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Chapter 1

Understanding Mitochondrial DNA in Brain Tumorigenesis

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Additional information is available at the end of the chapter

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1. Introduction

In developed countries, most studies reveal that the number of people who develop brain tumors and die from them has increased. Brain tumor, one of the most devastating central nervous system pathologies, is the leading cause of solid tumor death in children under the age of 15, and the second leading cause of cancer death in male adults ages 20-39. So far, researches on genesis and development of tumor are intensively focused and studied on alteration of the gene in nucleus and brain tumors is the one where most were reported arise as the result of progressive nuclear genetic alterations. Multiple genetic events have been identified in brain tumor cells involving some well-known susceptibility genes such as tumor suppressor and oncogenes that are encoded by the nuclear DNA (nDNA). For instance, the p53 tumor suppressor gene is frequently mutated and often detected altered or lost early in brain tumor mainly in astrocytic tumors formation [1-3]. Similarly, mutations or loss of PTEN (phosphatase and tensin homolog), p16, RB (retinoblastoma) and amplification of EGFR (epidermal growth factor receptor), MDM2, CDK4, CDK6 (cyclin-dependent kinase) are also involved in the pathogenesis of brain tumor [4,5].

Although, it is well established that multiple alterations in the nuclear-encoded genes are associated with tumor development, it is reasonable to consider and postulate that there is another factor or genome yet to be investigated. The involvement of the mitochondrial genome in tumorigenesis and cancer progression remains controversial to date. Mitochondria are cytoplasmic organelles in eukaryotic cell and recognized as "the power houses of the cell", thus one of their principal functions is providing cellular energy, adenosine triphosphate

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(ATP) through the oxidative phosphorylation (OXPHOS) [6]. OXPHOS can be defined as the oxidation of electron transfer chain by oxygen and the concomitant transduction of this energy into ATP. The OXPHOS system is composed of five protein complexes: NADH-ubiquinone oxidoreductase as complex I, succinate-ubiquinone oxidoreductase as complex II, ubiquinone-cytochrome *c* oxidoreductase as complex III, cytochrome *c* oxidase as complex IV and ATP synthase as complex V.

In addition to energy production, mitochondria are also key components in calcium signalling, regulation of cellular metabolism, haem synthesis, steroid synthesis and, perhaps most importantly, the initiation and execution of apoptosis [7,8]. Over the last 25 years, mitochondrial abnormalities that associated with mitochondrial DNA (mtDNA) alterations, has been identified in human disease, including seizure, ataxia, ophthalmoplegia, optic atrophy, short stature, sensorineural hearing loss, cardiomyopathy, diabetes mellitus and kidney failure [9,10]. Accumulation of altered mtDNA has also been widely believed to play the pivotal role in aging and the development of various age-related degenerative diseases [11]. In recent years, more attention has been directed towards the role of mitochondrial dysfunction in various cancer due to genetic defects of OXPHOS system [12-17]. Proteins that take part in the proper functioning of the OXPHOS system are encoded by both nDNA and mtDNA. Similar to nDNA, mtDNA mutations and deletions have been identified in a wide variety of cancers including brain tumor [18-26], although it is unclear whether these are causal or a consequence of the neoplastic process.

This chapter begins with a general overview of basic mitochondrial structure and OXPHOS system functions and then outlines more specifically the link between mitochondrial reactive oxygen spices (ROS) and apoptosis with tumorigenesis and genetic alterations in mitochondria associated with human cancers mainly brain tumor.

2. Mitochondrial structure

Mitochondria are seen by electron microscopy to be intracellular oblong or ovoid shaped organelles with a transverse diameter of 0.1-0.5 μm and a variable length [27]. The structure of mitochondria is shown in Figure 1. Most eukaryotic cells contain many mitochondria, which cover up to 25% of the volume of the cytoplasm. The number of mitochondria within a cell increases with the amount of substrate and oxygen. Mitochondria are large enough to be observed under a light microscope, but the detail of their structure can be viewed only with the electron microscope.

Initial studies based on electron microscopy investigations by two researchers Palade and Sjöstrand, revealed that mitochondria contain more than one membrane system with the existence of an outer membrane and of a highly folded inner membrane [28,29]. The baffle model which was coined by Palade has been accepted and currently depicted as a model of mitochondria structure in all the textbooks [28]. The baffle model describes mitochondria as having four compartments (Figure 1). The first compartment is termed the outer membrane. This smooth membrane surrounds with a very convoluted or folded inner membrane. The

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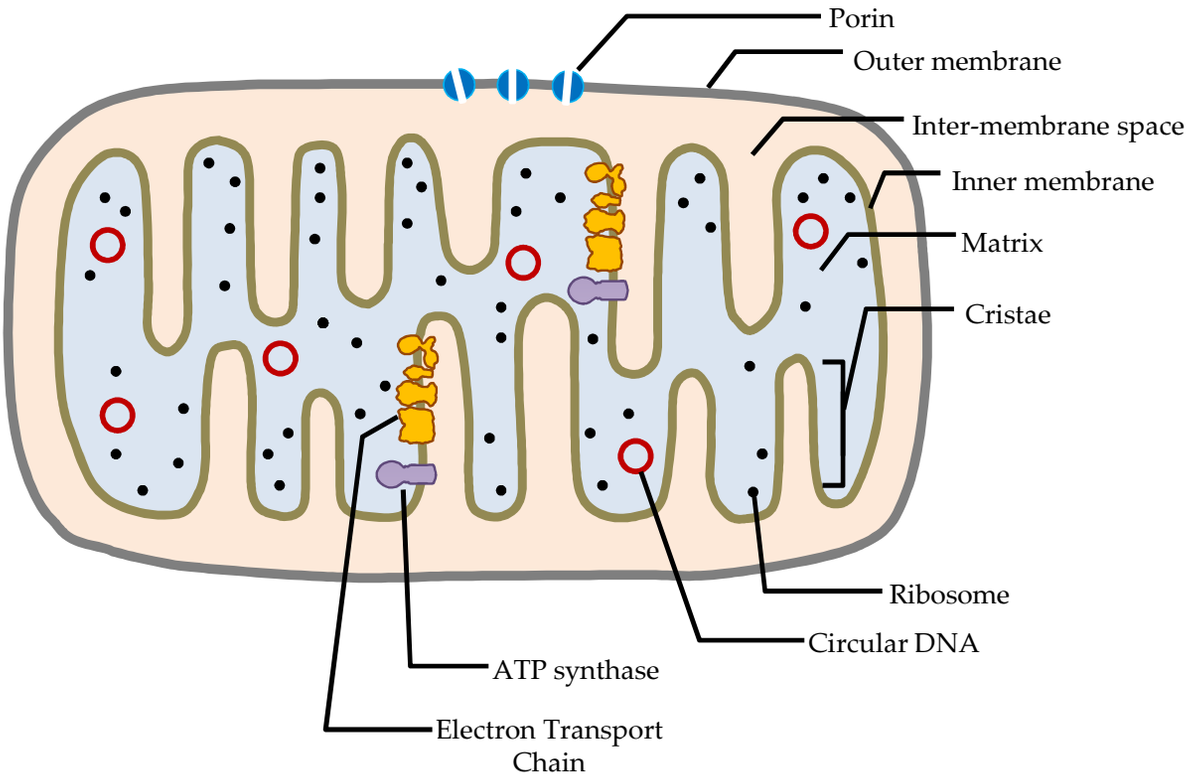

Figure 1. The structure of a mitochondrion

inner membrane is folded to create cristae. The outer and inner membranes have very different properties. Together they create two compartments, namely the intermembrane space (the space between the outer and inner membranes), and the matrix (closed by the inner membrane-the very interior of the mitochondria).

Nowadays, the baffle model has been shown to be inaccurate. Based on the investigations of 3-D structure of mitochondrial morphology by electron microscope tomography, the inner membrane is believed to be further divided into two distinct domains: an inner boundary membrane and cristae membranes [27, 30-32]. The inner boundary membrane is located close to the outer membrane and makes close contact with it at numerous positions. Cristae membranes protrude into the matrix compartment and are connected to the inner boundary membrane by narrow tubular structures called cristae junctions.

The outer bilayer lipid membrane contains channels made of voltage dependent anion channels called porins and are permeable to molecules < 10,000 Da. It is composed of approximately 50% lipids and 50% proteins. The inner bilayer lipid membrane is folded and impermeable to most molecules and protons. It is built up of 70% protein. The inner membrane is also the site of the electron transport chain and contains transport proteins for OXPHOS system. Within the matrix a large number of enzymes and other proteins and peptides, including DNA-polymerase, chaperones (heat shock proteins), ribosomes, mRNAs, tRNAs, and the mtDNA are located.

3. Mitochondrial function: OXPHOS system

Mitochondria play a central role in energy conversion processes (respiration) within the cell through the electron transport chain, the primary function of which is ATP synthesis via a complex mechanism referred to as "oxidative phosphorylation" (OXPHOS) (Figure 2). OXPHOS is the production of ATP using energy derived from the transfer of electrons in an electron transport system and occurs by chemiosmosis. As the process of mitochondrial electron transport takes place, energy is released in the form of a proton electrochemical gradient that can be used to make ATP. Though, the details regarding the conservation of this released energy are still being debated, most scientists accept the chemiosmotic hypothesis as the general mechanism for the energy transfer. The chemiosmotic hypothesis was formulated in the 1960s by Peter Mitchell [33,34]. This hypothesis states that hydrogen ions (H^+or protons) are transferred from mitochondrial matrix out across the inner membrane to the inter-membrane space as electron transport occurs by a series of reduction-oxidation reactions that establish an electrochemical gradient. The membrane is impermeable to protons, which flow back down the proton gradient through a large enzyme called ATP synthase or complex V, the energy from which is subsequently used to produce ATP.

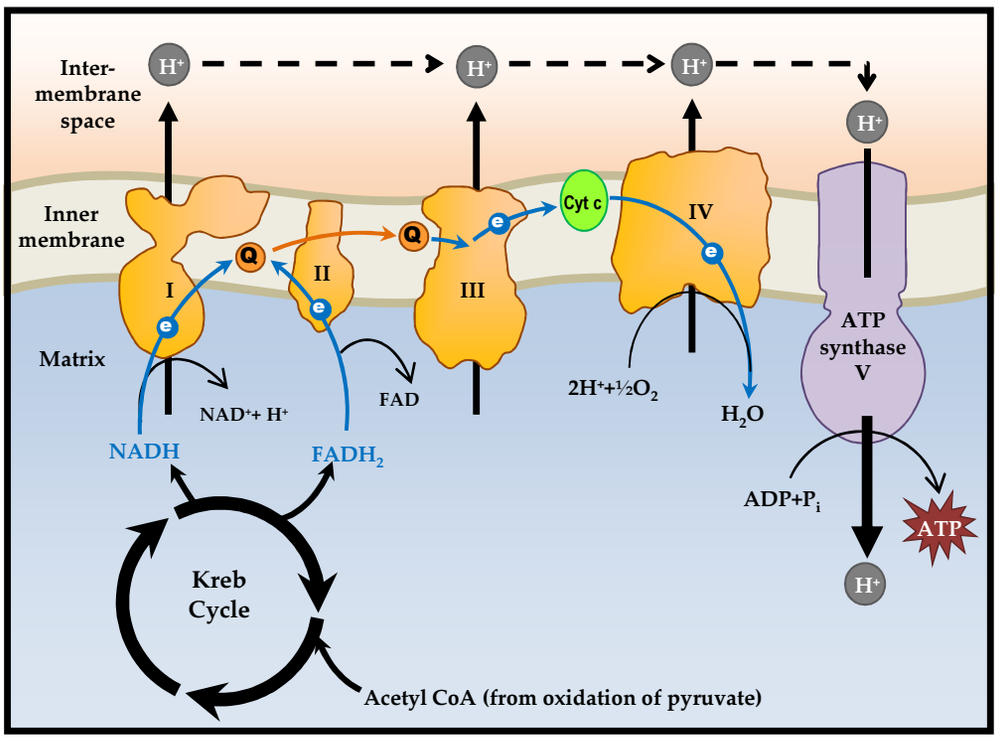

Figure 2. A schematic representation of the mitochondrial OXPHOS system

For achieving the whole process, in first stage pyruvate, which is generated in the cytosol during glycolysis, is transported across the double mitochondrial membranes and enters the matrix. The pyruvate molecules are produced by the breakdown of glucose molecules from carbohydrates via glycolysis. Once inside the matrix, pyruvate molecules are converted to the

two carbon compound acetyl coenzyme A (acetyl CoA). This oxidative decarboxylation reaction is catalyzed by the pyruvate dehydrogenase complex. The acetyl CoA is then taken into a sequence of enzymatically catalyzed reactions known as the citric acid cycle which completes the oxidation of carbon and regenerates an electron acceptor to keep the cycle going. The oxidation of acetyl CoA in the citric acid cycle (which is also called the Krebs cycle or tricarboxylic acid cycle) is catalyzed by a set of enzymes localized in the mitochondrial matrix. During this process, the released electrons are transferred to co-enzymes, $NAD^+$and FAD to form the reduced molecules NADH and $FADH_2$. Later, NADH and $FADH_2$ transfer electrons to acceptor molecules in the electron transport chain, in the inner mitochondrial membrane. Coenzyme Q (ubiquinone) and cytochrome c are also involved in mitochondrial respiration, serving as 'electron shuttles' or mobile electron carriers between the complexes.

Electrons donated from NADH to Complex I or from $FADH_2$ to Complex II are passed to coenzyme Q. Electrons then flow from coenzyme Q to Complex III which transfers the electrons to cytochrome c. From cytochrome c the electrons move to Complex IV and finally to ½ O_2 to produce H_2O [35]. As electrons pass through these complexes in a series of oxidation-reduction reactions, the energy that is released by this electron transport chain is used to pump protons out from the mitochondrial matrix to the inter membrane space via Complexes I, III and IV creating the electrochemical gradient. The electrochemical gradient allows protons to drive back into the matrix through a pore in Complex V (ATP synthase), using the released energy to catalyze the synthesis of ATP from ADP and phosphate.

4. Mitochondrial genome

Mitochondria have a genetic system of their own, separate from the nuclear one, with all the machinery necessary for its expression; that is, to replicate, transcribe and translate the genetic information they contain. The mitochondrial deoxyribonucleic acid (mtDNA) was discovered in 1963 [36] and the near complete sequence for human mtDNA was available in 1981 [37] and was minimally revised in 1999 [38]. Human mtDNA is mostly a double-stranded, closed circular molecule composed of 16,569 base pairs.

Figure 3 shows the human mitochondrial genome. It is very compact, containing little non-coding sequence, essentially just the 1.1 kb D-loop (displacement loop or non-coding) region, and having even some overlapping genes. The non-coding region that includes the D-loop is located between genes encoding tRNA phenylalanine (F) and proline (P). The two strands of mtDNA have been named light strand (L-strand, rich in cytosines) and heavy strand (H-strand, rich in guanines) according to their buoyancy through a denaturing caesium chloride gradient [39].

The D-loop region of mtDNA contains the origin of replication for H-strand synthesis as well as both mitochondrial transcription promoters (the light strand promoter, LPS and two heavy strand promoters, HSP1 and HSP2), and serves as the main site for mitochondrial genomic replication and transcription [40,41]. Between different mammalian species, the mtDNA is about the same size and has the similar organization and content of genes [42-44]. The

mitochondrial genome has been sequenced and mapped for many species yet the regulation of its expression is poorly understood.

The human mtDNA contains 37 genes coding mRNAs for 13 polypeptides that are part of four of the five multi-enzymatic complexes in the OXPHOS system, 22 tRNAs (that are able to decode all open reading frames) and 2 rRNAs (components of the specific mitochondrial ribosomes) necessary for synthesis of the polypeptides. Unlike nuclear DNA, mtDNA coding sequences have no introns. Seven of those polypeptides, ND1 to ND6 and ND4L are subunits of Complex I; one, cytochrome *b*, is part of Complex III; three, COX I, COX II and COX III, are the catalytic subunits of Complex IV, and ATPase 6 and 8 are subunits of Complex V (F_0F_1 ATP synthase). The heavy strand is the main coding strand, and codes for 2 rRNAs, 14 tRNAs and 12 polypeptides. The light strand codes for remaining 8 tRNAs and only one polypeptide, the ND6 subunit (NADH-dehydrogenase) [6].

Mammalian mitochondria are not self-supporting entities in the cell. Replication and transcription depend upon *trans*-acting nuclear-encoded factors. All proteins of mitochondrial ribosomes and their associated translation factors and, indeed, all other mitochondrial proteins including the components of the mitochondrial import machinery are encoded by the nuclear DNA. For instance, mitochondrial tRNAs are charged by imported aminoacyl-tRNA synthetases from nuclear genes.

There are approximately hundreds or thousands copies of mitochondrial genome in each somatic cell. Normally, all of the mitochondrial DNAs within the cells of an individual are identical, which is termed homoplasmy. However, in the presence of a mitochondrial DNA mutation, the affected individual cells will usually harbour a mixture of mutated and wild-type mitochondrial DNA. The condition of these two populations of mitochondrial DNA molecules is called heteroplasmy [45]. As cells divide, the mutant and wild-type mitochondrial DNA are randomly distributed to the daughter cells, so the proportion of mutant to wild-type mitochondrial DNA may increase or decrease with each subsequent generation of the cell line. If that proportion increases past a certain level, the cellular energy capacity will decline, and clinical signs appear. This is referred to as the threshold effect. The threshold may vary from tissue to tissue because the percent of mutant mitochondrial DNA needed to cause cell dysfunction varies according to the oxidative requirements of the tissue and the severity of the mutation. It has often been claimed that tissues with high requirements for oxidative energy metabolism, such as muscle and brain, have relatively low thresholds and are particularly vulnerable to mitochondrial DNA mutation.

Human mitochondrial DNA is a 16,569 base pair circle of double-stranded DNA that encodes 13 essential respiratory chain subunits. ND1–ND6 and ND4L encode seven complex I (NADH–ubiquinone oxidoreductase) subunits, CYT b encodes one subunit of complex III (ubiquinol:cytochrome *c* oxidoreductase), COX I–COX III encode the three major catalytic subunits of complex IV, and ATPase6 and ATPase8 encode two subunits of complex V (ATP synthase). Also shown are the two ribosomal RNA (12S rRNA and 16S rRNA) genes and the 22 transfer RNA genes (red spheres, depicted by single letter amino acid code abbreviation) required for mitochondrial protein synthesis. tRNAs are F, Phenylalanine; V, Valine; L, Leucine; I, Isoleucine; Q, Glutamine; M, Methionine; W, Tryptophan; A, Alanine; N, Asparagine; C, Cysteine;

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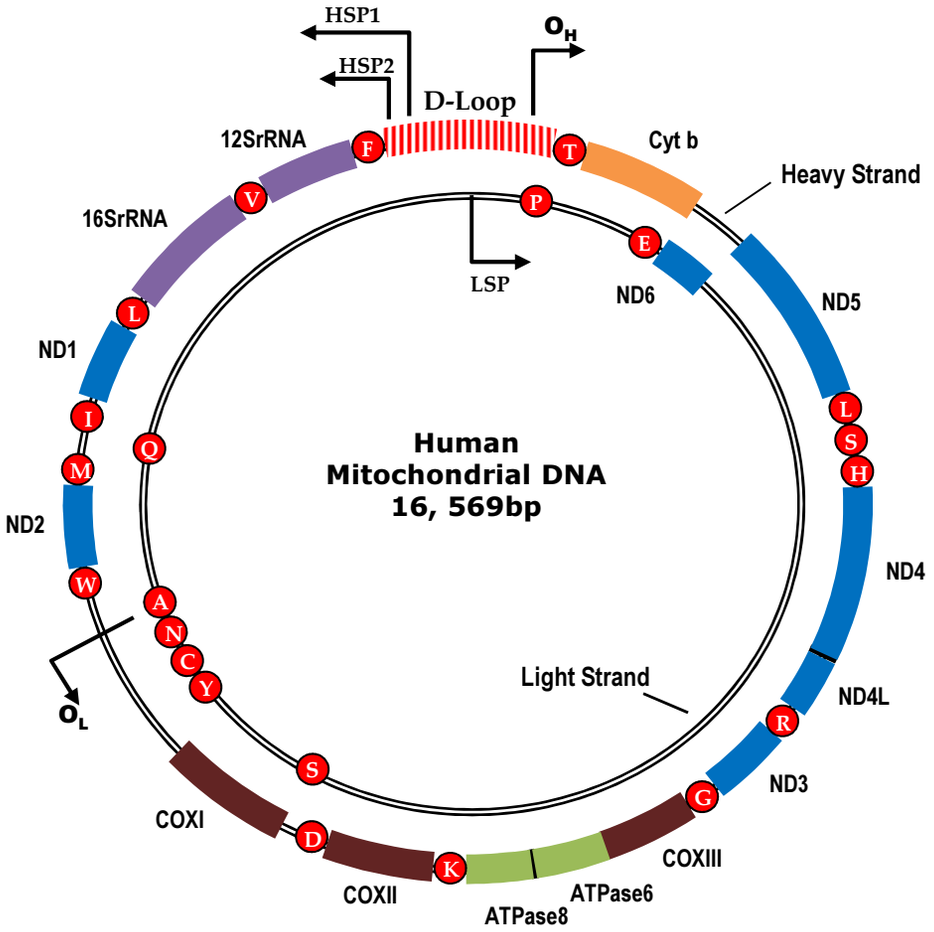

Figure 3. The human mitochondrial genome

Y, Tyrosine; S, Serine; D, Aspartic acid; K, Lysine; G, Glycine; R, Arginine; H, Histidine; E, Glutamic acid; T, Threonine; P, Proline. The genome is highly organised and shows little redundancy of its coding sequence. The displacement loop (D-loop), or non-coding control region contains the promoters for transcription of the L (LSP) and H strands (HSP1 and HS2) and the origin of replication of the H strand (O_H). The origin of light-strand replication is shown as O_L.

5. Warburg theory and mitochondrial dysfunction in cancer cells

In the 1930s, the German scientist, Dr. Otto H. Warburg pioneered the research specifically targeted to the alterations of mitochondrial respiration in the aspect of cancer. He reported that cancer cells exhibited a high glycolysis rate even in the presence of abundant oxygen. This phenomenon was known as the "Warburg effect". Cancer cells had to depend on anaerobic glycolysis rather than respiration to generate ATP [46]. He further proposed that defects in energy metabolism, especially due to mitochondrial malfunction, are involved in the initiation

or progression of cancer. Dr. Warburg's discovery encouraged many scientists to realize the potential role of mitochondria in cancer cells.

Since then, alterations of mitochondria in the number, shape and function have been reported in various cancers [47]. The conversion of ATP production from mitochondrial OXPHOS to glycolysis has been suggested to be the bioenergetic hallmark of cancer cells [48]. Furthermore, it has been shown that mitochondrial dysfunction is able to initiate critical signaling pathways that modulate cell proliferation or growth [49,50]. A study done by Pelicano's group found that mitochondrial respiration defects promoted to increased level of NADH, which could inactivate PTEN via a redox modification mechanism [51]. PTEN deactivation could lead to activation of the protein kinase B (Akt) survival pathway [51]. Akt was show to stimulate glycolysis and also trigger an increase in cell survival of cancer cells [52,53]. In addition, Lopez-Rios and colleagues showed that inhibition of OXPHOS activity by incubation of lung cancer cells with oligomycin could trigger a rapid increase in aerobic glycolysis [54]. This finding demonstrates that suppression of mitochondrial energy production can lead tumor cells become glycolytic [54]. However, when glycolysis was inhibited, tumor cells were unable to sufficiently upregulate mitochondrial OXPHOS and this indicating was due to partial mitochondrial impairment [55].

6. Reactive Oxygen Spices (ROS) and tumorigenesis

ROS such as superoxide anion radical (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH) are constantly generated during metabolic process in all living species [56]. Mitochondrial respiratory chain is a major intracellular source or producer of ROS generation, as some of the electrons passing to molecular oxygen are instead leaked out of the chain. Under normal physiological conditions, cellular ROS generation is counterbalanced by the action of the endogenous systems include mainly antioxidant enzymes for instance superoxide dismutases (SODs), cytosolic copper/zinc SOD (CuZnSOD) and mitochondrial manganese SOD (MnSOD). Low levels of ROS regulate cellular signaling and are essential in proliferation of normal cell. However, overproduction of ROS will lead to various cellular components injury, such as damage to DNA, proteins and lipids. Recent studies have demonstrated a role of ROS in promoting tumor development. The exposure of normal cells to ROS led to an increase in proliferation [57] and expression of growth-related genes [58-60]. Furthermore, cancer cells are commonly known to generate more ROS than normal cells [61,62]. These observations suggest that the stimulation of ROS may be an important contributing factor in the initiation, maintenance and development of cancer *in vivo*.

ROS are highly active and can also cause damage to mitochondrial genome [63,64]. It has been proposed that damage to mtDNA, if not repaired properly, could initiate tumorigenesis and promote cancer development [65,66]. Mutations in mtDNA may lead to a decreased efficiency of the OXPHOS system and increased leakage electrons as well as enhanced more mitochondrial and cellular ROS production. This situation may result in creating oxidative stress which will further accumulate more total damage to mtDNA because the location of mtDNA is in

close proximity to the ROS-generating electron transport system. Thus, it is possible that persistent oxidative stress on cells may favour the neoplastic process through induction of mtDNA damage which leads to mutations [67].

Moreover, in contrast to nDNA, mtDNA does not contain intronic sequences and not cover up with protective proteins such as histones. Due to these reasons, it has been suggested that most mtDNA mutations occur in coding sequences. However, more recent data shows that mtDNA can be almost completely covered by the DNA binding protein Tfam (mitochondrial transcription factor A) [68]. In addition, mtDNA also harbors limited effective DNA repair mechanisms. All these conditions are believed may contribute to the increased sensitivity of mitochondrial genome to damage, and ultimately leads to mutations. Whether mutations in mtDNA are a cause or a consequence of cancer is still debatable and need to be worked out. However, it is proven that mutations of mtDNA induced by oxidative damage could contribute significantly to OXPHOS defects and genetic instability in tumours and thereby promoting a higher propensity for tumour cell growth and progression [69]. This can be suggested that mutation of mtDNA may worsen oxidative stress or vice versa.

7. Apoptosis and tumorigenesis

Apoptosis, also called programmed cell death, is a crucial physiological process in the development and homeostasis of multicellular organisms which requires the involvement of mitochondria. Mitochondria have long been recognized for their essential role in regulating apoptotic signaling pathways [70,71]. Defects in apoptotic cell-death pathways are believed to contribute to genomic instability and tumorigenesis [72]. Study recently conducted shows that the mitochondrial respiratory chain has the ability to modulate apoptosis [73]. Respiratory chain dysfunction has been shown to either promote or suppress apoptotic cell death, relying on the specific alteration of electron flux [73]. Stimulation of ROS production can initiate apoptosis in the mitochondria. Mitochondrial defects normally can lead to reduced phosphorylation with low ATP generation and high cytosolic calcium and theses situations become a signal which triggers the apoptotic cell death [74]. Mitochondrial respiration defects in cancer cells can lead to activation of the Akt survival pathway which promotes cell death resistance. As mentioned earlier, this activation of Akt was suggested to result from increased level of NADH and inactivation of PTEN through a redox modification mechanism [51]. More interestingly, another study has elucidated the role of mitochondrial chaperones in modulating mitochondrial function for the survival of cancer cells [75,76]. Molecular chaperone heat shock protein 60 (Hsp60) was shown to orchestrate a broad cell survival program centered on stabilization of mitochondria and also to restrain p53 function [75]. Another chaperone, Hsp90 and its mitochondrial-related molecule, TRAP-1, were suggested to interact with cyclophilin D to suppress cell death [76].

8. Mitochondrial DNA mutations in cancer

Over 300 mtDNA mutations and even more mtDNA deletions have been reported that are associated with human diseases, since the first diseases caused by mtDNA damage were described 25 years ago [77-79]. Diseases that have been shown to be linked with mitochondrial dysfunction are diabetes mellitus, Parkinson's disease, Alzheimer's disease, epilepsy, sensorineural deafness and a variety of syndromes involving muscles and the central nervous system as well as a variety of forms of cancer [80-83]. The same mutation or different mutations in the same mtDNA gene may present with very different clinical manifestations, while the same clinical phenotype may be caused by different mutations (DiMauro and Schon, 2003). A large number of mtDNA mutations have been associated to a wide variety of clinical manifestations/ phenotypes of mitochondrial diseases include mitochondria encephalomyopathy, lactic acidosis and stroke-like syndrome (MELAS), myoclonic epilepsy and ragged red fiber disease (MERRF), Lebers hereditary optic neuropathy (LHON), Leigh's syndrome, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia (CPEO), neuropathy, ataxia, retinitis pigmentosa (NARP).

Although the role of nDNA mutations in carcinogenesis is well established, the importance of mtDNA alterations in the development and maintenance of cancers is only now beginning to be focused by researchers. Alterations in mtDNA which may lead to OXPHOS system destabilization seem to be particularly crucial because 13 proteins encoded by mtDNA are essential for complex I, and III–V respiratory chain assembly and these enzymatic complexes defects have been reported in human solid tumours [85]. There is considerable evidence suggesting that mitochondria may serve as potential contributors to carcinogenesis even though the exact mechanism of how mitochondria involved is still debatable and is not well-documented. Thus, mtDNA is now being targeted organelle by an increasing number of laboratories in order to investigate its potential role as biomarker for tumorigenesis in various types of tissues [86,87].

DNA alterations in mitochondria are believed to become fast hotspots of cancer research. Indeed, numerous mutations in mtDNA has now been observed in multiple cancer types (88-90] since the first somatic mtDNA mutation was detected 15 years ago by Bert Vogelstein's group in human colorectal cancer cells [91]. After these initial findings, mtDNA mutations or alterations have also been identified in bladder cancer [92], breast cancer [93-96], esophageal cancer [97-99], head and neck cancer [100], hepatocellular carcinoma [101-103], lung cancer [104-106], ovarian cancer [107,108], prostate cancer [109-111], renal cancer [112], thyroid cancer [113] and a number of blood cancers [114,115]. More recently, various types of molecular abberations in mtDNA such as point mutations, polymorphisms, depletion, insertions, microsatellite instability and changes in mtDNA copy number have been characterized throughout the mitochondrial genome in human cancers [89,90,116].

9. Somatic mitochondrial DNA alterations and brain tumors

Although there have been studies reporting about the association of mtDNA mutations with brain tumors, it is still no clear evidence whether mitochondrial abnormalities are contributing factors in brain tumorigenesis. Several types of somatic mtDNA alterations have been identified in brain tumors. These mtDNA alterations include point mutations, deletions, insertions, mtMSI (mitochondrial microsatellite instability) and copy number changes.

9.1. Point mutations

A number of studies have detected mtDNA point mutations in cancer of the brain and other central nervous system, including gliomas, astrocytomas, gliomatosis cerebri, medulloblastoma, meningiomas, schwannomas, and neurofibromas [19,20,117-120]. Mitochondrial genome somatic point mutations were most frequently found in the D-loop region, especially in a polycytosine (poly-C) mononucleotide repeat tract located between 303 and 315 nucleotides known as D310. This location has been identified as a hot spot region for somatic mtDNA mutations in various human cancers, including in brain cancer. In 2005, Montanini's groups analyzed the D-loop region of mtDNA in 42 patients affected by malignant gliomas and found sequence alterations in 36% of the patients including 16 somatic mutations, mostly in the D310 area. The authors suggested that mtDNA mutations were easily amplified from post-surgical tumor cavities and could be used for the clinical follow-up of malignant gliomas [121].

Instead of focusing on D-loop region, the complete of mitochondrial genome was also examined by various researchers in brain cancer patients. In a study that involved the entire mtDNA mutation scanning by temporal temperature gel electrophoresis (TTGE) in medulloblastomas, 40% of the cases (6/15) were found to have at least one somatic mutation [20]. Seven matched cerebrospinal fluid (CSF) samples were also analyzed to detect mtDNA mutations, where some of them were harbored mtDNA mutations in the tumors. This study suggests that somatic mtDNA mutations in CSF shows some promise as potentially useful biomarkers for disease prognosis. On the other hand, Lueth's group (2010) also reported the existence of somatic mtDNA mutations in 6 of 15 medulloblastoma patients. These results are in support of their previous findings on frequency of somatic mitochondrial mutations in medulloblastoma [23]. Before investigation on medulloblastoma patients, Lueth and colleagues have sequenced entire mitochondrial genome of tumor tissue and matched blood samples from 19 pilocytic astrocytomas patients and identified somatic mutations in as many as 16 (84%) cases [22].

In the cases of neurofibromas, Kurtz and team (2004) analyzed the whole mitochondrial genome in 37 neurofibromatosis type 1 patients and found somatic mutations in 7 individuals with cutaneous neurofibromas (37%) and 9 patients with plexiform neurofibromas (50%) [119]. All of the mtDNA somatic mutations detected in this study occurred in the D-loop region. The reason of most genetic mutations to occur in non-coding regions of the mitochondrial genome is currently unknown. However, mutations in the D-loop are believed to influence the origin of replication and promoter region and thus may lead to impair mitochondrial biogenesis and defective transcription and protein expression [122,123].

9.2. Deletion

Amongst the large-scale deletions identified in the mitochondrial genome, the 4977-bp deletion is the most common mtDNA deletion detected in various types of cancers including thyroid tumors, esophageal carcinoma, hepatocellular carcinoma, gastric cancer, and breast cancer [124-128]. This deletion recognized as "common deletion" removes all 5 tRNA genes and 7 genes encoding 4 complex I subunits, 1 complex IV subunit, 2 complex V subunits, which are essential for maintaining normal mitochondrial OXPHOS function. The consequence of this deletion could cause a complete failure of ATP production and abnormal ROS generation [129]. Although the 4977-bp deletion has been implicated in the process of carcinogenesis, the involvement or role of this deletion in brain tumors has not yet been investigated. Besides no study to date on the brain tumors, Wallace's group examined the existence of 4977-bp deletion in the aging process using brain normal individuals [130]. They found a significant increase in the 4977-bp deletion from young to old individuals, in different regions of the brain between cortex, putamen and cerebellum. Therefore, it was suggested that this mtDNA deletion might contribute to the neurological impairment associated with ageing. The 4977-bp deletion was also detected in the autopsied brains of patients with bipolar disorder [131].

9.3. Mitochondrial microsatellite instability

In 1999, Kirches and colleagues revealed high mtDNA sequence variants in 12 astrocytic tumors [117]. Two years later, the same group extended the study by examining 55 gliomas specimens for mtDNA instability in the poly-C tract of mitochondrial D-loop using a combination of laser microdissection and PCR technique [19]. They found a lower frequency of 9% of specimens with the poly-C tract alterations. In addition, they also sequenced the entire D-loop in 17 frozen glioblastoma samples and corresponding blood samples for detecting somatic mutation. In 2003, a follow up study of mitochondrial genome instability was carried out and the author later determined that poly-C tract of the hypervariable region (HVR2) as a clonal marker in gliomatosis cerebri patients [118].

Most recently, Yeung's team investigated the contribution of mitochondrial genome variants in glioblastoma multiforme (GBM) [132]. In this study, mtDNA variants were analysed in a series of GBM cell lines using a combination of next generation sequencing and high resolution melt (HRM) analysis. They reported a greatest frequency of mtDNA variants in the D-loop and origin of light strand replication in non-coding regions. Moreover, in coding region, ND4 and ND6 were the most affected genes to mutation which both of them encode subunits of complex I of the electron transport chain. The author concluded that these novel variants at the mitochondrial genome offer an advantage to cells for promoting GBM tumorigenesis [132].

9.4. Copy number changes

In addition to mtDNA mutations and deletion, changes in the mtDNA copy number have been studied in gliomas [133,134]. As first previously reported by Liang (1996), 15 of low-grade were assessed with cDNA homologous to mtDNA at position 1,679-1,946 and 2,017-2,057 and the results revealed that these tumors had increased mtDNA copy number when compared to

normal brain tissue controls [133]. In a separate study done by Liang and Hays (1999), 39 out of 45 (87%) examined gliomas, both low-grade and high-grade specimens, had increased up to 25-fold in mtDNA copy numbers [134]. They claimed that this frequency was much higher than erb-b gene amplification which was present in only 18% of these tumors.

9.5. Mitochondrial gene expression changes

In 2005, Dmitrenko's group screened cDNA libraries of human fetal glioblastoma and normal human brain samples and revealed 80 differentially expressed genes [135]. They identified 30 were corresponded to mitochondrial genes for ATP6, COXII, COXIII, ND1, ND4 and 12S rRNA. According to their data, all these mitochondrial transcripts were expressed at lower level in glioblastomas as compared to tumor-adjacent histologically normal brain [135].

10. Conclusion

The role of mtDNA mutations in cancer remains largely unclear and therefore more studies and attentions should been given before a clear conclusion could be achieved. There is a lot of evidence suggesting that some mtDNA mutations do play a role in certain stages of cancer development and progression, but further research is needed to clarify this possible link. There are still multiple potential experimental pitfalls and weaknesses, thus relevant caution and basic guidelines in research should be followed in order to obtain the best results [136,137]. Based on our ongoing research and previous studies from other researchers, it could be suggested that mtDNA mutations could be a genetic aberration target in cancer development, instead of nuclear oncogenes and tumor suppressor genes. Cancer cells are very mutagenic in the early stage either due to exposure to high levels of carcinogenic substances or conditions or because of lack of repair mechanism. Thus, mtDNA simply seem to be more prone to mutation at this stage and has a limited ability to repair itself.

Mitochondria produce energy and their genome is responsible for regulating OXPHOS function. Aberrations in mtDNA may interrupt this process and ultimately lead to abnormal function of the cell. The unique properties of mtDNA, including its high copy number, high susceptibility to mutations, and quantitative and qualitative changes in cancer, stimulate researchers to closely be involved in the clinical relevance investigation of mtDNA alterations in cancers. In addition, the screening of mtDNA mutations is more easy and cost-effective than nDNA analysis, due to several advantages that mtDNA have such as a simple circular structure with a short sequence length. It has been shown that the existence of mtDNA mutations in cancer cells is particularly consistent with the intrinsic sensitivity of mtDNA to accumulate oxidative damage. Impairment of mitochondrial OXPHOS activity and mtDNA damage seem to be a common feature of malignant cells. Instability and abnormality in DNA and protein of mitochondria have been identified in various solid tumors and hematologic malignancies. However, up to now many studies have been directed toward identifying and characterizing the altered mtDNA. There have been only limited studies, mainly in relation to its functional consequences and clinical relevance. The functional aspects of mtDNA mutations in cancer

development will provide a mechanistic link between mitochondria and carcinogenesis and also will translate into some useful prevention and therapeutic strategies of cancer in the future research.

Although to date mutations, polymorphisms, and variants of mtDNA have been described in brain tumors, there are more studies that need to be done to fully understand the role of mtDNA in these tumor cells. Further studies which include the assessment of the different types and stages of brain tumor need to be carried out. It is very crucial because perhaps that only certain stages and types will be sensitive to the effects of mtDNA mutations. Based on available evidence suggests that mtDNA may play a key role in the development and modulation of different steps of carcinogenesis. They could be used in the future as new potential target markers for rapid and effective early detection of brain tumorigenesis.

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