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Review

Genetic insights into OXPPOS defect and its role in cancer[☆]

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ABSTRACT

Warburg proposed that cancer originates from irreversible injury to mitochondrial oxidative phosphorylation (mtOXPHOS), which leads to an increase rate of aerobic glycolysis in most cancers. However, despite several decades of research related to Warburg effect, very little is known about the underlying genetic cause(s) of mtOXPHOS impairment in cancers. Proteins that participate in mtOXPHOS are encoded by both mitochondrial DNA (mtDNA) as well as nuclear DNA. This review describes mutations in mtDNA and reduced mtDNA copy number, which contribute to OXPPOS defects in cancer cells. Maternally inherited mtDNA renders susceptibility to cancer, and mutation in the nuclear encoded genes causes defects in mtOXPHOS system. Mitochondria damage checkpoint (mitocheckpoint) induces epigenomic changes in the nucleus, which can reverse injury to OXPPOS. However, irreversible injury to OXPPOS can lead to persistent mitochondrial dysfunction inducing genetic instability in the nuclear genome. Together, we propose that “mitocheckpoint” led epigenomic and genomic changes must play a key role in reversible and irreversible injury to OXPPOS described by Warburg. These epigenetic and genetic changes underlie the Warburg phenotype, which contributes to the development of cancer. This article is part of a Special Issue entitled: Bioenergetics of Cancer.

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1. Introduction

Mitochondria perform multiple cellular functions. Mitochondria produce ATP through oxidative phosphorylation (OXPHOS). Studies suggest that the OXPPOS system is severely compromised in cancer. Indeed, defect in OXPPOS is described as one of the most common and profound phenotypes of most cancers [1–19]. In 1930, Otto Warburg proposed that cancer was caused by defects in OXPPOS or respiration in the mitochondria, forcing cells to shift to an energy generation process through glycolysis despite aerobic conditions [16,20–22]. This characteristic of cancers is described as “Warburg effect.” During the past few years Warburg effect is being reconsidered and is the subject of increasing interest in cancer research [20,22–25]. Warburg effect plays an important role in tumor development by remodeling the metabolic profile of tumor cells, which allows cell survival under adverse conditions [23,26–29].

Since the description of the Warburg effect, studies have shown that cancer cell mitochondria have a characteristic shape and size [6–8]. Studies indicate that cancer cell mitochondria are small, possess few cristae, altered membrane composition, as well as altered membrane

potential [6–8]. Other types of mitochondrial abnormalities in cancers have also been described [3,10,14,30]. These include mitochondrial hyperplasia [3,4,10,30,31], differential expression of mitochondrial cytochrome c oxidase subunit II in benign and malignant tissues [10,32], and mammary adenocarcinoma with fewer mitochondria [33].

2. The OXPPOS system

OXPPOS system consists of five major protein complexes called complex I (NADH dehydrogenase or NADH:ubiquinone oxidoreductase), complex II (succinate dehydrogenase or succinate:ubiquinone oxidoreductase), complex III (the bc1 complex or ubiquinone:cytochrome c oxidoreductase), complex IV (cytochrome c oxidase, cytochrome c oxidoreductase), and complex V (ATP synthase); which are localized on the inner mitochondrial membrane. Additionally, OXPPOS system also involves two electron transport carriers, ubiquinone or coenzyme Q10 and cytochrome c [34]. The main function of OXPPOS is to transport two electrons from NADH or FADH₂ to oxygen molecules to generate water as a byproduct [34]. During electron transport, complexes I, III, and IV pump protons from the mitochondrial matrix to the intermembrane space resulting into increase in membrane potential across the inner mitochondrial membrane. In the presence of ADP, complex V actively allows flow of protons back to the matrix resulting into generation of energy in the form of ATP [34].

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OXPPOS proteins are encoded by both nuclear as well as mitochondrial DNA (mtDNA). The most important biological function of mtDNA is to encode enzyme subunits of the respiratory chain. Remarkably, human mtDNA is very small (16,569 bp). mtDNA is also extremely vulnerable to oxidative damage by reactive oxygen species (ROS) produced within mitochondria as a byproduct of OXPPOS. Of ~85 subunits as components of various OXPPOS complexes, 13 are encoded by mtDNA [35]. These 13 proteins constitute various subunits that make up four OXPPOS complexes (Complex I, III, IV, V). The rest of the subunits (>35 for Complex I, 10 subunits for protein Complex III and IV and 14 subunits for Complex V) are encoded by the nucleus, translated in the cytosol and imported into the mitochondrial compartment [5,36]. It is noteworthy that all four subunits constituting Complex II are entirely encoded by nuclear DNA. The mtDNA also encodes 22 tRNAs and two rRNAs involved in the synthesis of OXPPOS subunits. The D-loop region present in the mitochondrial genome controls both mitochondrial transcription and replication. Mutations in the D-loop regions, therefore, can result into inhibition of mitochondrial transcription and replication. mtDNA requires transacting nuclear encoded factors for its transcription and replication. To date genetic insights into OXPPOS defects in cancer are lacking, and very little is known about the genetic defects in DNA encoding various OXPPOS proteins or proteins involved in regulation and assembly of the OXPPOS system.

3. Nuclear genes involved in OXPPOS defect in cancer

The renewed interest in the Warburg effect has revealed that some mtOXPPOS proteins act as tumor suppressors. For example mtOXPPOS enzyme succinate dehydrogenase (SDHD, Complex II) is shown to be mutated in hereditary paragangliomas and pheochromocytomas [27,37,38]. SDHD oxidizes succinate to fumarate in the Krebs cycle and is involved in the mitochondrial electron transport chain. Mutations in three of the four subunits of succinate dehydrogenase, namely, SDHB, SDHC, and SDHD, have been involved in tumorigenesis [27,37,38]. Recently, mutations in SDHD5 gene encoding proteins involved in assembly of SDHD complex that contribute to hereditary paragangliomas have been described [25,39]. Interestingly, hereditary mutation in SDHA leads to typical mitochondrial disease such as Leigh syndrome characterized by severe progressive neurodegenerative disorder causing epilepsy, psychomotor retardation, and tetraspasticity [40]. However, recent evidence reveals that SDHA is also a tumor suppressor gene [41]. Mutation in SDHA gene causes paraganglioma and pheochromocytoma [41].

Paraganglioma and pheochromocytoma are rare benign tumors of chromaffin tissues and arise in the adrenal medulla (pheochromocytoma proper). Paraganglioma can also arise in extra-adrenal regions of the head and neck, thorax, abdomen or pelvis. Mutation in SDH genes led to tumorigenesis, and thus, should be considered as tumor suppressor genes [37,38,41,42]. In addition, hereditary mutations in the Krebs's cycle enzyme fumarate hydratase (FH) lead to leiomyomas, uterine fibroids, and renal cell carcinoma [43]. Inhibition of FH activity stabilizes hypoxia-inducing factor, which induces angiogenesis in cancer, and thus, promotes tumorigenesis [44].

In addition to hereditary mutations, somatic mutations involving genes in OXPPOS metabolism have been described. Indeed both germline and somatic mutations in NDUFA13/GRIM-19, a subunit of Complex I involved in mtOXPPOS, are linked to Hürthle cell tumors of the thyroid [45]. NDUFA13/GRIM19 is an indispensable component of complex I. NDUFA13/GRIM19 is essential for the assembly and enzymatic activity of complex I [46]. Loss of NDUFA13/GRIM19 in mice leads to embryonic lethality [46]. Down-regulation or loss of NDUFA13/GRIM19 expression has been reported in renal cell carcinomas (RCC) and colorectal carcinoma [45,47,48]. Altogether, these findings suggest a role for mtOXPPOS in tumorigenesis.

Somatic mutations affecting isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2), which catalyze the conversion of isocitrate to the Krebs cycle-intermediate α -ketoglutarate, have been identified in brain tumors [49,50]. Recent studies also indicate the presence of IDH1 and IDH2 mutations in other type of cancers such as prostate and B-acute lymphoblastic leukemias [51]. Mutation in IDH1 genes impairs its affinity for substrate and dominantly inhibits wild-type IDH1 activity through the formation of catalytically inactive heterodimers, which leads to the expression of hypoxia-inducing factor with subsequent promotion of tumorigenesis [52]. Singh's group [53] describe that tumor suppressor p53 regulates mtOXPPOS [53]. p53 also regulates glycolysis through TIGAR (TP53-induced glycolysis and apoptosis regulator) [54] or PGM (phosphoglycerate mutase) [55]. The p53 gene is mutated in a large number of human cancers. Interestingly, our study suggests that p53 also regulates mtDNA content via regulation of the RNR2 gene [56]. These findings suggest that p53 can modulate the balance between mtOXPPOS and glycolytic pathways in cancer cells.

Polymerase-gamma (POLG) is the only DNA polymerase known to function in human mitochondria [19,57]. POLG gene was mutated in 63% of breast tumors [19,58,59]. Mutations were found in all three domains of the POLG protein, including T251I (the exonuclease domain), P587L (the linker region) and E1143G (the polymerase domain). We have identified two novel mutations that include one silent (A703A) and one missense (R628Q) mutation in the evolutionarily conserved POLG linker region. Mutant POLG, when expressed in cancer cells, induced a depletion of mtDNA, decreased mitochondrial activity, decreased mitochondrial membrane potential, increased levels of reactive oxygen species and increased matrigel invasion. These studies suggest a role for POLG in OXPPOS dysfunction in cancers and in promoting tumorigenicity [19,57].

4. Mitochondrial genes involved in OXPPOS dysfunction in cancer

4.1. Somatic mutations in mtDNA

Mitochondrial DNA mutations have been increasingly identified in various types of cancer [60,61]. A number of mtDNA rearrangements and amplifications have been reported in acute myeloid leukemia [62]. Point mutations in mtDNA mutation have been reported in human colorectal cancer cells [60], esophageal, ovarian, thyroid, head, neck, lung, bladder, renal, and breast cancer cells [61,63–69]. These reports led to a suggestion that mutations in mtDNA D-loop can function as an independent prognostic marker for breast cancer [70,71]. Mutations in mtDNA have been described in tRNAs, rRNA, and protein encoding regions. Since these mutations affects the synthesis of peptides that are important components of various complexes, the ultimate outcome is likely to be defective OXPPOS [60,61,72].

There are various factors that contribute to mutations in mtDNA. For example lack of protective histones, limited DNA repair capability, lack of introns, and continuous exposure to ROS [73,74] are associated with increased rate of mutations in mtDNA. The AAA+ protein ATAD3, a component of mitochondrial nucleoids, has been shown to bind mtDNA but this process is transiently required only for nucleoid formation and segregation [75]. Therefore, ATAD3 may not play a role in protection of mtDNA like histones do for nuclear DNA. Other proteins such as mitochondrial transcription factor A (Tfam), the major mtDNA packaging protein [76], and Twinkle, a mtDNA helicase [77], mitochondrial single-strand binding protein, and DNA polymerase γ [78] have been associated with mtDNA, but their role in providing protection is not clearly defined [79].

4.2. Reduced mtDNA content (copy number)

Human mtDNA contains one single control region called the D-loop that controls mtDNA replication and transcription of mtDNA-

encoded OXPHOS genes. Mutation in the D-loop region is an important feature and has been reported in variety of tumors examined to date [15,16,80]. Mutations in the D-loop region result in altered binding affinities of the nuclear proteins involved in mtDNA replication and transcription leading to the depletion of mtDNA content [81,82]. Consistent with this notion, our laboratory recently reported a near absence of mtDNA-encoded cytochrome c oxidase subunit II expression in more than 40% of breast and ovarian tumors [32]. Other laboratories have also measured mtDNA content in tumors and report a decrease in mtDNA content in breast [71,83] renal [84] hepatocellular [83,85] gastric [86] and prostate tumors [87]. Depletion of mtDNA is also supported by a decrease in OXPHOS levels in renal tumors [88].

Reduced mtDNA leads to increased invasiveness and aggressive disease [88,89]. Reduced mtDNA has also been associated with liver cancer [85] as well as with higher histological grade of breast cancer in patients [71,90]. In order to establish the copy number of mtDNA as a marker for breast tumorigenesis, Shen et al. examined the copy number of mtDNA of noncancerous cells such as whole blood and observed high copy number in noncancerous blood cells of breast cancer patients as compare to healthy subjects [91]. Notably, mtDNA copy number was inversely proportional to several important endogenous antioxidant entities such as total glutathione, Cu-Zn SOD, and catalase. Interestingly, estrogen receptor (ER) positive normal breast tissues harbor higher level of mtDNA as compared to ER negative breast tissues [92], and ER localizes to mitochondria suggesting that ER presence in mitochondria regulates OXPHOS function [93–95]. Similar to ER, p53 also localizes to mitochondria and regulates mtDNA copy number [56,96]. Reduced mtDNA copy number has been associated with resistance to apoptosis and increased metastasis [73,88,97,98]. Reduced mtDNA represents a credible diagnostic or prognostic marker for breast cancer.

5. Maternally inherited predisposition to cancer

mtDNA is inherited maternally and genetic differences in mtDNA modulate the assembly of OXPHOS complexes [99] and its function [100]. Several studies have explored whether there is maternally inherited predisposition to cancer [101–109]. Tanaka's group analyzed a population with 1503 autopsied cases. The genotypes for 149 polymorphisms in the coding region of the mitochondrial genome were determined. The haplogroups were classified into 30 haplotypes. Subjects with the haplogroup M7b2 showed an increased risk for hematopoietic cancer. Results also indicated that haplogroup M7b2 is a risk factor for leukemia [101,102].

Booker and colleagues determined an association of U haplogroup with prostate and renal cancers [103]. They found that patients carrying U haplogroup had an increased risk of renal and prostate cancer. Bai and colleagues analyzed mtDNA polymorphism in European–American females and reported that A10398G and T16519C increase breast cancer risk [104]. In contrast, T3197C and G13708A were found to decrease breast cancer risk. Wang's group [105] evaluated polymorphisms in mtDNA associated with increased risk of pancreatic cancer. They screened Caucasian cases and found no significant associations with pancreatic cancer [105].

The 10398A allele localized in NADH dehydrogenase-3 locus (ND3) of mtDNA is associated with increased risk for invasive breast cancer in African–American women [106,107]. Similarly, 10398A mutation is also associated with breast and esophageal cancer in Indian women, whereas 10398G had been shown to increase the risk of breast cancer in European–American women [104,108]. G10398A along with other germline mutation such as G9055GA, T16519C, G13708A, T3197C, and A10398G also result in increased susceptibility to breast cancer in women [104,106]. Using cybrid approach, Singh's group analyzed tumorigenic potential of 10398A found in African–American woman [109] and found that 10398A induces complex I

activity resulting in increased ROS production. The 10398A also conferred resistance to apoptosis mediated by Akt activation. Additionally, Kulawiec and colleagues demonstrated that the G10398A leads to an increased tumorigenesis and metastases in mice [56,109].

6. Mitochondrial and nuclear intergenomic cross talk and its role in cancer

A highly coordinated retrograde cross-talk between mitochondria and the nucleus exists in eukaryotic cells [15,110–113]. Studies suggest that retrograde cross talk involves epigenetic and genetic changes, which play a key role in tumorigenesis.

6.1. OXPHOS induced epigenetic changes in the nucleus

Epigenetic modification in the nuclear genome plays a key role in human tumorigenesis. Smiraglia et al. [114] performed Restriction Landmark Genome Scanning (RLGS) with the methylation-sensitive enzyme NotI, which recognizes the sequence GCGGCCGC, and showed that 64 sites were hypomethylated and 50 sites were hypermethylated when mtDNA was depleted from four different cell lines [114]. The methylation changes affected more than 9% of the CpG regions tested. In one set of experiment, Smiraglia et al. [114] transferred the original mtDNA into the p0 cells (devoid of mtDNA) to create a cybrid line and then determined the reversibility of the 22 epigenetic changes that were found after the removal of mtDNA. Interestingly, when mtDNA was depleted, hypomethylation events outnumbered hypermethylation events 3-to-1, strikingly similar to the loss of imprinting events associated with increased tumorigenesis [115]. In p0 cells, 17 sites became hypomethylated, and 5 sites were methylated. After transfer of mtDNA, all 5 newly methylated sites remained methylated, and 12 of 17 (70%) of the hypomethylated sites remained hypomethylated. Only 5 of the 17 hypomethylated sites (30%) were remethylated after the reintroduction of mtDNA. These data suggest that OXPHOS impairment plays an important role in the aberrant methylation of CpG islands found in nearly all cancers. The identity of signal(s) that triggers epigenetic changes in the nucleus is not known at this time. Since OXPHOS defect leads to changes in redox status, membrane potential and the level of ATP, it is plausible that either a single intracellular change or a combination of these changes signal epigenetic changes [114].

6.2. OXPHOS induced genetic changes in the nucleus

In addition to epigenetic changes described above, studies indicate that the OXPHOS defect results in genetic changes in the nuclear genome [109,112,116]. This effect was due to an imbalance in nucleotide pools induced by depletion of mtDNA [117]. We found that nuclear genome instability was increased by injury to OXPHOS [109,112,117]. We also demonstrated that OXPHOS dysfunction activates an evolutionary-conserved error-prone DNA repair pathway involving Rev1, Rev3 and Rev7 proteins [116]. We determined gene expression changes associated with OXPHOS defect [110,113]. The DNA repair proteins APE1, p53 and SMC4 [56,112] were down-regulated in response to OXPHOS defective cells [112]. Importantly, expression of these genes was reversed if OXPHOS function is restored. These studies provide evidence for OXPHOS control of genetic changes in the nucleus.

7. Mitochondrial checkpoint in cancer

We previously described a conceptual framework of *mitochondrial checkpoint* that monitors the functional state of mitochondria and responds to spontaneous or induced injury to mitochondria [15,18,56,80,112,118,119]. The mitochondrial checkpoint coordinates and maintains the proper

balance between apoptotic and antiapoptotic signals. Upon injury to mitochondria, mitochekpoint is activated to help repair injury to mitochondria, restore normal mitochondrial function, and avoid induction of mitochondria-defective cells. Early response to restore normal mitochondrial function includes epigenomic changes in the nucleus [120]. Thus, mitochekpoint controls gene expression and helps restore the incurred damage (Fig. 1) [56,110,121].

If mitochondria are severely injured, such an event will trigger apoptosis (Fig. 1). If injury to mitochondria is persistent and defective mitochondria accumulate in a cell, it would lead to nuclear genome instability [109,112,116,117]. Accumulated nuclear genome instability can help cells acquire new functions such as resistance to apoptosis [109,121], migration, and invasive characteristics, which in turn, can induce tumorigenesis [109,113] (Fig. 1).

Recent studies suggest that cellular senescence provides an important barrier to tumorigenesis. Studies conducted in various cell types provide *in vivo* evidence that senescence is a defining feature in premalignant tumors [122–125]. Cellular senescence limits the capacity to replicate, thus preventing the proliferation of cells. Senescence bypass appears to be an important step in the development of cancer [126]. Our study suggests that injury to OXPHOS leads to cellular senescence [121] and a bypass induces genetic instability in the nucleus [56,117]. We propose that OXPHOS-induced cellular senescence may act as an additional checkpoint mechanism that suppresses tumorigenesis

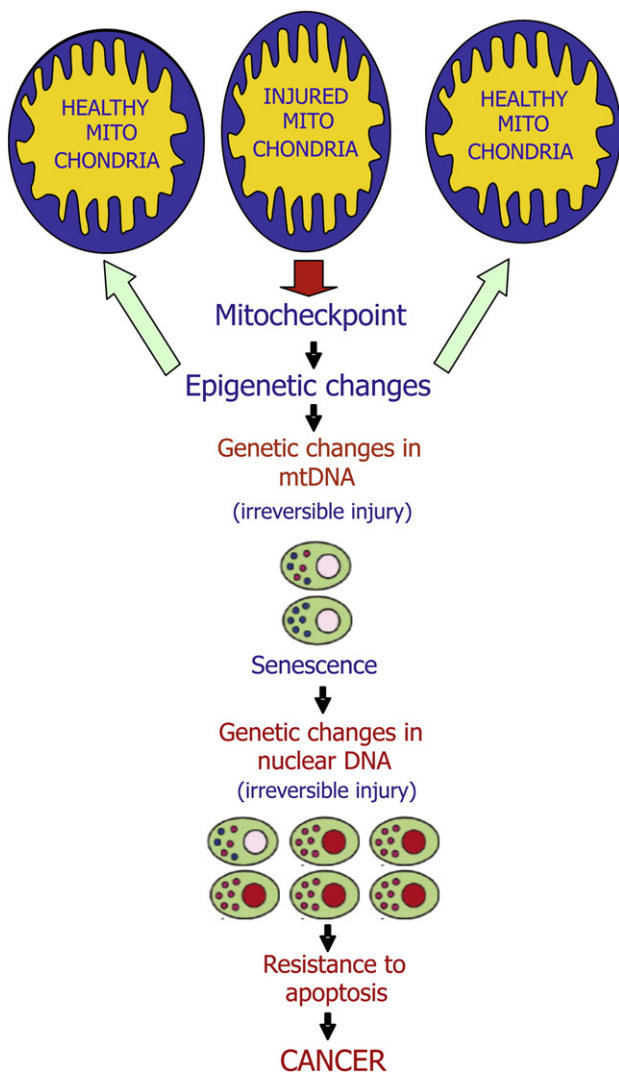


Fig. 1. Role of mitochekpoint in reversible and irreversible injury to OXPHOS and in development of cancer (see text for details).

(Fig. 1). In summary, we suggest that injured mitochondria activate mitochekpoint to restore normal mitochondrial function. When mitochondria are 1) injured severely or 2) damage is persistent (for example, mutation in mtDNA), mitochekpoint can trigger cellular senescence. Accumulation of mutations in mitochondrial and/or nuclear genome of cells containing severely damaged mitochondria may bypass cellular senescence leading to resistance against apoptosis and development of tumors. The mitochekpoint shares the characteristics of a signal-transduction pathway and may contain components, such as mitochondrial injury sensors, mediators, signal-transducers and effectors [55]. Sensor protein(s) recognizes injury to mitochondria and mediators signal the presence of injured mitochondria and initiate a biochemical cascade(s). Transducers are likely to be protein kinases that relay and amplify the signal. Effectors may include a transcription factor (such as p53; [55]), involved in regulation of DNA repair, cell proliferation, apoptosis, and tumorigenesis.

8. Conclusions

This review provides a genetic insight into the Warburg's observations of OXPHOS defect and its role in cancer. Warburg stated that cancer cells originate in two phases: 1: "The first phase is the irreversible injury to (OXPHOS) respiration." 2: "The irreversible injury to respiration (OXPHOS) is followed, by a long struggle for existence by the injured cells to maintain their structure, in which a part of the cells perish (apoptosis) for lack of energy, while another part succeed in replacing the lost respiration energy by aerobic glycolysis" [2]. We propose that injury to OXPHOS induces mitochekpoint response, which regulates reversible epigenetic modification (such as DNA methylation) and irreversible genetic changes in the nuclear genome. The genetic basis of underlying "irreversible injury" to OXPHOS includes mutations in mtDNA, reduced mtDNA content, and mutations in nuclear genes affecting OXPHOS. Altogether, the available evidences suggest that injury to OXPHOS may underlie development of cancer.

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