Increased expression of oxidative phosphorylation genes in breast cancer cells

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ABSTRACT

Aim: The aim of this study was to analyse the expression at the mRNA level of cytochromeb, subunits COI, COII, COIII of complex IV, ATP6 and ATP8 and to perform aquantitative analysis of the activity of ATP synthase as complex V of the respiratory chain, responsible for ATP synthesis and break down of ATP to ADP in breast cancer. **Methods and Results:** The level of gene expression at the mRNA level was evaluated on the basis of the light intensity of fluorochrome or fluorescein in the cells. Determination of the activity and location of the ATP synthase in cells was carried out using hybridization. In the formulations of breast cancer there was a higher genes expression at the mRNA level for all the examined genes as compared with non-cancerous tissue. The ATP activity was also higher in preparations obtained from breast cancer cells compared with the control tissue. **Conclusions:** The results confirm mtDNA incorporation to nDNA in neoplastic cells. They point to increased expression at mRNA level for COI, COII, COIII, ATP6 and ATP8 in breast cancer cells compared with control tissue. Increased amount of ATP synthase points to increased ATP in a neoplastic cell.

Keywords: breast cancer, mitochondrial genes, gene expression, oxydative phosphorylation

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INTRODUCTION

Because of the lack of protective effect of histone, mitochondrial DNA (mtDNA) is more susceptible to mutagenic effects of free radicals than the nuclear genome. Additionally, the closed-circular structure favours mtDNA binding alkalizing substances, such as N-nitrozomethylamine and benzopyrene. At the same time there is a build-up of those carcinogens in the mitochondrial lipid membrane, in which there is a combination of enzymes and mtDNA replication. Proteins involved in OXPHOS are located in the inner mitochondrial membrane and form part of the respiratory chain. The task of the respiratory chain is the transport of reducing equivalents, (hydrogen or electrons) detached from the substrate to oxygen. The energy released during the transport of electrons through the respiratory chain is used for the synthesis of adenosine triphosphate (ATP). The mitochondrial electron transport chain consists of four large complexes of respiratory enzymes. Complex III containing cytochrome b, is the first complex from which the electron transport starts. Complex IV or cytochrome c oxidase (CO) consists of 13 subunits, including three major subunits I, II, III. Three major subunits of cytochrome c oxidase I, II, III are encoded by the mitochondrial DNA, and constitute the core of the complex. The functioning of complex III and IV is extremely important for a cell.

Those are the last of the OXPHOS complexes before the ATP-synthase responsible for the synthesis of ATP, which terminates the respiratory chain. All changesin the respiratory chain have a great influence on the functioning of the protein. ATP synthase (F1F0 ATP-ase), also known as complex (De Paepe 2012; Fethiere et al. 2014; Wallace 2013),is protein composed of a part located in the mitochondrial membrane(F0) comprising a proton channel and its associated catalyst component (F1) located from the mitochondrial matrix (Wallace 2013). F0 component contains 6 and 8 subunit encoded by mtDNA (ATP6 andATP8).The aim of this study was to analyze the expression at the mRNA level of cytochrome b, complex IV (subunits COI, COII, COIII), ATP6 and ATP8 and to perform a quantitative analysis of the activity of ATP synthase as complex V of the respiratory chain, responsible for ATP synthesis and break down of ATP to ADP.

MATERIALS AND METHODS

Materials

The tested material were paraffin specimens of ductal carcinoma (carcinoma ductale) Tp1-2Np0-1M0, and non-cancerous tissue of the mammary gland (control) sampled from 30 breast cancer patients who had undergone surgery. The patients had received no chemotherapy or hormone therapy. They were all perimenopausal women. The Institutional Review Board at the Medical University of Lublin approved this study (approval no., KE-254/141/2009).

Hybridization reaction - detection of gene expression at the mRNA level.

Gene expression of cytochrome b subunits COI, COII, COIII, ATP6 and ATP8 paraffin performed

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in preparations in which the protein was digested with proteinase K (Boehringer Mannheim Germany) at a concentration of 100 μg /ml at 37^{0}C for 30 minutes. Pre-hybridization was used to block non-specific binding of the DNA probes, thus reducing background response. 50 μl prehybridisation mixture (Sigma) was applied on the sections and incubated on a sterile cover slip covering at 37^0 C for 45 minutes. Hybridization was carried out at a temperature appropriate for the respective probe for 2 hours with the prepared solution of fluorescein-labelled probe for the 5 'end (GENSET France). Molecular probes were used, complementary to portions of mRNA of the specific genes studied.

Antisense probes are known as R (left), and the probe sense F (right). The negative control preparations were added to them without probe. Detection was performed by incubation with the monoclonal anti-fluorescein antibody preparations labelled with alkaline phosphatase (Amersham England). This enzyme catalyses the oxidation of the cytochemical substrate, i.e. NBT / BCIP (Boehringer Mannheim Germany) to a blue coloured formazan. After incubation the preparation was washed twice with distilled water.

The level of gene expression at the mRNA level was evaluated on the basis of the light intensity of fluorochrome or fluorescein in the cells under the confocal microscope (Axiovert 200 M Zeiss) with a head LSM 5 Pascal. The experiment was performed in three independent replications.

Determination of the activity and location of ATP synthase in cells

To determine the activity and cellular localization of ATP synthase formulations we used paraffin sections, which were deparaffinised and rehydrated in alcohol. The formulations were evaluated histologically. Epitopes were uncovered by using 0.05% trypsin, and deproteinisation was performed by incubation with 20 μg/ml proteinase K. The blocking reaction was performed with 5% BSA and 0.5% Tween. Every piece was loaded with 100ml primary antibody and incubated for12 hours in a moist chamber. After washing the preparations with PBS 100μl of fluorescein-labelled secondary antibody was added and the preparations were incubated in the dark for 1 hour at room temperature in a humidified chamber. After washing with PBS, the sections were covered with cover slip and observed under a fluorescence microscope.

Method of mitochondrial preparations

Fresh examination material from breast cancer and the control tissue was crumbled, then homogenized mechanically using ball homogenizer in 0,02 M Tris HCL buffer with pH-7.5 containing 0.330 saccharose, 0.6 mM EDTA and PVS 4 μg/ml (Bugenhagen & Clayton 1974)

The homogenate was centrifuged for 5 minutes at 2.500xg twice in a MSE centrifuge to separate the tissue residue from cell nuclei. The obtained residue was thrown out and the supernatant was once again centrifuged at 15000xg for 30 minutes. The obtained residue was the mitochondria, which were subsequently suspended in the homogenizing buffer and purified in saccharose gradient made up of 15 ml 1.0 M saccharose, 5 mM NA_2EDTA layered on 15 ml 1.5 M saccharose, 5 mM NA_2EDTA, 10mM Tris HCL pH 7.5.

The mitochondria were centrifuged for 30 minutes at 20000xg. The obtained preparations were photographed in an electronic microscope.

RESULTS

Hybridization results

Gene expression at mRNA level for particular units are shown in the form of light emission by fluoresceine. In breast cancer preparations we deal with a higher expression of genes at mRNA level for COI, COII, COIII, cytochrome b and ATP6 and ATP8 compared with non-neoplastic tissue. In the preparation for COI (Figure 1-1A) in breast cancer cells there was a nuclear signal apart from a cytoplasmatic one. The nuclear signal did not occur in non-neoplastic tissue preparations. There was only a weak cytoplasmatic signal (Figure 1-1B). Similar results were obtained in the case of hybridization reaction for COII (Figure1-2A) and for cytochrome b (Figure1-3A). In non-neoplastic cell preparations there was only a weak signal from the cytoplasm (Figure 1- 1B,2B,3B,4B). Gene expression at mRNA level for COIII and ATP8 were also analyzed. In all the breast cancer cells there was a strong cytoplasmatic signal compared with the control. In the case of the control there was a weak cytoplasmatic signal.

Analysis of activity and location of ATP synthase.

In breast cancer preparations there was a strong expression of protein in the form of light emission emitted by fluoresceine in the cytoplasm (Figure 1-5A). Preparations of non-neoplastic tissue showed a weak protein activity were obtained. ATP synthase activity was higher in preparations obtained from breast cancer compared with the control tissue (Figure 1- 5A,5B).

Analysis of mitochondrial energy

It should be noted that in our study tumour mitochondria and those of normal cells showed a different energy status (Figure 2 and 3).

DISCUSSION

Changes in the gene expression of the mitochondrial proteins, and in particular membrane-associated proteins may interfere with mitochondrial apoptosis. Changes in the mitochondrial membrane cause opening of the mitochondrial mega-channels and an escape from the inner mitochondrial membrane of cell death promotion factors, such as cytochrome c, the apoptosis inducing factor (the apoptosis inducing factor-AIF) and caspases in the mitochondrial matrix (Chen et al. 2003; Kadenbach et al. 2004; Vaux 2011). Compounds which stimulate or inhibit the opening of the mitochondrial membrane channels simultaneously inhibit or stimulate apoptosis. Cytochrome c activates the caspase pathway in the cytosol, leading to degradation of the cell and passes into the nucleus AIF causing destruction of chromatin (Chen et al. 2003; Kadenbach et al. 2004; Vaux 2011). The inhibition of apoptosis is caused by respiratory chain inhibitors, either by affecting the process of oxidative phosphorylation, or inhibition of ATP synthase. This causes a decrease in the membrane potential without opening the channels in the membrane and an escape of the mitochondrial inducers of the mitochondrial pathway of apoptosis. This situation is the result of loss of accumulation of Ca^{+2} ions, which are an essential factor in the permeability of the membrane (Galitovsky & Gogvadze 1998; Kadenbach et al. 2004). The main components of the respiratory chain are synthesized in the mitochondria. Mutations in the genes can interfere with OXPHOS energy production in the mitochondria and damage the cellular processes including apoptosis (De Paepe 2012; Wallace 2013). The literature describes mtDNA mutations in the genes encoding OXPHOS (Canter et al. 2005; Czarnecka & Bartnik 2011; Grzybowska-Szatkowska, Slaska 2012). Some polymorphisms occurring in mtDNA seem to be related to the incidence of breast (Canter 2005; Czarnecka et al. 2010; Grzybowska-Szatkowska & Slaska 2012), prostate (Grzybowska-Szatkowska & Slaska 2012, Petros, Baumann & Ruiz-Pesini 2005; Sakr 2004) and endometrial cancers (Liu et al. 2003). The described differences in the mitochondrial membrane potential between the cancer cells and normal cells may be due to differences in the structure of the components responsible for the formation of the electron gradient. This alies to components of respiratory enzyme complexes, ATP synthase, ANT (adenine nucleotide translocator) and mitochondrial membrane lipid

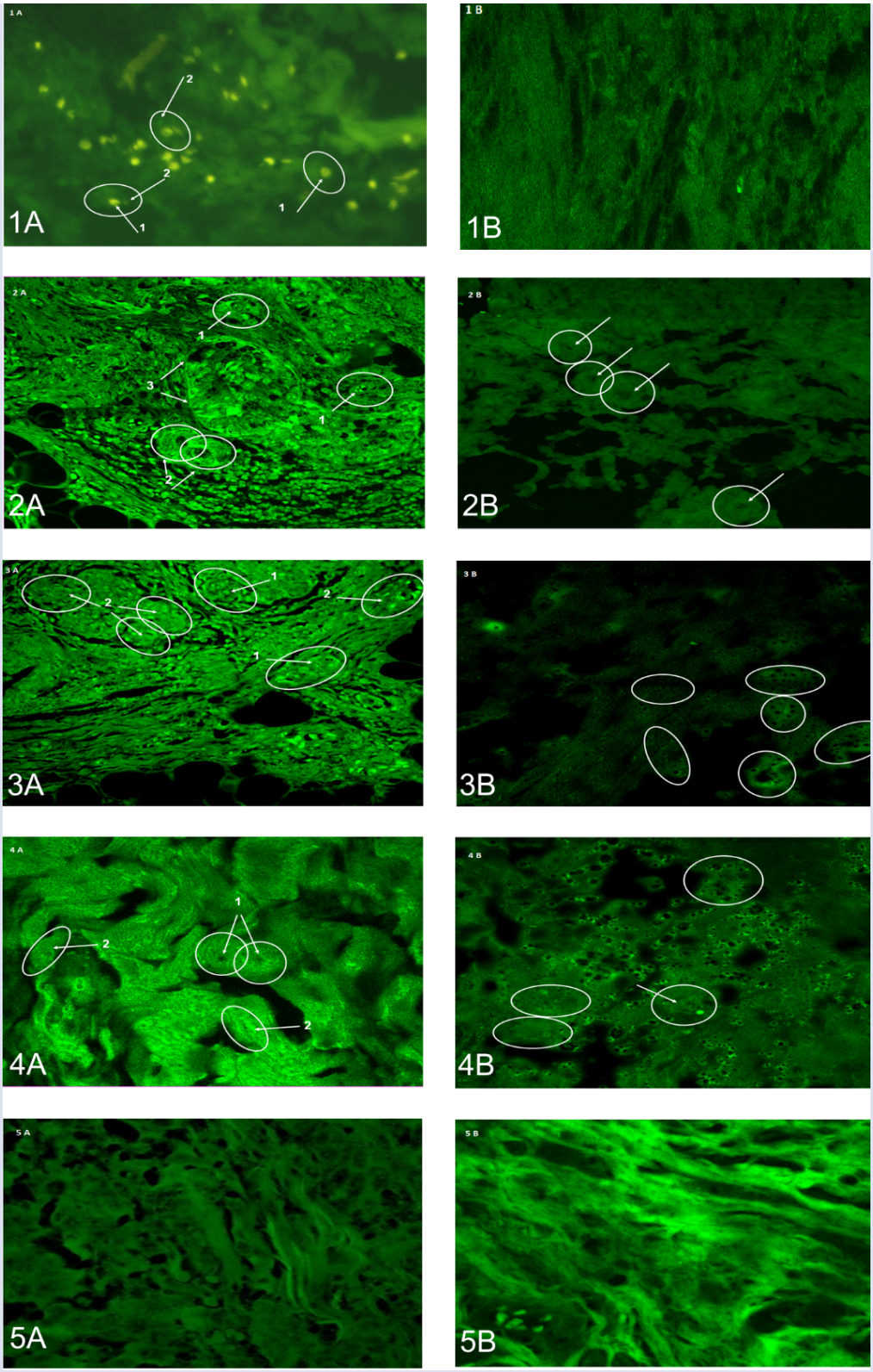

Figure 1. The expression at mRNA level for cytochrome b, COI,COII,ATP6 and ATP synthase activity 1.Expression of COI mRNA in: 1A) breast cancer cells – nuclear (1) and cytoplasmic (2) signal. 1B) normal tissue (Thefluorescence intensity: normal tissue: 1500, tumor tissue: - 12000. 2. Expression of COII mRNA in: 2A) breast cancer cells – nuclear (1) and cytoplasmic (2) signal. 2B) control tissue (The fluorescence intensity: normal tissue: 1500, tumor tissue: COII - 15000). 3. Expression at mRNA level for cytochrome b: 3A) breast cancer cells, clearly visible nuclear (1) and cytoplasmic (2) signals.3B) control tissue (The intensity of fluorescence intensity: normal tissue: 1000, tumor tissue: 10000). 4. High expression of mRNA for ATP6 in: 4A) breast cancer – (1) nucleus, (2) cytoplasmic signals. 4B) control tissue (The fluorescence intensity: normal tissue: 3000, tumor tissue: 12000). 5. ATP synthase activity. The intensity of fluorescence light: 5A) normal tissue: 2200, 5B) cancer cells: 10500

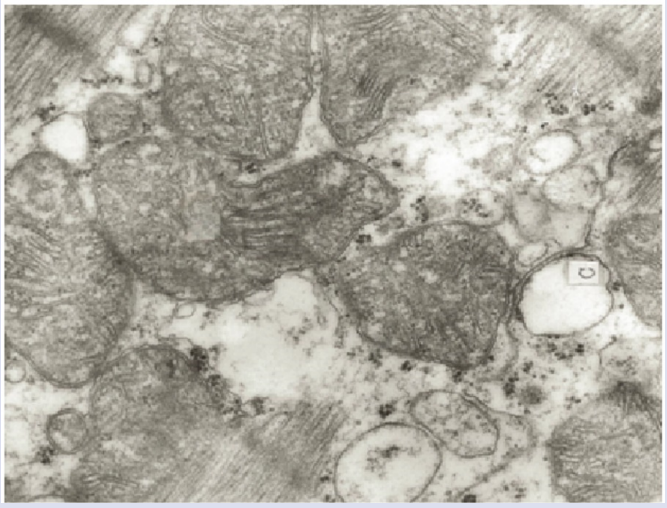

Figure 2. Low energy mitochondria obtained from breast cancer cells - 40 000 x magnification

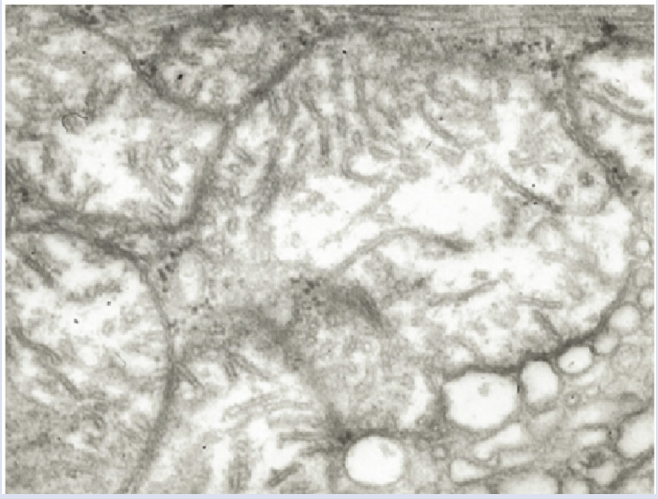

Figure 3. Mitochondria tissue cells obtained from control subjects. Accumulation of ATP in oxysomes, 40 000 x magnification

structure (Chen et al. 2003; Fethiere et al. 2004; Vaux 2011; Wallace 2013). In our studies we showed an increased activity of the Krebs cycle enzymes in the cells of various cancers, including breast cancer cells compared to normal tissue (Florianczyk et al. 1997; Grzybowska-Szatkowskaet al. 2005). There are some reports of reduced cytochrome c oxidase activity in prostate cancer cell lines (DU-145), breast cancer (MCF-7, T47D) (Modica-Napolitano, Touma 200) compared to the corresponding normal cell lines. Also, in the case of adenocarcinoma of the colon there was a reduced cytochrome oxidase activity as compared to non-malignant cells of liver and intestinal mucosa (Sun, Sepkowitz & Geller 1981). It is not clear whether it is accompanied by decreased expression of a particular gene. In the cell line of colon cancer, where a low level of mRNA COIII was found, there was a return in cytochrome c oxidase activity to normal after the exposure of the cells to sodium lactate (Heerdt et al. 1990). In Zajdel hepatoblastoma increased levels of mRNA were observed for subunits of the mtDNA COI and COII and nuclear component for CO IV (Luciakova & Kuzela 1992). The results of the hybridization showed a higher expression at the mRNA level for the complexes COI, COII, COIII and cytochrome b and for the 6 and 8 subunits of ATP synthase in all cases of breast cancer compared to normal cells. In the case of cytochrome b, COI and COII signal was present in the cell nucleus, which could indicate the presence of the nuclear genome sequence homologous to the mtDNA.

In situ hybridization a presence of mitochondrial DNA sequences in the nucleus and absence of nuclear signals in normal cells have been demonstrated in human low-grade gliomas and cervical cancer cells (Chen, Xue & Xiang 2008; Liang 1996; Liang & Hays 1996). The presence of mitochondrial sequences in the nuclear DNA is the result of the transition elements of mtDNA to nuclear DNA in the course of human evolution (Bensasson, Feldman & Petrov 2003; Hazkani-Covo, Zeller & Martin 2010) and in the process of carcinogenesis (Bagetto 1992, Ju et al. 2015, Wallace 2013). In the nuclear DNA mtDNA sequences were detected, so-called pseudogenes (Bensasson, Feldman & Petrov 2003; Hazkani-Covo, Zeller & Martin 2010) which is likely due to auto-fagocytosis passed to the nucleus during evolution (Bensasson, Feldman & Petrov 2003; Collura & Stewart 1995). Under the influence of carcinogene damage to mtDNA occurs and there is a creation of small mtDNA molecules that undergo auto-fagocytosis and thus pass on to the cytoplasm (Bagetto 1992). MtDNA fragments are then inserted into the nuclear DNA. Introduction of mtDNA molecules, especially in the vicinity of the promoters, can cause activation and expression of proto-oncogenes (Chen, Xue & Xiang 2008; Bagetto 1992). Confirmation of this hypothesis was demonstrated in chemically induced in rat haptomas and virus transformed fibroblasts SV-40 or in fibrosarcoma cell lines HT-1080 increased in comparison with the cell correct number of copies for pseudogenes COI, COII, COIII in the nuclear genome (Collura & Stewart 1995; Corral et al. 1989). In human cells, HeLa line was detected in mtDNA fragments belonging to the 12S rRNA gene, cytochrome oxidase subunit I and III, and NADH dehydrogenase introduced in the vicinity of the c-myc gene (Collura & Stewart 1995). As a result of over-expression of proto-oncogenes disturbances in protein synthesis occur, and thus disturbance in the growth and differentiation of cells takes place. Probably, complicity of mitochondria and mtDNA in the process of carcinogenesis is a complex phenomenon and both mechanisms are also involved. During this study, there were no nuclear signals in normal cells. In cancer cells the expression of ATP synthase was higher as compared with the control tissue. A signal in the tumour cells as oozed to the control tissue was strong, localized in cytoplasm. This indicates a high content of ATP synthase in cancer cells. In breast cancer patients in the study of antibody binding the expression of ATP synthase was higher in all the cases studied compared to control tissue. Comparing tumour mitochondria and mitochondria of normal cells in the study it should be noted that they show a different energy status (Figure 2 and 3). The mitochondria in tumour were in a state of low energy, as oosed to the high-energy state of the mitochondria of normal breast glandular cells. The mitochondria of tumour cells contain little ATP, as evidenced by the significantly thickened matrix and a small amount of the mitochondrial crests in contrast to the clear matrix with distinct ridges in the cell proper. This indicates the high consumption of ATP in cancer cell, which is dephosphorylated to ADP, with the participation of synthase ATP. This occurs in cells with high oxygen consumption and high amounts of free energy derived from the electron transport chain (Kudin et al. 2004). The aearance of mitochondria in some ways confirms the need for cell protein synthesis of the cytochromes and ATP synthase. Of course, this is not the proper functioning of the mitochondria. A reduction of cellular respiration related to the ATP synthesis and a reduction in phosphorylation ability have been reported in neoplasms of varying differentiation degrees as compared to normal tissue (Bianchi et al. 2015; Capuano 1997; Capuano et al. 1996; Krieg et al. 204; Solaini, Sgarbi & Baracca 2011). In hepatoblastomas of varied differentiation it was observed that there was a lowered degree of cell respiration connected with ATP synthesis and a reduction of phosphorylation ability compared with normal liver tissue. It is suggested that this may be associated with lower levels of β-subunit in the F1 component of mitochondrial ATP synthase or over expression of ATP synthase inhibitors in cancer cells (Capuano 1997; Capuano et al.

1996; Wallace 2013). It should be kept in mind that in cancer cells there is a multiplication of the number of copies of mtDNA (Liang & Hays 1996). The role of somatic mtDNA mutations in tumour progression has not been previously investigated. It is possible that mutations in conserved regions, places of replication of transcription promoters or a transcription factor binding site may affect both the efficiency of transcription, as well as the degree of ripeness of mitochondrial protein. So, the question remains open of whether protein overexpression is associated with the occurrence of mutations, or whether it is the result of increase in the amount of mtDNA?" (Torroni et al. 1990). Torroni, *et al.* (1990) showed that the increase in mtRNA for OXPHOS genes was not connected with mtDNA over expression (Juet al. 2015). The results of these studies indicate a relationship of mRNA over expression with changes in mtDNA.

The results confirm mtDNA incorporation to nDNA in neoplastic cells. They point to increased expression at mRNA level for COI, COII, COIII, ATP6 and ATP8 in breast cancer cells compared with control tissue. Increased amount of ATP synthase points to increased ATP in a neoplastic cell.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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