Mitochondrial DNA mutations in gynecological cancers

Mutacje mitochondrialnego DNA w nowotworach narządów płciowych i piersi u kobiet

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Summary

Mitochondria are metabolic organelles inherited only from the mother and possessing their own genome (mtDNA). The mt DNA is a circular, double-stranded molecule of 16.569 bp length containing 37 genes coding 13 polypeptides, 2 genes of rRNA (12S, 16S), and 22 genes of tRNA. All of these proteins are subunits of the oxidative phosphorylation system (OXPHO) localized at the mitochondrial inner membrane. Human mitochondrial dysfunctions have been linked to various metabolic diseases and cancer development. So far we have known several of the inherited and somatic mtDNA mutations predisposing to tumor development, occurring in both non-coding and coding regions. The genetic alternations in the mtDNA include point mutations, deletions, insertions, mtMSI (mitochondrial microsatellite instability). Most of mtDNA mutations in gynecological cancers are observed in the D-loop region. Studies suggest that both mtDNA polymorphism and classes of inherited haplogroups in the human population may be correlated with the risk of cancer development. Mitochondrial DNA mutation and polymorphism analysis may enable to identify individuals with high risk of cancer development, establish early detection or monitor the progression of cancer.

Key words: mtDNA, mutation, polymorphism, gynecological cancer.

Streszczenie

Mitochondria to metaboliczne organelle komórkowe zawierające własny genom (mtDNA) dziedziczony jedynie od matki. MtDNA jest kolistą cząsteczką o podwójnej nici wielkości 16,569 par zasad, zawierającą 37 genów kodujących 13 polipeptydów, 2 geny rRNA (12S, 16S) oraz 22 geny tRNA. Wszystkie te białka są podjednostkami systemu fosforylacji oksydacyjnej (OXPHO) zlokalizowanego na wewnętrznej błonie mitochondrialnej. Zmiany genomu mitochondrialnego mają wpływ na wystąpienie chorób metabolicznych oraz rozwój nowotworów. Do tej pory znanych jest kilka wrodzonych i somatycznych mutacji w obrębie mtDNA predysponujących do rozwoju nowotworu. Mutacje te pojawiają się w rejonach kodujących i niekodujących. Genetyczne zmiany w mtDNA zawierają: punktowe mutacje, delecje, insercje, mikrosatelitarną niestabilność mitochondrialną (mt MSI). Większość z tych mutacji zachodzących w nowotworach narządów płciowych obserwowana jest w regionie D-loop mtDNA. Badania sugerują obecność korelacji między wrodzonymi polimorfizmami i rozwojem nowotworów i innych chorób. Co więcej, klasy wrodzonych haplotypów w ludzkiej populacji mogą być powiązane ze wzrostem lub zmniejszeniem ryzyka rozwoju nowotworu. Badania wskazują, że zarówno analiza mutacji, jak i polimorfizmu mtDNA może ułatwić identyfikację osób z wysokim ryzykiem rozwoju raka oraz umożliwiać wczesną wykrywalność i prognozowanie w chorobie nowotworowej.

Słowa kluczowe: mtDNA, mutacja, polimorfizm, nowotwory narządów płciowych.

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Introduction

All human cells contain hundreds of mitochondria. They are metabolic organelles possessing their own genome (mitochondrial DNA, mtDNA) which is inherited only through the maternal lineage. The mtDNA is a circular, double-stranded molecule of 16.569 base pairs (bp) length containing 37 genes coding: two ribosomal ribonucleic acid (rRNA) molecules (12S, 16S) – 2 genes, transfer tRNA molecules – 22 genes and different polypeptides – 13 genes. All of these proteins are subunits of an oxidative phosphorylation system (OXPHO) localized at the mitochondrial inner membrane [1]. In addition, mitochondrial genome includes the displacement loop (D-loop), which contains the control region for replication and transcription of mtDNA. It is a "hot spot" region for mtDNA alterations. There are also 2 hypervariable regions (HV) localized in the control region of mtDNA: HV I (nucleotides 16024-16383) and HV II (57-372) [2, 3]. The hypervariable region has been given this name as it mutates several hundred times more frequently than other mtDNA regions. It is a place where multiple short tandem repeats (STR) are observed, and the majority of them are CA repeats (cytosine, adenine) and short base-repetitive sequences (microsatellite instability, MSI). MSI is diffused in the whole human genome.

High susceptibility of mtDNA to mutation is caused by its exposure to deleterious reactive oxygen species (ROS) generated by OXPHO, inefficient repair system and lack of protective histones. Therefore, the accumulation of mutations in mitochondrial DNA is approximately 10-100 times higher than that observed in nuclear DNA [4]. Most mutations in the regions of coding sequences lead to alterations in subunits of the oxidative phosphorylation system, and both rRNA or tRNA molecules. Mutations in the D-loop region may have an influence on replication and transcription of mtDNA [5].

Mitochondria could account, as one of the most powerful sources, for ROS generation, especially during inflammation. ROS belong to strong stimulators of pro-inflammatory cytokines, including IL-1, IL-2 and TNFα [6, 7]. Mitochondria are also both the target and source of reactive nitrogen species (RNS). Pro-inflammatory cytokines and ROS activate inducible nitric oxide synthase (iNOS), which produces nitric oxide (NO) accumulating inside mitochondria and reacting with superoxide to form peroxynitrite (ONOO-), which is responsible for disturbing OXPHOS function [8]. This sequence of events eventually leads to activation of transcription factor NF-κB [9]. As inflammation is one of the most important phenomena inside solid tumors, the aberrant function of mitochondria may enhance carcinogenesis.

Mitochondria have been also found to play a crucial role in the initiation of apoptosis, which ensures tissue homeostasis by regulation of the balance between cell growth and death [10, 11]. The key role of mitochondria is indicated by the observation that ROS production is an early event in apoptotic cascade, and that inhibition of OXPHOS seriously disturbs apoptosis [12]. Mitochondria-dependent apoptosis triggered by cytotoxic stress engages p53 oncogene, which simultaneously activates pro-apoptotic proteins while suppressing anti-apoptotic ones, like survivin and Bcl-2 [13]. After entering the mitochondrion, p53 increases ROS production and binds to the pro-apoptotic BAK protein, which initializes permeabilization of outer mitochondrial membrane, activation of both cytochrome c and caspases, which altogether contribute to the programmed cell death [14, 15]. These pathways are usually deregulated in tumor cells, which are capable of decreasing a ROS production, or change a cell redox state through overexpression of hypoxia-inducible factor HIF-1 and described earlier activation of factor NF-κB [16-18]. Disturbed apoptosis may contribute not only to malignant cell transformation but also alters cellular response to anticancer factors, thus enhancing cancer immortality [10, 11]. Cancerous transformation leads to overexpression of anti-apoptotic factors including Bcl-2 proteins, inhibitor of apoptosis proteins (IAP), or FADD-like interleukin-1β-converting enzyme-like protease (FLICE/caspase 8)- inhibitors. Alternatively, cancerogenesis causes decrease of the expression of pro-apoptotic BAK protein. These mechanisms may protect the cancer cells from death mediated by caspases 3 and 8, as well as trigger chemotherapy and radiotherapy resistance by activation of transport proteins (ATP-binding cassette proteins) responsible for removal of drugs from the cells [19, 20].

Seventy years ago, the first interest in mitochondrial involvement in carcinogenesis was brought by the work of Otto Warburg, a Nobel laureate. He suggested existence of differences in energy metabolism between normal and cancer cells. According to Warburg's hypothesis, the main way of energy generation in cancer cells is non-oxidative glycolysis, while normal non-cancerous cells generate energy mainly by oxidative breakdown of pyruvate subjected to further oxidation within the mitochondria. Therefore, the different glycolysis/respiration ratio characterizes cancer and normal tissues. This conclusion is known as the Warburg effect [21]. Hypoxia is a common phenomenon observed inside the solid tumors. Non-oxidative glycolysis inside tumors is perpetuated and enhanced by ROS production followed by HIF-1 over-expression. Factor HIF-1 induces transcription of genes undoubtedly engaged in tumor protection against hypoxia, like genes encoding glycolytic enzymes, glucose transporters and vascular-endothelial and insulin-like growth factors (VEGF, IGF-2) [22, 23]. HIF-1 regulates also mitochondrial cytochrome subunits activity and respiration rate [24]. Suppression of OXPHOS and non-oxidative glycolytic conditions stimulate in turn HIF-1 activity through blocking its proteasome-dependent degradation [25].

This metabolic adaptation is driven by oncogenes like *ras, Her-2/neu*, *c-myc* and *p53* [26-28].

The mutations of mitochondrial genome can be present both in somatic or germline cells. One of them, the germline mtDNA mutation might contribute to mitochondrial disease and certain cancer etiology in the offspring. In the germline cells, two mtDNA polymorphisms (in the NADH dehydrogenase 3 (ND3) gene at position 10398 G→A and in the cytochrome c-oxidase (COI) gene) have been linked to the risk of cancer. The first polymorphism was associated with an increased risk of invasive breast cancer in both pre- and postmenopausal Afro-American women. The mutations in COI gene are a frequent polymorphism met in the European population and have been linked to prostate cancer susceptibility [29-32].

MtDNA somatic mutations are linked to the cancer and aging. They are present inside the tumor but not in the normal tissue. Somatic mutations occur in the cells of various types of cancer including breast, ovarian, prostate, bladder, lung, and colon [3, 33, 34]. Moreover, somatic mutations were observed in premalignant conditions [35]. Most of them were detected in the control region of mtDNA. This region encompasses 1000 nucleotides (nt) of mtDNA genome and consists of the promoter for transcription of the G-rich heavy (H) strand (PH) and the adjacent promoter to transcribe the C-rich light (L) strand (PL), the intervening mitochondrial transcription factor (mtTFA)-binding sites, 3 conserved sequence boxes (CSB I-III), the origin of H-strand replication and the termination associated sequence (TAS) [31, 35].

Haplogroups in gynecological cancers

A haplogroup is a name for a group of similar DNA haplotypes having a common ancestor with a single nucleotide polymorphism (SNP) mutation. The patterns of mtDNA polymorphisms determine classes of inherence haplogroups. In Europe, macro-haplogroup N gave rise to the European specific haplogroups H, J, I, K, T, U, V, W and X. Haplogroups in mtDNA can be used to define genetic populations, human migrations and various individual predispositions to disease and cancers [32, 36]. The study devoted to endometrial cancer revealed differences of haplogroup distribution in the general Polish population, showing an overrepresentation of haplogroup U in most of the patients. Haplogroups I, V and X were not identified. Although haplogroups seem to be represented in patients with cancer and in the general population at a similar frequency, however, haplogroup H (characterized by T7028C polymorphism) was statistically more frequent in the general population than in patients with endometrial cancer. Most likely haplogroup H has protective potential in endometrial cancer development. However, a larger number of patients is needed before any practical application in clinics can be suggested [37, 38]. Inheritance of haplogroup U in the studied groups of prostate and renal cancer patients was suggested as a risk factor for development of these neoplasms in the population. Haplogroup K was also illustrated to increase the risk of breast cancer which developed among European-American women [39-41].

Mutations

So far we have known several inherited and somatic mt DNA mutations predisposing to cancer development. Mutations were demonstrated to occur in both the non-coding and coding regions. Most of them are located in the D-loop region, which is called a "hot-spot" in human cancer. The D-loop contains crucial elements for mtDNA replication and transcription and therefore, mutations in this region may cause a decrease in the copy number or alterations in the gene expression of mtDNA. It gives rise to deregulation of OXPHOS and other components of mitochondrial metabolism [42, 43].

The genetic alternations in the mtDNA include: point mutations, deletions, insertions, mtMSI (mitochondrial microsatellite instability), namely the change in length of short base-repetitive sequence of mtDNA [3, 32, 44, 45].

Breast cancer

Breast cancer is the most common malignancy in women and comprises 18% of all gynecological cancers [46]. Up to date, several authors have reported the presence of mtDNA mutations in breast cancer. Tan et al. [47] examined nineteen samples of paired normal and tumor tissues from the same patients. Studies illustrated the presence of somatic mutations in 74% of the patients. Most mutations (81.5%) were detected in the D-loop region. The remaining alterations were presented in 6 genes coding 16S rRNA, ND2 and ATP-ase [47]. Other investigators also showed the presence of mtDNA alterations in breast cancer. Among these, the majority (58%) of mutations were single-base substitutions in the coding (ND1, ND4, ND5, cytochrome b) and control regions (D-loop) of mtDNA. The remaining mutations were deletions or insertions in a homopolymeric C-stretch in the D310 region encompassed within D-loop. This region is a "hot spot" for mutations in breast cancer [48]. Investigators did not detect mutations in metastatic lymph nodes from patients with D310 aberration in tumor tissue. It can be assumed that mtDNA mutations occur at the early stage of the developing tumor [48].

There are still discussions about the influence of mtDNA polymorphism on ROS production and the breast cancer risk. Some researchers demonstrated the association of G10398A mtDNA variant with the increase in the breast cancer risk in African-American women.

Others did not prove the importance of this polymorphism in etiology of breast cancer. Undoubtedly, further studies on the role of mtDNA variants in etiology of breast cancer are necessary [49, 50]. Exposure to exogenous factors like estrogen intake, cigarette smoking, alcohol consumption or caloric intake might indirectly modify mitochondrial function and increase the risk of breast cancer. The activity of exogenous factors leads to an increased level of ROS, which through destruction of the mtDNA stability, cause impaired respiratory function, change activity of manganese superoxide dismutase Mn-SOD and disturb cell apoptosis. They are also capable of initiating the nuclear DNA damage, like activation of oncogenes or inactivation of tumor suppressor genes. Both processes may trigger breast carcinogenesis [51].

Cervical caner

Cervical cancer is the second most common cancer among gynecologic malignancies after the breast cancer [52]. Although molecular background of cancerous transformation in the cervical cells has been studied for a long time, the literature on the role of mtDNA mutations in cervical cancer is limited. Previous studies have only reported high frequency of the D310 region in cervical cancer [53]. Sharma et al. [54] compared 19 samples of cervical cancer, normal tissues and lymphocytes. Mitochondrial DNA mutations were found in all studied samples, however, their frequency in normal tissues and lymphocytes was lower than that observed in tumor samples. The main mutations were single base substitutions along with insertions and deletions. Moreover, a high frequency of mutations was associated with HPV infection, and HPV-positive cancer was characterized by an increased number of somatic mutations in comparison with precancerous stages [55]. Microsatellite insertions (mtMSI) were detected in CA repeats (514-523 nt position) region in D-loop and in common homopolymeric C stretch interrupted by a T (CCCCCTCCCC) at nucleotide position 303-315. The presence of high frequency of mtMSI in cervical neoplasm can result from a malignant transformation initiated by HPV [54].

Ovarian cancer

Ovarian cancer is the third most frequent gynecological cancer in Poland and the sixth cause of cancer-dependent death [56]. According to various clinical, histopathological and molecular features, ovarian neoplasms are a heterogeneous group. The majority of primary malignant ovarian tumors are epithelial carcinomas. Epithelial neoplasms with varied histology can be distinguished. These are serous, endometrioid, clear cells and mucinous tumors. The simplified classification based on clinical behavior, tumor progression and molecular genetic alterations divides ovarian cancers into two categories (type I and II), akin to the division adopted for endometrial carcinomas [57].

The role of mtDNA mutations in ovarian cancer has not been widely identified so far. One of the first reports analyzed mt DNA alterations in 15 primary ovarian cancers and matched control group (including normal cervix, endometrium tissues and lymphocytes). The localization of mtDNA somatic mutations was identified particularly in D-loop, 12S rRNA, 16S rRNA and cytochrome b (G-A transition) regions. These regions were proved to be especially relevant to ovarian cancer [58]. Various studies have suggested increased concentrations of mtDNA in the plasma of cancer patients. It might be a useful tool for the development of a noninvasive follow-up test for cancer. Nevertheless, somatic mtDNA mutations observed inside ovarian tumors were not detected in the patients' sera. Perhaps, less sensitive methods or too small population were used [58, 59]. Aikhionbare et al. [60] analyzed frequent mtDNA variants among three epithelial ovarian tumor subtypes (serous, endometrioid, mucinous). MtDNA mutations were observed over a span of 3.3 kb fragment, including D-loop, 12S r RNA, t RNA, COX I, COX II, ATPase 6, ATPase 8. These studies reported two novel mutations in 12S r RNA gene at nucleotide positions (np) 773del T and 780delC in FIGO stage IIIC endometrioid ovarian tumors. Moreover, two mutations at position 1657 del C in FIGO stage IV, as well as 8221 del A in benign cystadenomas and borderline tumors were detected in serous tumors. The authors suggested that certain mtDNA mutations can play a role in the differentiation of histological subtypes and stages of both benign and malignant epithelial ovarian tumors. Nevertheless, the analysis of a larger population will enable the confirmation of the authenticity of the postulated relationship [60].

An interesting finding of Bragoszewski et al. [61] study showed that clinical parameters (age, grade, FIGO stage) and expression of mitochondrially encoded 12S rRNA (MT-RNR1) gene in cancer tissue may be responsible for chemoresistance of ovarian tumor [61].

Endometrial cancer

Endometrial cancer is the most frequent gynecological malignant tumor in the Western countries and the United States [62, 63]. Differences in epidemiology, prognosis, clinical and histopathological factors show that two types of cancer exist: type I estrogen-related, responsible for approximately 80% of all cases, and type II estrogen-independent, much more rare, but with worse prognosis. Common molecular alterations in type I include: mutation in *PTEN*, *K-ras*, *β-catenin* genes and microsatellite instability. In type II, mutations of *p53* were documented [64, 65]. There are studies which document also the occurrence of mtDNA changes in endometrial cancer.

Many studies suggested that mutation in the D-loop region is frequent in endometrial cancer. Pejovic et al. [66] sequenced the D-loop region of mtDNA of endometrial serous type II carcinoma and matched results with these of normal endometrium. Their studies revealed the existence of somatic mtDNA alterations in 63% of tumor samples. The investigators identified 13 sequence variants by single-strand conformation polymorphism (SSCP) in 8 tumors. Between them there were 4 transitions: A16066G, A16211G, T16166C, A16327G (typical mutations for oxidative stress) and 1 insertion: G16320. All of these mutations were found in hypervariable area 1 (HV1) of the D-loop region in mtDNA. Unfortunately, the investigated group was too small for observation of correlations between the mtDNA mutations and clinical and pathological features [66]. Future studies are needed to prove the influence of oxidative stress on serous endometrial cancer development. Furthermore, somatic changes in mtDNA included deletions, point mutation and mtMSI. There was also change in the length of short base-repetitive sequences of mtDNA [45, 58]. The majority of somatic mutations were observed in D-loop, 16S r RNA and 12S r RNA genes [45]. Moreover, the presence of mtMSI in position 303-315 correlated with the increase of mtDNA content in the endometrial cancer [67].

Polymorphisms in endometrial cancers are mainly located in HV1 and HV2 regions of D-loop. Previous studies revealed that only the 16189T>C polymorphism was associated with susceptibility to endometrial cancer [29]. The recent studies have revealed other specific polymorphisms in D-loop observed in endometrial cancer. They were 16223C in 80%, 207A in 19%, 16126C in 23% of cases, respectively. Therefore, the probable correlation and association between 16223C/207A genotype and endometrial cancer development is high. Moreover, the studies showed overabundance of specific polymorphisms in some haplogroups. The 16126C polymorphism was specific to J or T haplogroups, 207A was characteristic of W haplogroup, while 16223T was typical of W, X and I haplogroups. In the nearest future, analysis of mtDNA polymorphism pattern may be a valuable tool to select populations at increased risk of developing cancer [37]. Moreover, the frequency of 16189T>C polymorphism found in the normal controls of Chinese ethnicity is statistically significantly lower than in Koreans and significantly higher than in white European population. In various human populations, the frequency of endometrial cancer associated with 16189T>C polymorphism can be different [29, 33, 68].

Vulvar carcinoma

Vulvar cancer is a rare female genital malignancy which accounts for approximately 5% of all gynecological cancers. It is the fourth cause of morbidity due to gynecological cancers [69, 70].

Till now, studies on patients with vulvar squamous cell carcinoma (VSCC) have not been widely performed. As a first investigator, Klemba et al. [71] identified pattern of inherited polymorphisms and haplogroup distribution among individuals with VSCC. The polymorphic regions for VSCC are located in D-loop, similarly like in the cases of endometrial cancer. The highly polymorphic region was observed in 303-315 np of CSB II part (299-315np) and other loci in 514-523np. These and other polymorphisms found can play a role in VSCC development and can become novel vulvar tumor biomarkers. Nevertheless, a more representative group of patients is necessary [71].

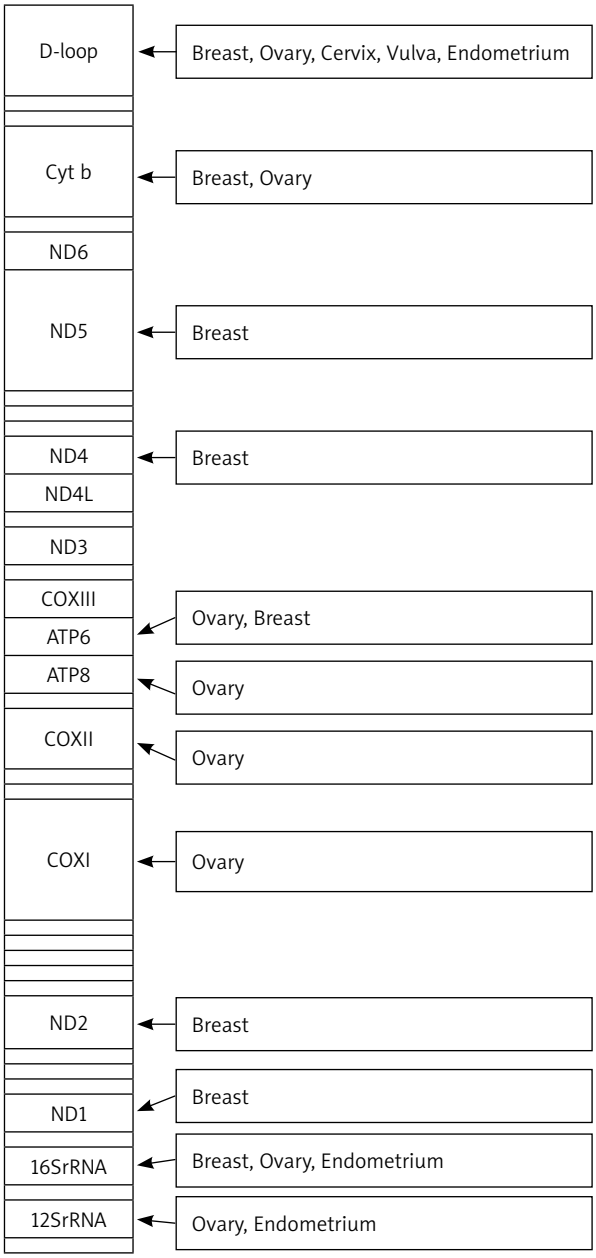

Fig. 1. The mitochondrial genome showing various mutations summarized in this review

Conclusion

Mitochondrial DNA mutations and polymorphism pattern have been observed in many human cancers. The functional defect of mitochondria has also suggested that expression of mtDNA encoded proteins can lead to OXPHOS deregulation [72]. The studies cited above show that mitochondrial alterations may enable the early detection of cancer, its progress and may allow for the identification of high risk individuals, thus may contribute to the development of a screening system. Research on the defects in OXPHOS and their reversal or inhibition may be useful in developing the therapeutic strategies in cancer [34, 41, 45, 72, 73].

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