Mitochondrial changes in endometrial carcinoma: Possible role in tumor diagnosis and prognosis (Review)

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Abstract. Endometrial carcinoma (EC) is a solid neoplasia for which a role for mitochondria in cancer progression is currently emerging and yet represents a diagnostic and prognostic challenge. EC is one of the most frequently occurring gynecological malignancies in the Western world whose incidence has increased significantly during the last decades. Here, we review the literature data on mitochondrial changes reported in EC, namely, mitochondrial DNA (mtDNA) mutations, increase in mitochondrial biogenesis and discuss whether they may be used as new cancer biomarkers for early detection and prognosis of this cancer.

1. Introduction

Endometrial carcinoma (EC) is a neoplasia for which a role for mitochondria in cancer progression is currently emerging. EC is the most common malignancy of the female genital tract. This cancer is usually grouped into 2 subsets: endometrioid carcinoma (type I, estrogen-dependent) and non-endometrioid carcinoma (type II, estrogen-independent). Type I is the most common form, displaying a less aggressive behavior than type II. The development of type I endometrial cancer is considered a multistep process, with slow progression from normal endometrium to hyperplasia and endometrial cancer as a result of an unopposed estrogenic stimulation (1,2).

Mitochondria are essential organelles in all eukaryotic cell systems, and are the powerhouse to provide ATP for a multitude of cellular processes by the oxidative phosphorylation (OXPHOS) system. They are the hub of metabolic pathways, primary sources of reactive oxygen species (ROS), regulators of apoptosis as well as signal transduction regulators and buffers of intracellular calcium (3-5). In addition, ATP production has to be continually adapted to cover current requirements, with marked changes in production levels in tissues alternating between different states (6).

Many years ago Otto Warburg observed that cancer cells actively metabolize glucose and produce an excess of lactate even in the presence of oxygen, the so-called reverse Pasteur effect or aerobic glycolysis. He hypothesized that malignant cells should harbor defects in the respiratory chain of mitochondria and uncovered that, although ATP production via glycolysis is a less efficient process, the increased glycolytic rate in cancer cells largely compensates the lower energy yield per single glucose molecule (7). Recently, it was observed
that different cancer cell types undergo different bioenergetic alterations and that a constant metabolic remodeling takes place according to the stages of cancer progression; thereby, tumors may be glycolytic, partial mitochondrial OXPHOS-dependent or complete OXPHOS-dependent (8,9).

Numerous studies have reported changes in the mitochondrial number (10), in mitochondrial DNA (mtDNA) content (11), in respiratory chain activity and in mitochondrial gene expression (9,12) in different human cancers. Different somatic mtDNA mutations have been reported in various types of human tumors (13,14). In addition to mutations that directly affect mtDNA, mutations in nuclear DNA affecting mitochondrial proteins such as tricarboxylic acid cycle genes (succinate dehydrogenase, fumarate hydratase and isocitrate dehydrogenase1 and 2) have been described (15-18).

This review aims to present the literature data on mitochondrial alterations in EC discussing the possible role of these alterations in EC diagnosis and prognosis. The reported data refer mostly to type I EC which accounts for the majority of cases and has been therefore more extensively investigated.

2. Mitochondrial genetics

Human mitochondria contain a small DNA, mtDNA, of ~16,569 bp (19) that codes for 2 rRNAs (12 and 16S), 22 tRNAs and 13 protein subunits of 4 of the 5 complexes of the respiratory chain. These proteins include: 7 subunits of NADH dehydrogenase (complex I), one of cytochrome c reductase (complex III), 3 of cytochrome c oxidase (complex IV) and 2 of ATP synthase (complex V). The non-coding region, the so-called D-loop region, is ~1.1 kbp long. It is the most variable part of the genome and contains regulatory signals for replication and transcription (20,21). The majority of mitochondrial proteins (~1500) are coded by nuclear DNA, transcribed and translated in the cytoplasm and then transported into the mitochondria. The mitochondrial genetic system has peculiar features with respect to the nuclear one.

mtDNA is maternally inherited and is present in a large number of copies per cell (~2-4000, polyploidy) (22,23). It is more susceptible to ROS-induced mutations (point mutations or deletions) than nuclear DNA since it is located close to the mitochondrial respiratory chain, the major source of ROS in the cell (24). mtDNA point mutations may be simple neutral polymorphisms with no important functional consequences for the cell or deleterious mutations potentially dangerous for the cell. The mtDNA in a cell or in a tissue of a single individual may be all of the same type, wild-type or mutant (homoplasy) or different genotypes may coexist (heteroplasy). Therefore, it is important to know what percentage of mutant mtDNA molecules (threshold) can lead to a dysfunction of the mitochondrial respiratory apparatus (25,26).

The sequential accumulation of de novo mtDNA point mutations in an individual mtDNA molecule generates a mtDNA haplotype. A group of related haplotypes, acquired along radiating maternal lineages, gives rise to haplogroups which tend to be restricted to specific geographic areas and/or ethnic groups (27). These ancient mtDNA variants related to haplogroups may influence individual predisposition to diseases (28).

3. mtDNA mutations in cancer

mtDNA point mutations and deletions have been extensively described in solid tumors. However, the functional relevance of these mtDNA changes in tumor formation and/or promotion is a matter of debate. Point mtDNA mutations could arise either in the female germ line (germline mutations) and predispose to cancer or in the mtDNA molecules of the affected tissues (tumor-specific somatic mutations) and participate in the tumor progression process. As suggested by Brandon et al (29) tumor-specific somatic mutations may be classified as tumorigenic and adaptive. The tumorigenic mutants are severe mutations (i.e. disruptive mutation, nonsense or frame-shift mutations) that alter the respiratory chain and may increase mitochondrial ROS production. ROS promote neoplastic transformation since they diffuse in the nucleus and induce mutations in genes which regulate cell replication, in proto-oncogenes and in tumor suppressor genes. Adaptive mtDNA mutations are instead mild mutations that allow an adaptation of cancer to adverse environments by participating in the metabolic remodeling recently included among cancer hallmarks (30). In fact, mtDNA-encoded proteins are de facto metabolic enzymes, whose function impinges directly on the same pathways as the well-known tumor suppressors succinate dehydrogenase, fumarate hydratase and isocitrate dehydrogenase (whose suppressor vs. oncogenic role is still debated) of the Krebs cycle. These genes have long been shown to contribute to tumorigenesis via stabilization of hypoxia inducible factor 1α (HIF1α) (31), thereby likely driving the glycolytic shift that tightly depends on this transcription factor. Similarly, adaptive mtDNA mutations may influence tumor progression conferring to cancer the ability to metastasize.

Germline mtDNA mutations in EC: Predisposing or protective modifiers of tumorigenesis? Screening tools that may enable to select populations at a high risk for EC and support the process of prevention and early diagnosis have been developed in recent years. The most common risk factors associated with the development of EC are: exposure to unopposed endogenous estrogen, as occurs in chronic anovulation (polycystic ovary syndrome), tamoxifen treatment, obesity, hypertension, type II diabetes, age, nulliparity, infertility, early age of menarche and late age of menopause (32). A familial risk for developing EC was found in women with Lynch syndrome or hereditary nonpolyposis colon cancer (HNPCC). This autosomal dominant syndrome is characterized by a germline mutation in one of the mismatch repair genes: MLH1, MSH2 and MSH6 (33). The association between germline mutations in the BRCA genes and the risk of EC remains controversial (34). Since mtDNA mutations have been described in EC, they have also been correlated with cancer risk. In particular, Liu et al reported that the m.16189T>C base change in the D-loop region was associated with susceptibility to EC (35). A study on a southwest China population pointed out that the mitochondrial polymorphisms associated to haplogroup D (such as m.5178A>C in the MT-ND1 gene) predispose to EC (36). Recently, in the Polish population, 3 polymorphisms of mtDNA, namely, m.16223C>A, m.207G>A and m.16126T>C in the D-loop region, were associated with an increased risk of EC, while
haplogroup H, with its defining polymorphism m.7028C>T in the COI gene, appeared to be a cancer protective factor (37). However, most of such studies have reported mere associations and lack functional proof that certain mitochondrial variants, many of which are common polymorphisms and even haplogroup-defining, may truly impinge on EC predisposition or be protective modifiers of EC tumorigenesis. Overall, it is interesting that evolution may have selected and fixed within certain populations advantageous nucleotide changes, perhaps able to allow a more efficient metabolism, that, however, as a double-edged sword, may facilitate EC occurrence. Functional studies with cybrid cells, i.e. cells in which different mtDNA genotypes may be investigated independently from the nuclear background, will help to clarify what evolutionary advantages these variants may present. However, if the variants reported to increase risk to EC truly constitute a predisposing background, it should be explained why this would occur only in the endometrium, since they are for the largest part homoplasmic within the germline. Moreover, since these polymorphisms are matrilinearly inherited, it would be of utmost importance to monitor the daughters of patients to verify whether such risk is increased in the generations to which the haplotype is passed on.

Somatic mtDNA mutations in EC: Possible molecular markers for cancer detection, diagnosis and prognosis. In EC, the prognosis still relies on conventional pathological features such as histological type and grade, as well as myometrial or lymphovascular space invasion. Unfortunately this analysis still does not provide a relevant prognosis. Many molecular biomarkers have also been defined (i.e. PTEN, K-ras, PT53, catenin, MSH2 and MSH6). However, not a single universally accepted predictive or prognostic marker exists to date to assist clinical decisions regarding EC (38).

Studies on somatic mtDNA mutations to ascertain their role as possible molecular markers for cancer detection, diagnosis and prognosis of EC have also been performed. Initial studies analyzed scattered regions of mtDNA, particularly the regulatory D-loop region and the 2 rRNA genes. Changes in length of short base-repetitive sequences of mtDNA (mitochondrial microsatellite instability, mtMSI), particularly in the D-loop region, 16S rRNA, the MT-ND4L gene and different tRNAs was performed in hyperplastic and cancer tissues. Somatic mtDNA mutations were not detected in hyperplastic endometrial tissues, however, they were found in 10% of analyzed patients and were unrelated to their clinicopathological data (age, clinical stage, histological grade and type or depth of myometrial invasion) (44).

Interestingly, these types of mutations were absent in hyperplastic tissues: all mtDNA variants detected in hyperplasia mtDNA) variants were detected and annotated. Tumor-specific mtDNA mutations were found in 69% of the analyzed cancer endometrial samples. Many of these mutations (59%) were predicted to be pathogenic by in silico analysis and had not been reported in the literature. Interestingly, these types of mutations were absent in hyperplastic tissues: all mtDNA variants detected in hyperplasia were in fact clear haplogroup determinants. A correlation between occurrences of mtDNA mutations and grading was not found, although, a clear-cut tendency for low-grade (G1-G2) compared with high-grade (G3) tumors to harbor clearly pathogenic mtDNA was observed. No other correlation between the occurrence of mtDNA mutations and other clinical data was found.

The sequencing of the entire mtDNA molecules in EC tumors and matched hyperplastic tissues allowed detection in a higher number of patients (70%) of a higher number of mtDNA mutations than previously reported. This frequency is very high compared to the other EC molecular biomarkers (38).
Furthermore, the presence of mtDNA mutations only in cancer tissues allowed distinguishing tumor vs. hyperplastic and non-malignant tissues. Therefore, mtDNA mutations can be considered useful biomarkers for cancer detection.

4. Increase in mitochondrial biogenesis in endometrial hyperplasia and type I EC

Mitochondrial biogenesis usually refers to an increase in the mitochondrial number and/or of the mitochondrial mass per cell. The cell increases mitochondrial biogenesis to overcome a bioenergetics deficit or to face an increased energy requirement (reviewed in refs. 47-49).

The number of mitochondria is generally expressed by the cellular content of mtDNA measured as mtDNA/nuclear DNA ratio whereas citrate synthase (CS) activity is considered a reliable marker of mitochondrial mass (50). The master regulator of mitochondrial biogenesis is the nuclear transcriptional coactivator PPARγ-coactivator-1α (PGC-1α) (51). This factor co-activates the nuclear respiratory factors 1 and 2 (NRF-1 and NRF-2) that, in turn, stimulate the expression of a large number of nuclear genes involved in mitochondrial respiration and in mtDNA replication and transcription (52). One of these genes, the one coding for mitochondrial transcription factor A (TFAM), regulates both mtDNA transcription and mtDNA replication (53).

In different human cancers, changes in the number of mitochondria (10) and/or in the level of mtDNA (54) have been reported. A 2-fold increase in mtDNA copy number was found in EC compared to normal endometrial glandular epithelial cells collected by laser capture microdissection (45). Moreover, a 2-fold increase in mtDNA content and in CS activity as well as TFAM, NRF-1 and PGC-1α protein content was found by our group (55) in a pooled group of type I EC endometrial tissues compared to a pooled group of endometrial proliferative control tissue. These results suggested an increase in mitochondrial biogenesis associated with the upregulation of the PGC-1α signaling pathway in type I EC tissue. The increase of mitochondrial biogenesis was evaluated also in hyperplastic endometrium since endometrial hyperplasia often precedes type I EC. The endometrial hyperplasia can be subdivided into hyperplasia with cytological atypia (atypical hyperplasia) and hyperplasia lacking these features (typical hyperplasia). The former frequently progresses to a well-differentiated type I EC (56). The mtDNA content and CS activity were measured in benign endometrial, in hyperplastic and in cancer tissue. It was found that the mtDNA content and CS activity increased in hyperplastic endometrium compared to the control tissues, even when their level remained lower compared to cancer tissue. mtDNA content increase preceded an increase in CS activity. In fact, mtDNA began to increase significantly already in typical hyperplasia while CS activity increased significantly only in atypical hyperplasia (57).

The increases in mtDNA content and CS activity could be envisioned in type I EC as potential molecular markers to establish the risk of malignant transformation of endometrial hyperplasia and may have a clinical value in patient management. However, due to the interindividual variability, a comparison of each hyperplastic tissue to matched control tissue is required. Further analysis in a higher panel of patients and prospective longitudinal studies are necessary to address this topic.

5. Association between pathogenic mtDNA mutations altering complex I and increase in mitochondrial biogenesis (oncocytic-like foci) in type I EC

It has been reported that a specific subset of tumors, namely oncocytic neoplasias, is characterized by the pathological hallmark of aberrant mitochondrial hyperproliferation. Oncocytic tumors harbor high loads of disruptive (nonsense or frameshift) mtDNA mutations, the large majority of which map in respiratory complex I genes and are associated with a disassembly of complex I (58-60). The mitochondrial hyperproliferation in these tumors has been hypothesized to be a compensatory effect triggered in response to a retrograde signaling from dysfunctional mitochondria to the nucleus (reviewed in refs. 61-63).

The association between mtDNA mutations in respiratory complex I genes, inefficiency of complex I and mitochondrial biogenesis was also verified in type I EC biopsies (46). In fact, in 72% of EC samples, previously characterized for tumor-specific mtDNA mutations by the sequencing of the entire mitochondrial genome, oncocytic-like foci were found. An immunohistochemical (IHC) staining of respiratory complex subunits revealed in 69% of EC samples with oncocytic-like foci, a partial or total loss of staining for the NDUB8 subunit of complex I suggesting at least a partial disassembly of complex I and confirming an association between the loss of the complex and oncocytic-like transformation. Approximately 70% of EC patients with loss of complex I harbored pathogenic mtDNA mutations, the majority in respiratory complex I genes. Moreover, in EC samples compared to matched hyperplastic tissues, an increase in the content of mtDNA, in structural mitochondrial proteins TFAM and porine, in some nuclear DNA encoded respiratory subunits NDFU19, SDHA, SDHB, Core II and mitochondrial antioxidant enzymes (Prx3 and MnSOD) was found, especially, in the EC samples harboring pathogenic tumor-specific mtDNA mutations. Oncocytic-like foci found in 72% of analyzed patients confirmed the increase of mitochondrial biogenesis already found by analyzing a pooled group of EC samples (46). The increase in mitochondrial biogenesis and antioxidant enzymes may be an attempt of EC tissues to overcome bioenergetic deficit and ROS production due to alteration of complex I, the major source of cellular ROS (64-66).

Previous studies indicate that most oncocytic tumors, harboring disruptive mtDNA mutations, retain a low-proliferating, benign behavior because of their inability to undergo adaptation to hypoxia and because of their deranged respiratory metabolism (59,67,68). Since type I EC prognosis is generally more favorable than that of type II EC, it can be hypothesized that in type I EC a combined action of deranged respiratory metabolism due to mtDNA mutations and an unopposed estrogen stimulation may induce mitochondrial proliferation, as found in oncocytic-like foci, thus contributing to maintain the tumor in a less aggressive stage. Studies on mitochondrial biogenesis in estrogen-independent type II EC are warranted to confirm whether this hypothesis holds true.
6. Estrogen stimulation may be responsible for the high frequency of mtDNA mutations and increase in mitochondrial biogenesis in type I EC

The role of estrogens in mitochondrial function is well established suggesting an important role in maintaining mitochondrial structure and function (69). The genomic activity of estrogens is mediated by ERα and ERβ that are members of the steroid/nuclear receptor superfamily of transcription factors. ERα and ERβ have been identified in mitochondria and bind to the D-loop of mouse and human mtDNA (70). However, mechanisms by which ERs coordinate the complex signal pathways between the membrane, mitochondria and nucleus remain to be fully determined.

Estrogen can also inhibit mitochondrial apoptosis since it increases anti-apoptotic Bcl-2 and can affect mitochondrial dynamics altering the fusion/tission ratio. Moreover, it was reported that estradiol stimulates mitochondrial biogenesis, in particular, increases mtDNA content in breast and lung adenocarcinoma cells by stimulating directly NRF-1 gene expression and consequently increasing TFAM, mitochondrial transcription and oxygen consumption (71). In human breast cancer cells, on the other hand, estradiol produces high rates of mitochondrial ROS that act as signal transducing factors activating NRF-1 (72). It can be envisioned that estrogen may favor the appearance of mtDNA mutations by 2 mechanisms: 1) stimulating mitochondrial biogenesis: excessive mtDNA replication, may favor replication errors and consequently mtDNA mutations; 2) inducing mitochondrial ROS: ROS may directly damage mtDNA and generate mtDNA instability. In cancer tissue, but not in hyperplasia, these mtDNA mutations, may reach detectable value probably due to positive selection and/or to tumor clonality. These mutations, above a threshold, may lead to respiratory dysfunction, in particular of complex I and consequently a bioenergetic deficit and ROS increase that generate, in turn, further mtDNA mutations.

In Fig. 1 a possible explanation of the effects of estrogen stimulation in progression from benign endometrium to hyperplasia and to cancer is schematically reported.

In hyperplastic tissue, which undergoes estrogen stimulation (56) and where potentially pathogenic mtDNA mutations have not been found, a mild increase in mitochondrial biogenesis occurs because of a direct interaction of estrogens with NRF-1. In cancer tissue the effect of estrogen stimulation on the increase in mitochondrial biogenesis is reinforced by the occurrence of pathogenic mtDNA mutations. These mutations, generated by estrogen-related ROS increase and by excessive mtDNA replication, may reach a threshold value and affect respiratory complexes, in particular complex I. The consequent bioenergetic deficit and ROS increase may trigger a retrograde signaling to the nucleus that, through the upregulation of the PGC-1α signaling pathway, stimulates mitochondrial proliferation and overexpression of antioxidant enzymes as a compensatory response. ROS may also induce mutations in mtDNA and in proto-oncogenes and tumor suppressor genes leading to nuclear genetic instability and to cancer. NRF-1, nuclear respiratory factor 1; mtDNA, mitochondrial DNA; ROS, reactive oxygen species.
7. mtDNA mutations within the progression model of EC

The screening of point mutations in 4 oncogenes commonly involved in type I EC pathogenesis, namely PTEN, KRAS, CTNNB1 and TP53 in the same patients in which mtDNA mutations were analyzed, allowed to place, for the first time, mtDNA mutations within the Vogelstein-like progression model of EC (46). In particular, it was observed that both canonical nuclear hits and mtDNA mutations occurred after hyperplastic development and before progression to high grade EC. In line with this, pathogenic mtDNA mutations were observed preferentially in low-grade (G1-G2) compared with high-grade (G3) tumors. Furthermore, the percentage of the analyzed patients harboring mtDNA mutations was higher compared to that of patients with mutations in oncogenes/tumor suppressors suggesting that mtDNA mutations may precede the genetic instability of nuclear genes (46). If so, an increase in ROS may be responsible for nuclear DNA damage and may induce genetic instability (Fig. 1) as reported in thyroid tumors (73). These results may be suggestive of a role of mtDNA mutations in the transition from simple hyperplasia to neoplasia. However, it should be considered that even if a high percentage (70%) of EC patients harbor tumor-specific mtDNA mutations, several tumor-specific mtDNA mutations were not potentially pathogenic and finally that not all mutations were homoplasmic or presented a mutation load over 50%, a threshold likely implying a phenotypic effect. Therefore, we cannot exclude that they may be regarded as side-effects of tumorigenesis, which may probably not impinge on tumor progression. More research is needed to assign a role to mtDNA mutations in tumor progression.

8. Tumor-specific mtDNA mutations: An additional diagnostic tool to reveal the synchronous nature of simultaneously detected endometrial and ovarian cancer

Recently, it was reported that the sequencing of the entire mtDNA helps to discriminate between the independent and metastatic origin of simultaneously detected tumors of the endometrium and ovary when histopathological criteria and canonical molecular methods fail or are ambiguous. The sequencing of the entire mtDNA from endometrial and ovarian cancer tissues of the same patient allows a comparison of tumor-specific mtDNA mutations eventually present in both tumors. The presence of one or more tumor-specific mtDNA mutations common to both tissues suggests a common clonal origin of the somatic mutation and the metastatic origin of 1 of the 2 cancers. On the contrary, the absence of tumor-specific somatic mtDNA mutations common to both tissues indicates an independent synchronous origin of the 2 cancers. In fact, it is very unlikely that the same somatic mutation may arise synchronously and independently in 2 tumors. This approach was applied for the first time to a patient carrying two simultaneously detected tumors in ovary and endometrium and a pelvic lymph node metastasis. Sequencing of the entire mtDNA molecule from the 3 different tissues of the patient revealed a frameshift deletion in the ND4 gene exclusively in the ovarian cancer, suggesting a different clonal origin of EC and lymph node metastasis. A comparative genome hybridization analysis revealed a duplication of 1qXq only in EC and lymph node metastasis suggesting that the lymph node metastasis was derived from the EC (74). Very recently the same approach was implemented in 11 additional cases of simultaneously detected endometrial and ovarian cancer. Histopathological criteria and canonical molecular analysis such as microsatellite instability, B-catenin immunohistochemical staining and CTNNB1 mutation screening provided ambiguous diagnoses in certain cases. The mtDNA genotype approach allowed to define the diagnosis in half of the analyzed cases (75). This new molecular approach has the advantages of requiring small amounts of starting material and has relatively low costs. However, it should be taken into account that not all analyzed tumor samples may harbor tumor-specific mtDNA mutations, although given the high percentage of EC samples with an accumulation of variants, this molecular method appears to be particularly suitable to aid diagnoses.

9. Conclusion

mtDNA mutations and mitochondrial proliferation are hallmarks of EC. The study of mitochondrial changes in EC, particularly in type I, reveal the following: i) multiple germline mutations are associated with EC, although, currently lack a functional proof that may truly impinge on EC predisposition or are protective modifiers of EC tumorigenesis; ii) somatic tumor-specific mtDNA mutations can be useful biomarkers for the distinction of tumor vs. hyperplastic tissues since they are present in high percentage only in EC; iii) somatic pathogenic mtDNA mutations may participate in the tumor progression process by contributing to genetic instability: they may not have a causative role but be responsible and provide an explanation for the respiratory dysfunction and the presence of oncocytic-like foci; iv) mtDNA mutations can be used to investigate tumor clonality and to discriminate between independent and metastatic tumors; v) the increase in mitochondrial biogenesis in endometrial hyperplasia could be envisioned as a potential biomarker to establish the risk of malignant transformation; vi) the presence of oncocytic-like foci in EC may be a prognostic marker of low-proliferating, more indolent cancer behavior.

In conclusion, studies of mitochondrial changes in EC should be implemented in the future since it requires small amounts of starting material and has a relatively low cost. This may open new horizons in the diagnosis and in the prognosis of EC especially when the screening of other diagnostic markers have failed or provide ambiguous diagnosis. Finally, similar studies in type II EC should be welcome to differentiate the two EC types and to better define the role of hyperestrogenism in this tumor.

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