Chapter 2
Mitochondrial DNA in Lung Cancer

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Abstract Mitochondrial DNA (mtDNA) variations are increasingly discovered and expected to be potential biomarkers to monitor severity, duration, stage, response to therapy, and prognosis in patients with lung cancer. The present article illustrates alterations of mtDNA in lung cancer, including alterations of mtDNA copy number and sequence mutations, as well as their possible mechanisms for carcinogenesis and development of lung cancer. The clear and comprehensive relationships between mtDNA variations and lung cancer are to be further confirmed to benefit effective strategies for lung cancer diagnosis and therapy.

Keywords Mitochondria • DNA • Mutation • Lung cancer • Diagnosis

1 Introduction

Lung cancer is an increasingly severe disease, accounting for 30% of all cancer-related deaths [1], and has the highest occurrence and mortality among malignancies. This will continue to increase if there are still no effective measures and therapies against lung cancer. Although the mechanism of lung cancer carcinogenesis remains unclear, tumor development is associated with mitochondrial DNA (mtDNA) mutations and alterations in mitochondrial genomic function [2, 3]. mtDNA mutations are found in various kinds of tumors, such as lung cancer [1, 4], bladder cancer [4], breast cancer [5], thyroid cancer [6], and prostate cancer [7], since mtDNA homogeneity mutation has been identified in colorectal cancer [8].

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H. Sun, X. Wang (eds.), *Mitochondrial DNA and Diseases*, Advances in Experimental Medicine and Biology 1038,
https://doi.org/10.1007/978-981-10-6674-0_2

Characterizations of mtDNA genes vary among lung cancer subtypes, stages, and severity [9, 10]. The present article aims at overviewing the understanding of mtDNA biology, the significance of mtDNA mutations and altered copy numbers in lung cancer, the potential of mtDNA-associated biomarkers, and the comparison between mtDNA and nDNA biomarkers.

2 mtDNA Biology

mtDNAs are double-stranded closed circular DNA with 16,596 base pairs, composed of coding regions without introns and noncoding region. The coding region contains 13 polypeptides, 22 transfer RNAs, and 2 ribosomal RNAs [11]. The noncoding region (also called D-loop region) is responsible for mtDNA replication and transcription [12, 13], which has significant regulatory elements, such as L-strand promoter, H-strand promoter, and H-strand replication origin. In coding regions, almost every base plays a role in gene assembly [14]. As a result, once mutations occur, DNA sequence will probably be altered and followed by the alteration of coding proteins and mitochondrial dysfunction, as an important cause of human pathology.

Compared with nuclear DNA (nDNA), mtDNAs have higher mutation rates, and there are hundreds of thousands of mtDNA copies per cell. Mitochondrion is a major source to generate adenosine triphosphate (ATP) for cells through oxidative phosphorylation [15], during which reactive oxygen species (ROS) are generated as by-products and lead to DNA damage. mtDNAs are in close physical proximity to the electron transport chain and superoxide anions generated in oxidative phosphorylation and easier to acquire oxidative damage [11] (Fig. 2.1). mtDNAs contain

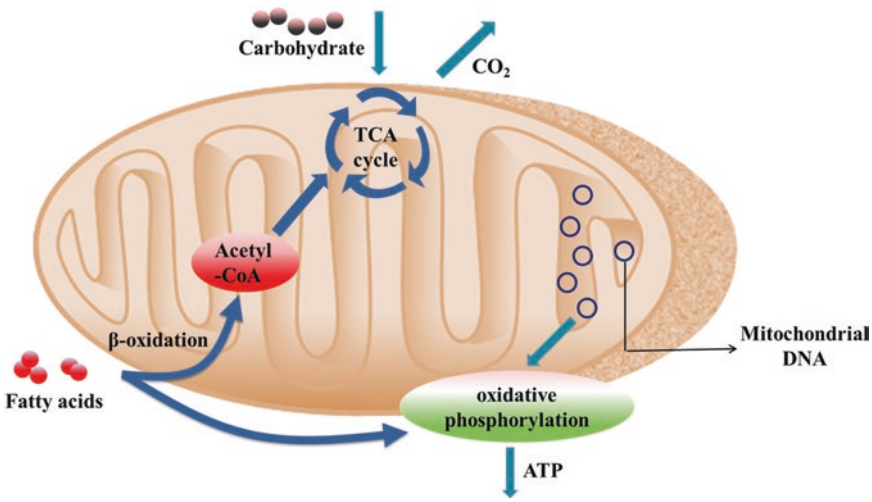


Fig. 2.1 An illustration of mtDNA distribution in mitochondria. mtDNAs are double-stranded closed circular DNA; they are in close physical proximity to the electron transport chain and reactive oxygen species produced in oxidative phosphorylation. It's more likely for mtDNAs to acquire oxidative damage

naked and lacked protective histones, more susceptible to the damage of carcinogens. Once mtDNA is compromised, mtDNA is hardly self-repaired due to the lack of DNA repair system and excision repair capacity in the mitochondria [14]. There are a large number of intra- and extracellular factors to contribute to the DNA damage of base pair mismatch and high mutation rates of mtDNAs, responsible for the development of mitochondrial dysfunction and cell susceptibility [15].

High mutations and copies of mtDNA as distinct features are involved in the carcinogenesis and are expected to be potential biomarkers for cancer detection and monitoring. The frequency of sequence mutations may increase during mtDNA copying and sequencing. The higher the number of mtDNA copies, the more susceptible mtDNAs are for mutation. The small size and closed circular structure of mtDNAs are more resistant to the DNA damages [11]. The appearance of the same mutation in mtDNAs and tumors indicates the clear relationship between [4], since it is questioned whether the gene mutation is from mtDNA to tumor tissue or reversely, genetically regulated from the source, and represent the targeting similarity between. It seems clear that mtDNAs can impact tumor cell growth and sensitivity to treatments [4, 16, 17].

3 The Significance of mtDNA Mutations

mtDNA may undergo mutations, e.g., insertion, deletion, or point mutations, in response to carcinogenetic factors [18, 19]. The mutation rate of mtDNA is much higher than that of nDNA due to its sensitivity to cancerogens. There are an amount of mutations in mitochondrial D-loop in lung cancer [19, 20]. mtDNA noncoding region is important in the transcription and duplication of mtDNA. D-loop is 1124 bp in size and a replicate origin where heavy and light chains of mtDNA are located [18]. There are two high-variable regions HVI and HVII located between 16,024–16,383 and 57–372 in D-loop, respectively. Alterations of D-loop region are possibly associated with mitochondrial dysfunction and mutation of nuclear genome. Single nucleotide polymorphisms of minor alleles of nucleotides 235A/G and 324A/G in D-loop region can be a risk factor of lung cancers. Of single nucleotide polymorphisms, the minor alleles 151C/T, 200A/G, 524C/CA, and 16274G/A are associated with the induction of squamous cell carcinoma, while the mutation of the minor allele 16,298 T/C may trigger the occurrence of small cell lung cancer [1]. In another sequencing of mtDNA, 8 of 27 primary lung tumors had mutations in the D-loop region, including a C-to-G transversion in nucleotide 16,114 and deletions/insertions in polyinosinic acid-polycytidylic acid [19]. In addition, 12 SCLC and 16 NSCLC cell lines of lung tumors have high frequency of homopolymeric C tract or single nucleotide polymorphisms in the D-loop region [18].

Mutations in mtDNA coding region are correlated with clinical characteristics in patients with lung cancer. Of those,36 mutations were detected in mtDNA coding region and 19 missense mtDNA mutations in 9 mtDNA coding region, including COI, COII, COIII, ATPase 6, ND2, ND3, ND4, ND5, and Cyt b [3]. These alterations of mtDNA may play an important role in tumorigenesis and metastasis of lung can-

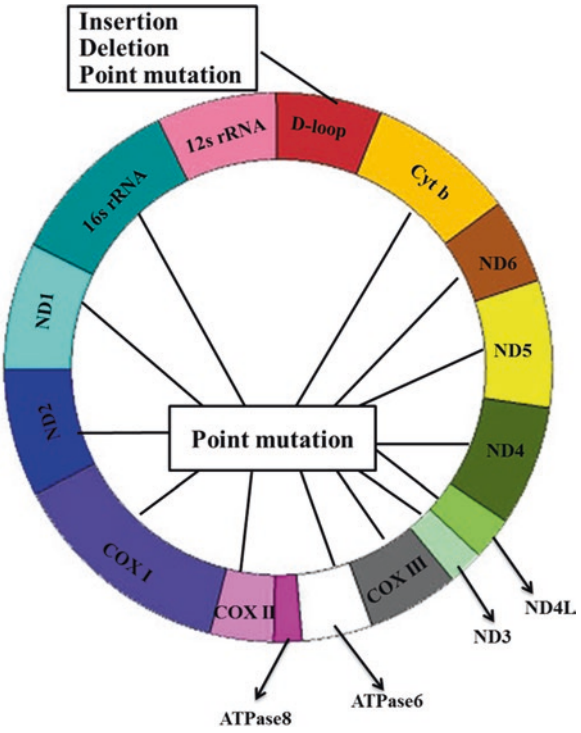


Fig. 2.2 Mutations in different regions of mtDNA. mtDNAs are composed of 16 coding and noncoding regions without introns. Several mutations of mtDNA in lung cancer were showed in this figure (insertion, deletion, or point mutations), according to the literature. The noncoding region D-loop is the "hot spot" of mutations

cer, as shown in Fig. 2.2. Mitochondrial DNA is vulnerable to alterations. When a mutation takes place, the altered mtDNAs can coexist with wild-type mtDNA in a heteroplasmy state [21, 22] . During cell replication, mtDNAs were divided into daughter cells randomly, and the percentage of variant mtDNAs in daughter cells is uncertain. After lots of passages of those heteroplasmic cells, the wild-type or mutation mtDNAs will transform into a predominant rate called homoplasmy. The heteroplasmic mutations result in highly variable inheritance and biological impact [22] due to the random distribution of genetic materials (Fig. 2.3). Thus, there are still several challenges to identify the association between mtDNA mutations and clinical phenotypes.

mtDNA mutations may contribute to carcinogenesis by decreasing cellular energy capacities, although the exact mechanism remains unclear. The mutation rate of mtDNA at a certain proportion can reduce the cellular energy capacity and cause the lack of cell and tissue bioenergetics to maintain normal functions. Or it is possible that tumors are induced by increasing mitochondrial oxidative stress [23]. The mitochondria are the primary source of endogenous ROS, including unpaired electrons and oxygen free radical. mtDNA encodes 13 polypeptides involved in electron transport chain, vulnerable to mutagens due to the lack of introns and protective histones. It is also possible that mtDNA mutations altered proteins and the function of respiratory chain is damaged [24]. The increased amount of electrons could result in more free radical production and interact with genome as tumor initiators, mutagenizing proto-oncogenes into oncogenes [25]. mtDNA mutations induce carci-

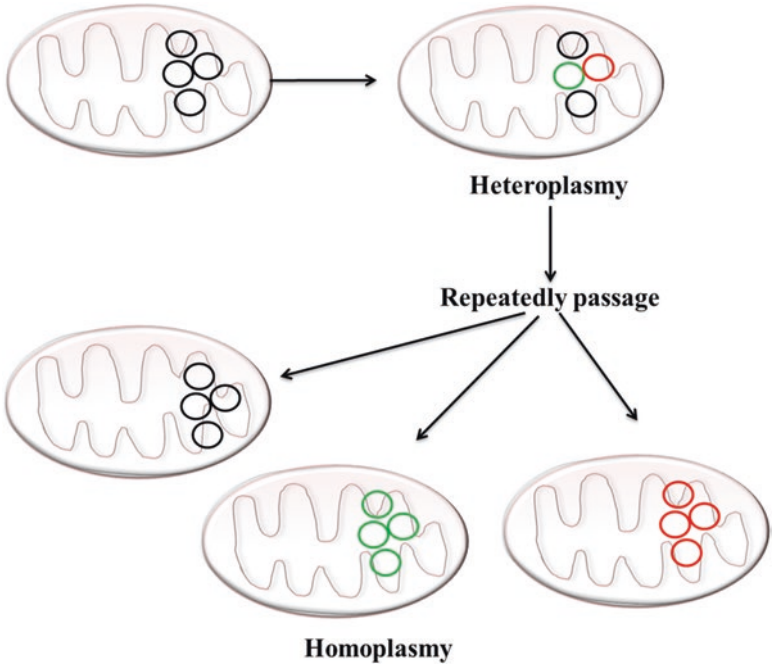


Fig. 2.3 The random genetic mutations of mtDNA. The altered mtDNAs can coexist with wild-type mtDNA in a heteroplasmy state. During cell replication, mtDNAs were divided into daughter cells randomly. After lots of passages of those heteroplasmic cells, the wild-type or mutation mtDNAs will transform into a predominant rate called homoplasmy that causes highly variable inheritance and biological impact

noma through modulating apoptosis controlled by electrochemical gradients. The reaction through mitochondrial electron transport chain can reduce electrochemical gradients, opening the mitochondrial permeability transition pore [22] and releasing cell death-promoting factors to destruct cytoplasm and chromatin. In cancer cells with mtDNA mutations, the electrochemical gradients increase more than in wild-type cells [26], possibly making carcinoma cells resistant to apoptosis (Fig. 2.4).

4 Altered Copy Number of mtDNAs

Each human cell contains an average of 100–500 mitochondria of which each has two to ten copies of mtDNAs [27]. The normal combination and operation of the respiratory chain require a complete and functional mitochondrial genome. mtDNA function depends not only on the integrity of mtDNAs' molecular structure but also on the copy number of mtDNAs in the cell. In addition to somatic mtDNA mutations including point mutation, deletion, and insertion, alterations of mtDNA copy number vary among human cancers. For instance, the copy number of mtDNAs

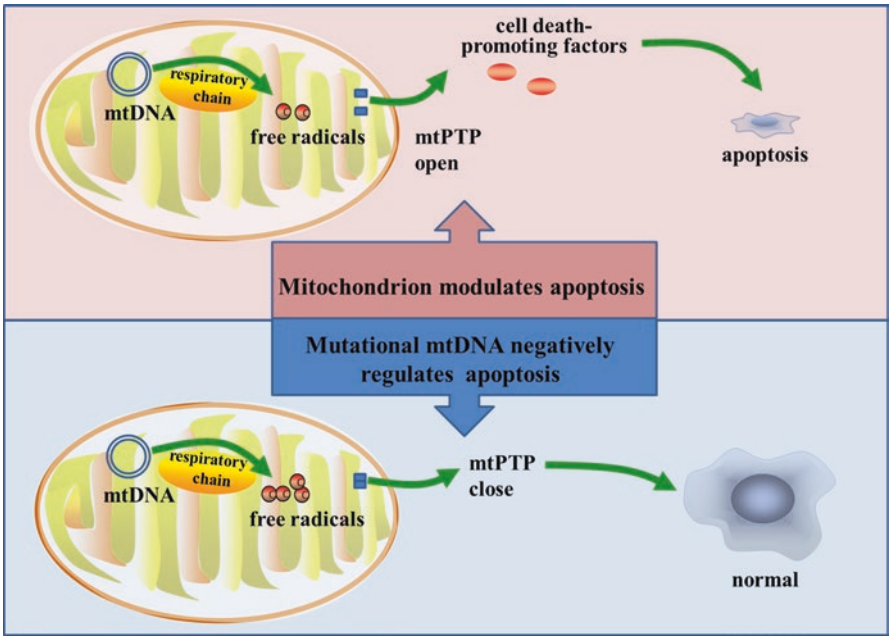


Fig. 2.4 Hypotheses about mtDNA mutations contributing to carcinogenesis. Proteins of electron transport chain are altered by mtDNA mutation, and the function of respiratory chain is damaged. The increased amount of electrons could result in more free radical production. In addition, mitochondria control cell apoptosis by electrochemical gradient ($\triangle\Psi$), produced by mitochondrial electron transport chain. Loss of $\triangle\Psi$ results in opening of the mitochondrial permeability transition pore (mtPTP). In cancer cells with mtDNA mutations, the $\triangle\Psi$ may increase, and mtPTP is closed; thus, the release of cell death-promoting factors was held back. By this way, mtDNA mutations possibly make carcinoma cells resistant to apoptosis

increased in prostate cancer cells [28] or in saliva of head and neck cancer [29] or serum levels of cell-free mtDNAs in testicular cancer [30]. Those data show that mtDNAs are altered not only in cancer cells but also in other body fluids. On the other hand, the contents of mtDNA reduced in 82% of cancerous breast tissues [31] and in hepatocellular carcinoma patients associated with poorer prognosis and shorter 5-year overall survival rates [32]. It indicates that the regulation of mtDNA copy number is out of control, with cancer site specificity [2, 33].

Alterations of mtDNA content also exist in patients with lung cancer. Lee et al. [34] found increased mtDNA content in about 50% of patients with lung cancers, while decreased mtDNA content was found in about 23%. Multiple factors influence alterations of mtDNA content, e.g., cancer type, DNA damage type, or sample size. The reduction of mtDNA copy number seems more common in lung cancer. For example, the copy number of mtDNAs is reduced in lung carcinoma tissues [35] and in advanced stages of the disease correlated with a shorter survival time [36]. There was no correlation between mtDNA content and gender, age, or smoking status [11] [36, 37]. Lee et al. reported that mtDNA contents initially increased with pack-years of smoking and then declined to levels below nonsmokers [38].

Different changes of mtDNA content in cancer may be caused by diverse mechanisms. D-loop region has regulatory elements containing promoters and replication origin and controls mtDNA replication and transcription. Once mutations occurred in D-loop region especially in regulatory elements, the replication and transcription rate of mtDNAs would be changed. The mutation in D-loop region was about 40% hepatocellular cancer, while decreased mtDNA content was more than 70% cancer with D-loop region mutation [34]. It is possible that the mutation in D-loop region decreases mtDNA content or a point mutation in coding region reduces mtDNA copy number. The introduction of mtDNA with mutant A3243G into mtDNA-deficient teratocarcinoma cells results in the depletion of mtDNA content [39].

Another possibility is that mtDNA contents are altered through ROS-mediated pathway. High levels of ROS would lead to mtDNA damage (oxidative damage), and 8-hydroxy-2-deoxyguanosine (8-oxo-G) as an indicator of oxidative damage increased in lung tissues of heavy smokers [27]. The 8-oxoguanine-DNA glycosylase 1 protein and polymerase γ are two key enzymes to repair 8-oxo-G damage in mtDNAs [40, 41]. Devitalized 8-oxoguanine-DNA glycosylase 1 and deficient polymerase γ lead to accumulation of mtDNA mutations responsible for changes of mtDNA content. The deficiency of repair system probably is responsible for the decrease of mtDNA content in ROS-mediated damage. ROS-mediated damage can also be a compensatory mechanism by which the process of mtDNA content to copy increases an oxidative stress [27]. When it comes to oxidative damage, the combination of mtDNA mutations and compensatory mechanism should be considered to estimate the changes of mtDNA copy number (Fig. 2.5).

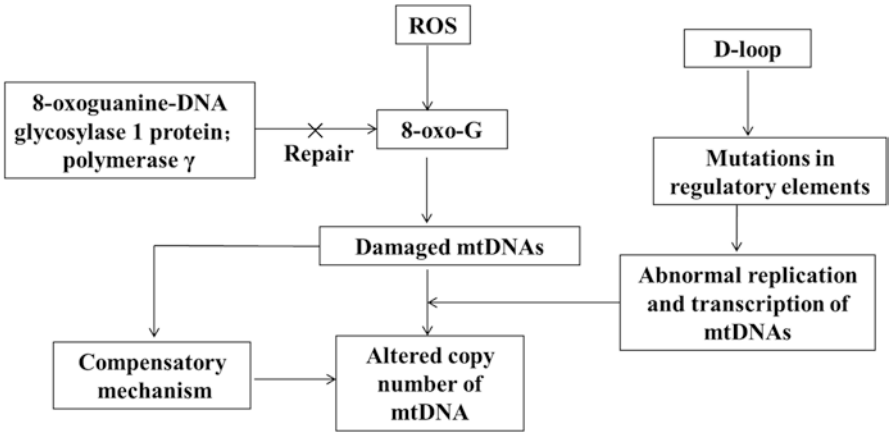


Fig. 2.5 Possible mechanisms of altered copy number of mtDNAs. When mutations occurred in regulatory elements in D-loop region, the replication and transcription rate of mtDNAs would be changed, decreasing mtDNA copy number. Another possibility is that high levels of ROS would lead to production of 8-hydroxy-2-deoxyguanosine (8-oxo-G) as an indicator of oxidative damage. Meanwhile, devitalized 8-oxoguanine-DNA glycosylase 1 and deficient polymerase γ lead to a failure of repairing 8-oxo-G damage in mtDNAs, which is responsible for changes of mtDNA content. ROS-mediated damage can also be a compensatory mechanism to estimate changes of mtDNA copy number

Loss of p53 protein is another reason to reduce mtDNA content through increased accumulation of mtDNA damage [42], since p53 protein regulates the response to DNA damage and can maintain the stability of mtDNAs [43]. In coping with mtDNA damage, p53 protein can move to mitochondria and interact with polymerase γ to strengthen the expression of polymerase γ to repair oxidative damage [42]. The alteration of mtDNA copy number in lung cancer is subject to the mtDNA mutations and oxidative damage. Although there are several causes to interpret the changes of mtDNA content, a clear and comprehensive explanation for increased or decreased mtDNA content of each case remains unknown. More research is required to determine the exact relationship between mtDNA content and lung cancer development.

5 Potential Value of mtDNA as Biomarkers for Lung Cancer Diagnosis

Although nuclear genome detection plays a significant role in cancer screening, the biological role of mtDNA alteration in tumor formation has drawn more and more attention in recent years. The alteration of mtDNA content or sequence mutations has evitable relationship with oncogenesis and becomes potential biomarkers for certain types of cancers [4, 44]. It is widely accepted that mtDNA is more vulnerable to mutagens by genotoxin, oxidative press, or other factors compared with nuclear genome [45, 46]. mtDNA has potential implications for lung cancer diagnosis, since mtDNA is easier to be detected and has a high copy number or mtDNA mutations have strong resistance to damage. The 16,596 base pairs make up 16 gene regions, arranging closely on the double-strand loop, which should be easier to be characterized with current advances of methodologies. There are several thousand copies of mtDNA in a cell [47], as compared to two copies of nuclear genome. Less samples were required for DNA extraction to evaluate mtDNA. For precious clinical samples, mtDNA content is usually enough for sequencing and other detection methods. On the other hand, mtDNA sequence alterations are more stable and can be detected with high repeatability.

Abnormal expression of mtDNA encoding proteins can also cause mitochondrial dysfunction and cell damage, due to the lack of introns and accumulation of mutations in coding regions. Changes of downstream proteins and clinical phenotypes can also imply the corresponding mtDNA mutations. Due to the high heterogeneity of mtDNA mutations, it is a challenge to identify lung cancer in an early stage. Sanger sequencing is a common type of mitochondrial sequencing technique, but as to heterogeneity detection, the next generation of sequencing will be more competitive. In addition, there are quantitative PCR techniques, array chips [48], and other measurement techniques, which can also achieve good detection results.

It is necessary for further study to identify and validate the function of mtDNA mutations in initiation and progression of lung cancer in order to be helpful to develop lung cancer detection and treatment strategies. It is also a challenge to

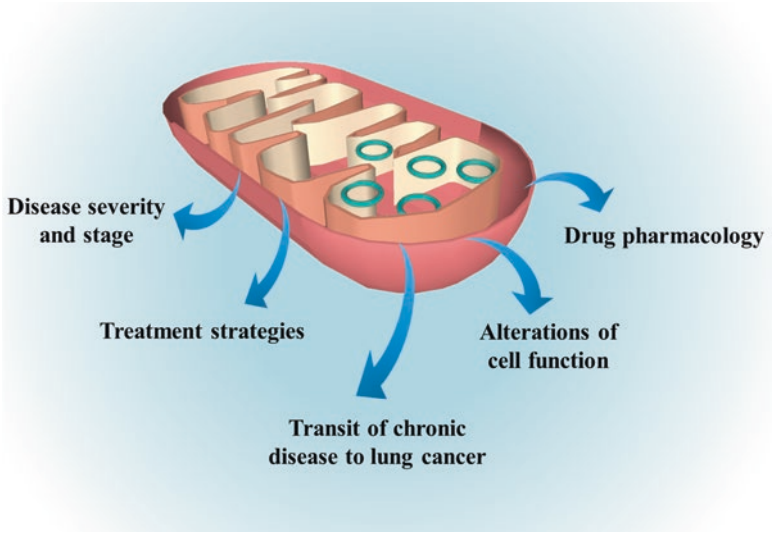


Fig. 2.6 Potential value of mtDNA as biomarkers. mtDNA has a prospect of becoming biomarkers to develop lung cancer detection and treatment strategies, to monitor disease severity and stage, to monitor the transit of chronic diseases especially chronic obstructive pulmonary disease to lung cancer, and to describe alterations of cell functions induced by mtDNA mutations. In addition, it will be a power if mtDNA alterations can act as a biomarker to measure the cell behavior in drug pharmacology

apply mtDNA changes for clinical application as biomarkers, especially to monitor the transit of chronic obstructive pulmonary disease to lung cancer [49–51], to integrate clinical phenotype mtDNA mutations for dynamic monitoring of disease severity and stage [52–54], and to describe alterations of cell functions induced by mtDNA mutations [55–58]. Mitochondrion is one of the most important organelles to regulate and control drug pharmacological profiles. It will be a power if mtDNA alterations can act as a biomarker to measure the cell behavior in drug metabolism [59–61], pharmacokinetics [62–64], and sensitivity to drug toxicity [65–68] (Fig. 2.6).

6 Conclusion

Alterations of mtDNA possibly are related to carcinogenesis of lung cancer, as well as their mechanisms for promoting the development of lung cancer, including alteration of mtDNA copy number and sequence mutations. Although the definite mechanism by which mtDNA is altered is to be further confirmed, it will be helpful in developing diagnostic and therapeutic strategies for lung cancer.

Acknowledgments The work was supported by Zhongshan Distinguished Professor Grant (XDW), the National Nature Science Foundation of China (91230204, 81270099, 81320108001, 81270131, 81300010), the Shanghai Committee of Science and Technology (12JC1402200, 12431900207, 11410708600, 14431905100), Operation funding of Shanghai Institute of Clinical Bioinformatics, Ministry of Education for Academic Special Science and Research Foundation for PhD Education (20130071110043), and National Key Research and Development Program (2016YFC0902400, 2017YFSF090207).

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http://www.springer.com/978-981-10-6673-3

Mitochondrial DNA and Diseases

Sun, H.; Wang, X. (Eds.)

2017, VII, 230 p. 89 illus., 62 illus. in color., Hardcover
ISBN: 978-981-10-6673-3