of growth promoting genes. Acetylation of GATA1 by p300/CBP within its Zn-fingers is important for chromatin binding and transcriptional activation resulting in hematopoietic terminal differentiation. NF-κB, which is a heterodimer of RelA/p65 and p50 or p52 subunits, is maintained in an inactive form in the cytoplasm complexed with IκB. Upon stimulation, IκB is phosphorylated by IκB kinase and degraded permitting NF-κB to be translocated to the nucleus. Acetylation of p65 by p300/CBP or PCAF at K218, K221, and K310 enhances DNA binding and transcriptional activity and inhibits IκB binding. Deacetylation by HDAC3 promotes IκB binding and nuclear egress. Deacetylation of NFκB by SirT1 at K310 decreases expression of NF-κB target genes (Glozak and Seto, 2007). Acetylation of PGC-1α by GCN5 attenuates its transcriptional co-activator activity suppressing mitochondrial biogenesis. Deacetylation by Sirt1 restores PGC-1α activity and increases mitochondrial biogenesis (Gerhart-Hines et al., 2007). Acetylation of FOXO by p300/CBP causes its removal from the nucleus, while deacetylation by Sirt1 facilitates its transfer back into the nucleus (Accili and Arden, 2004).

DNA methylation, DNA repair, and transcription come together through acetylation by the association of p300/CBP HAT, thymidine DNA glycosylase (TDG), and the bifunctional protein apurinic/apyrimidinic endonuclease /redox factor-1 (APE/Ref1$^{Red/Ox}$). Methylation of cytosine in CpG dinucleotides is important in regulation of gene expression. However, deamination of cytosine and methyl-cytosine result in uracil and thymine, respectively, accounting for approximately 30% of all *de novo* nDNA mutations. Correction of the resulting G/T and G/U base pairs involves DNA glycosylases that recognize and excise the mispaired thymine or uracil. Mammals have two thymine DNA glycosylases, TDG and MBD4. MBD4 is concentrated in heterochromatin, but TDG is enriched in transcriptionally active euchromatin. When TDG binds to the G/T or G/U base mismatches, this leads to the additional binding of both p300/CBP and APE-1/Ref1$^{Red/Ox}$. The p300/CBP acetylates the local histones to open the chromatin while the APE-1/Ref1$^{Red/Ox}$ cleaves the apyrimidinic DNA strand for repair (Tini et al., 2002). APE-1/Ref1$^{Red/Ox}$ is a bifunctional protein that not only participates in DNA repair, but also regulates a variety of transcription factors through thiol/disulfide conversions. Since thiol-disulfide chemistry is regulated by mitochondrial and cytosolic redox state (Hansen et al., 2006; Jones, 2006b, 2008; Kemp et al., 2008; Schafer and Buettner, 2001) the p300/CBP-TDG-APE-1/Ref$^{Red/Ox}$ complex integrates all aspects of the energetic regulation of the epigenome (Figure 1).

The coordination between cellular metabolism and transcriptional regulation is classically illustrated by the response of mammalian metabolism to the availability of carbohydrate calorie resources. When carbohydrates were abundant to our ancestors, such as during the

plant growing season, consumption of plant starch resulted in increased blood glucose levels. This stimulates the pancreatic β cells to release insulin. Insulin signals the availability of carbohydrates to the rest of the tissues in the body, shifting metabolism toward glycolysis for ATP generation and the storage of excess calories as fat. When carbohydrates are scarce, glucose becomes limiting to animals, serum glucose levels fall, insulin secretion declines, and the pancreatic α cells secrete glucagon. Glucagon then signals via cAMP to mobilize stored fat and up-regulate mitochondrial OXPHOS to burn fat and generate energy to survive periods of glucose deprivation (Wallace, 2007) (Figure 1).

When insulin is secreted due to increased serum glucose, it binds to insulin receptors of target tissue cells. This activates PI3 kinase (PI3K) which activates the Akt/PKB protein kinase. Akt then phosphorylates and inactivates the FOXO transcription factors. When unphosphorylated, FOXO transcription factors are active and bind to insulin response elements (IREs) in the promoters of nDNA genes. One FOXO target gene is the transcriptional co-activator, PGC-1α. PGC-1α interacts with a variety of tissue-specific transcription factors to induce key nDNA-encoded mitochondrial genes to up-regulate OXPHOS. Thus, when glucose is abundant, the FOXOs are phosphorylated and inactive, PGC-1α is down-regulated, mitochondrial OXPHOS is depressed, and metabolism shifts toward glycolysis. When blood glucose is low, insulin secretion decline, and the FOXOs are unphosphorylated and active. This induces PGC-1α and OXPHOS. Low blood glucose also stimulates glucagon secretion, which binds to the glucagon receptor of target calls and activates adenylylcyclase to produce cAMP. Elevated cAMP activates PKA to phosphorylate CREB which enters the nucleus and binds CRE cis elements, one of which is up-stream of PGC-1α. This up-regulates PGC-1α and OXPHOS expression. Therefore, when carbohydrates are limiting, the expression of PGC-1α is doubly induced by the dephosphorylation of the FOXOs and the phosphorylation of CREB, switching cellular metabolism toward OXPHOS to burn stored fats to survive periods of carbohydrate deprivation. Antioxidant defenses are also up-regulated in conjunction with OXPHOS to offset the effects of increased mitochondrial ROS production (Figure 1).

The switch from glycolysis to OXPHOS may also be mediated by the cytosolic NAD^+/NADH levels through Sirt1. Catabolism of glucose by glycolysis reduces cytosolic NAD^+ to NADH and produces pyruvate, which is further metabolized in the mitochondrion. By contrast, fatty acid oxidation occurs exclusively in the mitochondrion, leaving cytosolic NAD^+ oxidized. Therefore, when glucose in abundant, the cytosolic NAD^+ is reduced and the NADH can not be used by Sirt1 as a co-reactant to deacetylate the FOXOs and PGC-1α. Hence, the FOXOs and PCG-1α remain inactive down-regulating mitochodntrial biogenesis. When fats are oxidized, cytosolic NAD^+ remains abundant, permitting the deacetylation of the FOXOs and PGC-1α and the up-regulation of OXPHOS.

3.2.2.2. Metabolic Regulation via Nuclear Receptors: *PGC-1α* is one of three members of a gene family of transcriptional co-activators (PGC-1α, PGC-1β, and PERC) that modulate mitochondrial function by regulating genes for energetics including mitochondrial biogenesis, thermogenesis, and fatty acid oxidation (Kelly and Scarpulla, 2004; Scarpulla, 2002). PGC-1α was cloned through its interaction with PPARγ (Yang et al., 2006). PPARγ is a member of the nuclear receptor (NR) superfamily, a large family of ligand-dependent transcriptional factors. This superfamily consists of 48 members in human and 49 in mouse which are central to the regulation of metabolism, development, reproduction, and immune response. All members of the nuclear receptor superfamily share a common architecture containing a N-terminal ligand independent activation domain (AF-1), a DNA binding domain (DBD) consisting of two highly conserved zinc-finger motifs which interact with the hormone response elements (HRE, 5'-AGGTCA-3'), a hinge region, and the C-terminal ligand binding domain (LBD). Various members of the NR superfamily can bind to DNA as

monomers homodimers, or heterodimers. Based on their ligand binding, the NRs are divided into three major groups, “endocrine receptors” which encompass the steroid receptors and heterodimeric receptors, the “adopted orphan receptors” which include the lipid sensors and “enigmatic orphans,” and the “orphan receptors” whose ligands are unknown.

The steroid receptors of the endocrine class include the estrogen receptors (ER) α and β, androgen receptor, glucocorticoid receptor and others, all of which function as homodimers. The heterodimeric endocrine receptors include the thyroid hormone receptors α and β which dimerize with RXR.

The orphan receptors bind lipids and include PPARα, γ, and δ which also heterodimerize with RXR. PPARα is expressed in liver, heart, muscle and kidney and regulates fatty acid oxidation and apolipoprotein synthesis. PPARγ is most abundant in adipose tissue and regulates adipogenesis, but it is also expressed in liver and skeletal muscle. PPARδ is ubiquitously expressed and promotes mitochondrial fatty acid oxidation, energy expenditure, and thermogenesis. Mice over expressing PPARδ in skeletal muscle exhibit a shift in their muscle fiber distribution from glycolytic type II fibers to oxidative type I fibers with an associated remarkable increase in exercise endurance (Wang et al., 2004).

The enigmatic “adopted orphan receptors” include the estrogen-related receptors (ERR) α, β, and γ. The ERRs often act as monomers binding consensus half sites found in many genes involved in mitochondrial function. Under physiological conditions, the ERRs are not regulated by ligands, but instead by binding the inducible co-activators PGC-1α and PGC-1β. The interactions of ERRs with the PGC-1s then induce mitochondrial β-oxidation and oxidative metabolism. PGC-1α and β can interact with other NRs to up-regulate mitochondrial genes. While both can interact with PPARα and δ in muscle, heart, and white adipose tissue to induce mitochondrial fatty acid oxidation, PGC-1α can interact with FXR and HNF-4α in liver to induce gluconeogenesis during fasting, and PGC-1β can interact with SREBP-1c (steroid regulatory element binding protein-1c) and FOXA2 to promote lipogenesis. NR heterodimers involving RXR can interact with transcriptional co-repressors such as SMRT/NCOR plus HDACs in the absence of ligands to inhibit transcription, but in the presence of ligands can shift to binding transcriptional co-activators p300/CBP or SRC/p160 to activate transcription. On activation or induction of PGC-1, the ERR binds PGC-1 and this nucleates an active transcriptional complex that can include p300/CBP and SRC/p160 (Mangelsdorf and Evans, 1995; Shulman and Mangelsdorf, 2005; Sonoda et al., 2008).

While the interaction of PGC-1α and β with the NRs appear to be master regulators of oxidative metabolism, other steroid receptors also play an integral and often unexpected role in regulating mitochondrial function. It is now known that the estrogen receptors ERα and β are present not only in the nucleus-cytosol, but also in the mitochondrial matrix (Duckles et al., 2006; Pedram et al., 2006; Stirone et al., 2005). In cerebral vascular endothelial cells, estrogen induces mtDNA-encoded polypeptides such as COI and also the nDNA encoded mitochondrial polypeptides COX subunit IV (COX14), cytochrome *c*, and the nDNA gene mitochondrial nuclear transcription factor-1 (NRF1), as well as citrate synthetase and COX activities (Duckles et al., 2006; Stirone et al., 2005). Estrogen also decreases mitochondrial ROS production in association with an increase in MnSOD specific activity without increases in protein level in both vascular endothelial cells (Razmara et al., 2007; Razmara et al., 2008; Stirone et al., 2005) and also mammary tumor cells (Pedram et al., 2006). Therefore, the NR superfamily exerts broad control on many aspects of mitochondrial physiology in response to endogenous and exogenous environmental factors.

3.2.2.3. Metabolic Regulation via TOR Kinase: In addition to the transcriptional regulation of mitochondrial function, mitochondrial bioenergetics and biogenesis is

modulated by post-translational modifications. One important mediator of cellular and mitochondrial energetics is AMP-activated protein kinase (AMPK). Under conditions where energy production is compromised (e.g. hypoxia, starvation, OXPHOS inhibitors) or when energy consumption accelerates (e.g. muscle contraction), the ATP/ADP ratio declines. This drives the adenylate kinase reaction (2 ADP → ATP + AMP). The resulting increased AMP/ATP ratio then activates AMPK. Activated AMPK phosphorylates PGC-1α; up-regulates PGC-1α expression and OXPHOS (Jager et al., 2007); induces glucose uptake and glycolysis; activates fatty acid oxidation, and suppresses fatty acid synthesis; stabilizes p53, p21, and p27 to inhibit cell growth and proliferation; and represses the target of rapamycin (TOR) kinase to inhibit protein synthesis (Hardie, 2007). When nutrients again become available, the AMP/ATP ratio declines, AMPK activity is suppressed, and TOR signaling is activated to resume protein synthesis and stimulate cell growth (Wullschleger et al., 2006) (Figure 1).

The TOR serine/threonine kinases link nutrient availability to regulation of anabolism or catabolism. Mammalian cells have two TOR (mTOR) complexes: mTORC1 and mTORC2. mTORC1 consists of mTOR, raptor, and mLST8 and it regulates protein synthesis, metabolism, ribosomal biogenesis, transcription, and autophagy (Figure 1). mTORC2 is composed of mTOR, rictor, and mLST8 and it regulates via Akt/PKB cell proliferation, survival, metabolism, transcription and actin organization and thus motility. Rapamycin, when complexed with FKBP12, inhibits mTORC1 but not mTORC2.

mTORC1 is regulated by the insulin signaling pathway, stress and hypoxia, cellular energy levels through AMPK, and nutrient levels. Insulin and insulin-like growth factors activate the insulin receptor which phosphorylates insulin receptor substrate (IRS), thus activating phosphatidyl-inositol 3 kinase (PI3K). This activates Akt/PKB to phosphorylate and inactivate the tuberous sclerosis protein complex (TSC). TSC is composed of the proteins hamartin (TSC1) and tuberin (TSC2) and TSC2 acts as a GTPase activating protein (GAP) for the small GTPase Rheb. Rheb binds to the kinase domain of mTOR. When bound to GTP Rheb activates mTOR and when bound to GDP it inhibits mTOR. Thus, when insulin and IGFs are present, TSC is inactive, and Rheb retains GTP and activates mTOR. When insulin and IGF are absent, TSC is active, Rheb GTP is converted to GDP, and mTOR is inhibited. Activated mTORC1 phosphorylates downstream proteins S6K1 and 4E-BP to increase protein synthesis, and other targets to stimulate growth related processes. The Ras/ERK pathway can also phosphorylate TSC, stimulating growth. When ATP is limiting and the AMP/ATP ratio rises, AMPK is activated and phosphorylates TSC, enhancing GAP activity, converting Rheb GTP to GDP, and thus inhibiting mTOR. Therefore, ATP deficiency inhibits protein synthesis and growth processes. Similarly, hypoxia inhibits mTORC1 signaling and limits protein synthesis and growth via activation of hypoxia inducible factors-1α and 2α (HIF-1α, HIF-2α). The HIF-1α-HIF-1β complex induces the expression of the REDD complex (REDD1 & 2) which releases TSC2 from its association with the inhibitory 14-3-3 protein permitting TSC1/2 to inhibit mTORC1 and inhibit growth (DeYoung et al., 2008). Increased amino acids stimulate growth through mTORC1. The elevated amino acids, in particular leucine, induce an influx of Ca^{++} into the cell, which activates calmodulin. The Ca^{++}/calmodulin complex binds hVps34 which is attached to the mTORC1 complex. This activates hVps34 to generate PI(3)P which activates mTORC1 leading to phosphorylation of S6K1, 4E-BP, and other mTORC1 targets proteins and increased protein synthesis and growth (Gulati et al., 2008). Nutrient deprivation, by contrast, is associated with reduced cytosolic Ca^{++}, inhibition of mTORC1, dephosphorylation of target proteins and inhibition of protein synthesis and growth. mTORC1 also phosphorylates and inhibits the ATG1 protein kinase which mediates the early steps in autophagy. Therefore, when energy and nutrients are plentiful, mTORC1 is active, ATG1 is phosphorylated and autophagy is inhibited. When nutrients and energy are

limiting, mTORC1 is inactive, ATG1 becomes dephosphorylated, and autophagy recovers nutrients from cellular macromolecules (Wullschleger et al., 2006).

3.2.2.4. Metabolic and Circadian Regulation via Sirtuins & NAD^+: Cellular energetics is also modulated by the cellular redox state through the NADH/NAD^+ ratio. Since NAD^+, but not NADH, is a substrate for many of the class III sirtuin deacetylases, sirtuin activity links protein deacetylation to the cellular NADH/NAD^+ ratio. Mammals possess seven sirtuins: SIRT1, -2, -6, and -7 located in the nucleus; SIRT1 and -2 in the cytosol; and SIRT 3, -4, and -5 in the mitochondrion. SIRT1 is the best studied, deacetylating proteins using NAD^+. Acetylation of FOXO transcription factors by p300/CBP reduces their activities, while deacetylation by SIRT1 increases activity. Thus, when calories are limited, NADH is oxidized to NAD^+. This activates SIRT1 to deacetylate the FOXOs, up-regulating OXPHOS to begin oxidizing stored fat. PGC-1α can also be acetylated by GCN5 reducing its activity when calories are plentiful, and deacetylation by SIRT1 and NAD^+ when reducing equivalents are scarce increasing PCG-1α activity in muscle and up-regulating mitochondrial fatty oxidation (Gerhart-Hines et al., 2007). SIRT1 also regulates mitophagy through deacetylation of members of the Atg family of proteins (Lee et al., 2008). SIRT3 deacetylation of various OXPHOS proteins also modulates mitochondrial metabolic rate (Ahn et al., 2008).

SIRT1 deacetylase activity is also linked to circadian rhythms (Asher et al., 2008; Nakahata et al., 2008). Circadian rhythms are generated by a transcriptional negative feedback loop in which two transcription factors BMAL1 and CLOCK form a heterodimeric complex that drives the expression of two negative regulators, PER and CRY. Expression of PER and CRY attenuates the activity of the heterodimeric BMAL1/CLOCK complex and turns down PER and CRY expression. The CLOCK protein has HAT activity which is enhanced by BMAL1 and is essential to maintain the circadian rhythm (Doi et al., 2006). CLOCK-driven acetylation of histones H3 and H4 and BMAL1 are all cyclical, as is PER2 acetylation (Asher et al., 2008; Doi et al., 2006). BMAL1 and PER2 are also more stable when acetylated (Asher et al., 2008; Nakahata et al., 2008). SIRT1 also binds and deacetylates CLOCK, BMAL1, and PER2. Therefore, deacetylation by SIRT1 plus NAD^+ is also regulating circadian rhythm. SIRT1 expression level is circadian in mouse liver, being maximum at Zeitgeber time (ZT) 16 during the active dark period (ZT = 0 being the beginning of a 12 hour light cycle) and minimum at ZT4 during the quiescent light period. SIRT1 deacetylation is required for the oscillation of BMAL1 expression, since SIRT1 knockout cells have significantly reduced expression of the core circadian genes including *Clock*, *Bmal1*, *Per1*, and *Cry1* (Asher et al., 2008; Nakahata et al., 2008). Consistent with the SIRT1 requirement for NAD^+ for its deacetylase activity, oscillations of the circadian clock are coupled to oscillations of the cellular NAD^+ levels. The synthesis of NAD^+, in turn, is regulated by the expression of nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting step in mammalian NAD^+ synthesis. The *Nampt* gene in mouse contains an E-box (CACGTG) cis element that binds and is regulated by the CLOCK-BMAL1-SIRT1 complex. This causes the expression of NAMPT and thus NAD^+ levels to oscillate. Therefore, circadian rhythms are regulated both by the transcriptional CLOC-BMAL1 and CRY-PER feedback loop and also by the SIRT1-CLOCK-BMAL1 and NAMPT-NAD^+ metabolic feedback loop (Nakahata et al., 2009; Ramsey et al., 2009; Wijnen, 2009). Since cellular energetics drives oxidation-reduction reactions and modulates the NAD^+/NADH redox ratio, and the redox state of NAD^+ is modulated by caloric availability, circadian rhythms, food intact, and activity must interact (Eckel-Mahan and Sassone-Corsi, 2009).

The circadian oscillations of the *Clock*, *Bmal1*, *Per2*, and *Cry1* genes are also paralleled by oscillations in the expression of 28 of the 45 nuclear receptor genes (Yang et al., 2006). The mRNA levels of the PPAR family members showed tissue-specific oscillations that

correlated with those of the *Clock*, *Bmal1*, *Per2*, and *Cry1* genes in mouse white adipose tissue (WAT), brown adipose tissue (BAT), liver, and skeletal muscle (Yang et al., 2006). In BAT, all three *PPAR* genes, as well as *PGC-1α* and *UCP*-1, reach their maximal expression during ZT4, the light period when mice are at rest, and minimum at ZT16 during the dark period when mice are active. Thus, BAT thermogenesis is maximum during resting and minimum during periods of maximum activity, thus balancing heat generation by ATP hydrolysis during exercise with heat generation during rest by thermogenesis. In WAT, by contrast, *PPARγ* is maximum during the active dark period, ZT16, and minimal during the resting light period, ZT 4. This parallels the expression of the *SREBP-1c*, *adiponectin*, and *leptin* and is consistent with energy production being maximal during the dark period when mice are most active (Yang et al., 2006). Since the circadian regulation of the *PPAR* genes is at the transcription level, part of the regulation must be the result of changes at the chromatin level. Therefore, calorie intake and energy metabolism directly regulate epigenomic gene expression, and reciprocally epigenomic changes regulated food intake and energy metabolism.

3.2.2.5. PGC-1α and Sirtuin Mutant Mice: The spectrum of phenotypic and physiological parameters regulated by energy metabolism has been demonstrated by generating mice in which the genes of the PGC-1 and Sirtuin families have been inactivated. In mice lacking *PGC-1α* (−/−) only about half of the pups survive through early postnatal period into adulthood. These animals weigh 10–15% less at 2 months of age, and have abnormal BAT with large lipid droplets, but normal liver, heart, skeletal muscle, and pancreas (Lin et al., 2004). The *PGC-1β* knockout mice show grossly normal development, growth, and fertility (Sonoda et al., 2007).

Both the *PGC-1α* and *PGC-1β* knockout mice show reduced cold tolerance, decreased mitochondrial energy metabolism, and altered circadian rhythms indicating that the two transcription co-activators have overlapping functions. However, the two knockout mice differ in their tissue specificities demonstrating that *PGC-1α* and *PGC-1β* have different roles in regulating metabolism. *PGC-1α* knockout mice accumulate large lipid droplets in BAT and up-regulate gluconeogenesis in liver under normal conditions, while *PGC-1β* knockout mice accumulate large lipid droplets in their livers after being fed a high-fat diet. *PGC-1α* −/− mice are hyperactive in both light and dark cycles while *PGC-1β*-deficient mice have decreased activity during the dark cycle. Finally, *PGC-1α* –deficient but not *PGC-1β*-deficient mice develop neuronal degeneration (Lin et al., 2004; Sonoda et al., 2007).

The activation of PGC-1α by NAD^+-linked deacetylation by Sirt1 directly ties OXPHOS induction to calorie restriction (Cheng et al., 2003; McBurney et al., 2003) (Boily et al., 2008; Wallace, 2005c). SIRT1 is the mammalian orthologue of the yeast Sir2, and Sir2 orthologues which regulate life span in association with calorie restriction in multiple species (Lin et al., 2000; Rogina and Helfand, 2004; Wallace, 2005c). Thus, longevity and mitochondrial energetics are linked.

The homozygous knockout of *Sirt1* in the mouse on a 129/Sv background results in a 50% prenatal mortality, with the remaining animals being small and dying within a month. Sirt1 deficiency on a CD1 and 129/Sv mixed background results in animals which survive to adulthood, though both males and females are sterile (McBurney et al., 2003). On the 129/Sv background, the *Sirt1* −/− mutation is associated with retinal and heart defects (Cheng et al., 2003). Microarray analysis of *Sirt1*-silenced animals suggests that Sirt1 acts more on mammalian signal transduction pathways and transcription factors than on chromatin structure (McBurney et al., 2003).

Sirt1 −/− mice remain small and are also less active, yet their daily food intake is normal. This is because they are hypermetabolic, *Sirt1* −/− liver mitochondria being more uncoupled and thus less efficient at generating ATP. Caloric restriction of *Sirt1* −/− mice does not extend lifespan, supporting the hypothesis that life span is extended by the up-regulation of mitochondrial OXPHOS through the Sirt1-mediated deacetylation of the FOXO and PGC-1α transcription factors (Boily et al., 2008).

Mice in which the mitochondrial *Sirt3* and *Sirt5* genes have been inactivated are viable (Haigis et al., 2006; Lombard et al., 2007). *Sirt3* −/− mice have no histological abnormalities or marked changes in the expression of TFAM, MnSOD, COX IV, cyt c, and Ucp-1 in BAT even though mitochondrial proteins such as glutamate dehydrogenase (GDH) have markedly increased acetylated lysine levels (Lombard et al., 2007). However, the hyperacetylation of mitochondrial proteins seen in *Sirt3* −/− mouse embryo fibroblasts and *Sirt3* −/− tissues is associated with a 50% reduction in mitochondrial ATP production and complex I activity (Ahn et al., 2008). Thus, Sirt3 appears to be regulating mitochondrial basal metabolic rate. Since Sirtuins are activated by NAD^+, an increased NAD^+/NADH ratio resulting from a starvation state would deacetylate the OXPHOS proteins increasing mitochondrial basal metabolic rate and facilitating the oxidation of stored fats to generate ATP.

Sirt4 is an ADP-ribosylase. While *Sirt4* −/− mice appear normal in development, growth, and fertility, they show increased circulating insulin levels. Exposure of *Sirt4* −/− islets to glucose significantly increases insulin secretion. Injection of glutamine into *Sirt4* −/− mice also increases plasma insulin and *Sirt4* −/− islets exposed to glutamine or leucine have increased insulin secretion. These effects are mediated by the Sirt4-regulating ADP-ribosylation of pancreatic GDH which decreases its activity thus negatively regulating amino acid stimulated insulin secretion (Haigis et al., 2006).

Therefore, the acetylation of the FOXO transcription factors and the PGC-1α and β transcriptional coactivators via acetyl-CoA depress OXPHOS, shifting metabolism toward glycolysis in the fed state. However, during fasting the shift of the NADH/NAD^+ ratio toward NAD^+ results in the Sirt1-mediated deacetylation of these factors. Similarly, during fasting when NAD^+ is prevalent, GDH is ADP-ribosylated and inactivated, suppressing amino acid stimulated insulin secretion. This inhibits the storage of calories as fat, activates the FOXOs and induces and activates PGC-1α, thus inducing mitochondrial OXPHOS to oxidize fatty acids and amino acids to provide energy during fasting. Therefore, regulation of energetic gene expression and metabolism is directly linked to the availability and nature of the calories for the animal, intimately linking mitochondrial energy metabolism and the epigenome.

4. MITOCHONDRIAL GENETIC DISEASE

The elucidation of a broad spectrum of mtDNA and nDNA mitochondrial gene mutation diseases has revealed that mitochondrial dysfunction can result in the entire range of clinical phenotypes associated with metabolic and degenerative diseases as well as cancer and aging (Wallace et al., 2007). Mitochondrial diseases have been shown to affect the highly oxidative tissues including the brain, heart, muscle, kidney, and endocrine systems; as well as the metabolic systems resulting in diabetes, obesity, and influence a range of age-related disorders. Thus, the symptoms of mitochondrial diseases correspond to those attributed to epigenomic changes.

4.1. Recent mtDNA Mutations and Diseases

Clinically relevant mtDNA variants fall into three classes: recent deleterious mutations resulting in maternally transmitted disease, ancient adaptive variants that predispose individuals to disease in different environments, and the age-related accumulation of somatic mtDNA mutations that erode function and provide the aging clock. The extraordinary clinical variability of mtDNA diseases results from different mutations in the same gene causing different phenotypes and from the same mutation at different levels of heteroplasmy causing different phenotypes (Wallace, 2005c).

Pathogenic mtDNA mutations include both rearrangement mutations and base substitution mutations. Rearrangement mutations can either be *de novo* deletion mutations or maternally transmitted insertion mutations which are unstable and generate deletion mutations in post-mitotic cells. Most deletion mutations remove at least one tRNA and thus affect protein synthesis (Wallace et al., 2001). MtDNA rearrangement syndromes are invariably heteroplasmic and have been associated with maternally-inherited diabetes and deafness, Chronic Progressive External Ophthalmoplegia (CPEO), the Kearns-Sayre Syndrome (KSS), and the Pearson marrow/pancreas syndrome. Differences in mtDNA rearrangement phenotypes appear to stem from differences between insertions and deletions, the diversity of tissues that contain the rearrangement, and the percentage of mtDNAs harboring the rearrangement in each tissue (Wallace et al., 2007).

Base substitution mutations can alter either polypeptide genes (polypeptide mutations) or rRNAs and tRNAs (protein synthesis mutations). Pathogenic polypeptide mutations encompass a broad spectrum of multisystem diseases including LHON (Wallace et al., 1988a), Leigh syndrome (Holt et al., 1990), and mitochondrial myopathy (Andreu et al., 1999a; Andreu et al., 1998; Andreu et al., 1999b). Mitochondrial tRNA and rRNA protein synthesis mutations can result in multisystem diseases including Myoclonic Epilepsy and Ragged Red Fiber Disease (MERRF) (Shoffner et al., 1990; Wallace et al., 1988b); Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS) (Goto et al., 1990); encephalomyopathy; mitochondrial myopathy and exercise intolerance; CPEO and KSS; gastrointestinal syndrome; dystonia; diabetes; deafness; cardiomyopathy; renal failure, Alzheimer Disease (AD); Parkinson Disease (PD). (Wallace et al., 2007).

4.2. Ancient mtDNA Mutations and Disease

As modern humans migrated out of Africa, mtDNA mutations accumulated along radiating maternal lineages. When a mtDNA acquired a functional mutation beneficial in a particular environment, then that mtDNA became enriched by selection and radiated within that environment to give a cluster of related mtDNA haplotypes, known as a haplogroup. Hence, haplogroups correlate with the geographic origin of the indigenous population being studied and are designated by sequential alphabetical letters (Mishmar et al., 2003; Ruiz-Pesini et al., 2004; Ruiz-Pesini and Wallace, 2006; Wallace, 2005c; Wallace et al., 1999; Wallace et al., 2003).

These same ancient adaptive mtDNA mutations influence individual predisposition to a wide spectrum of common diseases today. Various mtDNA haplogroups have been associated with neurodegenerative diseases (Brown et al., 2002; Brown et al., 1997; Brown et al., 1995; Carrieri et al., 2001; Chagnon et al., 1999; Ghezzi et al., 2005; Jones et al., 2007; Khusnutdinova et al., 2008; Shoffner et al., 1993; Torroni et al., 1997; Udar et al., 2009; van der Walt et al., 2004; van der Walt et al., 2003), diabetes and metabolic syndrome (Crispim et al., 2006; Fuku et al., 2007; Mohlke et al., 2005; Nishigaki et al., 2007; Saxena et al., 2006), infectious disease including AIDS progression (Baudouin et al., 2005; Hendrickson et al., 2008; Hendrickson et al., 2009; Raby et al., 2007), longevity (De

Benedictis et al., 1999; Ivanova et al., 1998; Niemi et al., 2003; Rose et al., 2001; Tanaka et al., 2000; Tanaka et al., 1998), and cancer (Bai et al., 2007; Booker et al., 2006; Brandon et al., 2006; Darvishi et al., 2007; Gottlieb and Tomlinson, 2005; Wallace, 2005a). From these reports, it is clear that mtDNA functional variation modulates predisposition to a wide range of metabolic and degenerative diseases as well as influenceing cancer risk and longevity.

4.3. Somatic mtDNA Mutations in Aging and Cancer

Mutations in the mtDNA have been observed to accumulate with age in a variety of post-mitotic tissues in a wide range of species, and in a spectrum of complex of age-related diseases (Wallace, 2005c). Increasing the mtDNA mutation rate in mice increases their aging rate (Kujoth et al., 2005; Trifunovic et al., 2004) while decreasing the somatic mtDNA mutation rate by introducing catalase into the mitochondrial matrix extends mouse life span (Schriner et al., 2005). Therefore, the accumulation of somatic mtDNA mutations provides an aging clock that helps define an animal's life span and contributes to the delayed-onset and progressive course of complex diseases (Wallace, 2005c). Moreover, both somatic and germline mtDNA mutations have been associated with cancer (Brandon et al., 2006; Ishikawa et al., 2008; Petros et al., 2005; Wallace, 2005a).

4.4. Mitochondrial Diseases of nDNA-mtDNA Interaction

Mutations in nDNA-encoded OXPHOS genes have also been linked to a variety of multisystem disorders (Wallace et al., 2007). These include mutations that inactivate OXPHOS complex structural and assembly genes (Procaccio and Wallace, 2004; Zhu et al., 1998), mutations that destabilize the mtDNA (Carrozzo et al., 2007; Kaukonen et al., 2000; Mandel et al., 2001; Nishino et al., 1999; Palmieri et al., 2005; Saada et al., 2001; Spelbrink et al., 2001; Van Goethem et al., 2001), and mutations that perturb mitochondrial fusion and fission (Delettre et al., 2000; Zuchner et al., 2004).

5. MITOCHONDRIAL EXPLANATIONS FOR EPIGENETIC DISEASES

Therefore, mitochondrial gene defects can result in virtually all of the symptoms associated with the common "complex" diseases, confirming the importance of mitochondrial bioenergetics in health. Since mitochondrial metabolism also regulates the substrates for epigenomic regulation, it follows that changes in mitochondrial metabolism may also perturb the epigenomic state. Furthermore, in cells and animals in which the epigenomic elements NRs, PGC-1α and β, and the Sirtuins are inactivated, mitochondrial function is also perturbed. Similarly, compounds such as resveratrol and its derivatives, which activate SIRT1, can up-regulate mitochondrial energy production and have been found to ameliorate metabolic and age-related phenotypes (Baur et al., 2006; Baur and Sinclair, 2006; Feige et al., 2008; Figarella-Branger et al., 1992; Lagouge et al., 2006; Milne and Denu, 2008; Milne et al., 2007; Pearson et al., 2008; Wood et al., 2004). It therefore follows that alterations in the epigenome should also perturb mitochondrial function. Epigenetic alteration in mitochondrial function could occur at either the local intra-chromosomal domain level to suppress mitochondrial regulatory or maintenance genes or at the inter-chromosomal level to disrupt transcriptional factories resulting in the loss of coordinate regulation of energetic genes.

5.1. Altered Intrachromosomal Domains and Energetics

Evidence that mitochondrial dysfunction is associated with epigenomic changes can be found for a wide range of classical epigenomic diseases. In cancer, a genetic disease, changes in the epigenome such as "Loss of Imprinting" (LOI) and hypomethylation are common. LOI of the insulin-like growth factor II (IGF2) provides one example of how changes in the cancer epigenome might affect mitochondrial function. Half of Wilms tumors

as well as lung cancer, breast cancer, ovarian cancer, and glioma show LOI of the IGF2 locus. IGF2 is an imprinted locus normally expressed only from the paternal allele. Hence, LOI increases IGF2 expression (Bjornsson et al., 2007; Feinberg, 2007). In the mouse, LOI of Igf2 is associated with enhanced Igf2 signaling due to augmentation of Akt/PKB signaling (Kaneda et al., 2007). Activation of the Akt/PKB pathway suppresses mitochondrial OXPHOS and drives the cell toward glycolysis (Figure 1). Glycolysis is also enhanced in liver cancer by reversing the hyermethylation of the promoter of hexokinase II. Following epigenomic activation, hexokinase II transcription is further regulated by glucose; hypoxia via HIF-1α, cAMP via CREB, insulin and glucagon, and mutated p53 (Goel et al., 2003; Wallace, 2005a). Hexokinase II binds glucose and ATP, converting them into glucose-6-phosphate, the commitment step of glycolysis. Akt/PKB also phosphorylates hexokinase II causing it to bind to the mitochondrial outer membrane pore protein porin (voltage dependent anion channel, VDAC) with high affinity. The binding of hexokinase II to VDAC also antagonizes the pro-apoptotic action of Bax and Bak. The expression profile of the ANT isoforms is also altered in transformed cells (Torroni et al., 1990) and the ANTs export the mitochondrial ATP from the matrix to the intermembrane space so that VDAC can export ATP into the cytosol. Thus the binding of hexokinase II to VDAC means that ATP leaving the mitochondria binds preferentially to hexokinase II. This co-opts mitochondrial ATP production to drive glycolysis. Therefore epigenetic changes in cancer specifically suppress mitochondrial function in favor of glycolysis.

The chromatin modifications of cancer cells can be directly modulated by mitochondrial OXPHOS. Cancer cells which have been cured of their mtDNA but either chemical or genetic treatments have been found to have altered methylation patterns in 2–9% of the CpG islands surveyed. This is comparable to the 2–5% alteration in methylation regions associated with epigenomic changes during differentiation. In three out of four cases, removal of the mtDNA leads to the hypomethylation commonly associated with LOI in cultured cancer cells. When mtDNAs were reintroduced to the mtDNA-deficient cancer cells, 30% of the hypomethylated sitres become remethylated. Thus, there is a direct cause and effect relationship between mitochondrial function and epigenomic methylation in cancer cells (Naviaux, 2008; Smiraglia et al., 2008).

The p53 protein also regulates OXPHOS through induction of the complex IV chaperone protein “Synthesis of Ctyochrome c Oxidase 2” (SCO2) which is responsible for inserting Cu into COX. By contrast, p53 negatively regulates phosphoglycerate mutase of glycolysis and Akt. Therefore, mutational inactivation of p53 in cancer cells suppresses OXPHOS and induces glycolysis (Matoba et al., 2006).

Epigenetic alteration in genomic metylation in association and in part because of mitochondrial OXPHOS deficiency act in concert with alterations in the expression of IGF2, hexokinase II, the ANTs, and the inactivation of p53, to shift cancer cell energy production of toward glycolysis. This helps to explain Otto Warburg’s observation over 70 years ago that cancer cells generate excess lactate indicating hyperactive glycolysis, in the presence of oxygen, “aerobic glycolysis” (Wallace, 2005a).

LOI in the IGF2 gene region on chromosome 11q15.5 can also result in the dymorphology condition, Beckwith-Wiedemann Syndrome (BWS). About 15% of BWS of patients show LOI at the IGF2 locus reactivating the maternal allele and resulting in the overproduction of IGF2,. IGF2 overproduction leads to prenatal overgrowth, midline abdominal wall defects, ear creases and pits, and neonatal hypoglycemia. BWS cases associated with IGF2 LOI are also prone to Wilm’s tumor (Bjornsson et al., 2007; Feinberg, 2007, 2008). Again, over-expression of IGF2, acting via the PI3K-Akt-FOXO-PGC-1α pathway, would suppress mitochondrial OXPHOS (Figure 1).

In the mouse, the BWS locus is located on chromosome 7. The expression of the paternally expressed *Igf2* gene and the maternally expressed *H19* are regulated by the surrounding chromatin loop structure. The *Igf2* and *H19* genes are encompassed in an approximately 100 kb imprinted region, separated by a CTCF insulator site with an enhancer down stream of *H19*. The paternal and maternal transcription of the *Igf2* and *H19* genes is regulated by the interaction of differentially methylated regions (DMRs), three in *Igf2* and one at the CTCF insulator site. On the maternal chromosome, the DMR of *H19* associates with DMR1 near the 5' end of *Igf2*. This places *H19* in the active chromatin domain with the enhancer and the *Igf2* gene on the other side of the CTCF site in an inactive chromatin domain shutting off *Igf2*. On the paternal chromosome, the *H19* DMR interacts with the 3' *Igf2* DMR2 domain. This creates a loop which brings the *Igf2* gene adjacent to the *H19* enhancer on the same side as the enhancer, thus permitting its transcription. The *H19* gene on this chromosome is methylated and silenced (Murrell et al., 2004). Therefore, LOI in both cancer and BWS link epigenomic alterations to mitochondrial dysfunction.

Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are classical examples of epigenomic diseases resulting from genetic errors in imprinted loci on chromosome 15q11-13. Preliminary evidence is implicating mitochondrial dysfunction in AS as well. PWS is associated with hypotonia, hyperphagia, and obesity while AS is associated with hyperactivity, thinness, and autism. PWS involves a paternal deficiency in 15q11-13 while AS involves a maternal deficiency. Current evidence suggests that the expression of the small nuclear ribonuclear polypeptide N (*SNRPN*) and the adjacent imprinting control region (ICR) and the expression of the ubiquitin-protein ligase E3A (*UBE3A*) are reciprocally imprinted on the maternal and paternal chromosomes. Therefore, genetic inactivation of the expressed *UBE3A* gene is responsible for AS and inactivation of the expressed *SNRPN* and ICR loci are associated with the PWS phenotype (Feinberg, 2007). In an analysis of mice mutated at the *UBE3A* locus, we have found that the brain mitochondria are small and dense and that the activity of the combined respiratory complex III is reduced (Su et al., 2009). Therefore, mitochondrial dysfunction may contribute to the etiology of AS. While the mechanism by which UBE3A deficiency causes mitochondrial dysfunction is unknown, UBE3A is an E3 ubiquitin ligase and ubiquination is important in maintaining the structural and functional integrity of the mitochondrion (Escobar-Henriques et al., 2006; Neutzner and Youle, 2005). The mitochondrial ubiquitin ligase MARCH-V is important in regulating the mitochondrial fusion and fission dynamics through Drp1 and Fis1 (Karbowski et al., 2007; Nakamura et al., 2006) and the human deubiquitinating enzyme ubiquitin-specific protease 30 (USP30) is embedded in the mitochondrial outer membrane and important in maintaining mitochondrial morphology (Nakamura and Hirose, 2008). Therefore, loss of the 15q11-13 loci could perturb mitochondrial function and explain some of the pathophysiology of these diseases.

Tuberous sclerosis complex (TSC) is another cell over-growth disorder, which affects virtually every organ of the body. Clinical features include cutaneous hypomelanotic macules, facial angiofibromas, etc.; central nervous system subependymal nodules, and cortical tubers, learning difficulties, and seizures; renal angiomyolipomas and cysts; cardiac rhabdomyomas; and retinal hamartoma. TSC is caused by mutations in either the hamartin TSC1 gene or the tuberin TSC2 gene. TSC1 + 2 act through Rheb to regulate TORC1, and TOR is implicated in regulation of mitochondrial OXPHOS (Chen et al., 2008; Shadel, 2008)(Figure 1).

About 25–50% of TSC subjects manifest autistic traits. Autism has been associated with alteration in neurite growth and synaptic plasticity and there is growing evidence that the mitochondria play a central role in these processes (Kang et al., 2008; Li et al., 2004; Mattson and Liu, 2002; Schuman and Chan, 2004). Therefore, TSC forms a connection

between cell over-growth syndromes, neurological disorders such as autism, and mitochondrial energy metabolism.

The Fragile X Mental Retardation (FMR) Syndrome is also associated with mental retardation and autism. The FMR protein (FMRP) is an RNA binding protein that has recently been shown to be required for the expression of the mitochondrial and cytosolic Cu/Zn superoxide dismutase (SOD1) (Bechara et al., 2009). Since SOD1 functions to eliminate mitochondrial intermembrane space superoxide, its suppression could increase mitochondrial oxidative stress and thus cause symptoms through mitochondrial dysfunction (Wallace, 2005c).

Rett syndrome is an autism spectrum disorder caused by mutations in the X-linked *MeCP2* gene (Amir et al., 1999; Loat et al., 2008). Rett patients have been reported to harbor mitochondrial structural aberrations and reductions in skeletal muscle OXPHOS complexes I, III, IV, though not II. Furthermore, mice in which *MeCP2* is inactivated have increased complex III and core protein 1 gene (*Ugcrc1*) expression, together with reduced OXPHOS coupling (Eeg-Olofsson et al., 1989; Heilstedt et al., 2002; Kriaucionis et al., 2006). The MeCP2 protein binds to methyl CpG nDNA domains and modulates gene expression, either activation or repression, in part by recruiting histone-modifying enzymes such as deacetylases and methyltransferases (Chen et al., 2003b; Klein et al., 2007). MeCP2 can impart long-term silencing by binding to CpG rich domains and stimulating the deacetylation of histones H3 and H4 resulting in chromatin condensation. MeCP2 can also perform histone deacetylase-independent repression which is relevant to X chromosome inactivation and genomic imprinting (Matijevic et al., 2009). One of the targets of MeCP2 is promoter III of the neurotrophin gene, *BDNF* (Brain-Derived Neurotrophic Factor). It was first thought the MeCP2 repressed BDNF expression (Chen et al., 2003b), but MeCP2 was subsequently reported to enhance BDNF expression (Klein et al., 2007). Neurotrophic factors such as BDNF as well as cAMP stimulate the phosphorylation of CREB, which is important in neuronal plasticity and neurite outgrowth. Furthermore, the translation of *BDNF* mRNA and *p250GAP* mRNA are inhibited by the microRNA, miR132, and both BDNF and p250GAP regulate neuronal morphogenesis. The expression of miR132 is also induced by phospho-CREB demonstrating a feedback loop for regulating neuronal morphogenesis (Klein et al., 2007; Vo et al., 2005). Neurotrophic factors such as BDNF and NGF, bind and activate the tropomyosin-related kinase (Trk) receptor B (TrkB). Major down-stream pathways of the neurotrophic factors are the PI3K-Akt- and MAPK pathways and PKC. These in turn regulate AP1, NFκB, and the FOXOs to regulate energy production pathways, antioxidant enzymes, and anti-apoptotic proteins (Mattson, 2008).

In a rat brain preparation of mitochondria plus synaptosomal membranes, BDNF was found to act through the MAPK pathway to increase OXPHOS coupling efficiency, presumably increasing ATP production. This modulation occurs through complex I, not complex II, and occurs when glutamate and malate are used as the mitochondrial NADH generators, but not when pyruvate and malate were used. Thus, the BDNF regulation of mitochondrial respiration is specific for glutamate as a substrate, and glutamate along with γ-aminobutyric acid (GABA) are coupled through the TCA cycle to neuronal metabolism and transmission. BDNF can also modulate the stimulation of oxygen consumption by calcium, which is also consistent with increasing coupling efficiency (Markham et al., 2004). Surprisingly, the BDNF receptor, TrkB, has been localized to the mitochondrion, as well as to the plasma and endoplasmic reticulum membranes, in both muscle and nerve cells. The TrkB receptor has three isoforms, full length TrkB with tyrosine kinase activity, and two truncated forms (TrkB-T1 and TrkB-T2) without the tyrosine kinase domain. The truncated forms of TrkB appear to predominate in the mitochondrion, and preliminary studies suggest that they are localized to the mitochondrial inner membrane (Wiedemann et al., 2006). Since TrkB1 has

been reported to mediate BDNF-evoked calcium signaling in glial cells, it is possible that TrkB-T1 is directly regulating mitochondrial ATP production and mitochondrial calcium homeostasis through modulating the mitochondrial membrane potential. Therefore, inactivation of MeCP2 could selectively repress the expression of the nDNA encoded mitochondrial genes, providing a coherent argument that at least part of the pathophysiology of Rett syndrome involves mitochondrial dysfunction.

MeCP2 also binds to the PWS imprinting control region (ICR) and down-regulates *Ube3a* and the adjacent Gaba receptor gene (*Gabrb3*). MeCP2 also binds to the *H19* imprinted region altering regulation of the adjacent *Igf2* expression (Samaco et al., 2005). This co-regulation of the dispersed genes within a chromosomal region suggests that MeCP2 might regulate chromatin transcriptional loop domains (Murrell et al., 2004) and perhaps disrupts a mitochondrial gene transcriptional factory. Therefore, Rett Syndrome provides a strong case for how perturbation of the epigenome could reduce mitochondrial function.

Timothy syndrome, which presents with autism and Long QT syndrome, provides further evidence for connecting neurodegenerative disease with Ca^{++} regulation and thus mitochondrial function. Timothy Syndrome has been linked to mutations in the T-type voltage-gated $Ca_v1.2$ channel encoded by the *CACNA1C* gene, most commonly involving the G406R allele (Gargus, 2009). $Ca_v1.2$ shows its highest expression in the hippocampus, amygdale, and putamen. A survey of the *CACNA1H* gene, a close paralog of the Timothy syndrome Ca^{++} channel, in 461 autism DNAs revealed six new mutations. Functional studies of two of these mutant proteins, R212C and R902W, revealed extended Ca^{++} influx into the cytosol (Splawski et al., 2006). Cytosolic Ca^{++} levels are regulated by mitochondrial Ca^{++} uptake, driven by the mitochondrial inner membrane potential (ΔP). Excessive Ca^{++} uptake would limit ATP production, increase oxidative stress, and activate the mtPTP causing cell death.

Evidence is also accumulating implicating mitochondrial dysfunction in some forms of autism spectrum disorder (ASD), in addition to AS, TSC, Rett syndrome, FMR and Timothy syndrome. A subset of ASD patients is associated with chromosomal gene copy number variants (CNV). Ten percent of sporadic autism patients have CNVs, as compared to 3% of multiplex families and 1% of controls (Sebat et al., 2007; Zhao et al., 2007). A subset of these variants may coincide with important nDNA mitochondrial gene loci (Smith et al., 2008). Alterations in mitochondrial structure and function have been repeatedly observed in autistic patients (Correia et al., 2006; Filipek, 2005; Gargus and Imtiaz, 2008; Haas et al., 1996; Holtzman, 2008; Lombard, 1998; Oliveira et al., 2007; Poling et al., 2006), and alterations in the mtDNA have been observed in some cases of ASD (Fillano et al., 2002; Graf et al., 2000; Pons et al., 2004). The activity of the mitochondrial inner membrane Ca-regulated aspartate/glutamate carrier (AGC) gene, *SLC25A12*, and/or its expression have been reported to be increased in autistic patients, at least in part due to elevated brain calcium levels (Lepagnol-Bestel et al., 2008; Palmieri et al., 2008; Ramoz et al., 2004). *SLC25A12*-deficient mice show impaired myelination, confirming that alterations in AGC activity can affect neurological function (Hong et al., 2007). Since AGC regulates the increased flux of reducing equivalents into the mitochondrion, increased AGC activity would initially increase ATP production, but ultimately overload the ETC with electrons increasing oxidative stress and causing the loss of neuronal spines and synapses characteristic of autism pathology (Lepagnol-Bestel et al., 2008; Palmieri et al., 2008; Ramoz et al., 2004). Therefore, mitochondrial dysfunction may account for some forms of ASD.

The importance of mitochondrial ROS production in cell function and stem cell biology has been demonstrated in studies of mice in which the Bmi1 member of the Polycomb family

has been inactivated. The Polycomb family of transcription repressors mediates gene silencing by regulating chromatin structure. Bim1 is essential for the maintenance and self-renewal of both the hematopoietic and neuronal stem cells, and Bim1−/− mice have severe neurological abnormalities, alterations in hematopoietic cells, growth retardation, and shortened life span. Bone marrow cells from Bim1-deficient mice show an inhibition of mitochondrial ETC, reduced O_2 consumption, reduced ATP production, and increase mitochondrial ROS production. The increased mitochondrial ROS is a major factor for the reduced stem cell function. The reduction of the *Bim1* −/− induced ROS using N-acetylcysteine antioxidant is associated with the recovery of the bone marrow derived cells and partial restoration of thymic atrophy. In part, the effects of the increased mitochondrial ROS are due to activation of the DNA damage response pathway. This was confirmed by inactivation of the Chk2 gene which partially restored the normal phenotype (Liu et al., 2009). Therefore, genes central to stem cell function and thus development can be directly regulated by mitochondrial ROS signaling.

The mitochondrion also plays an important role in calcium homeostasis. In mice, neuronal spine formation and maintenance can be modulated by the inactivation of the mitochondrial anti-apoptotic protein, Bcl-w, and the glutamate receptor δ (Grid2), an excitatory Ca^{++} channel expressed in Purkinje cells. Bcl-w and Grid2-deficient mice develop enormously elongated mitochondria in their Purkinje dendrites indicating blocked mitochondrial fission. This is associated with aberrant dendrites, spines, and synapses and results in severe ataxia. Therefore, mitochondrial calcium not only regulates mitochondrial metabolism but also mitochondrial fission, directly affecting synapse formation, learning, and memory (Liu and Shio, 2008).

5.2. Altered Transcriptional Factories and Energy Deficits

While the above examples suggest the inhibition of mitochondrial function through alterations in the transcriptional regulation of individual chromosomal domains, the maintenance of the mitochondria likely also requires the coordinate expression of many mitochondrial loci dispersed across multiple chromosomes. These dispersed mitochondrial genes might require inter-chromosomal factories for coordinate expression. Therefore, we might expect that epigenomic defects that disrupt transcriptional factories might also be associated with mitochondrial dysfunction. The laminopathies could represent this class of epigenomic defect.

The laminopathies are caused by mutations in the *LMNA* gene, the product of which is involved in the production of the type V intermediate filament lamina that line the inside of the nuclear envelope, but are also found in the nucleoplasm. The lamina are produced from three genes: lamins A and C produced by alternative splicing from the *LMNA* gene, lamin B1 produced by the *LMNB1* gene, and lamins B2 + B3 produced from the *LMNB2* gene. The B-type lamins are ancient and constitutive and remain associated with the nuclear envelope at interphase and during mitosis. The A-type lamins (A/C) arose along with the metazoans, are expressed in association with differentiation, dissociate from the nuclear envelope during mitosis (Liu and Zhou, 2008), and a substantial portion are found centrally within the nucleus (Galiova et al., 2008).

The lamin A protein consists of a globular N-terminus domain, followed by an α-helical rod-like domain containing four coiled-coil repeats (1A, 1B, 2A, 2B), a nuclear localization sequence, an Ig-like domain, and a C-terminal domain which includes the end of the mature lamin A followed by a C-terminal pre-peptide extension ending in the sequence Cys-Ser-Ile-Met. In newly synthesized normal prelamin A, the Cys in the Cys-Ser-Ile-Met peptide is farnesylated by farnesyltransferase (FT) resulting in binding to the endoplasmic reticulum (ER). The ER metalloprotease, ZMPSTE24, then cleaves off the terminal Ser-Ile-Met

peptide, and the free Cys carboxyl group is methylated. ZMPSTE24 again cleaves prelamin A 15 amino acids N-terminal from the farnesylated Cys. This releases soluble lamin A to be imported into the nucleus where it is assembled with lamin B into the nuclear lamina as well as being located in the nucleoplasm. Lamin C encompasses the N-terminal 2/3 of the lamin A protein (Liu and Zhou, 2008). The lamin B proteins are also farnesylated, but not proteolytically processed. Hence, they remain membrane bound and diffuse along the ER into the nuclear envelope where they nucleate the assembly of the soluble lamin A and C polypeptides into the nuclear lamina.

Over 200 pathogenic mutations have been identified in the *LMNA* gene yielding a plethora of clinical phenotypes. These phenotypes can be recapitulated by the introduction of *Lmna* and *Zmpste24* gene mutations into the mouse, thus proving that lamin A and C defects cause these diseases (Stewart et al., 2007).

The pathophysiology of these diseases remains a mystery. A common finding among the *LMNA* mutations is the presence of highly distorted nuclei and marked repositioning of heterochromatin within the nucleus (Liu and Zhou, 2008; Park et al., 2009; Worman and Bonne, 2007). The nuclear lamina binds the Sun 1 and 2 proteins, which extend through the inner nuclear membrane, interact with the Nesprin-2 Giant and Nesprin 3 proteins that extend through the outer nuclear membrane, and which bind to the cytosolic actin cytoskeleton. Emerin, which interacts with lamin A, also links the nuclear envelope to the microtubule network and anchors the centrosome (Hale et al., 2008; Lee et al., 2007). LMNA-induced alterations in the cytoskeleton should alter the distribution and movement of mitochondria which are tethered to the cytoskeleton. Since treatment of cells with microtubule inhibitors alters mitochondrial OXPHOS activity and increases ROS production (Wagner et al., 2008), *LMNA* mutations could contribute to reduced mitochondrial function and increased ROS production.

Lamin A deficiency also results in redistribution of chromatin within the nucleus. In immortalized mouse embryo fibroblasts, 50% of the nuclear periphery is occupied by heterochromatin, but in *LMNA* −/− cells, the level of peripheral heterochromatin is significantly reduced. Moreover, the number of chromocenters is reduced in the nuclear interior of *LMNA* −/− cells and the heterochromatin clusters in larger internal nuclear aggregates. *LMNA* −/− cells also have smaller chromosomal domain areas than *LMNA* +/+ cells. Among the HP1α, β, and γ proteins important in heterochromatization, the HP1β develops chain-like aggregates. Treatment of *LMNA* +/+ or −/− cells with the HDAC inhibitor, Trichostatin (TSA), causes the areas of the chromosomal domains of *LMNA* −/− cell to increase and approach the size and distribution as those of *LMNA* +/+ cells and also restores the distribution of the HP1β and SC-35 foci (Galiova et al., 2008). Therefore, *LMNA* mutations that disorganize the chromatin domain structure and could result in loss of coordinate transcriptional control of the dispersed energy gene.

Consistent with this conjecture, lamin A mutations have been associated with an altered distribution and function of key transcription factors (e.g., c-fos, β-catenin, etc.) (Liu and Zhou, 2008; Pekovic et al., 2007; Pekovic and Hutchison, 2008), activation of the MAPK stress pathway (Muchir et al., 2007), and the Notch pathway (Scaffidi and Misteli, 2008). Lamin A alterations have also been associated with suppression of the Wnt and Mitf signaling pathways in epidermal stem cells (Espada et al., 2008) and of myogenin (*Myog*) expression in muscle cells. Increases in H3-K9me2 and failures to hypertrimethylate H3-K4 around *Myog* and the redistribution of H3-K27me3 away from the pericentric heterochromatin have also been observed (Hakelien et al., 2008). Therefore, lamin A appears to be important in maintaining an open chromatin conformation and thus the

sustaining of transcription, perhaps within transcriptional factories important for coodinate mitochondrial gene expression.

Patients with *LMNA* mutations have been classified into four classes based on clinical phenotypes (Liu and Zhou, 2008). However, *LMNA* mutations frequently exhibit pleiotrophy phenotypes and variable familial expressivity (Mercuri et al., 2005; Rankin et al., 2008). Class I laminopathies encompasses diseases of skeletal muscle and heart, including autosomal dominant (AD)-Emery-Dreifuss muscular dystrophy (EDMD), autosomal recessive (AR)-EDMD, AD-dilated cardiomyopathy 1A, and AD-limb girdle muscular dystrophy (LGMD). EDMD and LGMD *LMNA* mutations present with variable degrees of muscle weakness, cardiomyopathy, and contractures (Park et al., 2009). Cardiomyopathy patients are subject to cardiac conduction defects, sudden death, and dilated cardiomyopathy, with or without skeletal muscle weakness (Perrot et al., 2009; Wolf et al., 2008). EDMD mutations are distributed in lamin A from the N-terminal end through the Ig-like domain, but can be found elsewhere. DCM1A and LGMD1A mutations are found primarily in the coiled-coil protein domain (Liu and Zhou, 2008). Suggestive evidence that heart-muscle lamin A diseases are associated with mitochondria dysfunction comes for a boy who presented at six with delayed motor milestones, and proximal and truncal weakness. This progressed by nine years to severe, progressive cardiomyopathy necessitating heart transplant. His mother and brother had died at 31 and 8 years, respectively, of cardiomyopathy. Mitochondrial respiratory chain analysis of heart and skeletal muscle revealed a complex IV activity of 0.005 (normal being 0.014–0.034). Molecular studies failed to detect any of the known common pathogenic mtDNA mutations. Morever, nDNA studies revealed that the family harbored the common *LMNA* p.R644C missense mutation (Mercuri et al., 2005).

The Class II laminopathy involves AR-Charcot-Marie-Tooth (CMT) type 2B1, a peripheral neuropathy. The two *LMNA* mutations linked with AD-CMT2B1 are associated with mildly reduced nerve conduction, neuron demyelination, and axonal degeneration (Liu and Zhou, 2008), and both are adjacent to each other in the 2A coiled-coil domain (Liu and Zhou, 2008). Charcot-Marie-Tooth, Type 2A can also be caused by mutations in the nDNA-encoded mitochondrial fusion gene, mitofusin 2 (Zuchner et al., 2004)

Class III laminopathies encompasses the lipodystrophy syndromes and include AD-familial partial lipodystrophy, Dunnigan-type (FPLD2); AD-congenital generalized lipodystrophy type 2 (CGL2); and AR-mandibuloacral dysplasia. FPLD2 *LMNA* mutations are associated with loss of subcutaneous white adipose tissue (WAT) in limbs and the accumulation of WAT in the face, neck, and abdominal areas. The CGL2 *LMNA* mutations lead to diabetes with glucose intolerance, hepatic stenosis, hyperpigmentation, muscular atrophy, and hypertrophic cardiomyopathy (Araujo-Vilar et al., 2008; Liu and Zhou, 2008; Worman and Bonne, 2007). Women with FPLD2 from *LMNA* mutations can develop an array of fertility problems including polycystic ovaries, infertility, gestational diabetes, and preeclampsia (Vantyghem et al., 2008). Population variants in *LMNA* have also been associated with increased risk of diabetes (Duesing et al., 2008), and alterations in *LMNA* mRNA levels are observed in patients with diabetes and obesity (Miranda et al., 2008). FLPD mutations are often found in the Ig-like domain and the C-terminal region of the mature lamin A protein (Liu and Zhou, 2008).

A mitochondrial association with Class III laminopathies is supported by a study of cultured human fibroblast cell lines harboring six different heterozygous *LMNA* mutations (D47Y, L92F, L387V, R399H, L421P, and R482W) all derived from patients with insulin resistance and/or lipodystrophy. All of these cell lines were found by western blot to have a marked deficiency in the level of the mtDNA COII (COX2) protein but not the nDNA COX4

protein. These cell lines also showed increased ROS production which colocalized with the mitochondria (Caron et al., 2007).

All of these cells exhibit distorted nuclei have reduced proliferative capacity, increased tendency to generate senescent SA-β-galactosidase positive cells, and elevated prelamin A protein levels. Treatment of normal fibroblast cultures with the HIV anti-retroviral protease inhibitors indinavir and nelfinavir, which cause chemically-induced lipodystrophy syndromes, generated the same mitochondrial defects and cellular phenotypes as seen in the laminopathies (Caron et al., 2007). Furthermore, AIDS progression and drug-induced lipodystrophy have also been shown to be modulate mtDNA haplogroups (Hendrickson et al., 2008; Hendrickson et al., 2009).

Class IV laminopathies encompasses the accelerated aging syndromes, AD-Hutchinson-Gilford progeria syndrome (HGPS), AD-Werner Syndrome (WS), and AD-restrictive lethal dermopathy (Worman and Bonne, 2007). AD-HGPS individuals only live into their mid teens and exhibit an array of premature aging manifestations including ischemic heart disease, central nervous system problems, hearing loss, and insulin unresponsiveness (Korf, 2008; Merideth et al., 2008). *LMNA* mutations can also result in the later-onset Werner premature aging syndrome (Kudlow et al., 2007). Class IV *LMNA* mutations are primarily confined to the C-terminal end of the protein. The most common HGPS mutation is a synonymous mutation, p.G608G (Liu and Zhou, 2008), which exposes a cryptic splice site leading to a 150 nucleotide deletion in the transcript. As a result, 50 amino acids of the mature protein are deleted which eliminates the ZMPSTE24 proteolytic processing site for removal of the C-terminal prelamin A domain, while still retaining the C-terminal end of the lamin A protein with the Cys-Ser-Ile-Met sequence. The p.G608G mutation thus generates a novel protein, progerin, which remains attached to the ER and nuclear envelope membranes by its farnesyl group. This results in faulty assembly of the nuclear lamina, distortion of the nuclear shape, and a dominant negative gene action (Caron et al., 2007; Liu and Zhou, 2008; Scaffidi and Misteli, 2008). Since, the level of progerin has been found to correlate with the level of mitochondrial dysfunction in cells (Caron et al., 2007), the progeric laminopathies could also have a mitochondrial etiology.

In HGPS, the expression of progerin is also associated with reduced proliferative life span in cultured cells and increased telomere shortening rate. Telomeres, consist of thousands of copies of the TTAGGG repeat. They cap the ends of chromosomes and are maintained by the RNA-protein reverse transcriptase telomerase. The limited proliferative life span and rapid telomere decay of progeria and WS cells expressing porgerin can be ameliorated by introduction into these cells of the apoprotein of telomerase, TERT (Huang et al., 2008; Kudlow et al., 2008). Furthermore, lamin A has intrinsic affinities for binding DNA containing telomeric repeats (Shoeman and Traub, 1990) and telomeres are generally centrally localized within the nucleus of interphase cells (Scherthan, 2003).

WS can also be caused by mutations in the WRN helicase gene. The WRN helicase facilitates the opening of the ordered structure of the G-rich telomere sequences making it important in telomere maintenance and suppression of telomere sister-chromatid exchanges (Kudlow et al., 2007). Since *LMNA* mutations also cause WS, lamin A must be important in telomere decay. This creates a direct link between progeria and the mitochondrion. It is now clear that telomere decay is primarily due to mitochondrially-generated ROS which causes the oxidation and loss of telomere repeats (Parrinello et al., 2003; Passos et al., 2007; Passos and von Zglinicki, 2005; Richter et al., 2007; Richter and von Zglinicki, 2007; Saretzki et al., 2003; Saretzki et al., 2008; von Zglinicki, 2002; Yang et al., 2008). In cells expressing telomerase, increased ROS production activates a Src family tyrosine kinase located in the nuclear periphery which phosphorylates TERT. This causes TERT to be exported from the

nucleus and imported into the mitochondrion where it reduces ROS production, protects mtDNA from damage, and regulates apoptosis in a Bcl-2 dependent fashion (Ahmed et al., 2008; Del Bufalo et al., 2005; Haendeler et al., 2003; Haendeler et al., 2004; Santos et al., 2004). Since non-stem cells do not express TERT, the increased telomere shortening of progeria cells must be due to increased ROS production due to mitochondrial dysfunction.

6. PERSPECTIVE

The similarity in symptoms between mitochondrial and epigenomic diseases suggests that they have a common pathophysiology. Is so, alterations in mitochondrial function will have important effects on the epigenome and alterations in the epigenome will have significant effects on mitochondrial function (Borrelli et al., 2008).

The epigenome has been hypothesized to provide the interface between the environment and the regulation of nDNA gene expression (Feinberg, 2007, 2008). The most important factors in an organism's environment are the availability of calories and the demands made on the organism for the use of those calories. The mitochondrion lies between availability of environmental calories and their conversion to usable energy. This occurs by the conversion by the mitochondrion and glycolysis of energy rich compounds such as carbohydrates and fats into ATP, acetyl-CoA, SAM, and NADH. ATP, acetyl-CoA, SAM, and the NADH/NAD^+ ratio, in turn, are the high-energy substrates that drive the modification of the epigenome. Prevalent calories increase the ATP, acetyl-CoA, SAM and NADH, causing the modification of histones, the opening of the chromatin, increased gene expression, and the stimulation of growth and reproduction. Reduced calorie levels deplete ATP, acetyl-CoA, SAM, and increase NAD^+, reducing histone modification, compacting the chromatin, and reducing gene expression, growth and reproduction.

The mitochondrial genome encompasses over 1500nDNA genes plus the mtDNA genes. The nDNA mitochondrial genes plus the glycolysis genes are dispersed throughout the chromosomes. Therefore, the efficient exploitation of environmental calories requires the coordinate expression of the bioenergetic genes according to the availability of calories and the energy requirements of the organism. Procedures must then exist for regulating the expression of the nDNA bioenergetic genes in relation to calorie availability. The large number and random distribution of the bioenergetic genes would require both *cis* and *trans* regulation. The *cis* regulation of nDNA bioenergetic genes could occur within chromatin loops and be influenced by imprinting. The *trans* regulation of nDNA bioenergetic genes would require inter-chromosomal regulation by diffusible transcription factors or by the interaction of related genes through tertiary chromatin structures such as transcriptional islands and lamin A associated interactions.

Mutations in mtDNA or nDNA mitochondrial genes diminish energy production causing energy deficiency diseases. These preferentially affect the tissues most reliant on high energy flux: brain, heart, muscle, renal, and endocrine systems. Severe alterations of mitochondrial energy production should alter ATP, acetyl-CoA, SAM, and NADH levels and thus perturb the epigenome and the coordinate expression of bioenergetic genes.

Similarly, certain alterations in the epigenome should alter the coordinate expression of nDNA bioenergetic genes, thus diminishing bioenergetics and resulting in symptoms in the high energy flux tissues. Coordinate expression of bioenergetic genes could be perturbed through either *cis* or *trans* regulation systems. Alterations in the structure of chromatin loop domains should cause aberrant *cis* gene expression and are most apparent in imprinting diseases such as BWS, AS, PWS, etc. Alterations in the epigenome that affect *trans* interactions include mutations in *trans* acting factors such a PGC-1α, FOXOs, MeCP2, but

also could be affected by alterations in the overall chromatin arrangement in the nucleus as seen in the laminopathies.

Therefore, mitochondrial diseases and many epigenomic diseases may have a common pathophysiology, bioenergetic failure. If this continues to be shown to be true, then it will have major implications for the diagnosis and treatment of the common complex diseases associated with mitochondrial and epigenomic dysfunction.

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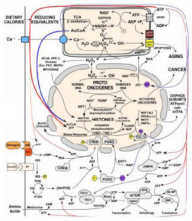

Figure 1. Energetic Regulation of the Epigenome

Mitochondrial energetics links the epigenome to calorie availability through high energy intermediates and redox reactions. The mitochondrion is at the top of the figure, the nucleus in the middle, and the cytosol in at the bottom. Calories as reducing equivalents enter the cell and mitochondria at the upper left resulting in generation of acetyl-CoA, reduction of NAD^+, and ATP. Energy then flows from top to bottom. ATP drives the phosphorylation of nuclear and cytosolic signal transduction proteins, acetyl-CoA acetylates chromatin and signal transduction proteins, and NAD^+ acts through the Sirtuins to deacetylate proteins. Abbreviations: AcCoA = acetyl-CoA, NAD^+ = nicotinamide adenine dinucleotide (oxidized) & NADH (reduced), mtPTP = mitochondrial permeability transition pore, GPx1 = glutathione peroxidase 1, mCAT = mitochondrially-targeted catalase, PARP = poly ADP ribose polymerase. Other abbreviations are described in the text.