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Nanoplateforms of Mitochondrial Dysfunction Oxidative Stress in Cancers

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Abstract

Mitochondrial major functions are ATP synthesis, regulation of Ca2+ homeostasis, generation of reactive oxygen species and programmed cancer cell death. They play as essential significant role in the generation of cell activation nano signals via released reactive species, as well as small GTPases, mitogen activated kinases located in the outer and inner membranes of cancer cell mitochondria. Several mutations in mitochondrial DNA led to synthesis of malfunctional proteins characterized by impaired energy metabolism due to presumed genetically based oxidative phosphorylation (OXPHOS) dysfunction. These proteins are potential nanoplatforms to indicate distinct cellular/organelle pathological changes. Several mitochondrial metabolic protein nanoplatforms screen the mitochondrial dysfunction induced oxidative damage to DNA, electron transport chain and structural proteins as etiologically important events in development and progression of mitochondrial driven cancer diseases. Literature data suggests several mechanisms of mitochondrial dysfunction indicated by protein and ROS nanoplatforms. One of the main challenges in using nanoplatforms seems to assess timely the functional/structural modulation to mitochondrial proteins and damage to DNA as potential causes or consequences of cancer diseases. Upon mitochondria dysfunction in oxidative stress mechanistic issues are resolved, use of mitochondria as a pharmacological nanoplatform target holds promise in the treatment of diseases. This paper presents a glimpse on application of mitochondrial nanoplatforms with newest supporting protein-based mechanisms of mitochondria in oxidative stress, inflammatory and apoptosis-based diseases, clinical management guideline and therapeutic failure if any.

Keywords: Mitochondria; Chemotherapeutics; Oxidative Stress; Lipid Metabolism; Oncometabolites

Abbreviations: OXPHOS: Oxidative Phosphorylation; TCA: Tricarboxylic Acid; SDH: Succinate Dehydrogenase; FH: Fumarate Hydratase; ROS: Reactive Oxygen Species; ETC: Electron Transport Chain; NOS: Nitric Oxide Synthase; TRAP-1: TNF Receptor-Associated Protein-1; HSP90: Heat Shock Protein 90; AML: Acute Myeloid Leukemia; IONP1: Ion Peptidase-1; PCR: Polymerase Chain Reaction; DHPLC: Denaturing High Performance Liquid Chromatography; DGGE: Denaturant Gradient Gel Electrophoresis; TGGE: Temperature Gradient Gel Electrophoresis; TTGE: Temporal Temperature Gradient Gel Electrophoresis; SSCP: Single-Strand Conformation Polymorphism; RFLP: Restriction Fragment Length Polymorphism; ASO: Allele Specific Oligonucleotide; FTICR-MS: Fourier Transform Ion Cyclotron Resonance Mass Spectrometry; ESI-TOFMS: Electrospray Ionization Time-of-Flight Mass Spectrometry; MERRF: Myoclonic Epilepsy and Ragged Red Fibers; PEO: Progressive External Ophthalmoplegia; POLG1: Polymerase Gamma; MRS: Magnetic Resonance Spectroscopy; TNBC: triple negative breast cancer; TFAM: Transcription Factor A Mitochondrial DNA; POLRMT: Mitochondrial RNA Polymerase; OMM: Outer Mitochondrial Membrane; CGN: Cerebellar Granule Neuron; ISP: iron-Sulfur Protein; LHON: Leber Hereditary Optic Neuropathy

Introduction

Mitochondria are unique energy storage organelles. Mitochondrial dysfunction and oxidative stress play a role in promoting tumor propagation and metastasis activity through ROS production and oncogenic transformation. Excessive mitochondrial oxidative stress triggers cell death in both transformed and non-transformed cells through proliferation, migration/invasion, angiogenesis, inflammation and cancer cell immnoescape towards adoption of new environment. As a result, oxidative stress causes malignant transformation to metastasis, dormancy and resistance to chemotherapeutics. In this process, ROS species and several proteins participate that serve as signals

on nanoplatforms to detect physiological stresses and changes in metabolic states of the cell [1]. These signals on nanoplatforms respond to new metabolic requirements by controlling ATP levels, lipid metabolism and/or promoting oxidative signaling during cancer diseases, cell migration, inflammatory responses, nutrient starvation, low oxygen, and oxidative stress or tumor progression during other diseases [2]. In adaptive mechanism, cancer cell mitochondria sustain tumor dissemination and optimize the production of oncoproteins, oncometabolites, energy, Ca_{2+} metabolism and generation of reactive species during cancer progression [3]. Mitochondrial functions proteins perhaps control the cellular responses to oncogene stimuli and regulation of cellular metabolism [4]. Mutations in mitochondrial enzymes of the tricarboxylic acid (TCA) cycle, such as succinate dehydrogenase (SDH), fumarate hydratase (FH), and isocitrate dehydrogenase 1, and 2 suggests that mitochondrial dysfunction enhances tumor growth or promotes cancer progression. Mitochondrial function, including oxidative phosphorylation (OXPHOS), is essential for cancer cell viability because the elimination of cancer cell mitochondrial DNA (mtDNA) reduces their growth rate and compromises tumorigenesis. These physiological processes affect cancer growth by modulating biosynthetic and cell signal pathways, transcription factors. Cancer cells have high anerobic glycolysis capacity znd active metabolic and proteotoxic stress. Presently, mitochondrial stress response targeting serves as an anti-cancer therapeutic method based on tumor cell growth suppression and prevention of metastasis.

Mitochondrial Electron Transport Chain and Tumor Initiation

Elevated reactive oxygen species (ROS) byproduct of OXIPHOS due to defective ETC activity drives towards more oxidized state in signal transduction cascades regulating cell proliferation, differentiation, oncogenic transformation and death [2]. The excessive ROS can cause DNA mutations in ETC genes that may contribute to genomic instability. Various cellular processes suggest a tight control for ROS production and function. There are at least three distinct signal mechanisms for ROS production in malignant transformations: 1) in cancer cells mutations in superoxide and SDH, FH and ICDH1 and oncometabolites 2, L- and D-2-hydroxyglutarate, succinate, fumerate, all these alter the signal transduction and mutation gene-expression regulation of hypoxia-inducing factor (cancer epigenome) towards low oxygen metabolic remodeling of malignant transformation. These accumulated oncometabolites inhibt Jumonji C domain-containing histone lysine demethylases; and suppress KG-dependent 10-11 translocation methylcytosine nucleotide dioxygenase that drives oncogenic transcriptional program. Thus high superoxide, ROS and oncometabolites contribute to malignant transformation (biosignal); 2), ROS are produced by various oxidases including lipoxygenases, cyclooxygenases, xanthine oxidase and nitric oxide synthase (biosignals); and 3) mitochondria are the most important source for ROS in every cell type, where 1-5% of the transported electrons are diverted to the formation of superoxide (O_2•-) instead of water [5]. Thus, accumulated mitochondrial oxidative stress causes metabolic re-programming leading to enzyme defects as observed mutations in SDH, FH, ICDH and ROS sensitive bio signal nanoplatforms to monitor the mitochondrial electron transport chain dysfunctions in human tumors.

Defects in the function of the mitochondrial electron transport chain (ETC) have been monitored as remarkable characteristics of several pathological conditions ranging from ischemia-reperfusion damage [6], diabetes [7], hypertension [8], liver damage by hepatitis B [9], allergic inflammation [10], cancer [11], cardiac impairment due to aging [12], neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis [13], among others. Mitochondrial nanoplatforms may detect mitochondrial dysfunctions in above pathological conditions. A common feature among these pathological conditions is the increased generation of ROS, which in some cases arise not only from the mitochondrial ETC but from other biosignal sources like NADPH oxidases (Nox) enzymes, cytochrome P450 enzymes, cyclooxygenases or uncoupled nitric oxide synthase (NOS) [14]. Therefore, ETC dysfunction during these pathologies has been monitored using biosignal nanoplatforms as ROS attack on the different components of the ETC. Furthermore, despite the prominent role attributed to mtDNA mutations in mitochondrial dysfunction, the direct damage by ROS on membrane lipids and proteins may be more relevant biosignals since it has been observed by nanoplatform experiments that accumulation of damage in ETC components is not codified by mtDNA [15].

Usually, it is assumed that ROS react preferentially with the bio signal molecules on nanoplatforms surrounding their generation site due to the short lifetimes of most of the radicals. For example, the steady-state concentration of hydroxyl radical (OH•) is practically zero because it reacts with very high-rate constants with almost every type of biomolecule [16]. In contrast, superoxide radical (O_2•-) is far less reactive with non-radical species and cannot cross membranes due to its negative charge. However, its reactivity and membrane permeability depend on the pH of the nanoplatform environment. Thus, at low pH values hydroperoxyl radical (HO_2•), the protonated form of superoxide, can cross the membranes more readily than O_2•- given its uncharged nature [16]. Hence, the low pH value generated by membrane potential in the intermembrane space might contribute to the formation of HO_2• from extra-mitochondrial sources to enhance the deleterious effects of non-mitochondrial-generated O_2•-. It has also been proposed that O_2•- can indirectly exert damaging effects on mitochondrial function through the opening of the mitoKATP channels, which may lead to increased K_+ influx, matrix alkalinization, swelling and ROS production [17]. Also, extra-mitochondrial-generated O_2•- has harmful effects on the ETC through its combination with NO• to form ONOO-, which can cause damage to respiratory complexes [18] possibly via tyrosine

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nitration [19]. Therefore, mitochondrial ETC dysfunction due to unregulated production of O_2•- by extra-mitochondrial bio signal systems such as Nox enzymes, cyclooxygenases or uncoupled NOS, may exacerbate and/or contribute to the loss of homeostasis observed in many of the pathological conditions mentioned above. For this reason, one of the main challenges in using mitochondrial nanoplatforms is to evaluate the exact contribution of the different extra-mitochondrial bio signal sources in ETC dysfunction during the development of diseases.

Mitochondrial ROS may be central in the cell death transduction pathways. Most investigators believe that most of the oxidants are produced by electron chain transport. The accumulation of high levels of ROS would induce necrosis, while programmed cell death (apoptosis) would be predominant in the presence of low levels of ROS. The ubiquinone site as nanoplatform in complex III appears as the major source of mitochondrial ROS production as this site catalyzes the conversion of molecular oxygen to O_2•-, which can lead to the formation of other potent ROS such as hydrogen peroxide (H_2O_2) and OH•. The release of cytochrome c must lead to a breakdown of the mitochondrial electron flow downstream of the ubiquinone site which in turn would result in an increased generation of ROS [20]. The decision of a cell to undergo apoptosis is mediated by a complex integration of signal transduction pathways [21] (Figure 1). Rho GTPases have been implicated as bio signals in the apoptosis of many cell types, but the mechanism by which they act is not fully understood. Several groups have reported both positive and negative involvement of Rho proteins in apoptotic program, depending on the cell line investigated. Thus, human RhoA, RhoC, Rac1, Rac2, and Cdc42 proteins have been involved in the induction of apoptosis in diverse cellular systems, including fibroblasts [22], thymocytes [23], neurons [24], and epithelial cells [25].

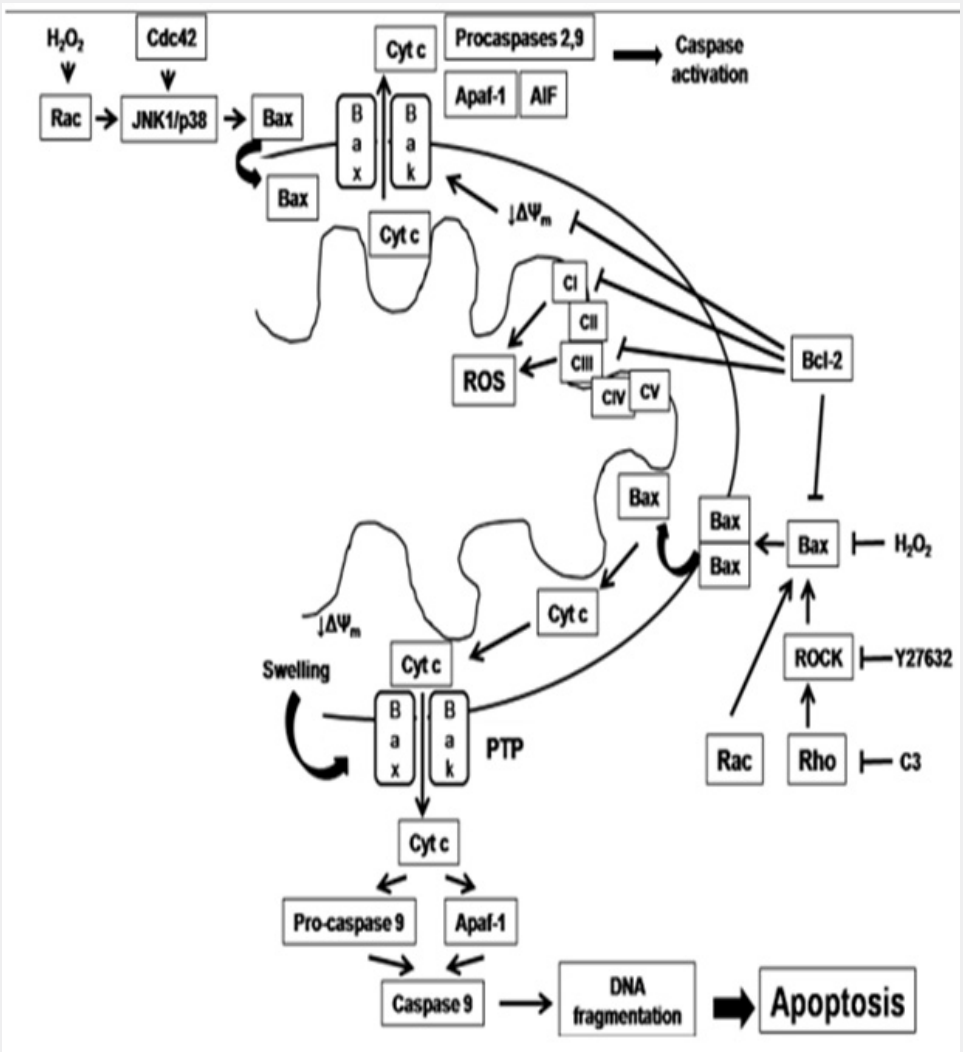

Figure 1: Model of the bio signal pathway of Rho protein induced apoptosis on mitochondrial nanoplatform.

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Tumor Growth

i. Mitochondrial enzymes for amino acid, fatty acids, androgen, estradiol synthesis in cancer cells support rapid cell division and membrane integrity in breast and prostate tumor progression as oncogenic factors for genetic alterations and metabolic rewiring.

ii. Major changes happen to be hypoxia, glucose and NADPH deficiency in tumor cell mitochondria to cause stress on TCA cycle intermediates needed for amino acid, nucleotides, lipids. So, mitochondria in tumors utilize lactate, serine, glycine and fatty acid oxidation in the pyruvate deficient acidosis conditions.

iii. In hypoxic conditions, mitochondria activate reductive carboxylation of glutamine metabolism for anaplerotic circuitry of TCA intermediates that render cancer cells reliant on reductive carboxylation of glutamine-derived α-ketoglutarate to fatty acids and redox balance for proliferation.

iv. Serine hydroxymethyltransferase-2 for serine catabolism provides NADPH/NADP while phosphoglycerate dehydrogenase for serine synthesis enhances ketoglutarate to support cancer growth.

v. Tumor cells secrete lactate and absorb it to fuel OXIPHOS at low glucose conditions.

vi. Cytosolic lactate makes pyruvate by LDH and in mitochondrial pyruvate makes acetyl-CoA by pyruvate dehydrogenase.

vii. In cancer cells, acetyl-CoA synthesizes fatty acids, isoprenoids, cholesterol to support proliferation in stressful conditions.

viii. Mitochondrial pyruvate carriers mediate pyruvate oxidation as on-off switch between OXIPHOS and glycolysis to support proliferation in breast, prostate, colon and liver cancers.

Metastasis and Survival

In nutrient starved, low oxygen and cytotoxic oxidative stressed harsh conditions leads to cancer cell death. However, metastatic cells easily evade these stressors to cause irreversible mitochondrial damage. Above all, malignant cells acquire alterations to maintain mitochondrial integrity and immortality. Hypoxia affects survival and metastasis in low oxygen fluctuating hypoxia-inducing conditions by oncogenic signaling pathways during tumor progression. These hypoxia-inducing factors HIF-1 trigger ROS production, proliferation, angiogenesis, migration, invasion, poor patient prognosis and therapeutic resistance. In cancer cells, the HIF-1 activates glucose transporters, hexokinase-2, pyruvate dehydrogenase kinase to accelerate glycolysis. HIF-1 reduces electron transport chain or mitochondriqal respiration by inhibiting pyruvate dehydrogenase to prevent oxidative stress. HIF-1 transcription is increased by mutations in TCA cycle SDH and FH genes to accumulate TCA cycle succinate and fumerate intermediates. These intermediates inhibit prolyl hydroxylase to disrupt HIF-1 activity. Cancer cells also activate HIF-1 to accelerate glycolysis and more ATP or relief from oxidative stress.

Mitochondrial Protein Quality Control in Cancer

Cancer cells evade environmental stress by monitoring the defensive mitochondrial repair defects before their cell death trigger. Initially, mitochondrial chaperones and proteases (mtUPR enzymes) degrade misfolded proteins to form protein aggregates in mitochondria by proteotoxic oxidative-hypoxic stressors. The heat shock protein 90 (HSP90) and TNF receptor-associated protein-1 (TRAP-1) chaperones are overexpressed in glioma cell mitochondria to control protein folding quality in tumor progression, survival and maintenance of OXIPHOS capacity during hypoxia and low glucose conditions. TRAP-1 induces HIF-1 stabilization and reduces mitochondrial respiration to confer tumorigenic potential.

Mitochondria dynamics in cancer cells promote mitophagy and remove damaged mitochondria during cytotoxic stress and survival. During this mitochondrial damage, proapoptotic factors release out to induce apoptosis and turnover older to new cells. Higher Ion peptidase-1 (LONP1) and Caseinolytic mitochondrial matrix peptidase proteolytic subunit (C1pP) amounts are in matrix of human colorectal cancer, glioma and melanoma as correlates of proliferation, high tumor grade, poor patient prognosis and survival. Low oxygen induced lower LONP1 expression arrests proliferation by OXIPHOS reduction and degrade misfolded ETC subunits. Thus, LONP1 impairs mitochondrial respiration, suppresses cell proliferation and cell metastatic dissemination, increases oxidative stress in human acute myeloid leukemia (AML). The C1pP expression is increased in breast, lung, liver, prostate, thyroid and melanoma cancers. In fact, LONP1 and C1pP genes share OXIPHOS, amino acid and lipid metabolism to maintain proteins in cancer cells to survive and evade the metabolic, oxidative and cytotoxic stress depleted.

Mitochondrial Dynamic Changes in Cancer

Continuously, hormones and cell signaling pathways alter cancer cell mitochondrial dynamics during tumor progression and survival in stress. The mitochondria change their shapes by fusion mitofusin (Mfn) 1 and 2 and OPA1 proteins and fission dynamin protein-1, mitochondrial fission factor proteins after lipid oxidation and mtDNA mutations in mitophagy process in liver, colorectal, brain, lung, breast cancers. Above proteins regulate mitochondrial pyruvate carrier in oncogenic pathways:

i. ERK1/2 signaling pathways responsible for MAPK-transformed tumor growth in melanoma and pancreatic cancers.

ii. CDK5 activates dynamin protein-1 phosphorylation to show poor outcome in glioblastoma cancer.

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iii. PI3K-Akt signaling in fragmented mitochondrial networks.

iv. Increased dynamin protein-1 expression or activated fission in lymph node metastasis in breast, thyroid, brain, prostate cancers.

v. Androgens hormones influence prostate cancer cell survival by androgen-receptor upregulated signaling in mitochondrial fission dynamics.

vi. The dynamin-1 protein enhances prostate cancer cell proliferation but weakens cell survival in hypoxic-oxidative stress, autophagy through voltage-dependent anion channel-mitochondrial pyruvate translocation carrier complex and TCA cycle rewiring.

vii. The dynamin-1 protein expression activates MFN2 downregulation to promote tumor survival or cancer related mortality through fragmented mitochondria in triple negative breast cancer (TNBC) cell mitochondria in hypoxic stress.

viii. The dynamin-1 receptor protein activates receptor MFF-VDAC complex protein phosphorylation through AMP-Protein Kinase in Myc targeting MFF and overexpressing it to induce mitochondrial fission, cell death in malignant primary and metastatic cancers. Thus, MFF upregulation and repression limits tumor growth by impairing cell division and loss of self-renewal.

Mitophagy in Cancer

Autophagosomes remove damaged mitochondria during hypoxia, nutrient deficiency and DNA damage in tumors by continued mitophagy. In case of mitophagy defects, dysfunctional mitochondria accumulate or excessive mitophagy induces loss of functional mitochondria by mitochondrial fission resulting with tumor cell death. Several mechanisms describe mitophagy:

i. An AMPK pathway initiates autophagy by unc-51, ULK-1 or TG1 (autophagy activating kinase-1 but AMPK inhibits rapamycin complex-1 (mTORC1). The absence of ULK1 in cancer cells does remove defective mitochondria and tumor cells die with oxidative stress-induced cell death by excessive lipid peroxidation.

ii. PTEN-induced kinase-1/ Parkin-mediated depolarized mitochondria accumulates PINK-1 on outer mitochondrial membrane to catalyze mitochondrial protein ubiquitination by E3 ubiquitin protein ligase and delivering defective mitochondria to autophagosomes.

iii. Parkin increases oxidative metabolic levels and inhibits aerobic glycolysis by p53 tumor suppressor during mitochondrial fission.

iv. Parkin binds to ubiquitin and degrades MFN2 (PINK1) during melanoma tumor formation and metastasis. The PINK1 silencing induces ROS overproduction to reduce lung cancer cell migration and its invasion capacity otherwise Parkin-deficient breast cancer cells show low proliferation and metastasis potential.

v. Many receptors NIX, BNIP3 and FUNDC1 bind to dynamin DRP1 on outer mitochondrial membrane to enhance mitochondrial fission during mitochondrial fission in hypoxic regions in glioblastoma for cancer stem cell maintenance, cell survival. The loss or inhibition of NIX slows down proliferation by redox homeostasis in pancreatic ductal adenocarcinoma.

vi. The BNIP3 inhibition reduces mitophagy in hypoxic adenoid cystic carcinoma invasion. Cisplatin promotes BNIP3-NIX co-upregulation to support mitophagy in lung cancer cells and depletes FUNDC1 expression to inhibit cell proliferation in cervical and colorectal cancers.

vii. Parkin protein prevents mitochondrial fission and fragmentation by dynamin DRP1 ubiquitination.

Cell Death Regulation

i. Cancer cells struggle till highest mitochondrial integrity threshold and slowly die (apoptosis) and finished (necrosis) through common stress response pathways and survival promoting B-cell lymphoma BCL-2 proteins against oxidative stress death. Mitochondrial fragmentation network enhances mitochondrial threshold for cell death, tumor expansion, metastasis and drug resistance. It all happens in a sequence of 1. Pro-apoptosis and antapoptosis balance due to mitochondrial permeability loss and induced targeting BH3 downstream cell-death proteins such as antiapoptotic BCL-2, BCL-XL, MCL1 regulator proteins (decreased mitophagy) and pro-apoptotic BAX, BAK proteins and upstream BAD, BIM, PUMA, BID, NOXA regulator proteins, to sense apoptosis and membrane permeability.

ii. Anti-apoptosis BCL-2 proteins (BCL-XL and MCL-1 complex) bind Parkin and stop Parkin translocation to depolarized mitochondria (fragmented across permeable outer membrane) while BH3 proteins enhance Parkin translocation.

iii. Molecular chaperone HSP60 enhances tumor growth. The HSP60-BAX upregulation (low HSP60 expression) due to stress-induced mitochndria damage quickly depletes mtDNA activity (BAX mitochondrial accumulation and cytochrome C caspase activation) to induce apoptosis and pro-apoptotic p53 protein function to prevent cancer cell death.

iv. Chaperone HSP10 overexpression accumulates anti-apoptotic BCL-XL and BCL-2 but reduces pro-apoptotic BAX.

v. Chaperone HSP90 inhibits cytochrome c-mediated protease cascade.

vi. Mitochondrial cyclophilin-D bound HSP90/60 promotes tumor growth, and its disruption causes caspase-dependent apoptosis.

vii. HSP27 overexpression delays caspase activation in

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etoposide treated cytotoxicity in human leukemia.

viii. High HSP70 inhibits mitochondrial BAX translocation, TRAP1 expression (silencing TRAP1 phosphorylation) and opens mPTP by apoptosis inducing drug to prevent stress-induced cell death. PINK1 protein phosphorylates TRAP1 and slows cytochrome c loss from mitochondria to protect cells from stress.

ix. BAX-Dynamin DRP1 colocalizes to reduce mitochondrial fission and caspase-dependent cancer cell death in autophagy.

x. In MFF deficient prostate cancer, AMPK signaling pathway and dynamin DRP1 depletion causes autophagy. The gene silencing or drugs inhibit autophagy and enhance caspase-dependent cell death.

Mitochondrial DNA in Cancer

Circular 16569 bp sized mitochondrial DNA encodes 13 ETC OXIPHOS proteins, two rRNA and 22 tRNAs. Mitochondrial DNA homeostasis is balanced by mtDNA repair and replication, mt DNA copy number alteration, mtDNA mutations and regulation of transcription-translation of mtDNA in tumorigenesis, tumor survival during dissemination and metastasis. The oxidative damage and mtDNA replication errors cause mutations. Thus, mtDNA integrity is related to mitochondrial function. So, mitochondrial dynamics (mitochondrial fission-fusion) and mitophagy (mitochondrial stress response) maintain mtDNA integrity, copy number, shape by fission-fusion processes to remove damaged mtDNA and accumulated mutations in high stressed conditions. Thus, increased mtDNA damage by mitochondrial fusion and reduced mitophagy produce bioenergetic defects of metabolic disorders and cell death.

Mitochondrial DNA mutation and Copy Number in Cancer

Mitochondrial DNA is most abundant in ovarian and lung adrenocarcinoma cancers and least abundant in myeloid, bladder, breast, kidney cancers. These mutations show specific patterns:

i. The low mtDNA content, heteroplasmic single nucleotide variant or D-loop mutations and copy number reflect the high cancer risk of lymphoma, breast cancer and colorectal cancer patients.

ii. The mtDNA mutations in 16S rRNA, ND2 and ATPase 6 genes reflect breast tumor small deletions and insertions in coding and non-codng regions.

iii. Synonymous and non-synonymous mtDNA mutations regulated by mtDNA repair in non-oncogenic mutations to keep tumor energy metabolism up in stressed conditions in kidney tumorigenesis.

iv. Low mtDNA deletions in dysfunctional mitochondria and apoptosis sensitized tumors. It helps to remove cancer cells having large scale mtDNA mutations during early tumor progression.

Mitochondria DNA Transcription and Translation

The role of mitochondrial transcription and translation in Mito ribosomes during cancer progression includes:

i. The mitochondrial gene regulation by chemical modification in heavy strands after inhibition of mitochondrial transcription and translation to proteins in Mito ribosomes affects cancer progression and metabolism.

ii. Mitochondrial DNA transcription factor A (TFAM), mitochondrial RNA Polymerase (POLRMT), mitochondrial transcription B1, B2 factors facilitate transcription in cancer. IMT1 inhibitors of POLRMIT sensitive OXIPHOS system inhibit mtDNA expression and OXIPHOS in tumors.

iii. The G1 arrest and growth inhibition through ROS-induced JNK/38 MAPK signaling leads to downregulation of TFAM in lung cancer cells.

iv. TFAM inhibition induces apoptosis and increases cisplatin sensitivity to mtDNA transcription in non-small lung cancer treatment.

v. All above antitumor effects of mitochondrial transcription inhibitors increase mtDNA gene expression to make more cellular metabolites by inhibiting mtTFAM downregulation for resistance in tumors.

vi. Orthogonal RNA sequencing shows lower mitochondrial RNA levels in breast, esophageal, head-neck, kidney cell, liver cancers.

vii. mitochondrial DNA copy number and lower mitochondrial RNA expression compensates for low mitochondrial RNA transcript levels.

viii. The abnormal translation (altered initiation, elongation mtEF4 factor, termination, ribosome recycling, translation factors) of mitochondrial encoded proteins, mtDNA polymerase in OXIPHOS system and gene mutations or deletions may cause apoptosis in leukemia cancer progression through lower cellular redox, mtRNA expression. Some of the above events may serve as nanoplatforms in oxidative stressed cancer detection and monitoring.

Mitochondrial Oxidative Stress Cancer and ROS induced Immunoescape

During oxidative stress, reactive oxygen species (ROS) are formed in mitochondria and mediate proliferation, migration/invasion, angiogenesis, inflammation and immunoescape in cancer cells to adapt to the stressed environment. ROS induces immunosuppression through immune cells, M2 macrophages, dendritic cells and T-cells to mitigate oxidative stress. Stress specific genome instability (replicative and mitotic stress), hypoxia (metabolic stress and angiogenesis), ROS production (mitochondrial stress) may cause carcinogenesis to support

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malignant behavior. Mitochondrial Lon-ROS supports cell proliferation, migration, angiogenesis, resistance towards apoptosis, inflammatory cytokine formation, mtDNA/Evs to escape immunosupressive environment in cancer. ROS-modulating anticancer immunotherapies show anticancer effects to avoid immunoescape and recurrence. In the next section, mitochondrial ROS signaling is described during cancer progression.

Rho Family GTPases in Mitochondria in Cancers

The Rho family GTPases are monomeric G-protein bio signals. These interact with intracellular target proteins or nanoplatform effectors to trigger a wide variety of cellular responses. Several responses may be the reorganization of the actin cytoskeleton, membrane trafficking, cell cycle progression, gene transcription, adhesion, migration, metastasis, and cell survival [26]. The three most studied Rho family member proteins as bio signals are RhoA, Rac, and Cdc42. Western blot analysis indicated the localization of Cdc42, Rac1, and Ras proteins in the mitochondrial fraction of pancreatic beta cells [27]. Besides, the presence of the Miro proteins (for mitochondrial Rho) has been identified as bio signal. Miro family members (1 and 2) function in a novel pathway that integrates cell bio signaling with mitochondrial dynamics and functions. These bio signal proteins are localized at the outer mitochondrial membrane (OMM).

Both bio signal proteins consist of 618 amino acid residues and were found to be 60% identical to each other [28]. Miro proteins are present in yeast (Gem1p) [1], Drosophila (dMiro) [29], and mammalian cells as well [28]. They have two potential Ca_{2+} binding domains, so called EF-hands. Functional EF-hand motifs exposed to the cytoplasm would be able to sense changing cytosolic calcium levels, whereas localization of these motifs to the mitochondrial matrix could allow Miro to monitor organellar calcium levels [1]. In neurons, Miro protein supports the distribution of mitochondria to the dendrites close to the Ca_{2+} entry sites and promotes the calcium bio signal propagation to the mitochondria [4]. The transport of mitochondria to specific neuronal locations is critical to meet local cellular energy demands and for buffering intracellular calcium levels. Miro1 and the kinesis adaptor Grif-1 play an important role in regulation of mitochondrial transport in neurons through the movement along microtubules. Thus, Miro1 is a key determinant of how energy supply is matched to energy usage in neurons [30].

Rho Proteins and Apoptosis in Cancer

In cardiomyocytes, RhoA activation bio signals act through effector Rho kinase to induce p53-mediated increases in the level of activated Bax protein and an increase in the amount of Bax associated with the mitochondria. Over time, however, Bax up-regulation appears to be sufficient to shift the balance in Bcl-2 family protein expression, induce mitochondrial permeabilization, facilitate cytochrome c release, initiate activation of caspase-9 and -3, and ultimately induce DNA fragmentation and cell death. The sustained RhoA activation (48h) can also increase the mitochondrial distribution of Bax, and increased RhoA bio signal protein activity following 'myocardial infarction'. It suggests that RhoA bio signal activation could play a role in ischemia/reperfusion-induced cell death [31]. In addition, the involvement of RhoA protein in hypertrophy of neonatal ventricular myocytes has been established [32]. Cultured cerebral cortical neurons undergo mitochondria-mediated apoptosis upon exposed to phenylalanine effector. The effector induces the RhoA/ROCK activation. Inhibition of the RhoA/ROCK bio signal pathway with effector C3 transferase or Y-27632 prevented the phenylalanine-induced caspase-3 activation (using nanoplatform) with result of rescued neurons from apoptosis. It indicated that the RhoA/ROCK bio signal pathway plays an important role in phenylalanine-induced neuronal apoptosis [33]. Membrane blebbing, cleavage of caspase 3, and release of cytochrome c from the mitochondria are unique nanoscale bio signals reduced by ROCK inhibition mechanism. In clinical practice, inhibition of Rho/ROCK bio signals may improve the survival of grafted cells in cell replacement therapy [34]. Rho proteins as nanoscale bio signals play an important role in physiological regulation of the apoptotic response to stress-inducing test drugs or agents because a dominant-negative mutant of Rac1 interferes with the induction of apoptosis by tumor necrosis factor-α [22]. Other studies indicate that over expression of Cdc42 induced apoptosis in Jurkat cells [35]. Transgenic mice carrying an activated version of the Rac2 gene nanoplatform showed an increased apoptosis in the thymus. In fact, it was the first in vivo demonstration of the role of Rho protein bio signal in apoptosis [23].

How the expression of Rac1 gene can induce apoptosis on nanoplatform?

The gene expression towards apoptosis takes place by a mechanism that involves mRNA and protein synthesis, activation of caspase-3 but not caspase-1. It may require the simultaneous production of ceramides and the synthesis of FasL protein by JNK- and NF-kB-dependent signals with no release of cytochrome c from mitochondria. In fact, an independent bio signal pathway was observed before the onset of the apoptotic program. Possibly, it was suggested as a pro-apoptosis pathway independent of cytochrome c release [36]. The pro-apoptotic role of Rac protein was correlated with a loss of plasma membrane-associated Rho family GTPases. These pro-apoptosis induction towards the apoptosis was reported in primary cortical neurons and brain neuroblasts [37]. Other pro-apoptosis inactivation of Rac GTPase stimulated the Bax protein translocation to mitochondria. Concurrently, it promoted a conformational change in Bax protein that is commonly associated with its cytochrome c-releasing activity [38]. While loss of Rac enzyme activity coincides with induction of apoptosis, Cdc42 activity is regulated independently of apoptotic signals. These indicate that Rac is the major Rho family GTPase. It is involved in promoting cerebellar granule neuron (CGN) survival and secondary role for Cdc42 [38].

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The Cdc42 protein is a major player in neuronal cell death. It involves the up regulation of the JNK pathway [24]. Two other proteins Ras and Rac1 are essential for Fas-mediated apoptotic death of Jurkat cells [39]. The ability of these GTP binding proteins to induce apoptosis originates from their ability to activate down-stream stress-activated kinases such as p38 and JNK proteins [40]. The Rac1 and Cdc42 proteins belong to the same family of Rho GTPases. Only Rac1 protein activates the p38 pathway. Thus, regulation of specific targets/signals by Myc upstream of Rho GTPases leads to specific activation of Rac1 and not Cdc42 [21]. Aberrant neuronal apoptosis is the sole cause of onset and progress of neurodegenerative disorders of Parkinson's disease and amyotrophic lateral sclerosis [38]. The Rho proteins may possibly regulate apoptosis [36].

Rho Protein Biosignals and ROS Species in Cancers

The ROS species are generated from nonenzymatic superoxide by-product of mitochondrial metabolism. The integrin proteins engage in mitochondria through the activation of Rac protein to change the mitochondrial function towards elevated levels of ROS [2]. The small GTPase Rac species mediates the ROS production in diverse signaling pathways. Eventually, ROS species trigger mitogenesis, gene expression, and stress responses [41]. Some are:

i. The ROS production in neutrophils evidenced the Rac2 binding to a NAD(P)H oxidase in response to above events [42].

ii. In Ras-induced NIH 3T3 cell transformation, Rac1 protein was necessary to induce the ROS production [43].

iii. The ROS species activated the Rho/ROCK pathway.

The ROS species lead to vasoconstriction. In experimental animal systemic arteries evidenced a cold-induced vasospasm (Raynaud`s phenomenon). It was exogenous H2O2 activated Rho kinase to increase the expression of ROCK-1 protein. The rise in PO2 increased the endogenous production of ROS in the mitochondria. The O2-dependent increased mitochondrial ROS might trigger the activation/induction of Rho-kinase [44]. The ROS inhibits the RhoA protein function by inducing the tyrosine phosphorylation of the RhoA GTPase activating protein p190Rho-GAP [45]. The exogenous ROS activated the RhoA in the smooth muscle of rat aorta [46].

Iron-Mediated Mitochondrial Dysfunction and Nanoplatforms

Another cellular oxidative stress bio signal is a free iron. Free iron causes several pathologies of Parkinson´s disease [47,48], neoplastic cancers [49,50], haemochromatosis [51], type II diabetes [52], cardiac and hepatic failure [53] and Friedreich's ataxia [54]. Free iron catalyzes the formation of highly toxic ROS like OH• radical, iron-centered ferryl and perferryl radicals [55,56]. Mitochondria plays an important role in iron mediated toxicity. The iron-driven oxidations require the interaction of iron metal with O_2•- and H_2O_2. The mitochondrial ETC is major source of O_2•- and H_2O_2 radicals [53]. Thus, mitochondrial compartments regulate iron homeostasis. The iron-sulfur (Fe-S) clusters and iron in protoporphyrin IX, both participate in heme synthesis in mitochondria [57]. Iron controls iron transport across the plasma membrane (i.e., Aft1/2p transcription factors), and transport into the mitochondrion (i.e., Mmt1/2p and Mrs3/4 transporters) to make Fe-S clusters. Inside mitochondria, iron is sequesterized by human mitochondrial protein frataxin. This protein participates in assembling of Fe-S clusters with other mitochondrial scaffold proteins Isu1/2p and ferredoxin Yah1p, the ferredoxin reductase Arh1p, and chaperone pair Ssq1p and Jac1p, to transfer the assembled Fe-S clusters from Isu1/2p scaffolds to apo-Fe-S proteins [57,58]. Thus, quantity of bio signal proteins in mitochondrial iron metabolism reflects the management of minimum mitochondrial free iron concentration to avoid mitochondrial ROS generation.

In an inherited neurological disorder FRDA, disrupted iron handling occurs in the mitochondria due to mutations in the frataxin gene [59]. Mitochondria in cultured fibroblasts and mitochondria from FRDA patients had more iron than mitochondria from control fibroblasts. Interestingly, cardiac and neural tissues had more iron deposits [59]. In affected tissues, a decrease in several Fe-S containing proteins was reported [60]. Moreover, skeletal muscle from FRDA patients presented a decreased oxidative metabolism. The FRDA patients had mutation in human frataxin gene with accumulated high levels of iron [61], reduced activity of several Fe-S mitochondrial proteins and defective mitochondrial respiration [62].

Molecular Aspects of ETC Dysfunction by Lipoperoxidation

As mentioned above, mitochondria are exposed to oxidative attack during several pathological conditions characterized by an increment in cytosolic and mitochondrial ROS production. Thus, exhaustive research has been done about the effects of ROS on ETC complex function and the mechanism by which oxidative alterations on ETC components lead to an increase in ROS production with the objective to identify the main molecular targets of ROS attack to design future strategies to minimize the damage in mitochondrial function and improve the bioenergetics status of the cell during such diseases.

Numerous reports have identified lipoperoxidation and sulphydryl group oxidation as the main factors that decrease ETC activity under oxidative stress conditions generated in vitro or during pathological situations. In the case of lipoperoxidation, this process has been generally stimulated through the addition of nanomolar and micromolar concentrations of Fe alone [63] or in combination with ascorbate [13,15,64,65]. ADP/NADPH [66] or ADP/ascorbate [67]. The mitochondrial lipoperoxidation has been observed with H_2O_2 [68], O_2•- [69] and ischemia-reperfusion models as well [70-72]. A remarkable feature of the mitochondrial inner membrane is the presence of cardiolipin, a

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tetra-acyl phospholipid essential for the proper structure and activity of ETC complexes except in succinate dehydrogenase (complex II) as recently reviewed [73]. Thus, lipoperoxidation has been associated with cardiolipin loss and inactivation of NADH: ubiquinone oxidoreductase (complex I) [72,74], ubiquinol: cytochrome c oxidoreductase (complex III) [70,71,75] and cytochrome c oxidase (complex IV) [76-78]. In agreement with the lack of cardiolipin requirement for proper function of complex II, lipoperoxidation does not participate in complex II inactivation given that the treatment with the anti-lipoperoxidative agent butylated hydroxytoluene cannot protect enzymatic activity the treatment with Fe_{2+} or Fe_{3+}/ascorbate/ADP [63,67].

Another component of ETC, highly sensitive to lipoperoxidation, is the liposoluble electron carrier ubiquinone, which transfers electrons between complexes I and II to complex III. Oxidative modifications that impair the ability of ubiquinone for electron transfer, as well as the loss of the ubiquinone pool, have been associated with inactivation of partial reactions involving ubiquinone, i.e., NADH- and succinate-ubiquinone and cytochrome c reductases [67]. This fact and the finding that ubiquinone is more important for the protection of ETC against oxidative inactivation than the liposoluble antioxidant vitamin E, have led to the proposal that ubiquinone serves as an important lipophilic antioxidant system in mitochondria besides its function as an electron carrier [66]. Indeed, the maintenance of the ubiquinone pool in a reduced state through the feeding of ETC with succinate prevents lipoperoxidation and ubiquinone loss [64,67]. However, the ubiquinone loss during lipoperoxidation progression seems to be controversial since it has been observed in liver mitochondria treated with iron/ascorbate that the total ubiquinone content (reduced plus oxidized forms) remains constant and only the reduced fraction becomes exhausted. This observation seems to be tightly correlated with a rapid decay in the content of vitamin E [64]. Although this fact is also controvertial with the proposal that vitamin E is less important than ubiquinone for ETC protection as mentioned above, it was suggested instead that vitamin E and ubiquinone act through a synergistic fashion, where ubiquinone would act as a substrate to convert vitamin E radicals to reduced vitamin E and ubiquinone would not act as an antioxidant per se [64].

Despite the importance of ubiquinone and cardiolipin damage during lipoperoxidative injury to ETC, the damage to proteins is also relevant to the mechanism of ETC inhibition by lipoperoxidation since it is well known that lipoperoxidation inactivates several enzymes bound to membranes due to a decrease in membrane fluidity and the reaction of polypeptidic chains with several products of lipoperoxidation [79,80]. The analysis of the protein content of ETC complexes from liver mitochondria during lipoperoxidation induced by iron/ascorbate have revealed that protein degradation is more rapid and pronounced in complex I than in complex III, while complex IV is the least sensitive complex to lipoperoxidation [65]. These observations agree with the facts that these complexes require interaction with cardiolipin for a proper function and conformation [73] and hydrophobic antioxidants like butylated hydroxytoluene or vitamin E protect their activity from oxidative inactivation [63,81]. However, these observations do not correlate with the extent of loss of complex I and III activity observed during the treatment of rat liver mitochondria [64,82,83] and synaptosomes with iron/ascorbate. In contrast, the rate of complex IV and complex III degradation correlates well with the degree of its inactivation in beef heart [67], liver submitochondrial particles [66], rat testis mitochondria [15], liver mitochondria [64], gerbil liver [83] and Saccharomyces cerevisiae mitochondria with manipulated fatty acid content [63] treated with Fe_{3+}/ascorbate/ADP, Fe_{3+}/NADPH/ADP/, Fe_{2+}/ascorbate, Fe_{2+}/ascorbate, subcutaneous injection of iron/dextran and Fe_{2+} alone, respectively.

It has been suggested that the lack of correlation between the decline in the complex III activity and the rate of its protein degradation could be due to specific impairment of the redox-active centers (i.e., Fe-S clusters or cytochromes) caused by changes in phospholipid-protein interactions induced by lipoperoxidation [64]. In agreement with this idea, some studies have found that treatment with Fe_{3+}/ascorbate/ADP or Fe_{2+} impairs electron transfer to cytochrome b without altering the concentration and structure of b hemes [63,67]. Furthermore, the analysis of cytochrome b reduction in mitochondria from the yeast S. cerevisiae, confirms that impairment in electron transfer to b hemes can be attributed to lipoperoxidation, because the treatment with Fe_{2+} does not impair cytochrome b reduction by succinate or dithionite in this organism [63], which is intrinsically resistant to lipoperoxidation due to its membrane fatty composition constituted by saturated and monounsaturated fatty acids [84].

Iron treatment also affects the content of hemes in both yeast and rat models. However, in contrast with hemes b, this effect cannot be attributed to lipoperoxidation given that c+c1 hemes loss was also observed in yeast mitochondria [63,67]. The alteration on electron transfer to cytochrome b by lipoperoxidation is consistent with its hydrophobic character [85] and the requirement of this subunit for lipids to achieve an adequate stabilization of its structure as delipidation of complex III impairs antimycin A binding in a reversible way through cardiolipin addition [86]. Therefore, these observations indicate that lipoperoxidation possibly alters electron transfer through destabilization of cytochrome b conformation without altering heme b center. However, this may impair redox potential of b hemes to an unfavorable value that impairs electron transfer to these prosthetics' groups. A mechanism has been proposed by which lipoperoxidation may impair complex III activity and promote ROS generation in the basis of knowledge in the Q-cycle operation and the next observations:

i. Lipoperoxidation is associated with increments in the

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production of ROS [12,63,70,71,75].

ii. Lipoperoxidation impairs electron transfer to cytochrome, but it may not affect ubiquinol oxidation at the QO site [63,67].

iii. Lipoperoxidation induces resistance to the inhibitory effects of antimycin A in cytochrome c reduction [63].

iv. The subunits that constitute QO site require specific interactions with membrane phospholipids to achieve a proper conformation and function [86,87].

v. The disruption in the electron transfer between b hemes impairs the movement of the head domain of reduced iron-sulfur protein (ISP) [88].

In such a mechanism, lipoperoxidation would affect cytochrome b conformation, disrupting electron transfer to b hemes and the ISP movement between heme bL and cytochrome c1, which in turn, would lead to decreased catalytic cytochrome c reduction and accumulation of electrons at the QO site. The failure in electron transfer to cytochrome b and the impaired ISP movement would lead to a leak of electrons arising from partial ubiquinol oxidation by ISP to yield ubisemiquinone, which may react with oxygen to produce O_2•-.

Thiol Oxidation in the Mechanism of ETC Inhibition by ROS in Cancer

Thiols (-SH) have been known to play an important role in regulating cellular function through redox changes in cysteine residues from peptides and proteins. Mitochondrial function seems not to be an exception since the existence of reactive –SH groups from cysteine residues of ETC complexes has been demonstrated which modulate their enzymatic activity through redox changes under oxidative stress conditions. Many ROS oxidize -SH directly to thiyl radical, yielding different protein -SH alterations including formation of mixed disulfides or internal disulfides from vicinal dithiols, S-nitrosation, and the formation of higher oxidation states [89]. H_2O_2, one of the most important ROS produced from the ETC, does not react at physiologically significant rates with -SH unless the reaction is catalyzed or under conditions that promote formation of thiolate (S-) species, which react with hydroperoxides at rates varying from ~10–105 M-1 · s-1 [90]. Thus, the reaction of –SH in mitochondria with H_2O_2 is highly favored by S- formation due to the high matrix pH (~8.0) and pKa values of protein -SH of 8–8.5 [91]. Nonetheless, although S- rather than -SH reacts with H_2O_2, the rate constants for some S- are still relatively slow and may require catalysis [90], which may explain the different sensitivity of –SH to oxidation as remarked below.

Proteomics approaches have demonstrated the presence of –SH on ETC complexes with different sensitivity to ROS attack. For example, in a study carried out in the presence of exogenous oxidants or stimulators of endogenous ROS production, it was found that core protein I of complex III is the only protein from the ETC that contains thiols sensitive to oxidation stimulated by endogenous ROS. Since two-dimensional electrophoresis may restrict detection of hydrophobic membrane proteins, there were no other identified ETC proteins with sensitive –SH groups [92]. In another study, the reactivity of thiol groups with lipophilic cations which accumulate in mitochondria in response to membrane potential and form stable adducts in a thiol-specific reaction was evaluated. This approach showed the presence of free reactive -SH residues on the matrix surface of complexes I, II, and IV [91]. Therefore, it can be concluded from these studies that all complexes from the ETC contain free -SH residues prone to oxidative modifications. Several functional studies indicate that reversible –SH oxidation modulates ETC activity at the level of all ETC complexes, except in complex IV. For example, the treatment of yeast mitochondria or rat synaptosomes with micromolar concentrations of hydrogen peroxide H_2O_2 or ascorbate/iron, respectively, inhibit activities of complex II and complex III [68,81]. A role was attributed to protein –SH oxidation as treatment with the thiol reductant β-mercaptoethanol in yeast almost completely reverted the inhibition in both complexes II and III [68], while in synaptosomes, glutathione alone prevented complex II inhibition and a mixture of glutathione and lipophilic antioxidants prevented complex III inhibition, suggesting that in complex III, lipoperoxidation and –SH oxidation impair enzyme function [81]. The presence of reactive –SH groups in complex II agrees with earlier reports about the existence of two classes of –SH groups in complex II with different reactivities to alkylating agents, with the most sensitive groups being those localized in the substrate site of the enzyme [93].

Despite the presence of reactive –SH groups in complex IV [91], these groups do not seem to participate in activity modulation since the treatment of mitochondria with milimolar concentrations of H_2O_2 or H_2O_2/protein ratios as high as 3000 nmol/mg protein caused a null or slight loss of activity, respectively [94]. One possible explanation for this phenomenon may reside in the fact that complex IV can function in the presence of H_2O_2 as a peroxidase using reduced cytochrome c as an electron donor. During complex IV turnover, the dioxygen bound to the Fe_{3+} atom from heme a3 (Fe_{3+}-O-O=) undergo a double protonation to give a peroxide (Fe3+-HO-OH), which is unstable and suffers immediate heterolytic cleavage resulting in H_2O release [95]. In a similar fashion, H_2O_2 can bind to heme a3, forming the complex Fe3+-HO-OH and undergo a heterolytic cleavage in the same way as the intermediate peroxide generated during normal complex IV turnover [96]. Thus, H_2O_2 can be considered a substrate of complex IV rather than an oxidant agent that modifies its structure and function, which may explain the observed resistance of this complex to high H_2O_2 concentrations.

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In contrast, complex I activity is highly sensitive to –SH oxidation as demonstrated in dopaminergic cells subjected to oxidative stress through glutathione depletion. Because complex inhibition can be reversed by addition of the thiol reductant agent dithiotreitol, the participation of –SH oxidation through mixed disulfide or intramolecular disulfide formation from vicinal thiols has been suggested [97]. Additional evidence that complexes I is inactivated by –SH reversible oxidation due to glutathione depletion has been obtained from mitochondria subjected to ischemia-reperfusion [98] or haloperidol exposure [99]. A possible role for reactive –SH groups in the protection of complex I against oxidative damage has been proposed based on the observation that complex I activity is inhibited without promoting ROS production by selective glutathionylation of only two of six free cysteine residues (Cys-535 and Cys-704). Glutathionylation of these exposed surface –SH groups could proceed through oxidation of –SH to sulfonic acid and its posterior reaction with reduced glutathione to form a mixed disulfide, which then reacts rapidly with GSH in a reaction catalyzed by mitochondrial glutaredoxin Grx2 to regenerate thiol, thus creating a cycle of –SH oxidation-regeneration that may protect other essential amino acids residues from oxidative damage [100]. Therefore, the hypothesis is plausible that -SH groups from ETC complexes may serve as a redox sensor that modulates ETC activity in function of the redox state of mitochondria. This could decrease ROS generation by limiting electron fluxes to mitochondrial sites of ROS generation (i.e., quinone sites of complex III). The operation of this system would be optimal under high GSH/GSSG ratios and moderate levels of oxidative stress. Otherwise, -SH modification would be irreversible due to further –SH oxidation to sulfinic or sulfonic acid species, thus inactivating the protection to ETC conferred by -SH from oxidative damage to essential amino acid residues and leading to irreversibly damaged ETC complexes and further ROS formation. Hence, this picture may also, in part, explain the irreversible damage to ETC proteins observed under strong oxidative conditions like iron overload. However, it must be pointed out that although sulfinic or sulfonic acid formation in proteins has long been viewed as an irreversible process, it has been demonstrated that sulfinic acids can be reduced to thiols in vivo by an enzyme with sulfinic acid reductase activity called sulfiredoxin [101].

Despite the growing body of data showing the direct interaction of H_2O_2 with –SH groups, there is some contradictory evidence indicating that H_2O_2 inhibits ETC function without directly altering the enzymatic activity of ETC complexes [102,103]. In heart mitochondria, H_2O_2 exposure inhibited respiration in state 3 using glutamate/malate as a substrate. This effect was attributed to inhibition of α-ketoglutarate dehydrogenase activity and a consequent decrease in NADH production to feed the ETC. A short time of H_2O_2 exposure (3 min) may account for the lack of direct effects on ETC function, since in other reports, longer incubations were needed to observe direct effects on ETC activities. Similar results were obtained using α-ketoglutarate as a substrate, but in this case, succinate dehydrogenase and aconitase were also susceptible to H_2O_2 inactivation. Remarkably, enzyme activities and respiration were recovered several minutes after oxidant addition except for aconitase. Since this phenomenon was only observed in intact mitochondria but not in solubilized mitochondria, it was suggested that inactivation of enzymes was due to glutathionylation rather than direct interaction of H_2O_2 with proteins, while NAD(P)H depletion was also explained because of its utilization for a system present only in intact mitochondria (i.e., glutaredoxin) that carries out reversion of glutathionylation [102]. In summary, the ambiguous effects of H_2O_2 on mitochondrial function may be related to the concentrations and time of exposure used as well as whether H_2O_2 was added exogenously or generated through the inhibition of ETC complexes or reverse electron transfer, which may influence the proximity of –SH groups to the site of H_2O_2, its reactivity or its conversion to thiolate form.

Mitochondrial Dysfunction Evaluation Methods

Mitochondrial diseases are genomic in origin with multiorgan system manifestations and phenotypes. Diagnostic evaluation includes blood analytes and tissue histochemical measurements, neuroimaging, enzymatic assays in tissues or cultured cells and DNA analysis indicating grade of disease burden and its progress according to mitochondrial society in-depth evaluation stretagy [104]. Primary mitochondrial disorders follow patterns of maternal inheritance (i.e., mitochondrial DNA (mtDNA) mutations) or classical Mendelian inheritance (i.e., nuclear DNA (nDNA) mutations). Mitochondrial disease in children is caused by nDNA autosomal recessive pattern of inheritance confirmed by mtDNA analysis and molecular testing.

The biochemical analysis is done by lactate and pyruvate analysis. For it, sample is taken 30 minutes after placement of an intravenous catheter. Lactic acid is seen minimally elevated in mitochondrial polymerase gamma (POLG1)-associated diseases, Leber Hereditary Optic Neuropathy (LHON), Leigh disease, Kearns-Sayre syndrome, and complex I deficiency [105]. CSF lactate is elevated in CNS infection, stroke, malignancy, inflammation, and seizures [106]. Blood lactate/pyruvate ratios reflect the NAD+/NADH cytoplasmic redox state. Pyruvate is quite unstable. Blood and/or CSF pyruvate may be elevated in pyruvate metabolic defects such as pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency, or biotinidase deficiency. CSF lactate or pyruvate levels may be elevated in mitochondrial disease patients with predominant brain manifestations [107]. Pyruvate metabolism defects are genetic based mitochondrial diseases of oxidative phosphorylation dysfunction [108,109].

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Amino acid analysis is performed using tendem mass spectrometry (MS/MS) for amino acid analysis of any change in cystine, homocystine, lysine, tryptophan, and GABA neurotransmitters involved in methylation reactions. Reverse-phase HPLC is another high throughput method for amino acid analysis. Elevated alanine: lysine ratio > 3:1 and alanine: phenylalanine + tyrosine (normal ratio < 4:1) indicate true hyperalaninemia [110]. An absolute elevation in alanine above 450 uM indicates Nijmegen diagnostic protocol. Aminoaciduria with renal tubular acidosis and glycosuria indicates renal Fanconi syndrome with mtDNA deletions [111]. Alanine, proline, glycine, and sarcosine amino acids elevate in mtDNA depletion syndrome (OXPHOS disease with severe infantile-onset liver disease). Elevated tyrosine withourt rise in succinylacetone in newborn screening studies indicate type 1Tyrosinemia [112].

Methods of organic acid quantification mass spectrometry extracted ion ratio method and semi-quantitative analysis utilizing gas hromatography flame ionization with mass spectrometry identify organic acid peaks [113]. Elevated organic acid mevalonate indicates diagnosis of mild mevalonic kinase deficiency or hyper IgD syndrome). Elevated CSF organic acid analysis has utility in select disorders of GABA metabolism. Urine organic acid analysis is routinely obtained in infants with sudden-onset encephalopathy, organic acidopathies and dicarboxylic acid in β-fatty acid oxidation disorders. Increased excretion of tricarboxylic acid (TCA) cycle intermediates, ethylmalonic acid, and 3-methyl glutaconic acid jndicate renal immurity due to microsomal fatty acid oxidation [114-116].

Blood total and free carnitine levels along with free and acyl-carnitine ester profiling indicates fatty acid oxidation defects of primary aminoacidemias, organic acidemias, secondary fatty acid oxidation defects and carnitine deficiency in primary OXPHOS disorders. Quantitative acyl-carnitine analysis is performed by either tandem mass spectrometry (MS/MS) or HPLC followed by electrospray ionization (ESI)-MS/MS [117]. A filter paper blood spot can be used. (Figures 2-4).

Proton magnetic resonance spectroscopy (MRS) is used for neurometabolic evaluations of mitochondrial diseases [118-124] to detect lactate (1.33 ppm), N-acetyl-L-aspartate (2.02 ppm), succinate (2.39/2.40 ppm), total creatine (3.03 ppm), choline (3.22 ppm), and myo-inositol (3.55 pm). The author established a method of metabolite concentration based on peak area proportional to the number of spins to calculate disease burden. The prominent lactate peak resonance at 1.33 ppm at short TE times (i.e., 35 milliseconds) is inverted down at intermediate TE times (i.e., 135 milliseconds) and long TE time (i.e., 288 milliseconds) to reduce lipid contamination. Clinical spectroscopy centers still report peak area ratios. Lactate is elevated in anaerobic glycolysis and Leigh syndrome or mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) in range of 0.5 – 1 mM as shown in Figure 3 by Barkovich [118-123]. Patients with respiratory chain deficiencies showed blood lactate elevated levels with moderate sensitivity18 % to 27% depending on acute, subacute, or chronic [124].

N-acetyl-L-aspartate (NAA) in neurons, axons, and dendrites is synthesized within the mitochondria and decreased NAA indicates neuronal integrity loss in mitochondrial diseases. The NAA/Cr ratio is different in cerebellum in 93% and in cortical gray matter regions in 87%, appearing normal on MRI [125]. The NAA/Cr ratio signal changes in patients with detectable Lac peaks. In some studies, the apparent decrease in the NAA/Cr signal was reversible [126,127]. As with elevated Lac, decreased NAA is not specific for mitochondrial or even metabolic disease [128,129]. The choline (Cho) signal on MRS includes free choline, phosphorylcholine, and phosphatidylcholine in brain myelin and cell membranes [130,131]. Cho elevation reflects membrane turnover and demyelination in patients with mitochondrial disease. The Cho/Cr ratio in 40% of patients showed reduced NAA/Cr and 53% of patients showed reduced NAA/Cr ratio with elevated Lac [132]. Succinate is present in brain at low concentration 0.5 mmol/kg wet weight [140]. Succinate peak is not visible on MRS [133] due to overlapping with glutamate and glutamine [134]. Significant increases in 2.4 ppm succinate peak by multiple voxel MRS indicated complex II deficiency with reduced NAA/Cr in white matter and cortical gray matter and increased Lac signals within white matter [135]. This highlights the importance of utilizing multivoxel acquisition.

The diagnostic value of glucose or fructose loading provocative clinical tests is poor. Other exercise bicycle and trademill decreased exercise tolerance, lactate production and slow lactate clearance tests indicate mitochondrial myopathy [136]. The venous oxygen saturation in skeletal muscle results in poor extraction of oxygen from blood in mitochondrial disease [137,138]. Invasive skin biopsy investigations in many children OXPHOS defects in skeletal muscle might show change in respiratory chain enzyme activities in cultured skin fibroblasts [139]. Detectable respiratory chain enzyme defects were reported in liver [140] or cardiac muscle [141] and skeletal muscle activities. Skeletal muscle biopsy analysis is used for mitochondrial histochemical, immunohistochemical, and even ultrastructural study to evaluate for morphologic evidence of primary OXPHOS disease by respiratory chain enzyme activity analysis, integrated OXPHOS capacity, and extraction of DNA for genetic testing. The mitochondrial proliferation or regged-red fiber deposits by Trichrome Gomori stain within myofibers in sarcolemma space suggests mitochondrial atropy OXPHOS disorder. The mitochondrial enzyme activities of NADH dehydrogenase, succinate dehydrogenase (SDH), and cytochrome c oxidase histochemistry staining indicated complex II disease encoded by nuclear genes and subsarcolemmal mitochondrial accumulation [141]. Change in normal brown fibers to COX-deficient blue fibers evaluated the complex IV mitochondrial and nuclear genomes [142]. However, RRF are rarely seen in childhood but frequent sarcolemma accumulation as mild manifestation of mitochondrial proliferation in pediatric muscle biopsy [143].

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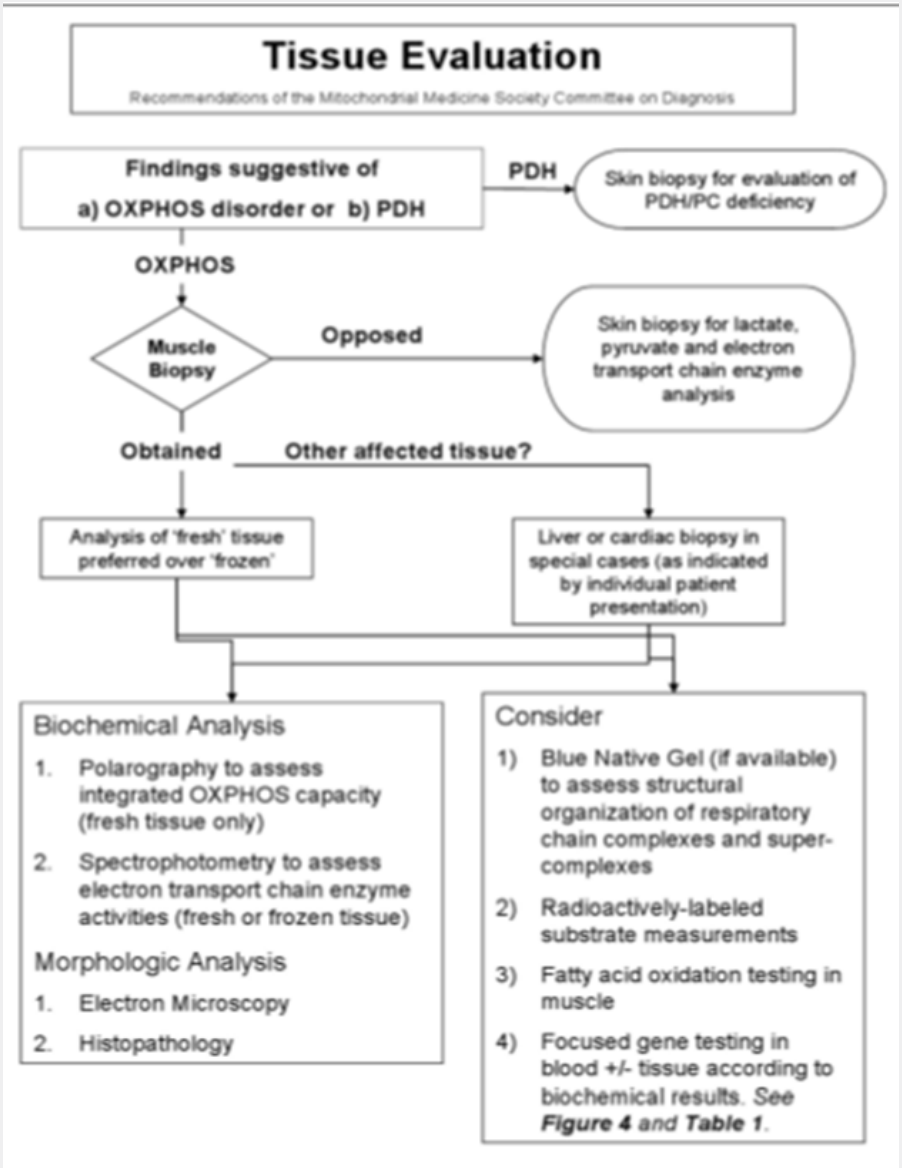

Figure 2: An overview of findings presents minimally invasive analyte screening in mitochondrial disease.

Moreover, age-related muscular dystrophies, myotonic dystrophy, inflammatory myopathies, glycogenoses, and congenital myopathies also show COX-deficient non-specific muscle OXPHOS disorders including neurogenic atrophy, internal nuclei, abnormal variation in fiber size, and accumulations of glycogen or lipid [144,145]. Staining for glycogen and lipid is the gold standard to evaluate glycogen or lipid storage disorders. Rhabdomyolysis and dystrophic changes are rare in mitochondrial OXPHOS disorders. The presence of RRF with strong subsarcolemmal SDH activity and low COX activity are due to mtDNA deletions (i.e., Kearns-Sayre Syndrome or progressive external ophthalmoplegia (PEO)) or tRNA mutations (i.e., myoclonic epilepsy and ragged red fibers (MERRF)) indicating impaired mitochondrial protein synthesis [143]. The reason for COX deficiency is speculated when wildtype mtDNA levels fall below the threshold necessary for COX protein subunit expression. As a result, only few COX-deficient fibers or none may be present while high percentages of mtDNA mutation evenly distributed mutant and wild-type mtDNA throughout the fiber in MELAS due to an A3243G tRNALeu gene mutation in which RRF are often COX-positive. An increase in vascular smooth muscle SDH activity frequently is also seen in MELAS [146]. The mosaic and segmental pattern of COX activity indicates

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heteroplasmic mtDNA disorder while decreased COX activity throughout the length of the muscle fibers sparing spindles indicates the mutation in a nuclear gene encoding of SURF1 in homoplasmic tRNA mutations of fatal and benign forms of infantile COX-deficient myopathy [147]. Mutations in the mtDNA protein-encoding genes are occasionally associated with RRF but COX-positive fibers in cytochrome b, COX IIII, and some mutations in complex I (ND1-6, ND4L) genes.

In contrast, mutations associated with NARP/MILS (T8993G/C mutation in the ATPase 6 mtDNA gene) and ND mutations indicate LHON specific changes on muscle biopsy. Mitochondrial myopathy is OXPHOS disorder with absent nDNA mutations in nuclear-encoded complex I and II subunits. However, CoQ10 deficiency, benign infantile COX-deficient myopathy are exceptions [148]. Electron microscopy ultrastructural changes as increased mitochondrial number and size distorted or absent cristae, and osmophilic or paracrystalline inclusions are well documented in patients with mitochondrial myopathic and neuropathic diseases [149]. Ultrastructural changes of mitochondria have been described in muscle biopsies of patients with no RRF or COX deficient fibers [144].

Biochemical analysis of skeletal muscle distinguishes classical syndromic presentations (i.e., Kearns-Sayre syndrome, Pearson syndrome, Leigh syndrome, MELAS, MERRF, or LHON). Over 1,000 genes are involved in the mitochondrial function [150]. For OXPHOS biochemical investigation, spectrophotometric assays of enzyme activity in isolated in vitro tissue mitochondria or cultured cells predict the diagnosis of an OXPHOS disorder [151]. Spectrophotometric data gives valuable information of respiratory complexes following either detergent- or freeze-thaw disruption of the inner mitochondrial membrane [152,153]. However, in vitro conditions do not correspond to the physiological, cytosolic environment of mitochondria. Spectrophotometric assays of the different electron transport chain (ETC) enzyme complexes measure the complex I (NADH-ubiquinone oxidoreductase), complex II (succinate-ubiquinone oxidoreductase), complex III (decylubiquinone-cytochrome c reductase) or complex IV (cytochrome c oxidase), or they can be studied together as complex I+III (NADH-cytochrome c reductase) or complex II+III (succinate-cytochrome c reductase) [154]. Direct assays of ATP synthase (complex V) hydrolytic activity are available by spectrophotometric analysis. Citrate synthase enzyme distinguishes primary electron transport chain mitochondrial OXPHOS defects from secondary deficiencies [147,153,155]. However, these assays use artificial substrates in disrupted mitochondrial preparations different from intact cellular mitochondrial respiration in a stereochemical environment of multi-enzyme complexes and supercomplexes. Isolated one complex defect may point out a mutation of either an mtDNA-encoded or nDNA encoded subunit or assemblyfactor of that complex (i.e., SURF1 mutation in COX deficiency). Partial enzyme deficiencies involving complexes I, III and IV may not distinguish patients with a generalized translation defect due to either mtDNA deletions or tRNA mutations [156,157]. Complex I activity is decreased in patients with MERRF, MELAS, COX deficiency and mitochondrial polymerase deficiency [156]. The combined measurements of I+III and II+III predict treatable coenzyme Q10 deficiency disorders or CoQ10 binding/electron exchange disorders by simple coenzyme Q10 quantification in muscle [158,159]. Earlier, polarographic oxygen consumption by Clark electrode in various substrate mixture (e.g., malate + pyruvate or malate + glutamate to donate NADH, succinate to donate FADH2, or TMPD+ ascorbate to donate electrons directly to cytochrome C) indicated mitochondrial respiratory burst or oxidation rates [155].

In complex I deficiency patients, impaired respiration with NADH–producing substrates was seen while normal oxidation rates with other substrates. Patients with complex II deficiency showed reduced oxygen consumption with FADH2 producing substrates [155]. Low respiratory rates with both NADHand FADH2-producing substrates but normal oxidation of durohydroquinone and TMPD+ascorbate suggested deficiency of coenzyme Q10 otherwise with low oxidation of durohydroquinone suggested a deficiency of complex III. Diminished oxidation rates in the presence of all substrates tested for deficiency of complex IV. Polarographic studies may indicate a possible pyruvate dehydrogenase complex (PDHC) deficiency by measuring a reduced oxidation of pyruvate in the presence of normal oxidation of glutamate [160].

Respiratory chain function can be measured by isotopic $14CO_2$, and ATP produced from radioactively labeled substrates (e.g., [1-14C] pyruvate, [U-14C] malate and [1,4-14C] succinate) in the absence or presence of inhibitors. Citrate synthase activity is a biomarker of mitochondrial function. Various ratios can be determined to pinpoint the deficiency to a single respiratory chain complex [161]. Muscle mitochondria in muscle fibers placed in saponin housed in polarographic chamber can quantify oxygen consumption rates in presence of several substrates [162] Fresh muscle tissue is ideal for measuring oxygen consumption with polarography, substrate oxidation, or ATP production rates. Alternatively, high resolution respirometry of muscle fibers to measure oxygen consumption in isolated mitochondria or a fresh, needle biopsy of muscle or liver from 2 milligrams to evaluate all complexes' activities in OXPHOS system [163,164]. The isolated mitochondria under in vivo like conditions identify mitochondrial defects by polarographic ETC assays such as identification of coenzyme Q10 synthetic defects [165,166], abnormal PDHC deficiency, tricarboxylic acid cycle enzymes, beta-oxidation, coenzymes, complex V, and transmembrane carriers [51], deficiency of pyruvate and phosphate transport carriers in fresh muscle mitochondria [167,168]. Coenzyme Q10 is an electron carrier to shuttle electrons to complex III from I, II, electron transfer factor (ETF), or other electron donors. It recycles tocopherol and ascorbate and has proxidant functions [169]. Impaired coenzyme Q10 dependent respiratory chain activity

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suggests primary coenzyme Q10 deficiency manifested as four phenotypes:

i. An encephalomyopathy with exercise intolerance, myopathy, myoglobinuria, seizures, and ataxia.

ii. Severe infantile encephalopathy with renal tubulopathy.

iii. Myopathic form with exercise intolerance, myopathy, and rhabdomyolysis.

iv. Encephalopathy with ataxia, seizures, and basal ganglia disease [170,171].

The impaired coenzyme Q10-dependent respiratory chain activity and plasma Q10 levels may indicate secondary coenzyme Q10 deficiency in muscles of Kearns-Sayre syndrome patients [172,173]. The concentration of coenzyme Q10 in heart muscle is highest at 114 ug/gram [174]. The coenzyme Q10 is lipoprotein bound reflects the cholesterol normative values established as a function of age [175]. Skeletal muscle coenzyme Q10 concentrations are two-fold high in healthy children [176].

Defects in mitochondrial oxidative phosphorylation found in both hypertrophic and dilated cardiomyopathy [177,178]. Dilated cardiomyopathy reflects pump failure arising from hypertrophic cardiomyopathies. Chamber dilation increases wall tension, cardiac output and blood pressure through equilibrium of Laplace (pressure-volume) and Frank-Starling (wall tension force) principles. Multisystemic dysfunction with isolated cardiomyopathy [155,179] arise due to mitochondrial dysfunction primary or secondary to a failing heart [180,181] in cardiac aging and cardiac disease [182,183]. Therefore, cardiac muscle biopsy may evaluate the respiratory chain OXPHOS defects secondary to primary mechanical or coronary vascular insufficiency [178]. In a severely ill neonate, infant or young child, direct gene testing by mutations in SCO2, COX-10, and COX-15 can give rise to cardiac hypertrophy.

Liver dysfunction is clinically hepatic or hepatocerebral mitochondrial disease. It is evaluated by blood DNA testing for POLG, dGUOK, or MPV17, SCO1 and SUCLA2 mutations indicating ketoacidosis (SCO1) or myopathy (SCO1 and SUCLA2) (see Table 1). More extensive evaluation is indicated by simultaneous biopsy and DNA studies at earliest. Needle biopsy yields sufficient tissue for histology, electron microscopy, and miniaturized respiratory chain polarography and biochemistry to confirm abnormal liver histologies of mitochondrial disease [179,180]; COX deficiency in respiratory chain biochemical testing; multiple ETC deficiencies with mtDNA depletion associated with POLG, dGUOK, MPV17, or SUCLA2 mutations; quantitative Southern analysis or real-time quantitative PCR to detect mtDNA depletion; normal mtDNA content on liver biopsies of POLG disease and Alpers syndrome [181] as routine liver biopsy tests.

Table 1: Biochemical Analysis for Mitochondrial Dysfunction.

Biochemical Analysis for Mitochondrial Dysfunction		
Amino Acid (plasma / CSF)	**Organic Acid (urine)**	**Acylcarnitines (plasma)**
Elevated alanine Elevated glycine, proline, sarcosine or tyrosine	TCA cycle intermediates Ethylmalonate. • 3 - methyl glutaconate. • Dicarboxylic acids	· Low free carnitine Elevated acyl: free carnitine ratio Elevations suggestive of disrupted fatty acid oxidation

A skin biopsy is very simple office procedure done with local anesthesia using a disposable 3- or 4-mm punch biopsy without stitches to study mitochondrial disease biochemistry [182]. Cultured skin fibroblasts can be stored indefinitely as a renewable source of DNA but not useful in mitochondria phenotyping or respiratory chain defect expression [183,184] due to altered heteroplasmy and a high tissue regeneration rate of fibroblasts [183]. In cultured skin fibroblasts, biochemical analysis includes electron transport chain enzyme analysis via spectrophotometry and radiolabeled isotope fatty acid oxidation, measurements of lactate and pyruvate [184], and ATP production and consumption in fibroblasts [185]. Fibroblasts are best for protein studies by western blot and blue native polyacrylamide gel electrophoresis (BN-PAGE) analysis [186]. BN-PAGE analyzes multisubunit mitochondrial electron transport protein complexes to identify complex abnormalities SURF1 defects [187] or tissue-specific mitochondrial translation defects [188]. The 2-dimensional BN-PAGE/SDS-PAGE was performed in combination with Western analysis using antibodies directed proteins [189,190].

Mitochondrial DNA Analysis

Mitochondrial DNA analysis is done for mitochondrial DNA mutation types. The types of mitochondrial DNA abnormalities include single basepair point mutations, several basepair insertions or deletions, large scale deletions on the order of 100s to 1000s of basepairs, or relative depletion of total mitochondrial DNA content. Routine PCR with restriction fragment length polymorphism (RFLP) analysis screens specific mutations with allele specific oligonucleotide (ASO) analysis to screen for multiple known mutations simultaneously. Other methods are Single-strand conformation polymorphism (SSCP) [191], heteroduplex screening assays (such as temporal temperature gradient gel electrophoresis (TTGE) [192-194], temperature gradient gel electrophoresis (TGGE) [195], denaturant gradient gel electrophoresis (DGGE) [196,197], denaturing high performance liquid chromatography (dHPLC) [198], and DNA sequencing. DNA sequencing is the gold standard for mutation detection in nuclear genes. For mtDNA sequencing, interference by nuclear pseudogenes exclusion is done by use of rho- cells for new PCR-based assays. Point mutations or deletions may not be

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present in all mtDNA genomes within a cell or tissue, but rather be heteroplasmic with wildtype to varying degrees. Quantification of mutant heteroplasmy is performed by densitometer scanning utilizing RFLP or realtime ARMS qPCR [199]. Southern blot analysis is the method most often used for the detection of large-scale mtDNA deletions and duplications, although these can be detected by long range polymerase chain reaction (PCR) analysis. Finally, depletion testing utilizes either Southern densitometry scanning or real time qPCR to quantify mtDNA copy number in reference to a nuclear gene [199].

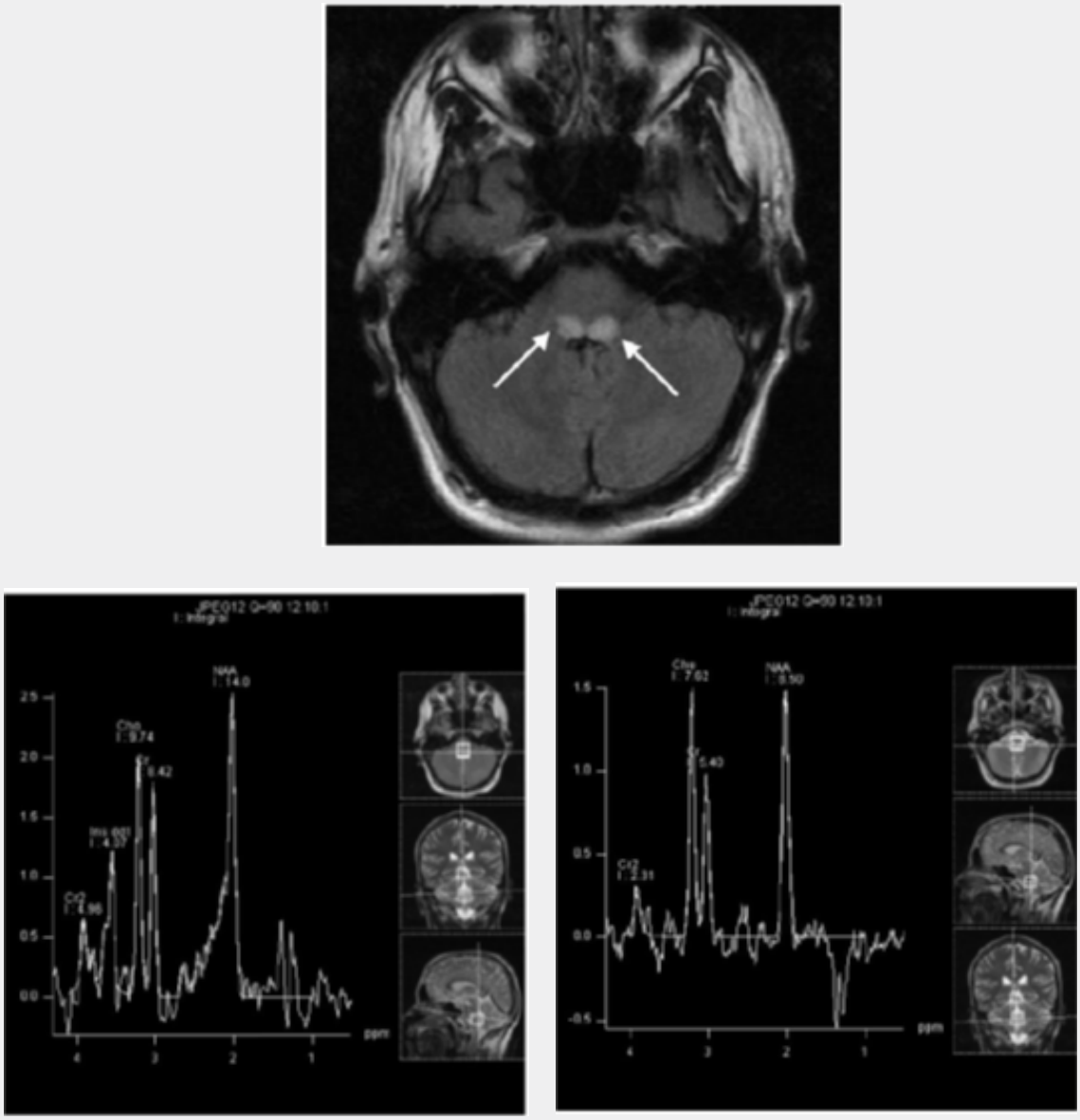

Figure 3 (panel on top) Brain MRI demonstrating an axial FLAIR sequence of a 17-year-old boy with new-onset respiratory difficulty, episodic vomiting, and extreme fatigue. This figure represents the symmetric regions of elevated T2/FLAIR signal located within the tegmentum (arrows). The diagnosis was Leigh syndrome. (at bottom) On left, brain MRS scan represents a 1.6 × 1.6 cm voxel within the hyperintense FLAIR signal region. The exact location can be seen on the MRI images represented on the right of the picture. The time to echo (TE) was 35 msec. There is a upward lactate peak (Lac) located at 1.33 ppm, N-acetyl-L-aspartate (NAA) peak at 2.02 ppm, total creatine peak (Cr) at 3.03 ppm, choline peak (Cho) at 3.2 ppm, and inositol peak (Ins) at 3.8 ppm. It is likely that the voxel may include some cerebral spinal fluid. There was no detectable lactate in the cerebral spinal fluid several days before the image was acquired. On the right, MRS scan represents the same 1.6 × 1.6 cm voxel as figure 3A. The time to echo (TE) was 135 msec. Notice the downward Lac peak at 1.3 ppm, while the NAA peak at 2.02 ppm, Cr peak at 3.03 ppm, and Cho peak at 3.2 ppm remain upward. At this TE, the ins peak is not well visualized.

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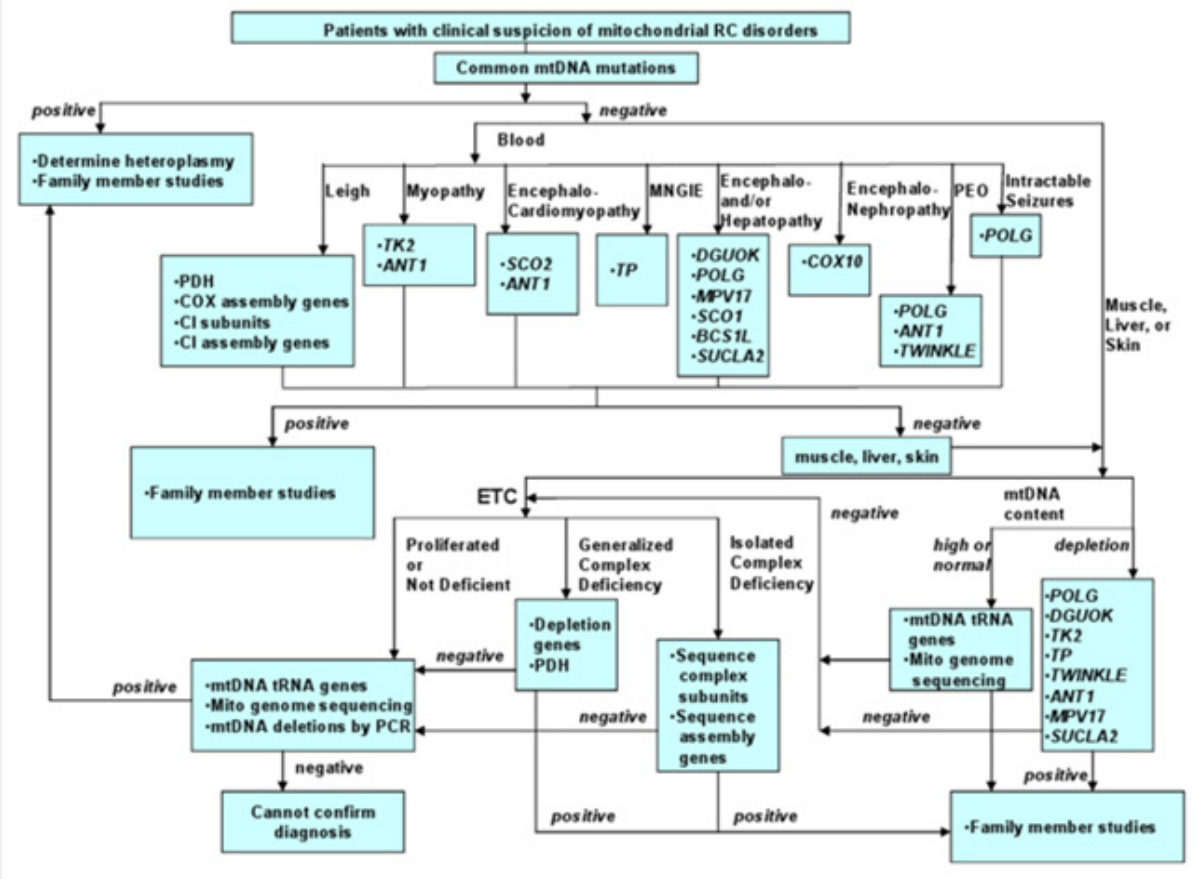

Figure 4: Clinical algorithm for genetic diagnostic testing of mtDNA and nDNA genes in patients suspected of mitochondrial disorders.

Nuclear DNA Analysis

Nuclear DNA Analysis measures 75%-90% pediatric primary mitochondrial disease resulting from nDNA mutations. (Figure 2)

Complex I structural subunits [151], B17.2L & NDUFAF1 [151], SDHA [152], SDHC [153], SDHD [153],

BCS1L [154,155], SURF1 [156], SCO1 [157], SCO2 [158], COX10 [159], COX15 [160,161], ETHE1 [162], LRPPRC (LSFC) [138], ATP12 [163],

PDSS1 [164], PDSS2 [165], COQ2 [164], APTX [166], ADCK3 [167], ETFDH [168], TSFM [169], TUFM [170], EGF1 [170], MRPS16 [171],

PUS1 [172], DARS2 [173], PDHA1 [14], POLG1 [107], TK2 [174,175], DGUOK [176], MPV17 [137], SUCLA2 [177], SUCLG1 [177], RRM2B

[178], TWINKLE [179], ANT1 [180], ABC7 [181], FXN [182], OPA1 [183], DDP1 [184], SPG7 [185,186], TAZ [187].

[b]Sensorineural hearing loss localized to the central brainstem or peripheral cochlear in pediatric and adult patients, can be seen in virtually any mitochondrial disease.

A sample algorithm of DNA-based analyses in mitochondrial disease is shown in Figure 2. Specific nuclear genes in mitochondrial disease in each patient show a detailed compilation of biochemical and clinical findings associated with pathogenic mutations in nuclear DNA genes currently implicated in primary mitochondrial diseases.

Regular clinical signs and symptoms in mitochondrial disorders are developmental and degenerative. Alpers or Kearns-Sayre syndrome presents the full clinical spectrum of mitochondrial disease. Establishing a genetic diagnosis permits accurate etiologic, prognostic, recurrence risk, and management counseling. In the future, it is hoped that this will also permit accurate subgrouping among the heterogeneous category of mitochondrial disease patients to develop disease-focused interventions. DNA-based new emerging Techniques are mtDNA

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Sequencing Microarray such as Affymetrix oligonucleotide resequencing microarray (MitoChip 2.0) to yield sequence data on the complete coding region and 15,452 of the 15,569 bp mtDNA [200] without amplifying pseudogenes by first amplifying mtDNA in 3 long overlapping fragments do not present in the nDNA. It detects heteroplasmy down to about 2-5% [201]. ESI-TOF Mass Spectrometry screens the PCR-amplified fragments of mtDNA by electrospray ionization time-of-flight mass spectrometry (ESI-TOF MS), Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS) [202] and ion-pair reverse phase HPLC time-of-flight mass spectrometry (ICEMS) [203]. ESI-TOF-MS and ICEMS are economical and well-suited for rapid sequence screening and the quantitation of heteroplasmy in the range of 1-2%.

Protein-based Immunocytochemistry is based on monoclonal antibodies for diagnosis of selected OXPHOS defects [204] using the expression of the mitochondrial protein defect in cultured skin fibroblast pyruvate dehydrogenase E1α defects [190]. However, background autofluorescence complicates the use of immunofluorescent probes in muscle biopsies. Selected use of OXPHOS antibodies in Western immunoblot analysis [204] and immunocapture of assembled complexes [205] have proven powerful analytical techniques. Proteomics and Systems Biology in purified mitochondria from different tissues combined with gel and chromatography-enhanced mass spectrometry methods, offer tissue-specific mitochondrial proteome characterization [206] and examination of tissue-specific heterogeneities [207]. A powerful bioinformatics tool "Maestro" identified 1,451 mitochondrial proteins out of 33,860 proteins in the Ensembl human protein data set [208]. Application of "Maestro" identified MPV17 as a cause of mtDNA depletion syndromes [209] and LRPPRC as the cause of Leigh syndrome [210].

31P and 13C NMR Spectroscopy measures the dynamic capacity of mitochondria during changing physiologic conditions in real-time determines. In vivo 31Phosphorus magnetic resonance spectroscopy (31P-MRS) monitors baseline, exercise, and recovery measurements of ATP and phosphocreatine to reveal very subtle derangements in mitochondrial function [211]. 13C-MRS is another emerging technology [212]. Optics, Biophotonics, and Nanotechnologies are emerging. Bio cavity Laser Spectroscopy uses the bio cavity laser, a semiconductor nanolaser about the size of a dime. Cells or mitochondria that flow through the bio cavity laser trigger the emission of photons of laser light. Measurement of the red shift of this emitted laser light provides information of the biophysical composition of healthy and diseased mitochondria. The bio cavity laser can measure the overall biophysical state of the cell and mitochondrial dysfunction in cancer [213] and primary OXPHOS disease [214].

Nanomedicine—Mitochondria have the unique electrophysical property of concentrating or attracting amphipathic, charge-delocalized, cationic molecules and nanoparticles. This allows for the rational design of a variety of cargo-delivery systems. Indeed, mitochondriotropic tags incorporated into paclitaxel-bearing nanoliposomes inhibited tumor cell growth in a mouse model, whereas free paclitaxel had no effect [215]. The selective delivery of DNA to mitochondria in cell culture is state of art [216]. Mitochondria Light Interactions might stimulate incipient mitochondria cells [217]. Traces of important light interactions of mitochondria with specific wavelengths in the red and near infrared ranges (ca 600-1200 nm) are known to stimulate expansion of cardiac stem cells in culture [218] and accelerated healing of chemotherapy-associated mucositis [219]. Low level laser treatment using an 808 nm light source over mitochondria has shown promise in a blinded, prospective clinical trial in acute stroke patients [220].

In nutshell, an in-depth evaluation of mitochondrial disease is possible and indeed warranted to obtain a clear diagnosis for individual patients. This is necessary to minimize the cost of duplicate investigations, correct misinformation to families and health care providers, and provide accurate prognostic and recurrence risk counseling. Recognized mitochondrial diagnostic centers working in close collaboration with referring clinicians can successfully navigate the complexities of the diagnostic evaluation and work towards the development of quality assessment programs in the laboratory-based investigations of mitochondrial disease.

Conclusion

Mitochondria are unique energy generating and storage cellular organelles. Mitochondrial density varies in hundreds to thousands per cell. Every mitochondrion house five to ten copies of mitochondrial DNA to encode almost 13-16 bio signal mitochondrial proteins as subunits of the mitochondrial respiratory chain. Mitochondrial genetics evolved over years to recognize several nanoplatforms to confirm mtDNA-related disorders, mostly inherited maternal diseases. Mitochondria are the primary source of redox ROS radicals and ATP molecules. These bio signals control many programmed cell-death events or apoptosis. Mitochondria plays a major role in ATP synthesis, regulation of cellular oxidative state, and Ca_{2+} homeostasis to control cell activation bio signaling. In the case of mitochondrial dysfunctions, several clinically heterogeneous diseases are developed in a single or multiple organs. The disturbances in mitochondrial metabolism and oxidant formation alter the biology of aging and age-associated metabolic diseases, such as diabetes, cardiovascular diseases, and multiple disorders of the central and peripheral nervous system. Now, mitochondrial oxidative stress nanoplatforms may facilitate the early detection of ROS towards prevention and/or decreased mitochondrial dysfunction to restrict the generation of ROS, and mitochondrial abnormalities. Such monitoring may have benefits in lowering the disease symptoms and increasing health and lifespan of humans.

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