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Mitochondrial DNA mutations and breast tumorigenesis

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Abstract

Breast cancer is a heterogeneous disease and genetic factors play an important role in its genesis. Although mutations in tumor suppressors and oncogenes encoded by the nuclear genome are known to play a critical role in breast tumorigenesis, the contribution of the mitochondrial genome to this process is unclear. Like the nuclear genome, the mitochondrial genome also encodes proteins critical for mitochondria functions such as oxidative phosphorylation (OXPHOS), which is known to be defective in cancer including breast cancer. Due to limited repair mechanisms compared to that for nuclear DNA (nDNA), mitochondrial DNA (mtDNA) is more susceptible to mutations. Thus changes in mitochondrial genes could also contribute to the development of breast cancer. In this review we discuss mtDNA mutations that affect OXPHOS. Continuous acquisition of mtDNA mutations and selection of advantageous mutations ultimately leads to generation of cells that propagate uncontrollably to form tumors. Since irreversible damage to OXPHOS leads to a shift in energy metabolism towards enhanced aerobic glycolysis in most cancers, mutations in mtDNA represent an early event during breast tumorigenesis, and thus may serve as potential biomarkers for early detection and prognosis of breast cancer. Because mtDNA mutations lead to defective OXPHOS, development of agents that target OXPHOS will provide specificity for preventative and therapeutic agents against breast cancer with minimal toxicity.

Keywords

Mitochondrial DNA; OXPHOS; breast cancer; Warburg effect; mtDNA mutations; homoplasmy and heteroplasmy

Introduction

Breast cancer remains a major cause of cancer related death in women despite significant progress in understanding its causes, genesis, detection, and treatment [1]. Tremendous progress has been made as a result of extensive research focusing on the nuclear genome. For example, mutations in the *BRCA1* and *BRCA2* genes encoded by the nuclear DNA (nDNA) are associated with a high risk of developing breast cancer [2, 3]. Similarly, mutations in *TP53*, *PTEN* (phosphatase and tensin homolog), and *CHEK1* and *CHEK2* (checkpoint kinases 1 and 2) are also associated with increased susceptibility to breast cancer development [4]. Current evidence suggest that mitochondrial function is severely impaired in various cancers including breast cancer [5–16] due to genetic defects of

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oxidative phosphorylation (OXPHOS) system. Proteins that participate in the proper functioning of the OXPHOS system are encoded by both nDNA and mitochondrial DNA (mtDNA). Similar to nDNA, mtDNA deletions and mutations have been shown to play critical roles in breast tumorigenesis [5, 17–23]. Cancer associated mtDNA mutations can be germline or somatic mutations [24, 25]. Currently it is unclear whether mtDNA mutations or copy number determine the fate of cells undergoing transformation and how homoplasmic (cells harboring identical mtDNA genotype) or heteroplasmic (occurrence of more than one mtDNA genotype) states affect breast tumorigenesis. It is important to critically evaluate the relative contributions of nDNA and mtDNA, and the crosstalk between these two genomes in the regulation of OXPHOS. We expect that detailed analysis of the effects of mtDNA mutations on OXPHOS will not only shed light on breast tumorigenesis, but will also be important for early detection and predicting the prognosis of breast cancer patients.

The OXPHOS system

Although cancer cells are not entirely reliant on energy production through OXPHOS, they do contain necessary components of this system and functional OXPHOS (albeit reduced) similar to those of non-cancerous cells [26, 27]. The OXPHOS system is comprised of five large multi-subunit complexes as follows: 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, cyclooxygenase or reduced cytochrome c:oxygen oxidoreductase), and complex V (F_oF_1-ATP-synthase). These complexes are localized at the inner mitochondrial membrane and made up of proteins encoded by nDNA and mtDNA. Apart from these five multi-subunit complexes, cytochrome c and ubiquinone (coenzyme Q10) are also required as electron carriers to generate energy in the form of ATP [28–30]. NADH and $FADH_2$ oxidation reactions feed electrons to respiratory chain (complexes I–IV) that are transferred to molecular oxygen to form water as a byproduct and generate a proton (H^+) gradient [28–30]. H^+ pumping at complexes I, III, and IV from the mitochondrial matrix into the inter membrane space leads to an increase in the H^+ gradient across the inner mitochondrial membrane. Finally, the dissipation of the H^+ gradient via complex V provides energy for combining the ADP and inorganic phosphate (Pi) to form ATP [28–30]. Several questions remain unanswered about the structural and functional integrity of the OXPHOS system in cancer cells. Do cancer cells have normal OXPHOS system, and if so, why are they dependent more on glycolysis than OXPHOS for ATP generation? Do cancer cells harbor defects in mtDNA and nDNA encoding various proteins that are part of OXPHOS system?

Molecular genetics of the OXPHOS system

OXPHOS system consists of 92 structural subunits (Figure 1) [29, 31]. Most of the proteins of OXPHOS system are encoded by the nDNA except for the following 13 polypeptides that are encoded by the mtDNA: seven subunits of complex I, one subunit of complex III, three subunits of complex IV, and two subunits of complex V. In addition to these 13 polypeptides, the 16.6-kb mitochondrial genome also encodes 22 tRNAs and 2 rRNAs [29, 32]. This suggests that mutations in the regions of mtDNA or nuclear DNA that encode components of the OXPHOS system can affect its function. Indeed, mutations in regions of the mitochondrial and nuclear genes encoding OXPHOS proteins have been reported in a variety of cancers [22, 25, 33–41]. However, little is known about the mtDNA-mediated impairment of mitochondrial function caused by mutations in mtDNA in breast cancer cells.

The copies of mtDNA per mitochondrion and mitochondria per cell vary with cell types. Each mitochondrion contains 2–10 copies of mtDNA, and each cell may harbor hundreds to

thousands mitochondria. Damage to mtDNA and change in its copy number can affect OXPHOS function. Multiple factors contribute to the increased vulnerability of mtDNA to damage, and thus mutations. During replication, mtDNA contains a short triple-stranded DNA structure (known as the D-loop), in which a single strand of mtDNA is displaced [42–44]. Unlike nuclear DNA, the mtDNA does not contain the well-known protection mechanisms such as protective histones, harbors limited DNA repair capability, and lacks introns. In addition, since mitochondria are the source of reactive oxygen species (ROS), continued exposure to ROS [45, 46] contributes to the increased susceptibility of mtDNA to mutation.

Multiple copies of mtDNA exist in association with key maintenance proteins in structures known as mitochondrial nucleoids. The mitochondrial D-loop region recruits and binds ATAD3 (ATPase family AAA domain-containing protein 3), a component of many, but not all, mitochondrial nucleoids. The interaction between ATAD3 and D-loop region of mtDNA is required for the purpose of forming and segregating mitochondrial nucleoids [47]. This association is transient, thus ATAD3 may not protect mtDNA as histones do for nDNA. Mitochondrial transcription factor A (Tfam) is the main factor packaging mtDNA into nucleoids or mitochromosome formation and is essential for mtDNA transcription initiation [48]. The interaction between hexameric mtDNA helicase Twinkle [49], tetrameric mitochondrial single-strand DNA binding protein (mtSSB), and the heterotrimeric mtDNA polymerase γ (pol γ) [50] forms mtDNA replisome, which promotes proper mtDNA replication. This suggests that these proteins interact with mtDNA but their function in terms of providing protection is still not clearly defined. There is evidence that a reduced level of Tfam results in increased levels of ROS and mtDNA instability and a subsequent increase in tumor number and growth in the small intestine, suggesting that defects in OXPHOS lead to tumorigenesis [51]. Furthermore, cybrids (a fusion of whole cell with a cytoplasm) with benign mitochondria can reverse oncogenic characteristics of cancer cells [52]. Additional proteins have been co-purified with frog oocyte mtDNA [53] but their roles in mtDNA maintenance are uncertain. Although many details remain to be clarified, it is clear that mtDNA is more susceptible to damage than nDNA, and that mutations of mtDNA could contribute to defects in OXPHOS leading to the development of various disease processes including breast cancer.

Mitochondrial DNA mutations in breast cancer

Although the role of nDNA mutations in cancer development is well established, the importance of mtDNA mutation in the disease process is only now beginning to receive attention. Mutations in mtDNA are expected to destabilize the OXPHOS system because 13 proteins encoded by mtDNA are essential for structural and functional integrity complex I, and III–V. Deficiency of OXPHOS in cancer cells was first described by Otto Warburg who hypothesized that cancer cells rely more on glycolysis for their bioenergetic needs instead of OXPHOS even in the presence of abundant oxygen [54, 55]. However, the Warburg hypothesis does not apply to all types of tumor cell or in all conditions. Several reports suggest that OXPHOS accounts for approximately 40–80 % of the total ATP produced by cells in glucose-enriched medium [26, 56–60]. In addition, lack of oxygen or intermittent hypoxia and/or glucose limitation contributes to a shift toward high glycolysis or glucose-independent respiration in cancer cells in order to generate the required ATP [61–65]. Overall, it is now clear that mtDNA mutation influences OXPHOS function and consequently might play a role in tumor initiation and progression.

Indeed, mtDNA mutations have been identified in various types of cancer [25, 66–69]. Although a number of mtDNA rearrangements and amplifications were reported in acute myeloid leukemia [70], the first somatic mtDNA mutation was detected by Polyak et al., in

human colorectal cancer cells [66]. After these initial findings, mtDNA mutations have been reported in esophageal, ovarian, thyroid, head and neck, lung, bladder, renal, and breast cancer cells [25, 67, 71–73]. Mutations in nDNA such as those in *p53*, *BRCA-1* and *BRCA-2*, *PTEN*, *CHEK2*, *ATM* (ataxia telangiectasia mutated), XPD (xeroderma pigmentosum group D)/ERCC2 (excision repair cross-complementing rodent repair deficiency, complementation group 2 protein), and *HER-2* (human epidermal growth factor receptor) have been extensively studied in breast cancer [2–4, 74], whereas mtDNA mutations are only now becoming recognized as an important aspect of breast cancer development and resistance to apoptosis. Studies performed in the last few years have characterized various alterations in mtDNA in breast cancer, including point mutations, mtDNA polymorphisms, mtDNA depletion, microsatellite instability, insertions, changes in mtDNA copy number, homoplasmy, and heteroplasmy of mtDNA [18, 33, 51, 68, 69, 75–99]. Breast nipple aspirate fluid (NAF) with mtDNA mutations at position 204, 207, and 16293 has been suggested to be indicative of breast cancer and mtDNA D-loop mutation has also been proposed as an independent prognostic marker for breast cancer [100, 101]. In addition to a deleterious effect on genes encoding OXPHOS components, mutations in mtDNA could involve tRNAs and rRNA [25, 102, 103] required for the synthesis of peptides that are important in the assembly of various complexes. Therefore, the ultimate outcome of mtDNA mutation is defective OXPHOS function, which leads to a moderate increase in ROS production that in turn may promote tumorigenesis [66, 67, 104].

Germline mtDNA mutations and breast tumorigenesis

DNA instability can be caused by various factors such as lack of DNA repair and proof reading, and instability of nuclear DNA is known to be a major cause of tumorigenesis. Nuclear DNA-encoded proteins are an integral part of the OXPHOS system and, conversely, defects in OXPHOS induce irreversible changes in the nuclear genome [30, 105, 106]. Mitochondria-nucleus crosstalk and mitochondrial retrograde signaling play important role in tumor development [16, 41, 107–111], supporting the notion that mtDNA instability also plays an important role in tumorigenesis. Indeed, various cancer cells including breast cancer cells, harbor instability in the mitochondrial genome [68, 108, 112, 113].

In mtDNA T16189C germ-line mutation, various factors contribute to the substitution of T by C at the nucleotide position (np) 16189, for example, lack of repair and proof reading play a critical role in this transition. Although a large data set is needed, but this study provides evidence that T to C substitution at np 16189 is associated with susceptibility to breast cancer development [114]. The 10398A allele of the NADH dehydrogenase-3 locus (ND3) of mtDNA is associated with increased risk for invasive breast cancer in African-American women [33, 115]. Similarly, 10398A allele is also associated with breast and esophageal cancer in North Indian women [22]. However, other studies demonstrate that mtDNA G10398A polymorphism do not associate with breast cancer in African-American or South Indian women [116, 117]. In contrast, the 10398G polymorphism of ND3 has been shown to increase the risk of breast cancer in European American, Polish, and Malay populations [22, 78, 96, 118, 119]. Therefore, more studies involving larger population sizes are needed to clarify this association. It is also possible that, polymorphisms in the mitochondrial genome could also be influenced by life styles such as alcohol consumption [120]. Chronic alcohol use may cause OXPHOS deficiency and other cellular changes. The mechanism by which the presence of these mutations leads to mitochondrial dysfunction is not clearly defined but the G10398A variant of mtDNA may result in defective complex I function, and thus lead to increased ROS production [22, 121]. Whether ROS produced due to the G10398A polymorphism is sufficient to induce tumor formation remains to be determined, but the presence of other mutations combined with G10398A may contribute to breast tumorigenesis.

Other single nucleotide polymorphisms (SNPs) in mtDNA including G9055A, T16519C, T239C, A263G, and C16207T, also result in increased susceptibility to breast cancer [78, 87]. MtDNA T3197C and G13708A SNPs decrease breast cancer risk [78], and a reduced incidence of mtDNA A73G, C150T, T16183C, T16189C, C16223T, and T16362C SNPs was noted in breast cancer patients compared to database controls [87]. Recent studies have also identified multiple novel mtDNA mutations and polymorphisms in breast cancer patients [79]. Analysis of the sequence of genes encoding complex I in cancer tissues and corresponding normal tissues has led to the discovery of very rare mtDNA polymorphisms, including A4727G, G9947A, A10044G, A10283G, T11233C, and C11503T, that may have implications in breast cancer development [122].

Somatic mtDNA mutations and risk for breast cancer

Although germline mutations have been linked to breast tumorigenesis, the majority of breast cancers are not inherited. In such cases, somatic mtDNA mutations may lead to selective transformation of breast epithelial cells and tumorigenesis. Various somatic mtDNA mutations have been detected in breast cancer [21, 23, 80, 81, 83, 85, 91, 101, 123–127], and here we will discuss a few of these mutations. It is important to note that the prevalence of germline mutations is significantly higher than that of somatic mutations, and most of the patients with germline mutations have multiple mutations [128]. The majority of somatic mutations occur in the D-loop region, which is considered a hot spot for mutation [23] because this region is ~60 times more susceptible to mutations than the coding regions, although others report only a 7-fold increase in susceptibility [100]. The D-loop itself is a non-coding region of mtDNA, but mutations in this area contribute to alterations in the coding sequence of mtDNA and modification of transcription, and thus affecting the expression and function of 13 core proteins of the OXPHOS system.

Somatic mutations of mtDNA can be point mutations, deletions or insertions, or missense mutations. In a study on invasive ductal carcinoma, 11 out of 18 tumor samples showed somatic mtDNA mutations [127]. Similarly, somatic mutations were observed in 14 out of 19 tumor samples, of which only 4 mutations were in polypeptide coding regions and one of these was a missense mutation [23, 129]. In another study, 15 among a total of 45 mutations detected in 15 tumor samples were missense mutations [100, 130]. By targeting *Mnl*I restriction site between nucleotides 16,106 and 16,437 within the D-loop region of mtDNA, Ye et al. [131] showed that somatic mutation at this site occurred more frequently in breast cancer cells than in benign epithelial cells. Their study involved 501 patients with breast cancer and 203 with benign breast disease, and the findings suggest that somatic mutations at the *Mnl*I site in mtDNA may lead to the development of breast cancer. In another study, screening of the D-loop region demonstrated that 8 out of 22 cancer tissues had somatic mutations; of these 6 had a single somatic mutation and 2 had 7 somatic mutations [124].

Deletion of 4977 base pairs ($\Delta mtDNA^{4977}$ mutation) was also observed in breast cancer tissues and surrounding normal breast cells patients [132]. Although the $\Delta mtDNA^{4977}$ mutation has been implicated in the process of carcinogenesis, its occurrence in breast cancer tissue, breast benign tissues, and surrounding normal tissues suggests that it does not play a significant role in breast tumorigenesis [133]. Other groups have reported conflicting data on the role of $\Delta mtDNA^{4977}$ mutation in breast cancer [101, 130]. David Sidranski's group analyzed 18 primary breast tissues and observed 12 somatic mutations in 11 tumor samples. Out of the 12 mutations, 5 were deletions or insertions within the D310 repeat region of the D-loop, whereas the remaining 7 were single base substitutions in the coding regions and D-loop of mtDNA. The mutations detected in coding regions lead to alterations in the polypeptides encoded by mtDNA. Using D310 as a clonal marker, they concluded that D310 alteration in primary breast cancer may represent a clinical marker for breast

tumorigenesis [127]. Recent studies also detected a high frequency of D310 mutations (32.5%) in Asian Indian patients with breast cancer [76], supporting the role of mtDNA instability at D310 as a marker for breast cancer.

Because a normal cell contains multiple copies of mtDNA compared with two copies of nDNA, determination of mtDNA mutations in blood or biofluids with low cellularity such as NAF, which contains shed ductal epithelial cells may represent a better biomarker for breast cancer. In this regard, several studies have been performed in this direction to establish mtDNA somatic mutation as a biological marker for breast tumorigenesis [81, 95, 100, 124, 127, 134–137]. Sauter and colleagues detected mtDNA mutations in primary breast tumor and matched breast NAF [100]. Similarly, other studies have shown a correlation between mtDNA mutations in breast tumor tissues and in biological fluids including serum [81, 95, 99, 127, 137]. However, in some studies, mtDNA mutations were undetectable or follow-up was not available [134], therefore, further studies with more advanced techniques and long-term follow-up are necessary to robustly establish whether mtDNA mutations in blood, NAF, or other biological fluids could be used for early detection of breast cancer.

Reduced level of mtDNA and breast tumorigenesis

Although OXPHOS dysfunction is known to be associated with tumorigenesis in several types of cancer, including breast cancer [9, 11, 138–140], some studies also suggest that OXPHOS dysfunction could play a causative role in cancer development [5, 141, 142]. Because OXPHOS deficiency suppresses p53 expression/function and p53 function declines with age [141, 142], increased mtDNA mutations or reduced mtDNA content-mediated OXPHOS dysfunction may facilitate the suppression of p53 function causing higher tumor incidence. There is evidence that either mtDNA mutation or a reduced mtDNA content in tumor cells can contribute to OXPHOS dysfunction and tumorigenesis [25, 30, 103, 138, 143]. A reduced level of mtDNA associates with increased resistance, invasiveness, and aggressive disease in multiple types of cancer including breast, renal, and thyroid [5, 10, 19, 82, 84, 109, 144–147]. In addition, reduced level or lack of mtDNA has also been associated with resistance to apoptosis, increased proliferation, and increased metastasis [45, 145, 146, 148–150]. The aberration of mitochondrial complex I function has been associated with the enhanced aggressiveness of human breast cancer cells [103].

Although a reduced mtDNA content has been associated with higher histological grade in breast cancer patients in some studies [82, 101]; no correlation between the reduced mtDNA content and tumor grade or metastasis was observed in other studies [144, 151]. A study demonstrated high mtDNA copy number in whole blood cells of breast cancer patients compared to control healthy subjects [75]. High mtDNA content was also associated with decreased endogenous antioxidant system including total glutathione, Cu-Zn superoxide dismutase (SOD1), and catalase [75]. Our recent findings suggest that a reduced level of mtDNA is associated with high incidence and poor prognosis of prostate cancer [152]. Decreased levels of mtDNA in the peripheral blood were reported in breast cancer patients with stage I disease [147], suggesting that a reduction in mtDNA represents an early stage in breast tumorigenesis, which could have significance in early detection of breast cancer.

Comparison of mtDNA content with other prognostic markers such as estrogen receptor (ER) demonstrated a reduced level of mtDNA in ER-negative normal breast tissues compared with ER-positive normal breast tissues [151]. ER localizes to the mitochondria [153, 154], therefore the presence of ER may regulate the level of mtDNA or OXPHOS function [154–156]. Since p53 also localizes to mitochondria and interacts with ER [157], the ER-p53 may regulate mtDNA content, and thus OXPHOS function. Although mtDNA content was highly reduced in breast tumor tissues, the level of mtDNA was similar between

ER-negative and ER-positive cancerous breast tissues [151]. These findings indicate that a reduced level of mtDNA alters ER and/or ER-p53 functions during breast tumorigenesis.

Although it is unclear whether the decreased level of mtDNA is due to alterations in copy number per cell or in the number of mitochondria per cell, several lines of evidence suggest decreased mtDNA copy number per cell. Regulation of mtDNA integrity and replication by p53 and pol γ might be defective in cancer cells, causing reduced mtDNA content [105, 158]. Since replication of mtDNA is controlled by the D-loop region, the presence of mutations in the D-loop region in various cancers, including in breast cancer, could also contribute to a reduced copy number of mtDNA [42, 113, 159, 160]. Additionally, mtDNA is especially susceptible to damage caused by the high levels of ROS production in mitochondria of cancer cells, which may lead to degradation of damaged mtDNA [159, 161, 162].

Homoplasmic and heteroplasmic mutations in breast cancer

The number of mtDNA molecules in a typical cancer cell is in the range of thousands and these molecules can be present in homoplasmic or heteroplasmic states. Because the inheritance of mtDNA is maternal with no or minimal intermolecular recombination events [163], the vast majority of mtDNA copies are identical (either wild-type or mutant) at birth, which is called a state of homoplasmy. As mitochondria are the key source of ROS, mtDNA is highly susceptible to damage and mutations from ROS, and as a result multiple subpopulations of mtDNA could exist, creating a heteroplasmic condition in cancer cells [113]. Thus, heteroplasmic state could arise in cells during their life span but most breast tumors whether mitochondrial *Mnl*I restriction site variants or mitochondrial microsatellite instability (MSI) were reported to be homoplasmic [164]. Other groups have also provided evidence that most mtDNA mutations are homoplasmic [66]. For example, Tan et al. [23] identified 27 mutations in 19 tumor samples. Of the 27 mutations, 17 were homoplasmic and the remaining 10 were heteroplasmic. It is unclear how certain mutations are selected towards homoplasmic state during breast cancer development. Because cancer is an age-related disease and takes a long time to develop, it is reasonable to hypothesize that during the course of breast tumorigenesis a particular mutation may be selected and propagated through multiple cell divisions, creating a homoplasmic condition. Two main hypotheses have been proposed to explain the dominance of homoplasmy over heteroplasmy [66, 165–167]. In the first, some of the mtDNA mutations confer a selective growth advantage, allowing the mtDNA with that particular mutation to outgrow others in the mitochondrial genome. Ultimately, cells harboring this selective advantageous mtDNA mutation overpopulate the tumor [166, 168]. In the second hypothesis, mtDNA with the selective mutant over-replicates to maintain OXPHOS function and over multiple cycles of cell division the over-replicated mtDNA replaces the original mtDNA in cells and tissues thus creating a homoplasmic condition [24, 66, 67, 166]. During the course of multiple generations mtDNA may acquire various mutations, some of which may not be advantageous for cell survival and will be eliminated. Mutations in the mtDNA that complement the nuclear genome function may dominate and lead to homoplasmy [169]. Apoptotic sensitivity of proliferating cells is often reduced by impaired OXPHOS [149, 170–172]. Therefore, it is possible that mtDNA mutations impairing OXPHOS system may be positively selected because they will be relatively protected from apoptosis, a key mechanism of cellular culling that provides protection against tumorigenesis.

Conclusions and future perspectives

MtDNA plays an important role in regulating OXPHOS function. Defective OXPHOS will lead to production of ROS, which may enhance cell transformation and ultimately lead to

tumor initiation, promotion, and progression. It has also been suggested that the function of an early moderate increase in ROS is to provide protection, which could lead to enhanced survival of cancer cells [173]. Various proapoptotic BH3-only and antiapoptotic Bcl-2 family proteins also regulate glycolysis and respiration [174], thus mtDNA-mediated OXPHOS defects could lead to suppression of apoptosis in cancer cells. Although based on our current knowledge, we can not conclude that mtDNA mutation is a determining factor in breast tumorigenesis, the evidence suggests that OXPHOS dysfunction caused by mtDNA mutations and/or reduced mtDNA copy numbers might suppress p53 function [141], and result in breast tumorigenesis. Additionally, OXPHOS deficiency is known to cause constitutive activation of AKT that is linked with tumorigenesis [175]. Current findings using an animal model derived from inactivation of SUV3, a mitochondrial helicase, suggest that increased mtDNA mutations and decreased mtDNA copy numbers can predispose mice to tumor development in various tissues [5]. Germline introduction of a tumor-associated somatic G13997A mutation in ND6 subunit of complex I predispose mice to lymphoma formation and enhanced metastasis [176]. Future technical advances may allow us to elucidate the effect of key mtDNA mutations and mtDNA copy numbers on OXPHOS dysfunction and cancer, including breast tumorigenesis. Polymorphism in mtDNA has been detected in certain populations. Therefore, it is tempting to assume that the presence of germline mtDNA polymorphisms/mutations might predict susceptibility to developing breast cancer. Since somatic mtDNA mutation is an early event during breast tumorigenesis, such mutations could be used as early detection marker for breast tumor formation and might also predict disease outcome. Although further studies with large data sets and more sensitive methods are needed to determine whether mtDNA mutations and/or mtDNA content in biofluids could be used as biomarkers for early detection of breast cancer, the followings points should be considered with regard to biomarker development. While multiple germline and somatic mutations have been detected, there is no consensus to conclusively identify that a particular mutation is a potential biomarker for breast cancer. Based on the accumulating evidence and our current understanding, reduced mtDNA content in breast tumor compared with matched normal breast tissues could be a viable biomarker for early detection, although available studies related to mtDNA content in biological fluids such as blood, urine, and NAF are not conclusive. Therefore, a reasonable approach may be to combine mtDNA mutations in biolfluids such as blood or NAF with mtDNA content analysis of biopsy tissues for early detection of breast cancer.

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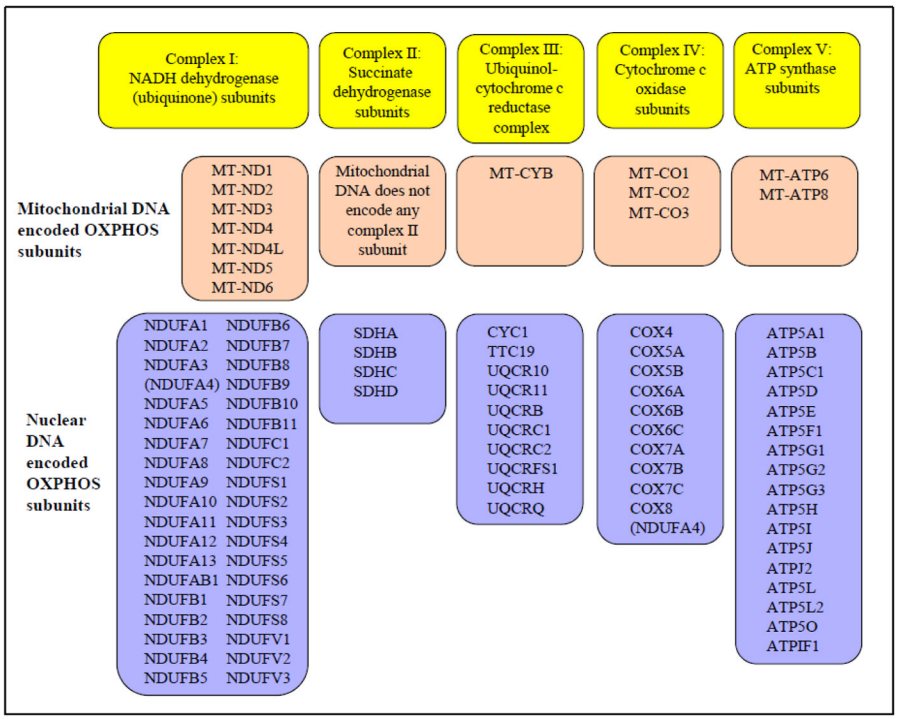

Figure 1. Components of OXPHOS system

Mitochondrial OXPHOS complexes are encoded by the nuclear and mitochondrial genome. NDUFA4 was previously classified as a part of complex I, recent findings (see reference 30) suggest that NDUFA4 belongs to complex IV. Therefore, NDUFA4 is mentioned in both complex I and IV.

Gene name abbreviations for mitochondrially encoded subunits are:

MT-ND mitochondrially encoded NADH dehydrogenase

MT-CYB mitochondrially encoded cytochrome b

MT-CO mitochondrially encoded cytochrome c oxidase

MT-ATP mitochondrially encoded ATP synthase

Gene name abbreviations for nuclear DNA encoded subunits are:

NDUFA NADH dehydrogenase (ubiquinone) 1 alpha subcomplex

NDUFAB1 NADH dehydrogenase (ubiquinone) 1 alpha/beta subcomplex 1

NDUFB NADH dehydrogenase (ubiquinone) 1 beta subcomplex

NDUFC NADH dehydrogenase (ubiquinone) 1 subcomplex unknown

NDUFS NADH dehydrogenase (ubiquinone) Fe-S protein

NDUFV NADH dehydrogenase (ubiquinone) flavoprotein

SDHA	succinate dehydrogenase complex subunit A
SDHB	succinate dehydrogenase complex subunit B
SDHC	succinate dehydrogenase complex subunit C
SDHD	succinate dehydrogenase complex subunit D
CYC-1	cytochrome c-1
TTC19	tetratricopeptide 19
UQCR	ubiquinol-cytochrome c reductase complex III
UQCRB	ubiquinol-cytochrome c reductase binding protein
UQCRC	ubiquinol-cytochrome c reductase core protein
UQCRFS1	ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1
UQCRH	ubiquinol-cytochrome c reductase hinge protein
UQCRQ	ubiquinol-cytochrome c reductase complex III subunit VII
COX4	cytochrome c oxidase subunit IV
COX5A	cytochrome c oxidase subunit Va
COX5B	cytochrome c oxidase subunit Vb
COX6A	cytochrome c oxidase subunit VIa
COX6B	cytochrome c oxidase subunit VIb
COX6C	cytochrome c oxidase subunit VIc
COX7A	cytochrome c oxidase subunit VIIa
COX7B	cytochrome c oxidase subunit VIIb
COX7C	cytochrome c oxidase subunit VIIc
COX8	cytochrome c oxidase subunit VIII
ATP5A1	ATP synthase H+ transporting mitochondrial F1 complex, alpha subunit 1

ATP5B	ATP synthase H+ transporting mitochondrial F1 complex, beta polypeptide
ATP5C1	ATP synthase H+ transporting mitochondrial F1 complex, gamma polypeptide 1
ATP5D	ATP synthase H+ transporting mitochondrial F1 complex, delta subunit
ATP5E	ATP synthase H+ transporting mitochondrial F1 complex, epsilon subunit
ATP5F1	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit B1
ATP5G	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit C
ATP5H	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit d
ATP5I	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit E
ATP5J	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit F6
ATP5J2	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit F2
ATP5L	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit G
ATP5L2	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit G2
ATP5O	ATP synthase, H+ transporting, mitochondrial Fo complex, O subunit
ATPIF1	ATPase inhibitory factor 1