Review Article

Mitochondrial Markers for Cancer: Relevance to Diagnosis, Therapy, and Prognosis and General Understanding of Malignant Disease Mechanisms

Boel De Paepe

Laboratories for Neuropathology & Mitochondrial Disorders, Ghent University Hospital, Building K5 3rd Floor, De Pintelaan 185, 9000 Ghent, Belgium

Correspondence should be addressed to Boel De Paepe, boel.depaepe@ugent.be

Received 25 September 2012; Accepted 15 October 2012

Academic Editors: B. Azadeh, T. Kovács, P. J. Twomey, and T. Yazawa

Copyright © 2012 Boel De Paepe. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Cancer cells display changes that aid them to escape from cell death, sustain their proliferative powers, and shift their metabolism toward glycolytic energy production. Mitochondria are key organelles in many metabolic and biosynthetic pathways, and the adaptation of mitochondrial function has been recognized as crucial to the changes that occur in cancer cells. This paper zooms in on the pathologic evaluation of mitochondrial markers for diagnosing and staging of human cancer and determining the patients' prognoses.

1. Introduction

Mitochondria are membrane-enclosed cell organelles that can be found in all human cells, except for the peripheral red blood cells. An eukaryote cell contains around 1000 to 2000 mitochondria, with diameters varying between 0.5 and 1.0 μm. The mitochondrion is a key venue for cellular metabolism and the powerhouse of the cell. As a consequence, mitochondrial content is influenced by cellular energy demand. Exercise training for instance, increases the amount of mitochondria per fiber and the volume of organelles in skeletal muscle tissue [1, 2].

1.1. Mitochondrial Metabolic Pathways.

To understand the crucial role played by mitochondria in cancer, it is necessary to fully grasp the extent of their metabolic activity.

1.1.1. Glycolysis. Glycolysis is the sequence of cellular reactions that converts glucose into pyruvate, with the concomitant production of a relatively small amount of energy. Glycolysis occurs throughout the cell and is considered the basis of all energy processes. The 2 ATP and 2 NADH molecules it produces can enter the oxidative phosphorylation (OXPHOS) cycle, which then produces larger quantities of ATP.

1.1.2. Oxidative Phosphorylation. In the Krebs or OXPHOS cycle, sequential oxidation and reduction reactions take place upon a chain of four multiprotein complexes: (1) complex I is composed of 45 protein subunits and displays NADH dehydrogenase activity. In the process, four hydrogen ions are pumped out of the mitochondrial matrix. (2) Complex II: the succinate dehydrogenase complex catalyzes the oxidation of succinate to fumarate, with concomitant reduction of ubiquinone. (3) In two cycles, complex III or coenzyme Q cytochrome c oxidoreductase reduces coenzyme Q, extracting 4 protons from the mitochondrial matrix. (4) On complex IV or cytochrome c oxidase, electrons are donated one at a time to cytochrome c and passed on to O2, producing 2 H2O molecules. In addition to the protons utilized in the reduction of O2, there is electron transfer-linked transport of 2 protons from the matrix to the mitochondrial intermembrane space.

The translocation of protons across the inner mitochondrial membrane, established by the respiratory chain, creates an electrochemical gradient (Δψ) that is utilized by complex V, the ATP synthase, to generate ATP from ADP and inorganic phosphate. Complex V is composed of a catalytic component on the matrix side (termed F1) and a hydrophobic membrane component (termed F0) that contains the proton...
channel, linked by a stalk. The membrane-associated OXPHOS complexes are co-assembled into higher-order supercomplexes within the inner mitochondrial membrane [3].

1.1.3. Tricarboxylic Acid Cycle. In the tri-carboxylic acid (TCA) cycle, a series of chemical reactions generates energy through the oxidation of acetate derived from carbohydrates, fatty acids, and proteins. In addition, the cycle provides precursors (amino acids for instance) as well as the reducing agent NADH that is used in numerous biochemical reactions. The series of oxidation reactions that occurs is connected to the electron transport chain and generates ATP. Acetyl CoA is oxidized by the pyruvate dehydrogenase complex, which is located in the mitochondrial matrix.

1.1.4. Fatty Acid Oxidation. β-oxidation is the process by which fatty acids are broken down to generate acetyl CoA, the latter being the entry molecule for the TCA cycle. The β-oxidation pathway involves 4 enzymes that are present in the mitochondrial matrix and function in a repetitive cycle. The process continues until the original fatty acid molecule is completely degraded to acetyl CoA. Acetyl coA can subsequently enter the TCA cycle, undergoing oxidation to CO₂. Under conditions of starvation, acetyl coA can alternatively be converted into ketones.

1.1.5. Urea Cycle. The urea cycle is a cycle of biochemical reactions that produces urea from ammonia at the cost of 3 ATP molecules. The urea cycle consists of five reactions of which the first two occur in the mitochondrial matrix.

1.1.6. Gluconeogenesis. Gluconeogenesis is a metabolic pathway that generates glucose from substrates such as lactate, glycerol, and glucogenic amino acids. It is one of the two main mechanisms to keep blood sugar levels from dropping when glucose intake is low and takes place mainly in the liver. Gluconeogenesis is a pathway consisting of a series of eleven enzyme-catalyzed reactions, starting in the mitochondria with the formation of oxaloacetate by the carboxylation of pyruvate. Oxaloacetate is reduced to malate using NADH, a with the formation of oxaloacetate by the carboxylation of enzymes that convert phosphoenolpyruvate to glucose are present in both the cytosol and the mitochondria. Phosphoenolpyruvate carboxykinase activity is present in both the cytosol and the mitochondria. The enzymes that convert phosphoenolpyruvate to glucose are found in the cytosol. Transport of phosphoenolpyruvate across the mitochondrial membrane is accomplished by dedicated transport proteins.

1.2. Dual Genetic Origin of Mitochondria. A unique feature of mitochondria is that these organelles contain their proper genome. The human mitochondrial genome (mtDNA) is a 16,569 base-pair long circular DNA molecule that contains genes for 13 structural subunits of oxidative phosphorylation: (1) 7 subunits of complex I encoded by ND1, ND2, ND3, ND4L, ND4, ND5, and ND6 genes, (2) one complex III subunit encoded by the CYTB gene, (3) 3 complex IV subunits encoded by COXI, COXII, and COXIII genes, and (4) 2 complex V subunits encoded by the ATP6 and ATP8 genes. The mtDNA also contains sequence information for 2 rRNAs and 22 tRNAs essential for translation of mitochondrial proteins. The mtDNA is exclusively maternally inherited and a variety of polymorphisms is present in the human population [4]. Multiple copies are present in each mitochondrion. When mtDNA with different sequences coexists within a single cell or tissue, this is defined as heteroplasmy. Many disease-causing mtDNA mutations have been shown to display heteroplasmy, and the percentages of mutated mtDNA determine the severity of mitochondrial dysfunction [5].

1.3. Mitochondrial Morphology. Historically, mitochondria were described as free-floating vesicles in the cell [6]. They consist of an outer mitochondrial membrane (OMM) and an inner mitochondrial membrane (IMM) that contains convolutions termed cristae, forming the compartments of intermembranous space (IMS) and mitochondrial matrix. The development of cellular imaging techniques, however, has since cast new light onto mitochondrial structure, revealing it as a network of long tubules rather than a collection of individual small vesicles. Mitochondria are highly dynamic organelles that can fuse, divide, and form an interconnected network throughout the cell that stretches from the nucleus to the plasma membrane [7].

The mitochondrial network is shaped through the equilibrium obtained by regulation of the mitochondrial fusion/fission machinery. Two mitofusins, MFN1 and MFN2, are dynamin-related GTPases located to the OMM. They can form homo- and heterodimers and, fueled by GTP, will make the OMM of adjacent mitochondria fuse. MFN2 is also responsible for the tethering between mitochondria and the endoplasmic reticulum. The related dynamin GTPase optic atrophy 1 (OPA-1) is located to the IMM and controls fusion at this level. Other proteins that are involved in mitochondrial fusion are leucine zipper-EF-hand containing transmembrane protein 1 (LETM1), phospholipase D, and prohibitins. Dynamin-related protein 1 (DRP1) is a cytosolic GTPase that, when recruited to the OMM, oligomerizes forming ring-shaped structures and inducing mitochondrial constriction and subsequent fission. Mitochondrial fission factor (MFF) is an adaptor of DRP1 on the OMM, and mitochondrial elongation factor (MIEF) binds DRP1 inhibiting the latter’s activity [8]. Fission 1 (FIS1) can interact and sequester MIEF function. Other proteins involved in mitochondrial fission are endophilin B1, a fatty acyl transferase that acts downstream of DRP1, mitochondrial 18 kDa protein (MTP18) [9], mitofusin binding protein (MIB), and ganglioside-induced differentiation associated protein 1 (GDAP1) [10].

Mitochondrial morphology and OXPHOS function are strongly associated. Impaired OXPHOS function leads to mitochondrial network fragmentation. Structural defects in complex V lead to severe morphological alterations to
the mitochondria [11], and the oligomeric state of F1F0 ATP synthase determines cristae morphology [12].

2. Metabolic Cancer Markers

Cancer is strongly associated with perturbations in cellular metabolism, with a characteristic metabolic shift toward aerobic glycolysis in transformed cells.

2.1. Markers of Aerobic Glycolysis. In cancer cells, pyruvate is abundantly transformed to lactate by aerobic glycolysis [13], and the overexpression of glycolysis genes is the general rule [14]. Physical association between glycolytic enzymes and the mitochondrion has been firmly established using the yeast cell model [15].

Enolases catalyze the conversion of 2-phosphoglycerate to phosphoenolpyruvate. These enzymes are classically regarded as cytosolic, yet they tightly associate with the mitochondrial surface [16]. In human tissues, three genetic loci, termed α, β, and γ, encode the different enolase isoforms. Enolase 1 is present in almost all adult tissues, enolase 2 is found in neuronal and neuroendocrine tissues, and enolase 3 is found mainly in muscle. They form hetero- and homodimers that dehydrate 2-phosphoglycerate in the glycolysis or the reverse reaction in the gluconeogenesis. The enzyme is upregulated under stress conditions, via activation of hypoxia-inducible factor-1 (HIF-1). Overexpression of α-enolase is associated with tumor development and represents a potential diagnostic and prognostic marker [17]. In breast cancer, α-enolase gene expression correlates with tumor size and shorter disease-free interval [18]. In head and neck [19] and non-small-cell lung cancer [20], higher expression of α-enolase is associated with poorer clinical outcome in patients.

Pyruvate kinase (PK) is a rate-limiting glycolytic enzyme that converts phosphoenolpyruvate into pyruvate with the generation of one ATP molecule. Its PKM1 and PKM2 isoforms are encoded by the same gene and are generated by alternative splicing. PKM1 is found mainly in normal cells, whereas PKM2 is an embryonic isoform expressed in cancer cells [21]. Both plasma and fecal PKM2 can be used as a marker for gastrointestinal cancer, showing good diagnostic accuracy [22]. In addition, PKM2 plasma levels appear predictive for disease severity and outcome. Elevated levels have been found to associate with aggressive breast carcinomas [23]. In breast cancers lacking caveolin-1, PKM2 immunostaining is confined to the stromal cells and sometimes the extracellular matrix [24].

Pyruvate, the end product of the glycolysis, enters the mitochondria where it is transformed to acetyl CoA, producing NADH and CO₂. Acetyl CoA can subsequently enter the TCA cycle. This process is regulated by the pyruvate dehydrogenase complex (PDH), which is composed of the E2 core bound to the E1 and E3 components. PDH activity is controlled by pyruvate dehydrogenase kinases (PDK) 1 to 4, which phosphorylate and suppress the E1 subunit [25]. PDH levels are dramatically decreased in hepatomas [26] and skin carcinomas [27]. While normal lung tissue stains strongly for PDH and PDK1, a large proportion of cancer cells in patients with non-small-cell lung carcinomas show diminished expression. The lack of PDH expression was shown to be associated with HIF-1α stabilization [28].

2.2. Oxidative Phosphorylation Markers. Warburg hypothesized as early as the thirties of the last century that the increased rates of aerobic glycolysis he observed in tumor cells, might be due to their impaired respiratory capacities [13]. Reduced respiration is indeed associated with cancer, however, the OXPHOS is not always compromised as a whole. For instance, the OXPHOS enzyme activities and protein levels are not uniformly decreased in breast cancer cell lines. The spectrum of decrease is MCF7 (complexes II, III, and V), T47D (complexes I, III), SKBr3 (complexes III, IV, and V), and MDA-MB-231 (complexes I, III, IV, and V) [29]. Interestingly, the most aggressive breast cancer line (MDA-MB-231) displays the broadest OXPHOS defect. In support, a correlation was shown between low overall OXPHOS activity and tumor aggressiveness in renal carcinoma [30].

2.2.1. Complex I. Complex I loss of function has been shown many times in cancer tissues. In renal oncocytomas, complex I activity is reduced by 50% [31] to 65% [32], with blue native PAGE immunoblot revealing the lack of assembled complex I. All 17 oncogenic thyroid adenomas tested display greatly reduced or absent complex I subunit NDUF4 immunoreactivity, compared to expression levels of complex II, III, IV, V, and porin, which are higher in the tumor cells than in the adjacent normal tissue [33].

2.2.2. Complex II. A reduction of complex II activity is associated with human cancer. In a series of 31 renal carcinomas, complex II activities are 6-fold lower than in controls [34]. Complex II activity was found decreased in breast cancer cell lines [29].

2.2.3. Complex III. In addition to reduced activities [29], complex III activation has also been reported in cancer. Complex III subunits UQCRFS1 and UQCRH are overexpressed in a variety of tumors. The complex III subunits Rieske iron-sulfur protein and Hinge protein are encoded by the UQCRFS1 and UQCRH gene, respectively. Expression studies reveal that transcripts of UQCRFS1 and UQCRH are increased in breast tumors compared to normal breast tissue. Immunohistochemical staining for UQCRFS1 shows higher expression scores in breast cancer compared to benign breast tissue [29]. Also, UQCRFS1 gene amplification has been detected in breast tumors [35].

2.2.4. Complex IV. Both compromised and induced complex IV function have also been observed in cancer. COXI, COXII, and COXIV, mRNA levels are increased in hepatoma compared with normal liver [36]. A proteomic study shows a 2-fold upregulation of COXII protein in breast cancer cells [37]. On the other hand, complex IV activity is 5-fold decreased in renal carcinomas compared with controls [34]. Also, COXIII mRNA levels are lower in colonic carcinoma versus normal mucosa samples [38]. Differential complex
IV activity could be relevant to therapeutic outcome. Adriamycin-resistant leukemia cells, for instance, contain alterations in complex IV subunits and decreased activity of the complex [39].

2.2.5. Complex V. The relationship between complex V function and cancer appears to be complicated. Complex V activity was shown to be reduced in high grade but normal in low grade renal carcinomas [30], but another report did not find a tumor grade correlation [34]. A proteomic study shows a 2-fold increase of the ATP synthase f chain in breast cancer cells [37].

2.3. Other Metabolic Markers. Being such a crucial venue of metabolism, many other mitochondrial metabolic factors are continuously surfacing as possible biomarkers for cancer. A selection is discussed hereunder.

2.3.1. Hydratases. Fumarate hydratase (FH) is a nuclear-encoded mitochondrial enzyme that takes part in the TCA cycle, catalyzing the formation of L-malate from fumarate. Mutations in the FH gene are associated with an autosomal dominant tumor syndrome causing uterine, skin, and kidney cancer [40] and hereditary leiomyomatosis and renal cell cancer [41]. Mitochondrial enoyl-CoA hydratase 1 catalyzes the second step of the β-oxidation. Its expression is 10-fold increased in a human gastric cancer cell line [42]. NAD-dependent bifunctional methylenetetrahydrofolate dehydrogenase/cyclohydrolase (MTHFD) regulates the biosynthesis of tetrahydrofolate, providing precursors for nucleotides and methylation reactions. There is a strong association between MTHFD genetic variants and gastric [43] and bladder [44] cancer risk. MTHFD2 protein content is 3-fold decreased in breast cancer cell lines [37].

2.3.2. Dehydrogenases. Isocitrate dehydrogenases (IDH) are important players in the exchange of metabolites within the cell, and two IDH isoforms can be found within the mitochondrion. NADP-dependent IDH2 has a role in shuttling of electrons between the mitochondrion and the cytosol. The mitochondrial matrix enzyme NAD-dependent IDH3 is involved in the TCA cycle. Breast cancer cell lines display high levels of IDH2, and expression is positively associated with overall survival in breast cancer patients [45], possibly due to enhanced reactive oxygen species (ROS) protection.

2.3.3. Oxidases. Coproporphyrinogen III oxidase (HemN), an enzyme required for heme synthesis, is present in the IMM. It’s expression is increased in adriamycin-resistant breast cancer cells [46].

3. Genetic Cancer Markers

Due to their genetic complexity, both the nuclear (nuDNA) and the mitochondrial genome are suitable for investigation in regard to carcinogenesis.

3.1. mtDNA Alterations in Cancer. The mtDNA is particularly susceptible to mutations due to its proximity to ROS generation and the relatively inefficient DNA repair system the mitochondrion possesses [47]. The frequency of mtDNA mutations in cancer cells is 10-fold higher than nuDNA mutations [48], and many alterations to the mtDNA that can be detected in tumor cells potentially alter mitochondrial function. Also, mtDNA alterations can often already be detected in the premalignant stage. mtDNA is abundant and readily detectable in blood, urine, and saliva samples, making it an attractive subject for diagnostic investigations.

3.1.1. Alterations in ND Genes. The mtDNA encodes for seven complex I subunits (ND1–ND6 and ND4L) and alterations in cancer cells are plenty. Somatic mutations of ND genes are associated with thyroid oncocytoma [49]. A study of 10 colorectal cancer cell lines reveals 1 ND1, 1 ND4L, and 1 ND5 sequence alterations [50]. Of 45 colorectal carcinomas tested, 3 contain ND1 and 3 ND5 gene mutations [51]. Of 18 primary oral squamous cell carcinomas tested, 3 contain ND2, 1 ND3, and 1 ND4 somatic mutations [52]. In a series of 15 patients with renal oncocytoma and compromised complex I function, 4 patients harbor ND1, 3 patients ND4, and 3 patients ND5 sequence alterations. The alterations are most often single-nucleotide insertions (6/10) or deletions (3/10) [32]. In 31 urothelial cell carcinoma patients, tumor cells contain ND1 (n = 2), ND2 (n = 3), ND4 (n = 2), and ND6 (n = 1) frequency variations [53]. In a study examining 38 bladder tumors, 73% contain at least one base-pair alteration in the ND1 gene [54].

3.1.2. Alterations in the CYTB Gene. The mtDNA contains one gene that encodes a structural unit of complex III, namely, cytochrome b (CYTB). In 10 colorectal cancer cell lines, 2 CYTB sequence alterations could be found [50]. Tumor cells from 3 of 31 patients with urothelial cell carcinoma contain CYTB alterations [53]. In 81% of bladder carcinomas, at least one base-pair substitution is present in the CYTB gene [54]. In a human bladder cancer model, CYTB alteration is shown to generate higher levels of ROS and lead to increased tumor growth [55].

3.1.3. Alterations in COX Genes. The mtDNA encodes three structural components of complex IV: COXI, COXII, and COXIII. In 10 colorectal cancer cell lines, 1 COXI, 1 COXII, and 1 COXIII sequence alterations are present [50]. Of 18 oral squamous cell carcinomas, 1 contains a COXIII somatic mutation [52]. In 31 urothelial cell carcinoma patients, tumor cells are found to contain altered sequence in COXI (n = 2) and COXIII (n = 2) genes [53]. 11% of prostate cancer patients harbor COXI mutations in conserved sequences compared to less than 2% in healthy controls [56].

3.1.4. Alterations in ATPase Genes. The mtDNA encodes two structural units of complex V, being ATPase6 and ATPase8. ATPase6 is central to the proton channel of the ATPase [57]. Mutations in the ATP6 gene are present in 24 of
39 patients with osteosarcoma [58]. In 1 of 31 urothelial cell carcinoma patients, an ATP6 sequence variant is found [53]. 71% of bladder tumors tested contain at least one base-pair substitution in the ATP6 gene [54]. In a series of 102 epithelial ovarian tumors, 12 contain ATP6 and 21 contain ATP8 sequence variations [59]. ATP6 mutant cybrids of prostate cancer cells display enhanced ROS generation accompanied by increased tumorigenicity [56].

3.1.5. Alterations in tRNA Genes. The mtDNA encodes 22 transfer RNA (tRNA) molecules necessary for mitochondrial protein translation. tRNA is the adaptor used to bridge the four-letter genetic code in messenger RNA (mRNA) to the twenty-letter code of amino acids present in proteins. In one of the 15 tested patients with renal oncocytoma, the 3243G mutation was shown in the mtDNA tRNALeu gene [32]. In urothelial cell carcinoma patients, tumor cells contain tRNA sequence variants in 4 of 31 patients tested [53].

3.1.6. Alterations in rRNA Sequences. The mtDNA encodes both a small (12S) and a large (16S) ribosomal RNA (rRNA) gene. In 10 colorectal cancer cell lines, 3 16S rRNA and 1 12S rRNA sequence alteration are found [50]. In 31 urothelial cell carcinoma patients, 5 tumors contain rRNA somatic gene variations: 4/31 in the 16S and 1/31 in 12S rRNA [53].

3.1.7. mtDNA Displacement-Loop Alterations. Replication of mtDNA starts in the displacement loop (D-loop) region located between nucleotides 16024 and 16576. mtDNA replication involves DNA polymerase γ (POLG) and transcription factor A mitochondrial (TFAM), the latter being the key transcription factor regulating mtDNA copy numbers [60]. Mutations in the D-loop can therefore lead to decreased mtDNA copy numbers and subsequent OXPHOS dysfunction and increased ROS. Intriguingly, the most frequent mtDNA alterations in human cancers are in fact located in the D-loop region [61]. mtDNA alterations within the D-loop could be detected in 77% [52] or 64% [62] of oral squamous cell carcinomas and 44% of colorectal carcinomas (n = 45) [51]. Of 9 renal cell tumors tested, 3 contain D-loop sequence changes [63]. In breast cancer patients, the occurrence of D-loop mutations is associated with an older onset age [64], suggesting that age-related DNA damage contributes to the disease mechanism.

A homopolymeric C-stretch within the D-loop, between nucleotides 303 and 315 termed the 310 microsatellite sequence, is a relatively conserved region. It includes a replication origin for the mtDNA heavy-strand, and sequence variations in D310 are thought to affect mtDNA replication [65]. Many reports have shown D310 sequence alterations in human cancers. In 34% of rectal carcinomas (n = 38) and 38% of sigmoid carcinomas (n = 25), D310 sequence alterations could be detected [66]. In breast cancer patients, 68% of ductal carcinomas in situ (n = 23) and 71% of invasive ductal carcinomas (n = 26) harbor D310 sequence alterations [67]. In 11 of 18 breast cancers, mtDNA mutations could be detected, of which 42% are D310 alterations [68]. 38% of gallbladder carcinomas (n = 123) contain D310 alterations [69] and 62% of multicentric hepatocellular carcinomas [70].

D310 mutation detection could represent a potential early marker for premalignant human disease. Histologically normal breast epithelial cells, adjacent to invasive ductal carcinomas that carry D310 mutations, already display D310 alterations [67]. D310 alterations are also present in normal-appearing (46%) and dysplastic (57%) gallbladder epithelia accompanying gallbladder carcinomas [69]. It seems that D310 alterations are an early event in malignity, and detection could serve as an early detection strategy. In addition, D-loop alterations have been put forward as a possible prognostic marker for therapeutic outcome. Three-year survival rates of patients with stage III colorectal cancer are 70% without and 47% with D-loop mutations. In combination with fluorouracil as adjuvant chemotherapy, the difference is even more pronounced, being 78% versus 45%, respectively [71].

3.1.8. Alterations in mtDNA Abundance. Each mitochondrion contains multiple copies of the mtDNA, and this copy number changes in response to energy demands. Either increased or reduced mtDNA content has been reported in cancer cells [72, 73]. mtDNA content is elevated in head and neck [74] and esophageal [75] squamous cell carcinoma and increased in malignant compared to premalignant lesions [76]. Also, mtDNA levels are increased in papillary thyroid carcinomas [77], endometrial cancer [78], and oncocytomas [79]. Quantitative real-time PCR amplifying mtDNA-encoded COXI and nuDNA-encoded β-actin revealed a significant increase of mtDNA content in the tumors of 76% of urothelial cell carcinoma patients compared to the matched lymphocytes [53]. Nonetheless, increased mtDNA content does not appear to be firmly associated with carcinogenesis. In prostate cancer, it has been observed that cells with an amplified mtDNA copy number coexist with cells displaying a diminished or depleted copy number [80]. In a study that quantified mtDNA content using RT-PCR with ND1 primers in 31 gastric cancers, 23% of patients displayed a significant increase, but 55% displayed a significant decrease of mtDNA content [81]. Moreover, the relative ratio of mtDNA over nuclear 18S rDNA, as determined by Southern blot, is 3-fold lower in renal carcinoma tissues than in controls [34]. Also, mtDNA content was found reduced in the majority of breast tumors, with mean mtDNA content, as determined by quantitative RT-PCR using ND1 gene primers, being significantly lower than that of the adjacent nontumorous tissue [64]. In lung cancer, mtDNA depletion has been associated with progressive disease [82].

Circulating mitochondrial nucleic acids could be a prognostic marker for cancer. Patients with prostate, head and neck, kidney and colorectal cancer, and blood mitochondrial RNA concentrations above the 95th percentile found in healthy subjects demonstrate decreased survival after a two-year follow-up period [83]. Also, mtDNA content may be a potential biomarker for prediction of the response to chemotherapy. Breast cancer patients with lower copy number of mtDNA have better disease-free survival than patients.
with high mtDNA content, when treated with anthracycline after surgery [84]. Possibly, low mtDNA content enhances ROS and sensitizes the cancer cells to anticancer agents.

3.2. nuDNA Alterations Affecting Mitochondrial Function in Cancer. The repertoire of nuclear-encoded genes involved in mitochondrial function continues to expand [85]. They include, but are not limited to, mutations in genes encoding structural OXPHOS subunits, OXPHOS assembly factors, and components of the mitochondrial protein translation machinery. nuDNA alterations have not been studied as extensively as mtDNA alterations, but are more and more recognized in cancer. SNP-analysis of the mitochondrial biogenesis pathway (25 genes), for instance, reveals a pathway-wide association with a risk of developing epithelial ovarian carcinoma [86]. Mitochondrial biogenesis is crucial because of the constant battle of the organelle against ROS and DNA damage.

3.2.1. Complex I. The nuDNA encodes several structural complex I subunits, as well as complex-specific assembly factors. Single-nucleotide polymorphisms in NDUF9, NDUF52, and NDUF9 genes are associated with prostate [87] and NDUF810, NDUA11, and NDUF12 with epithelial ovarian [86] cancer risk.

3.2.2. Complex II. Complex II contains four nuclear-encoded structural subunits designated SDHA to D. The subunits are imported into the mitochondria, where they are modified, folded, and assembled to functional complex II. The genes encoding complex II subunits behave as tumor suppressors. Hereditary paraganglioma has been linked to SDHA [88], SDHB [89], SDHC [90], and SDHD [91] gene mutations. SDHB mutations have also been shown in pheochromocytoma [92] and renal cell carcinomas [93]. Also, mutations in SDH assembly factor 2 (SDHAF2) cause head and neck paranggliomas [94]. SDHAF2 is essential for the incorporation of FAD cofactor in the SDHA subunit. It has been suggested that loss of complex II function induces HIF, which promotes glycolysis and angiogenesis and thus tumor growth and survival.

3.2.3. Complex III. Of the 11 structural subunits that make up complex III, 10 are encoded by nuclear genes. Genetic amplification of the UQCRFS1 gene has been reported in leukemia [95], ovarian [96], and breast carcinoma [35].

3.2.4. Complex IV. In addition to structural subunits, the nuclear genome encodes many assembly factors necessary for complex IV formation. Single-nucleotide polymorphisms in the COX7A2 gene have been linked to an increased risk of developing prostate cancer [97], while COX7A1 and COX8C alterations have been shown to associate with epithelial ovarian cancer risk [86].

3.2.5. DNA Polymerase γ, POLG is responsible for the replication of the mtDNA, and mutations cause multiple large scale deletions and mtDNA depletion, leading to compromised OXPHOS functioning. Mutations in the POLG gene have been detected in breast cancers and are associated with mtDNA depletion in cancer cells [98]. The POLG gene contains a polymorphic CAG repeat of a dominant length of 10. Men with homozygous deviations from this length have an increased risk of developing seminomas [99]. The percentage of the homozygous non-10 allele is significantly higher in cancer patients than in the general population, yet is only present in low frequencies.

4. Mitochondrial Stress Markers

4.1. ROS Damage Control. Mitochondrial respiration inherently produces ROS, and OXPHOS dysfunction further increases its generation. In cancer cells, a consistent increase of ROS can be observed. NADPH oxidase 1, a major source of ROS in the cells, predominantly localizes to the mitochondria and is highly expressed in breast (86%) and ovarian (71%) tumors [100]. To counter the damaging effect of ROS, cells contain a multilayered system of antioxidant defences executed by three types of enzymes: superoxide dismutases (SOD), peroxidases (POD), and catalases (CAT).

MnSOD is constitutively present in the mitochondrial matrix, but expression can be further induced by hypoxia. MnSOD levels are low or below the detection limit in healthy human pleural mesothelium, but highly increased in tumor biopsies of malignant mesothelioma [101]. MnSOD levels are increased in ovarian cancer [102]. In breast cancer patients, strong MnSOD staining can be observed in neoplastic cells, moderate-to-strong staining in adjacent hyperplastic ducts and weak-to-moderate staining in normal epithelium [103]. A histochemical study on the other hand reveals lower expression in breast cancer cells compared to the adjacent normal epithelia [104]. MnSOD expression levels have been put forward as a prognostic factor for glioblastoma [105, 106].

Glutathione POD is present in different cellular compartments, including the mitochondria. A polymorphism variant of the glutathione POD1 gene is associated with lung cancer risk [107]. In women with papillary serous ovarian cancer, serum glutathione POD3 levels are significantly lower than in controls, and the decrease is stage-dependent [108]. In endometrial adenocarcinoma on the other hand, glutathione POD3 is uniformly downregulated regardless of tumor grade or histopathological subtype, which would imply that it is an early event in tumorigenesis [109].

Mitochondrial expression of CAT has been shown, and in vitro studies have indicated that decreased levels of CAT correlate with invasive and migratory capacities of cell lines and resistance to chemotherapeutic drugs [110]. Gene therapy that results in mitochondrial CAT overexpression renders transgenic mice less susceptible to metastatic breast cancer [111]. Thus, increasing the antioxidant capacity of the mitochondrial compartment could be a rational therapeutic approach.

Prolonged hypoxia and failing ROS neutralization activates HIF proteins that in turn increase the expression of the oncogenes RAS, MYC, and p53. MYC stimulates
4.2. Apoptosis Markers. Mitochondria are regulators of apoptotic processes. Oxidative stress accompanied by calcium overload, ATP depletion, and elevated phosphate levels induce mitochondrial permeability transition (MPT) with formation of nonspecific MPT pores (MPTP). Three proteins are key structural components of the MPTP. Adenine nucleotide translocase (ANT) in the IMM, cyclophilin D in the matrix, and the voltage-dependent anion channel (VDAC) in the OMM [114]. Opening of MPTP causes mitochondria to become permeable to all solutes up to a molecular mass of 1500 Da. Pore opening results in mitochondrial dysfunction, through uncoupling of OXPHOS from ATP hydrolysis. Osmotic forces make the mitochondrion swell and the OMM rupture, releasing apoptogenic proteins into the cytosol. Released proteins include cytochrome c, apoptosis inducing factor (AIF), and endonuclease and second mitochondria-derived activator of caspases (direct IAP-associated binding protein with low pI (Smac/DIABOL0), which, in conjunction with apoptosis protease activating factor (APEF-1), activate caspase 9. The ultimate result is DNA fragmentation and cell death. Additionally, mitochondrial membrane permeability is further regulated by Bcl-2 proteins, including the proapoptotic Bax, Bak, Bid, and Bad [115]. Bax is a known tumor suppressor protein [116]. The MPTP, that contains both repressors and inducers of apoptosis, has been ascribed a target for anticancer drugs [117].

Repression of apoptosis is a hallmark of tumorigenesis [118]. Many immunohistochemical markers of apoptosis have become available to the pathologist, including cleaved caspase 3 and AIF, and have become indispensable for tissue evaluation. Cyclophilin D was found significantly increased in tumors of the breast, uterus, and ovary but not in kidney, gastro-intestinal, and lung cancers [119]. Proapoptotic Bcl-2 interacting protein 3-like (BNIP3L) immunostaining is elevated in the stroma of human breast cancers that lack caveolin-1 [120]. Cofilin, an inducer of the release of cytochrome c, is a small cytoskeletal protein that depolymerizes actin filaments. Apoptosis is mediated through mitochondrial shuttling of actin- and cofilin-interacting protein 1 [121]. Gene associated with retinoid-interferon-induced mortality-19 (GRIM-19) is a cell-death regulator that works through inhibition of signal transducer and activator of transcription 3 (STAT3). Loss or dysregulation of GRIM-19 provides growth advantage to cancer cells. Intriguingly, it has been demonstrated that GRIM-19 localizes to OXPHOS complex I [122], and that its dysfunction results in complex I disassembly and disruption of electron transfer [123]. GRIM-19 mRNA and protein expression are severely reduced in primary renal cell [124], colorectal [125], and cervical [126] carcinoma. In normal prostatic tissues, the epithelium stains intensely, while in prostatic adenocarcinomas, GRIM-19 staining is focally lost [124]. In lung cancer, GRIM-19 expression is reduced and translocates to the nucleus. GRIM-19 downregulation in non-small-cell lung carcinoma correlates with advanced disease stage [127]. Delivery of GRIM-19 has been put forward as a plausible therapeutic approach [128].

4.3. Molecular Chaperones. Mitochondrial molecular chaperones play important roles in protein transport, protein complex assembly, refolding of misfolded proteins, and, when all else fails, sentencing proteins to degradation by the proteasome. They represent a heterogeneous group of proteins subdivided into families according to their molecular weight: large HSP, HSP90, HSP70, HSP60, and HSP40 and small HSP families. In cancer cells, the network of molecular chaperones appears altered compared to normal cells.

4.3.1. HSP90 Family. Molecular chaperones of the HSP90 gene family are considered indispensable regulators of protein folding. The HSP90 proteins HSP86 and HSP84 are mainly found in the cytoplasm of normal cells, but in contrast are found to accumulate in the mitochondrial matrix and IMS of tumor cell mitochondria [129]. Bladder specimens stain strongly for HSP90 in all cells, but in primary bladder transitional cell carcinoma, loss of expression is observed in 24% of tumors. In superficial bladder carcinoma, loss of HSP90 expression is associated with the risk of developing an infiltrating recurrence [130]. TNF receptor-associated protein 1 (TRAP1) is a member of the HSP90 family that is considered mostly mitochondrial. In vivo studies in the rat have shown that TRAP1 protects against hypoxia, by reducing generation of ROS, improving mitochondrial complex IV activity, and preserving ATP levels [131]. TRAP1 expression is induced in tumor cells. As revealed by immunohistochemistry, TRAP1 staining appears intense in pancreas, breast, colon, and lung adenocarcinomas, while normal matched epithelia stain weakly [132].

Accumulating evidence points to a protective role against apoptosis for the HSP90 family. TRAP1 and HSP90 are involved in the mitochondrial pathway that antagonizes the proapoptotic activity of cyclophilin D [132]. This interaction occurs in a multichaperone complex that is selectively assembled in tumor cells and is not present in normal mitochondria [133]. Also, TRAP1 has been shown to directly interact with members of the MPTP, inhibiting its opening and the subsequent release of cytochrome c [134].

4.3.2. HSP70 Family. The human HSP70 family encompasses a member present in the mitochondrial matrix and two cytosolic members: HSP73 is largely constitutive, while HSP72 can be induced by cellular stress. HSP70 levels are increased in cancer cells, including osteosarcoma [135] and renal cell carcinoma [136]. In urothelial carcinoma of the bladder, HSP70 immunostaining is significantly linked with tumor grade [137]. This upregulation increases the tumorigenic potential through the chaperone's anti-apoptotic properties.
4.3.3. HSP60 Family. In human cells, HSP60 is largely but not exclusively mitochondrial and localizes to the mitochondrial matrix and the OMM. HSP60 is constitutively expressed, but its expression increases in response to mitochondrial damage and mtDNA depletion [138]. The chaperone appears to have both prosurvival and proapoptotic functions, and the relationship between HSP60 and tumor prognosis and clinical outcome remains unclear. Upregulation has been described in several cancers including colorectal [139] and cervical [140] carcinomas. Western blot analysis revealed significantly higher HSP60 protein levels in cervical cancer compared to normal tissue, but semiquantitative RT-PCR showed no difference in expression of the corresponding mRNA [141]. HSP60 protein is overexpressed in prostate cancers compared with normal prostate epithelium and hyperplasia. Immunostaining is relatively homogeneous, coarsely granular and confined almost exclusively to neoplastic epithelial cells. Western blotting analyses show that high Gleason score tumors have significantly higher levels of HSP60 protein than tumors of low to moderate Gleason score [142]. In oesophageal squamous cell carcinoma [143] and ovarian cancer [144] on the other hand, positive HSP60 expression correlates with good prognosis.

4.3.4. Small HSP Family. HSP27 is mainly cytosolic, but a small fraction localizes to the mitochondria. HSP27 expression may be a useful prognostic marker of poor survival in human cancers. HSP27 is upregulated in the serum of breast cancer [145] and ovarian cancer [146] patients and correlates with poor clinical outcome. mRNA and protein levels are significantly higher in epithelial ovarian cancer with peritoneal metastasis than without [147]. A clinical evaluation of breast cancer and melanoma patients correlates expression of HSP27 with tumor aggressiveness and decreased survival [148]. HSP10 staining is present in the mitochondria and correlates with high grading of urothelial bladder carcinoma [137].

5. Mitochondrial Membrane Markers

5.1. Mitochondrial Depletion and Proliferation Markers. Mitochondrial membrane proteins can serve to quantify the mitochondrial load of tumors, and porin (VDAC) is often used as a marker for mitochondrial abundance. Quantified to porin content measured by Western blot, no obvious mitochondrial reduction was seen in renal carcinoma compared to control kidney. However, citrate synthase activity, another frequently used marker for mitochondrial load, was 2-fold lower in renal carcinoma tissues [34]. Oncocytomas show a 5-fold increase of citrate synthase activity and an increase of the number of mitochondria [30].

5.2. Mitochondrial Import Channels. Mitochondrial function is profoundly dependent on the import of cytosolic proteins. Complex protein structures form channels that allow preproteins to translocate from the cytosol to the mitochondrial matrix. The proteins that constitute these channels are the translocase of the outer mitochondrial membrane (TOMM) and translocase of the inner mitochondrial membrane (TIMM) proteins [149]. TOMM20 selectively stains metastatic breast cancer cells and is largely absent from the adjacent metastatic lymph node stroma [150]. Proteomic analysis shows a 5-fold increase of TIMM17A protein levels in breast cancer cells, and the increase could be validated by western blot and immunohistochemistry. The latter shows strong staining in ductal carcinoma in situ and invasive ductal carcinoma of the breast, while the adjacent normal epithelia and stromal cells are negative. All normal breast tissues are TIMM17A negative. Quantitative RT-PCR confirms significantly higher levels in invasive carcinoma compared to normal breast tissue [151]. A recent study confirms upregulation of TIMM17A mRNA, when normalized against the housekeeping gene cytokeratin 19 [152]. Both studies have shown TIMM17A expression to be associated with poorer disease-free and overall survival. Thus, TIMM17A offers a promising diagnostic as well as prognostic marker for breast cancer patients.

5.3. Other Mitochondrial Membrane Proteins. Translocator protein (TSPO), also known as peripheral-type benzodiazepine receptor, is a well-conserved protein located at the OMM-IMM contact sites and is closely associated with VDAC and ANT. TSPO has been shown to participate in apoptotic processes but has been ascribed both anti- and proapoptotic properties. Administering TSPO ligands increases the antineoplastic properties of cytostatic drugs in human hepatocellular cancer cells [153]. Overexpression of TSPO is associated with aggressive tumor subtypes in breast, colorectal, and prostate carcinomas and correlates with advancing stages of malignancy. Metastatic breast and colorectal adenocarcinomas manifest increased TSPO expression relative to their primary malignancies. In contrast, adrenocortical hepatomas display decreased TSPO levels compared to the strongly staining normal hepatocytes [154].

6. Mitochondrial Morphology Markers

The classical way to study mitochondrial morphology is transmission electron microscopy. Using such techniques, changes in mitochondrial morphology have been shown to accompany alterations in mitochondrial function. Increasing evidence shows the involvement of mitochondrial dynamics in cancer development, but the structural mitochondrial alterations appear heterogeneous and nonspecific to neoplasias. In addition, in all instances where mitochondrial pleomorphism could be observed, normal mitochondria were equally present.

Mitochondrial morphological changes associated with cancer are varied and include: (1) increased mitochondrial mass as seen in breast carcinomas [49] and pancreatic tumors [155] (2) reduced numbers and degradation to mitochondrial remnants in hepatocellular carcinoma [156] (3) swollen mitochondria as in clear cell carcinoma [157] and undifferentiated retinoblastoma [158] (4) elongated tubular
mitochondria in aldosterone-producing adrenal cortical ade-
nomas [159] and (5) aberrations to the cristae varying from 
reduced amounts in osteosarcoma cell lines [160] to densely 
packed villiform and lamelliform cristae in Warthin's tumor 
[161].

When comparing a human gastric cancer cell line with 
normal rat gastric mucosal cells, electron microscopy reveals a 
significant decrease in both the numbers per cell and the 
size of mitochondria [162]. An ultrastructural study of renal 
cancer observes most severe mitochondrial aberrations in 
eosinophilic clear cell renal cell carcinomas, where most 
mitochondria appear swollen with loose matrix and short 
attenuated cristae [163]. Percentages of mitochondria with 
damaged cristae are 72% in a primary mammary carcinoma 
cell culture, compared to 20% in a control mammary 
epithelial cell line [164].

Several cristae remodeling markers have been described 
and include Mitofilin [165]. Many mitochondrial fusion/
fission factors are involved in maintaining mitochondrial 
integrity. tBid binds to cardiolipin, a negatively charged 
phospholipid present in the IMM [166, 167]. Optimal 
mitochondrial membrane potential is necessary for mito-
chondrial fusion [168]. Cancers exhibit an imbalance of 
mitochondrial fission factors. In tumor tissue from lung 
cancer patients, increase of DRP1 is accompanied by decrease of 
MFN2 levels when comparing with adjacent healthy tissue 
[169]. Immunohistochemistry and immunoblotting reveals 
DRP1 overexpression in 89% of tested lung adenocarcinomas 
(n = 202). DRP1 is mostly found sequestered within 
the nucleus [170]. Nuclear DRP1 overexpression correlates 
with tumor staging, smoking, resistance to chemotherapy, 
and worse prognosis. FIS1 is upregulated in subtypes of 
melanoma [171].

7. Conclusions and Perspectives

Assaying mitochondrial factors has long been recognized 
as a diagnostic approach for metabolic disorders. Con-
venient methods have been developed for human tissues 
[172] and cultured skin fibroblasts [173, 174]. In addition, 
diagnostic and prognostic mitochondrial markers have 
been developed for cancer. An overview is given in this 
paper (Figure 1). These include classical histopathological 
evaluation of mitochondrion-related proteins, as well as 
molecular techniques. Detection of mtDNA alterations 
offers the advantage of allowing low invasive methods, including 
analysis in urine for bladder cancer or saliva for head and 
nack cancers [70]. Also, screening tools such as MitoChip
oligonucleotide arrays [175] make it possible to screen for many factors at the same time.

Mitochondria have not only become valuable subjects for the early detection of cancer, but, moreover, may become cellular targets for future cancer therapy. Mitocans, that is, anticancer agents that act through the mitochondria, provide a strategy for targeting of mitochondrial metabolism and apoptotic processes. The vitamin E analog alphatocopheryl succinate (alpha-TOS) is a mitocan that inhibits the mitochondrial electron redox chain by interfering with and apoptotic processes. The vitamin E analog alpha-

provide a strategy for targeting of mitochondrial metabolism cellular targets for future cancer therapy. Mitocans, that therapeutic trials with great interest.

breast cancer model [178]. The clinic awaits results of many factors at the same time.

inner membrane potential of proliferating endothelial cells This selectivity is attributed to the greater mitochondrial tumor neovascularization and suppressing cancer growth. alpha-TOS, termed MitoVES, is more potent in preventing and translates in reduced tumor progression in an in vivo breast cancer model [178]. The clinic awaits results of therapeutic trials with great interest.

Conflict of Interests

The author declares to have no conflict of interests.

References

[1] J. O. Holloszy, “Regulation by exercise of skeletal muscle content of mitochondria and GLUT4,” Journal of Physiology and Pharmacology, vol. 59, supplement 7, pp. 5–18, 2008.
[2] A. R. Coggan, W. M. Kohrt, R. I. Spina, D. M. Bier, and J. O. Holloszy, “Endurance training decreases plasma glucose turnover and oxidation during moderate-intensity exercise in men,” Journal of Applied Physiology, vol. 68, no. 3, pp. 990–996, 1990.
[3] R. A. S. Stuart, “Supercomplex organization of the oxidative phosphorylation enzymes in yeast mitochondria,” Journal of Bioenergetics and Biomembranes, vol. 40, no. 5, pp. 411–417, 2008.
[4] MITOMAP, “A human mitochondrial genome database,” 2008, http://www.mitomap.org/MITOMAP.
[5] M. Zeviani and S. Di Donato, “Mitochondrial disorders,” Brain, vol. 127, no. 10, pp. 2153–2172, 2004.
[6] C. Benda, “Weitere Mitteilungen über die Mitochondria,” Verhandlungen Physiologische Gesellschaft Berlin, vol. 99, no. 4–7, pp. 376–383, 1898.
[7] M. P. Yaffe, “The machinery of mitochondrial inheritance and behavior,” Science, vol. 283, no. 5407, pp. 1493–1497, 1999.
[8] H. Otera, C. Wang, M. M. Cleland et al., “Mff is an essential factor for mitochondrial recruitment of Drp1 during mitochondrial fission in mammalian cells,” Journal of Cell Biology, vol. 191, no. 6, pp. 1141–1158, 2010.
[9] D. Tondora, F. Czaundera, K. Paulick, R. Schwarzer, J. Kaufmann, and A. Santeil, “The mitochondrial protein MTP18 contributes to mitochondrial fission in mammalian cells,” Journal of Cell Science, vol. 118, no. 14, pp. 3049–3059, 2005.
[10] A. Niemann, M. Ruegg, V. La Padula, A. Schenone, and U. Suter, “Ganglioside-induced differentiation associated protein I is a regulator of the mitochondrial network: new implications for Charcot-Marie-Tooth disease,” Journal of Cell Biology, vol. 170, no. 7, pp. 1067–1078, 2005.
[11] M. Zick, R. Rabl, and A. S. Reichert, “Cristae formation-linking ultrastructure and function of mitochondria,” Biochimica et Biophysica Acta, vol. 1793, no. 1, pp. 5–19, 2009.
[12] P. Paumard, J. Vaillier, B. Coulayr et al., “The ATP synthase is involved in generating mitochondrial cristae morphology,” European Molecular Biology Organization Journal, vol. 21, no. 3, pp. 221–230, 2002.
[13] O. Warburg, “On the origin of cancer cells,” Science, vol. 123, no. 3191, pp. 309–314, 1956.
[14] B. Altenberg and K. O. Greulich, “Genes of glycolysis are ubiquitously overexpressed in 24 cancer classes,” Genomics, vol. 84, no. 6, pp. 1014–1020, 2004.
[15] S. Ohlmeier, A. J. Kastaniotis, J. K. Hiltunen, and U. Bergmann, “The yeast mitochondrial proteome, a study of fermentative and respiratory growth,” The Journal of Biological Chemistry, vol. 279, no. 6, pp. 3956–3979, 2004.
[16] N. Entelis, I. Brandina, P. Kamenski, I. A. Krasheninnikov, R. P. Martin, and I. Tarassov, “A glycolytic enzyme, enolase, is recruited as a cofactor of tRNA targeting toward mitochondria in Saccharomyces cerevisiae,” Genes and Development, vol. 20, no. 12, pp. 1690–1620, 2006.
[17] M. Capello, S. Ferri-Borgogno, P. Cappello, and F. Novelli, “α-enolase: a promising therapeutic and diagnostic tumor target,” The Federation of the Societies of Biochemistry and Molecular Biology Journal, vol. 278, no. 7, pp. 1064–1074, 2011.
[18] S. H. Tu, C. C. Chang, C. S. Chen et al., “Increased expression of enolase α in human breast cancer confers tamoxifen resistance in human breast cancer cells,” Breast Cancer Research and Treatment, vol. 121, no. 3, pp. 539–553, 2010.
[19] S. T. Tsai, I. H. Chien, W. H. Shen et al., “ENO1, a potential prognostic head and neck cancer marker, promotes transformation partly via chemokine CCL20 induction,” European Journal of Cancer, vol. 46, no. 9, pp. 1712–1723, 2010.
[20] G. C. Chang, K. J. Liu, C. L. Hsieh et al., “Identification of α-enolase as an autoantigen in lung cancer: its overexpression is associated with clinical outcomes,” Clinical Cancer Research, vol. 12, no. 19, pp. 5746–5754, 2006.
[21] S. Mazurek, C. B. Boschek, F. Hugo, and E. Eigenbrodt, “Pyruvate kinase type M2 and its role in tumor growth and spreading,” Seminars in Cancer Biology, vol. 15, no. 4, pp. 300–308, 2005.
[22] Y. Kumar, N. Tapuria, N. Kirmani, and B. R. Davidson, “Tumour M2-pyruvate kinase: a gastrointestinal cancer marker,” European Journal of Gastroenterology and Hepatology, vol. 19, no. 3, pp. 265–276, 2007.
[23] D. Lüftner, J. Mesterharm, C. Akrivakis et al., “Tumor type M2 pyruvate kinase expression in advanced breast cancer,” Anticancer Research, vol. 20, no. 6, pp. 5077–5082, 2000.
[24] B. Chiavarina, D. Whitacker-Menezes, U. E. Martinez-Outschoorn et al., “Pyruvate kinase expression (PKM1 and PKM2) in cancer-associated fibroblasts drives stromal nutrient production and tumor growth,” Cancer Biology and Therapy, vol. 12, no. 12, pp. 1101–1113, 2012.
[25] R. A. Harris, M. M. Bowker-Kinley, B. Huang, and P. Wu, “Regulation of the activity of the pyruvate dehydrogenase complex,” Advances in Enzyme Regulation, vol. 42, no. 1, pp. 249–259, 2002.
[26] M. L. Ebeli, “Pyruvate dehydrogenase levels in Morris hepatomas with different growth rate,” Cancer Letters, vol. 26, no. 2, pp. 183–190, 1985.
[27] M. L. Eboli and A. Pasquini, “Transformation linked decrease of pyruvate dehydrogenase complex in human epidermis,” Cancer Letters, vol. 85, no. 2, pp. 239–243, 1994.

[28] M. I. Koukourakis, A. Giatromanolaki, E. Sivridis, K. C. Gatter, and A. L. Harris, “Pyruvate dehydrogenase and pyruvate dehydrogenase kinase expression in non small cell lung cancer and tumor-associated stroma,” Neoplasia, vol. 7, no. 1, pp. 1–6, 2005.

[29] K. M. Owens, M. Kulawiec, M. M. Desouki, A. Vanniarajan, and K. K. Singh, “Impaired OXPHOS complex III in breast cancer,” PlosOne, vol. 6, no. 8, Article ID e23846, 2011.

[30] H. Simonnet, N. Alazard, K. Pfeiffer et al., “Low mitochondrial respiratory chain content correlates with tumor aggressiveness in renal cell carcinoma,” Carcinogenesis, vol. 23, no. 5, pp. 759–768, 2002.

[31] H. Simonnet, J. Demont, K. Pfeiffer et al., “Mitochondrial complex I is deficient in renal oncocytomas,” Carcinogenesis, vol. 24, no. 9, pp. 1461–1466, 2003.

[32] J. A. Mayer, D. Meierhofer, F. Zimmermann et al., “Loss of complex I due to mitochondrial DNA mutations in renal oncocytoma,” Clinical Cancer Research, vol. 14, no. 8, pp. 2270–2275, 2008.

[33] F. A. Zimmermann, J. A. Mayer, D. Neureiter et al., “Lack of complex I is associated with oncogenic thyroid tumours,” British Journal of Cancer, vol. 100, no. 9, pp. 1434–1437, 2009.

[34] D. Meierhofer, J. A. Mayer, U. Foetschl et al., “Decrease of mitochondrial DNA content and energy metabolism in renal cell carcinoma,” Carcinogenesis, vol. 25, no. 6, pp. 1005–1010, 2004.

[35] Y. Ohashi, S. J. Kaneko, T. E. Cupples, and S. R. Young, “Ubiquinol cytochrome c reductase (UQCRFS1) gene amplification in primary breast cancer core biopsy samples,” Gynecologic Oncology, vol. 93, no. 1, pp. 54–58, 2004.

[36] K. Luciakova and S. Kuzela, “Increased steady-state levels of several mitochondrial and nuclear gene transcripts in rat hepatoma with a low content of mitochondria,” European Journal of Biochemistry, vol. 205, no. 3, pp. 1187–1193, 1992.

[37] K. D. Yu, A. X. Chen, C. Yang et al., “Current evidence on the relationship between polymorphisms in the COX-2 gene and breast cancer risk: a meta-analysis,” Breast Cancer Research and Treatment, vol. 122, no. 1, pp. 251–257, 2010.

[38] B. G. Heerdt and L. H. Augenlicht, “Effects of fatty acids on expression of genes encoding subunits of cytochrome c oxidase and cytochrome c oxidase activity in HT29 human colonic adenocarcinoma cells,” The Journal of Biological Chemistry, vol. 266, no. 28, pp. 19120–19126, 1991.

[39] M. Denis-Gay, J. M. Petit, J. P. Mazat, and M. H. Ratinaud, “Modifications of oxido-reductase activities in adriamycin-resistant leukaemia K562 cells,” Biochemical Pharmacology, vol. 56, no. 4, pp. 451–457, 1998.

[40] N. A. Alam, A. J. Rowan, N. C. Wortham et al., “Genetic and functional analyses of FH mutations in multiple cutaneous and uterine leiomyomatosis, hereditary leiomyomatosis and renal cancer, and fumarate hydratase deficiency,” Human Molecular Genetics, vol. 12, no. 11, pp. 1241–1252, 2003.

[41] P. J. Ratcliffe, “Fumarate hydratase deficiency and cancer: activation of hypoxia signaling?” Cancer Cell, vol. 11, no. 4, pp. 303–305, 2007.

[42] K. K. Hyoung, S. P. Won, H. K. Sung et al., “Mitochondrial alterations in human gastric carcinoma cell line,” American Journal of Physiology, vol. 293, no. 2, pp. C761–C771, 2007.

[43] L. Wang, Q. Ke, W. Chen et al., “Polymorphisms of MTHFD, plasma homocysteine levels, and risk of gastric cancer in a high-risk Chinese population,” Clinical Cancer Research, vol. 13, no. 8, pp. 2526–2532, 2007.

[44] A. S. Andrew, J. Gui, A. C. Sanderson et al., “Bladder cancer SNP panel predicts susceptibility and survival,” Human Genetics, vol. 125, no. 5–6, pp. 527–539, 2009.

[45] T. Geiger, S. F. Madden, W. M. Gallagher, J. Cox, and M. Mann, “Proteomic portrait of human breast cancer progression identifies novel prognostic markers,” Cancer Research, vol. 72, no. 9, pp. 2428–2439, 2012.

[46] R. Strong, T. Nakanishi, D. Ross, and C. Fenselau, “Alterations in the mitochondrial proteome of adriamycin resistant MCF-7 breast cancer cells,” Journal of Proteome Research, vol. 5, no. 9, pp. 2389–2395, 2006.

[47] D. L. Croteau and V. A. Bohr, “Repair of oxidative damage to nuclear and mitochondrial DNA in mammalian cells,” The Journal of Biological Chemistry, vol. 272, no. 41, pp. 25409–25412, 1997.

[48] M. Verma, R. K. Naviiaux, M. Tanaka, D. Kumar, C. Franceschi, and K. K. Singh, “Mitochondrial DNA and cancer epidemiology,” Cancer Research, vol. 67, no. 2, pp. 437–439, 2007.

[49] G. Gasparre, A. M. Porcelli, E. Bonora et al., “Disruptive mitochondrial DNA mutations in complex I subunits are markers of oncogenic phenotype in thyroid tumors,” Proceedings of the National Academy of Sciences of the United States of America, vol. 104, no. 21, pp. 9001–9006, 2007.

[50] K. Polyak, Y. B. Li, H. Zhu et al., “Somatic mutations of the mitochondrial genome in human colorectal tumours,” Nature Genetics, vol. 20, no. 3, pp. 291–293, 1998.

[51] W. Habano, T. Sugai, T. Yoshida, and S. Nakamura, “Mitochondrial gene mutation, but not large-scale deletion, is a feature of colorectal carcinomas with mitochondrial microsatellite instability,” International Journal of Cancer, vol. 83, no. 5, pp. 625–629, 1999.

[52] D. I. Tan, J. Chang, W. L. Chen et al., “Somatic mitochondrial DNA mutations in oral cancer of betel quid chewers,” Annals of the New York Academy of Sciences, vol. 1011, pp. 310–316, 2004.

[53] S. Dasgupta, C. B. Shao, T. E. Keane et al., “Detection of mitochondrial deoxyribonucleic acid alterations in urine from urothelial cells carcinoma patients,” International Journal of Cancer, vol. 131, no. 1, pp. 158–164, 2012.

[54] A. I. Guney, D. S. Ergenc, H. H. Tavukcu et al., “Detection of mitochondrial DNA mutations in nonmuscle invasive bladder cancer,” Genetic Testing and Molecular Biomarkers, vol. 16, no. 7, pp. 672–678, 2012.

[55] S. Dasgupta, M. O. Hoque, S. Upadhyay, and D. Sidransky, “Mitochondrial cytochrome B gene mutation promotes tumor growth in bladder cancer,” Cancer Research, vol. 68, no. 3, pp. 700–706, 2008.

[56] J. A. Petros, A. K. Baumann, E. Ruiz-Pesini et al., “MtDNA mutations increase tumorigenicity in prostate cancer,” Proceedings of the National Academy of Sciences of the United States of America, vol. 102, no. 3, pp. 719–724, 2005.

[57] J. A. Smeitink, M. Zeviani, D. M. Turnbull, and H. T. Franceschi, and K. K. Singh, “Mitochondrial DNA and cancer epidemiology,” Cancer Research, vol. 67, no. 2, pp. 437–439, 2007.

[58] X. G. Guo, C. T. Liu, H. Dai, and Q. N. Guo, “Mutations of the mitochondrial ATase6 gene are frequent in Chinese patients with osteosarcoma,” Experimental and Molecular Pathology. In press.
[59] F. O. Aikhionbare, S. Mehrabi, K. Kumaresan et al., “Mitochondrial DNA sequence variants in epithelial ovarian tumor subtypes and stages,” *Journal of Carcinogenesis*, vol. 6, article e1, 2007.

[60] M. I. Ekstrand, M. Falkenberg, A. Rantanen et al., “Mitochondrial transcription factor A regulates mtDNA copy number in mammals,” *Human Molecular Genetics*, vol. 13, no. 9, pp. 935–944, 2004.

[61] S. Horai and K. Hayasaka, “Intraspecific nucleotide sequence differences in the major noncoding region of human mitochondrial DNA,” *American Journal of Human Genetics*, vol. 46, no. 4, pp. 828–842, 1990.

[62] S. A. Liu, R. S. Jiang, F. J. Chen, W. Y. Wang, and J. C. Lin, “Somatic mutations in the D-loop of mitochondrial DNA in oral squamous cell carcinoma,” *European Archives of Oto-Rhino-Laryngology*, vol. 269, no. 6, pp. 1665–1670, 2012.

[63] A. Nagy, M. Wilhelm, and G. Kovacs, “Mutations of mtDNA in renal cell tumours arising in end-stage renal disease,” *Journal of Pathology*, vol. 199, no. 2, pp. 237–242, 2003.

[64] L. M. Tseng, P. H. Yin, C. W. Chi et al., “Mitochondrial DNA mutations and mitochondrial DNA depletion in breast cancer,” *Genes and Chromosomes and Cancer*, vol. 45, no. 7, pp. 629–638, 2006.

[65] H. C. Lee, S. H. Li, J. C. Lin, C. C. Wu, D. C. Yeh, and H. C. Lee, “Somatic mutations in the D-loop and decrease in the copy number of mitochondrial DNA in human hepatocellular carcinoma,” *Mutation Research*, vol. 547, no. 1-2, pp. 71–78, 2004.

[66] M. Pinheiro, I. Veiga, C. Pinto et al., “Mitochondrial genome alterations in rectal and sigmoid carcinomas,” *Cancer Letters*, vol. 280, no. 1, pp. 38–43, 2009.

[67] C. Xu, D. Tran-Thanh, C. Ma et al., “Mitochondrial D310 mutations in the early development of breast cancer,” *British Journal of Cancer*, vol. 106, no. 9, pp. 1506–1511, 2012.

[68] P. Parrella, Y. Xiao, M. Fliss et al., “Detection of mitochondrial DNA mutations in primary breast cancer and fine-needle aspirates,” *Cancer Research*, vol. 61, no. 20, pp. 7623–7626, 2001.

[69] M. Y. Tang, S. Baez, M. Pruyas et al., “Mitochondrial DNA mutation at the D310 (displacement loop) mononucleotide sequence in the pathogenesis of gallbladder carcinoma,” *Clinical Cancer Research*, vol. 10, no. 3, pp. 1041–1046, 2004.

[70] M. S. Fliss, H. Usadel, O. L. Caballero et al., “Facile detection of mitochondrial DNA mutations in tumors and bodily fluids,” *Science*, vol. 287, no. 5460, pp. 2017–2019, 2000.

[71] A. Lièvre, C. Chapusot, A. M. Bouvier et al., “Clinical value of mitochondrial mutations in colorectal cancer,” *Journal of Clinical Oncology*, vol. 23, no. 15, pp. 3517–3525, 2005.

[72] J. S. Carew and P. Huang, “Mitochondrial defects in cancer,” *Molecular Cancer*, vol. 1, article 9, 2002.

[73] H. C. Lee and Y. H. Wei, “Mitochondrial DNA instability and metabolic shift in human cancers,” *International Journal of Molecular Sciences*, vol. 10, no. 2, pp. 674–701, 2009.

[74] W. W. Jiang, B. Masayesva, M. Zahurak et al., “Increased mitochondrial DNA content in saliva associated with head and neck cancer,” *Cancer Research*, vol. 11, no. 7, pp. 2486–2491, 2005.

[75] C. S. Lin, S. C. Chang, L. S. Wang et al., “The role of mitochondrial DNA alterations in esophageal squamous cell carcinomas,” *Journal of Thoracic and Cardiovascular Surgery*, vol. 139, no. 1, pp. 189–197, 2010.

[76] M. M. Kim, J. D. Clinger, B. G. Masayesva et al., “Mitochondrial DNA quantity increases with histopathologic grade in premalignant and malignant head and neck lesions,” *Clinical Cancer Research*, vol. 10, no. 24, pp. 8512–8515, 2004.

[77] E. Mambo, A. Chatterjee, M. Xing et al., “Tumor-specific changes in mtDNA content in human cancer,” *International Journal of Cancer*, vol. 116, no. 6, pp. 920–924, 2005.

[78] Y. Yang, V. W. S. Liu, W. C. Xue, P. C. K. Tsang, A. N. Y. Cheung, and H. Y. S. Ngan, “The increase of mitochondrial DNA content in endometrial adenocarcinoma cells: a quantitative study using laser-captured microdissected tissues,” *Gynecologic Oncology*, vol. 98, no. 1, pp. 104–110, 2005.

[79] G. Tallini, M. Ladanyi, J. Rosai, and S. C. Jhanwar, “Analysis of nuclear and mitochondrial DNA alterations in thyroid and renal oncocytic tumors,” *Cytogenetics and Cell Genetics*, vol. 66, no. 4, pp. 253–259, 1994.

[80] T. Mizumachi, L. Muskeshishvili, A. Naito et al., “Increased distributional variance of mitochondrial DNA content associated with prostate cancer cells as compared with normal prostate cells,” *Prostate*, vol. 68, no. 4, pp. 408–417, 2008.

[81] C. W. Wu, P. H. Yin, W. Y. Hung et al., “Mitochondria DNA mutations and mitochondrial DNA depletion in gastric cancer,” *Genes Chromosomes and Cancer*, vol. 44, no. 1, pp. 19–28, 2005.

[82] C. S. Lina, L. S. Wang, C. M. Tsaiq, and Y. H. Wei, “Low copy number and low oxidative damage of mitochondrial DNA are associated with tumor progression in lung cancer tissues after neoadjuvant chemotherapy,” *Interactive Cardiovascular and Thoracic Surgery*, vol. 7, no. 6, pp. 954–958, 2008.

[83] N. Mehra, M. Penning, J. Maas, N. Van Daal, R. H. Giles, and E. E. Voest, “Circulating mitochondrial nucleic acids have prognostic value for survival in patients with advanced prostate cancer,” *Clinical Cancer Research*, vol. 13, no. 2, pp. 421–426, 2007.

[84] C. W. Hsu, P. H. Yin, H. C. Lee, C. W. Chi, and L. M. Tseng, “Mitochondrial DNA content as a potential marker to predict response to anthracycline in breast cancer patients,” *The Breast Journal*, vol. 16, no. 3, pp. 264–270, 2010.

[85] X. Zhu, X. Peng, M. X. Guan, and Q. Yan, “Pathogenic mutations of nuclear genes associated with mitochondrial disorders,” *Acta Biochimica et Biophysica Sinica*, vol. 41, no. 3, pp. 179–187, 2009.

[86] J. Permuth-Wey, Y. A. Chen, Y. Y. Tsai et al., “Inherited variants in mitochondrial biogenesis genes may influence epithelial ovarian cancer risk,” *Cancer Epidemiology Biomarkers and Prevention*, vol. 20, no. 6, pp. 1131–1145, 2011.

[87] L. Wang, S. K. McDonnell, S. J. Hebbering et al., “Polymorphisms in mitochondrial genes and prostate cancer risk,” *Cancer Epidemiol Biomarkers*, vol. 17, no. 12, pp. 3558–3666, 2008.

[88] N. Burnichon, J. J. Brière, R. Libé et al., “SDHA is a tumor suppressor gene causing paraganglioma,” *Human Molecular Genetics*, vol. 19, no. 15, pp. 3011–3020, 2010.

[89] B. E. Baysal, J. E. Willett-Brozick, E. C. Lawrence et al., “Prevalence of SDHB, SDHC, and SDHD germline mutations in clinic patients with head and neck paragangliomas,” *Journal of Medical Genetics*, vol. 39, no. 3, pp. 178–183, 2002.

[90] S. Niemann and U. Müller, “Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma, type 3,” *Nature Genetics*, vol. 26, no. 3, pp. 268–270, 2000.

[91] B. E. Baysal, R. E. Ferrell, J. E. Willett-Brozick et al., “Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma,” *Science*, vol. 287, no. 5454, pp. 848–851, 2000.
[121] C. Wang, G. L. Zhou, S. Vedantam, P. Li, and J. Field, “Mitochondrial shuttling of CAPI promotes actin- and cofilin-dependent apoptosis,” Journal of Cell Science, vol. 121, no. 17, pp. 2913–2920, 2008.

[122] I. M. Fearnley, J. Carroll, R. J. Shannon, M. J. Runswick, J. E. Walker, and J. Hirst, “GRIM-19, a cell death regulatory gene product, is a subunit of bovine mitochondrial NADH:ubiquinone oxidoreductase (complex I),” The Journal of Biological Chemistry, vol. 276, no. 42, pp. 38345–38348, 2001.

[123] G. Huang, H. Lu, A. Hao et al., “GRIM-19, a cell death regulatory protein, is essential for assembly and function of mitochondrial complex I,” Molecular and Cellular Biology, vol. 24, no. 19, pp. 8447–8456, 2004.

[124] I. Alchanati, S. C. Nallar, P. Sun et al., “A proteomic analysis reveals the loss of expression of the cell death regulatory gene GRIM-19 in human renal cell carcinomas,” Oncogene, vol. 25, no. 54, pp. 7138–7147, 2006.

[125] L. B. Gong, X. L. Luo, S. Y. Liu, D. T. Ong, J. P. Gong, and J. B. Hu, “Correlations of GRIM-19 and its target gene product STAT3 to malignancy of human colorectal carcinoma,” Ai Zheng, vol. 26, no. 7, pp. 683–687, 2007.

[126] Y. Zhou, M. Li, Y. Wei et al., “Down-regulation of GRIM-19 expression is associated with hyperactivation of STAT3-induced gene expression and tumor growth in human cervical cancers,” Journal of Interferon and Cytokine Research, vol. 29, no. 10, pp. 695–703, 2009.

[127] X. Y. Fan, Z. F. Jiang, L. Cai, and R. Y. Liu, “Expression and clinical significance of GRIM-19 in lung cancer,” Medical Oncology. In press.

[128] S. Moreira, M. Correia, P. Soares, and V. Máximo, “GRIM-19 function in cancer development,” Mitochondrion, vol. 11, no. 5, pp. 693–699, 2011.

[129] B. H. Kang and D. C. Altieri, “Compartmentalized cancer drug discovery targeting mitochondrial Hsp90 chaperones,” Oncogene, vol. 28, no. 42, pp. 3681–3688, 2009.

[130] T. Lebret, R. W. G. Watson, V. Moliné et al., “Heat shock proteins HSP27, HSP60, HSP70, and HSP90: expression in bladder carcinoma,” Cancer, vol. 98, no. 5, pp. 970–977, 2003.

[131] L. Xu, L. A. Voloboueva, Y. Ouyang, J. F. Emery, and R. G. Giffard, “Overexpression of mitochondrial Hsp70/Hsp75 in rat brain protects mitochondria, reduces oxidative stress, and protects from focal ischemia,” Journal of Cerebral Blood Flow and Metabolism, vol. 29, no. 3, pp. 365–374, 2009.

[132] B. H. Kang, J. Plescia, T. Dohi, J. Rosa, S. J. Doxsey, and D. C. Altieri, “Regulation of tumor cell mitochondrial homeostasis by an organelle-specific HSP90 chaperone network,” Cell, vol. 131, no. 2, pp. 257–270, 2007.

[133] J. C. Ghosh, M. D. Siegelin, T. Dohi, and D. C. Altieri, “Heat shock protein 60 regulation of the mitochondrial permeability transition pore in tumor cells,” Cancer Research, vol. 70, no. 22, pp. 8988–8993, 2010.

[134] F. Xiang, Y. S. Huang, X. H. Shi, and Q. Zhang, “Mitochondrial chaperone tumour necrosis factor receptor-associated protein 1 protects cardiomyocytes from hypoxic injury by regulating mitochondrial permeability transition pore opening,” The Federation of the Societies of Biochemistry and Molecular Biology Journal, vol. 277, no. 8, pp. 1929–1938, 2010.

[135] S. Moalic-Juge, B. Liagre, R. Duval et al., “The anti-apoptotic property of NS-398 at high dose can be mediated in part through NF-kappaB activation, hsp70 induction and a decrease in caspase-3 activity in human osteosarcoma cells,” International Journal of Oncology, vol. 20, no. 6, pp. 1255–1262, 2002.

[136] C. Gaudin, F. Kremer, E. Angevin, V. Scott, and F. Triebel, “A hsp70-2 mutation recognized by CTL on a human renal cell carcinoma,” Journal of Immunology, vol. 162, no. 3, pp. 1730–1738, 1999.

[137] F. Capello, S. David, N. Ardizzzone et al., “Expression of heat shock proteins HSP10, HSP27, HSP60, HSP70, and HSP90 in urothelial carcinoma of urinary bladder,” Journal of Cancer Molecules, vol. 2, no. 2, pp. 73–77, 2006.

[138] J. J. Hansen, P. Bross, M. Westergaard et al., “Genomic structure of the human mitochondrial chaperonin genes: HSP60 and HSP10 are localised head to head on chromosome 2 separated by a bidirectional promoter,” Human Genetics, vol. 112, no. 1, pp. 71–77, 2003.

[139] F. Cappello, S. David, F. Rappa et al., “The expression of Hsp60 and Hsp10 in large bowel carcinomas with lymph node metastases,” BioMedCentral Cancer, vol. 5, article 139, 2005.

[140] P. E. Castle, R. Ashfaq, F. Ansari, and C. Y. Muller, “Immunohistochemical evaluation of heat shock proteins in normal and preinvasive lesions of the cervix,” Cancer Letters, vol. 229, no. 2, pp. 245–252, 2005.

[141] Y. J. Hwang, S. P. Lee, S. Y. Kim et al., “Expression of heat shock protein 60 kDa is upregulated in cervical cancer,” Yonsei Medical Journal, vol. 50, no. 3, pp. 399–406, 2009.

[142] C. Castilla, B. Congregado, J. M. Conde et al., “Immunohistochemical expression of Hsp60 correlates with tumor progression and hormone resistance in prostate cancer,” Journal of Urology, vol. 76, no. 4, pp. 1017.e1–1017.e6, 2010.

[143] A. Faried, M. Sohda, M. Nakajima, T. Miyazaki, H. Kato, and H. Kuwano, “Expression of heat-shock protein Hsp60 correlated with the apoptotic index and patient prognosis in human oesophageal squamous cell carcinoma,” European Journal of Cancer, vol. 40, no. 18, pp. 2804–2811, 2004.

[144] J. Schneider, E. Jiménez, K. Marenbach, H. Romero, D. Marx, and H. Meden, “Immunohistochemical detection of HSP60-expression in human ovarian cancer. Correlation with survival in a series of 247 patients,” Anticancer Research, vol. 19, no. 3, pp. 2141–2146, 1999.

[145] Z. Rui, J. Jian-Guo, T. Yuan-Peng, P. Hai, and R. Bing-Gen, “Use of serological proteomic methods to find biomarkers associated with breast cancer,” Proteomics, vol. 3, no. 4, pp. 433–439, 2003.

[146] S. P. Langdon, G. J. Rabiasz, G. L. Hirst et al., “Expression of the heat shock protein HSP27 in human ovarian cancer,” Clinical Cancer Research, vol. 1, no. 12, pp. 1603–1609, 1995.

[147] M. Zhao, F. Shen, Y. X. Yin, Y. Y. Yang, D. J. Xiang, and Q. Chen, “Increased expression of heat shock protein 27 correlates with peritoneal metastasis in epithelial ovarian cancer,” Reproductive Science, vol. 19, no. 7, pp. 748–753, 2012.

[148] O. Straume, T. Shimamura, M. J. G. Lampa et al., “Suppression of heat shock protein 27 induces long-term dormancy in human breast cancer,” Proceedings of the National Academy of Sciences, vol. 109, no. 22, pp. 8699–8704, 2012.

[149] N. Pfänner and N. Wiedemann, “Mitochondrial protein import: two membranes, three translocases,” Current Opinion in Cell Biology, vol. 14, no. 4, pp. 400–411, 2002.

[150] F. Sotgia, D. Whitaker-Menezes, U. E. Martinez-Outschoon et al., “Mitochondrial metabolism in cancer metastasis,” Cell Cycle, vol. 11, no. 7, pp. 1445–1454, 2012.
Submit your manuscripts at http://www.hindawi.com