Review

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CLINICALLY SIGNIFICANT MOLECULAR ALTERATIONS OF MITOCHONDRIA IN CARCINOGENESIS AND AGE-RELATED DISEASES: PART 2. EXPOSOME INFLUENCES, BIOMARKERS AND THERAPEUTIC STRATEGIES

The second part of the review presents an analysis of a number of exposome factors that influence the development of molecular disorders and metabolic shifts in mitochondria in cancer and age-related diseases. A number of mitochondrial biomarkers have been demonstrated to serve as biochemical, genetic, and molecular biological indicators for the diagnosis, prognosis, and treatment of cancer and age-related diseases. Certain areas of therapy and new modern therapeutic approaches to the treatment of cancer and age-related diseases are analyzed in the context of the pathogenetic effect on mitochondrial dysfunction in human cells and organs for the improvement of pathological conditions and the promotion of healthy longevity.

Keywords: *mitochondrial dysfunction, molecular alterations, cancer, age-related diseases, exposome, biomarkers, therapeutic strategies, hormesis*

Introduction

The first part of this review already discussed the main structural and functional mitochondrial features that are important for many physiological and pathological cellular processes exhibiting distinct tissue-specific manifestations [1]. Multilevel mitochondrial dysfunction has been observed in a variety of human diseases, including cancer and age-related diseases. This phenomenon is influenced by a combination of endogenous and exogenous factors that exert their influence throughout the human lifespan [2, 3]. This section of the review will emphasize several critical factors that influence the genetic and metabolic state of mitochondria. The genetic features of mitochondrial DNA, encompassing both germinal (haplotypes, familial, and individual) and somatic alterations, exhibit a close correlation with mitochondrial metabolism and the development of diseases. These features are

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frequently detected in patients with age-related and oncological diseases [4]. Metabolic dysfunction of the mitochondria is prevalent, manifesting in a broad spectrum of both general and specific forms These include changes in the levels and activities of proteins and their complexes, as well as structural mitochondrial aberrations. These phenomena are detected in the development and progression of age-related and oncological diseases [5]. A number of these features have been previously discussed in the initial section of this review. The subsequent stage in the analysis of clinically significant mitochondrial disorders is to identify the most significant groups of human life factors that lead to the mitochondrial metabolic dysfunction and promote the development of diseases. Another salient aspect of this subject is the establishment of informative biomarkers and clinically relevant indicators of the metabolic mitochondrial disorders, which facilitate the assessment of the patient's condition and the extent of the pathological process. These biomarkers also allow us to predict the course of disease , to determine the effective treatment methods and the recovery of mitochondrial function [6, 7]. The therapeutic interventions developed by scientists and doctors are aimed at the structural and functional regeneration of mitochondria in age-related diseases and differentiated effects on the mitochondria of cancer cells and normal cells of the body for the treatment of oncological diseases [8, 9]. The present review will concentrate on these aspects with the objective of providing a more comprehensive overview of the current state of research on clinically significant molecular alterations of mitochondria in age-related and oncological diseases.

Exposome factors in the development of mitochondrial dysfunctions in age-related and oncological diseases

The exposome concept, as it was defined in molecular epidemiology, is the combination of exogenous and endogenous factors that have the capacity to affect human health and the development of diseases, including age-related and oncological diseases, as well as the body's response to these influences [10, 11]. A schematized representation of the impact of the most potent and widely studied groups of exposome factors on the mitochondrial state is illustrated in Fig. 1. These factors can influence, starting from the prenatal period through all subsequent stages of the human life cycle, the health and illness of individuals [12]. Exposomes are conventionally categorized into three distinct classifications: external, general, and specific exposomes, as well as internal exposomes. In the context of disease development, these groups include harmful environmental, physical, lifestyle factors, psychosocial influences, and the body's response to these exposures [13]. Multilevel mitochondrial dysfunctions play an important role in this concept, both in the transduction of biological effects of exogenous influences and in the pathogenesis of cancer and age-related diseases [2, 14].

In contrast, positive exogenous exposures of the exposome have the potential to support human health and promote mitochondrial function. This assumption is confirmed by studies of exogenous protective factors of the exposome and reduced levels of age-related and oncological diseases in people from different populations in the so-called Blue Zones [15, 16, 17, 18]. Recent studies have demonstrated that specific factors, such as clean air, mineral-rich water, balanced nutrition patterns, support for circadian rhythms, an active lifestyle, and strong social cohesion, can promote metabolic, energetic, and neuroimmune homeostasis, protect against age-related diseases, and promote healthy longevity [19].

Among the damaging factors of the exposome, the effects of air pollution (particularly polycyclic aromatic compounds, heavy metals, nanoplastics, and others) and environmental pollution with chemicals (pesticides, herbicides, carcinogens, and others) have been the focus of active research in recent decades [20, 21]. Consequently, these effects have been shown to result in an increase in mtDNA heteroplasmy, an increase in the generation of reactive oxygen species (ROS), and

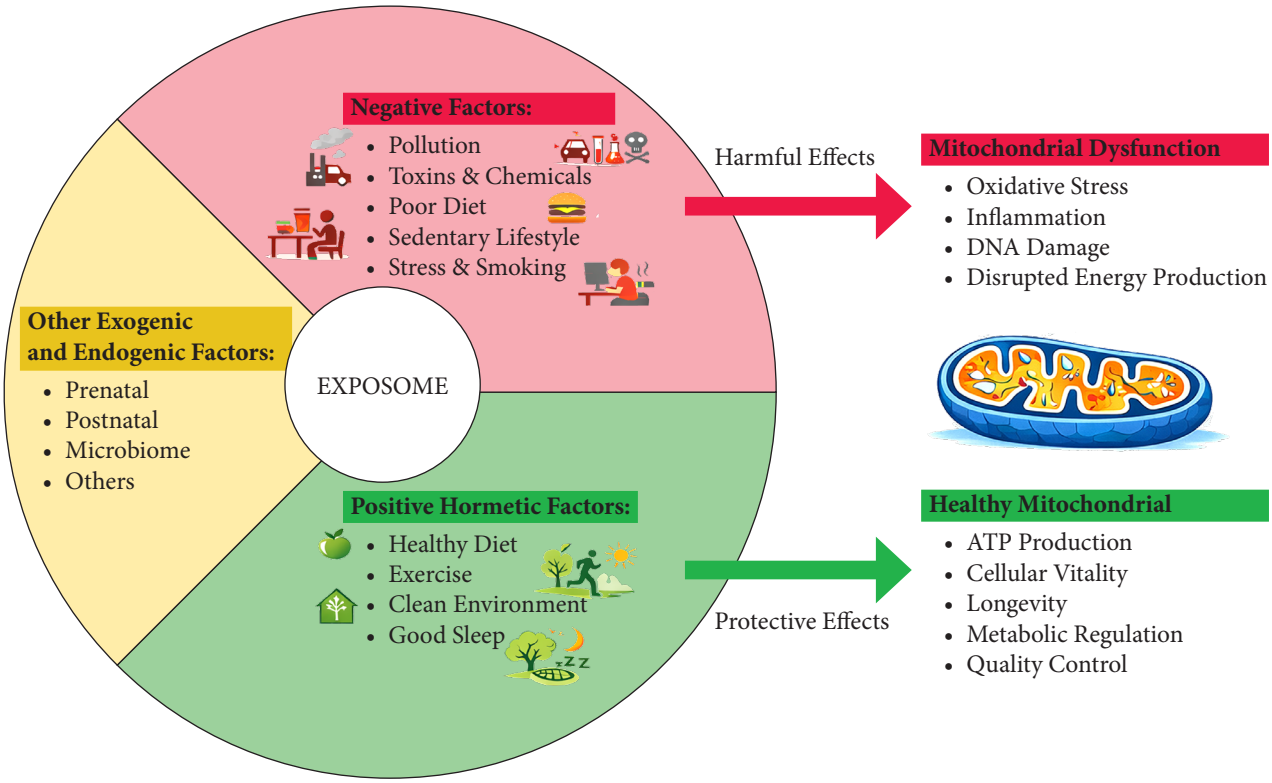


Fig. 1. Influence of some exposome factors on the mitochondrial states

a disruption of the regulation of mitochondrial structure and their interaction with other cell components, particularly the nucleus and endoplasmic reticulum [20]. These disturbances manifest directly in mitochondrial metabolism, specifically in alterations of mitochondrial membrane potential, calcium levels, and ATP levels [22]. They have been shown to affect the functioning of most organs and systems of the body, as well as to accelerate the development of age-related diseases and the induction of cancer [21, 23].

The next group of harmful factors of the exposome is related to the lifestyle of modern humans. These factors include a sedentary lifestyle, a diet high in carbohydrates and unhealthy foods, disruption of circadian rhythms, and harmful habits such as smoking, alcohol consumption, and drug use [13, 14]. It has been established that a sedentary lifestyle constitutes a primary risk factor for the escalating prevalence of non-infection diseases among adults worldwide. Among these non-infection diseases, age-related and oncological diseases are the foremost contributors to mortality [24]. A significant component of the etiology of these diseases is mitochondrial metabolic dysfunction, impaired regulation of AMPK, SIRT1/3, PGC-1α, increased ROS, mitochondrial metabolic reprogramming, decreased OXPHOS/ETS capacity, and impaired mitochondrial quality. This, in turn, leads to chronic inflammation, activation of pro-oncogenic pathways, and dysfunction of both links of immunity [25, 26]. The impact of a sedentary lifestyle on mitochondrial dysfunction is also manifested in accelerated loss of cardiovascular and strength fitness, reduced healthspan, and earlier onset of the first chronic age-related disease [27]. A diet with a high carbohydrate content has been shown to lead to persistently elevated glucose

and insulin levels, as well as the development of insulin resistance. This phenomenon is particularly pronounced in individuals who maintain a sedentary lifestyle, a condition that can result in the onset of mitochondrial dysfunction in various organs and body systems [28]. Signs of mitochondrial dysfunction manifest in a high-glucose diet include increased mito-ROS, damage to OXPHOS/intermembrane potential, and impaired mitochondrial dynamics/quality control [29]. Chronic activation of the insulin/IGF-1 pathway has been demonstrated to result in increased functioning of PI3K-AKT-mTOR Raf/MAPK signaling pathways and aberrant expression of oncogenes, particularly KRAS and MYC. These alterations, in turn, contribute to the formation of the Warburg phenotype of cells and the metabolic reprogramming of epithelial cells into cancer cells [30]. The typical Western diet is characterized by a high consumption of carbohydrates and unhealthy fats. This combination is considered the most significant damaging factor in the functioning of mitochondria in terms of diet due to a decrease in mitochondrial respiration, a decrease in mitochondrial bioenergetics, and a disruption in the functioning and dynamics of mitochondria [31—34].

The modern lifestyle has been shown to promote the disruption of natural circadian rhythms, which, with prolonged exposure, can result in a range of health imbalances. These imbalances may include metabolic dysfunction, cognitive decline, immunosenescence, sleep disturbances, and an elevated risk of developing age-related and oncological diseases due to the occurrence of various cellular and molecular changes [35]. The proteins involved in circadian rhythms have been shown to directly affect mitochondrial function, for example through DRP1 on mitochondrial biogenesis [36], or indirectly through disruption of the circadian clock network (CLOCK/BMAL1, PER/CRY). This aberration has been shown to induce metabolic dysregulation, inflammation, decreased mitochondrial function, and accelerated aging phenotype [37]. Furthermore, the circadian rhythm hormone melatonin has been demonstrated to exert a direct influence on cell proliferation, including cancer cells, without altering the expression of clock genes, but rather through modulations in the activity of cell mitochondria [38]. Conversely, diminished expression of clock genes has been linked to telomere shortening, resulting in telomere attrition. This, in turn, can lead to mitochondrial dysfunction in three ways: PARP1-NAD+-SIRT1, ATM/R-P53-PGC1α/β, and ATM-AKT-mTOR-PGC1β. The combination of these two dysfunctions has been demonstrated to significantly exacerbate the aging process and the development of age-related diseases [8].

The next group of negative exposome factors that enhance mitochondrial dysfunction is psychotraumatic factors, chronic stress, and social maladjustment. Chronic psychosocial and metabolic stress could create chronically elevated levels of cortisol and, as a result, glucose, leading to mitochondrial allostatic load. This phenomenon is characterized by the impairment of both mitochondria and mitochondrial DNA, resulting in the production of toxic byproducts. These byproducts, in turn, induce alterations in the expression of pro-inflammatory genes, which can contribute to systemic inflammation and accelerate cellular aging [39].

Chronic psychological stress has been demonstrated to induce metabolic and neuroendocrine mediators that result in structural and functional mitochondrial defects, which in turn affect the brain, endocrine system, and immune system. These defects serve to modulate the rate of cellular and organismal aging [40, 41]. Chronic psychological stress activates neuroendocrine pathways, particularly β-adrenergic and glucocorticoid signals. These pathways have been associated with tumor progression, decreased immune surveillance, and reduced survival in some types of cancer [42].

Disruption of the microbiome in various organs and systems of the body is considered an endogenous factor that is closely related to many negative exogenous factors, including a sedentary lifestyle, poor diet, and chronic stress [43]. The pathophysiological role of microbiome-derived metabolites,

including amino acids, fatty acids, and extracellular vesicles, in the development of mitochondrial disorders has been proven [44]. Changes in the microbiome have specific effects and mechanisms on the development of mitochondrial dysfunction in cancer and age-related diseases [45].

Thus, to date, the influence of a number of genetic factors on mitochondrial function and the development of multifactorial diseases, such as age-related and oncological diseases, has been studied. However, exposome factors that act throughout life play a very important role in the onset, progression, course, and prognosis of a number of these pathologies [15, 46]. A comprehensive investigation of the interaction and interrelationships between endogenous and exogenous factors is necessary to identify the most critical polygenic combinations and exposome influences. This investigation will facilitate the identification of risks and characteristics associated with the development of age-related and oncological diseases in humans. These findings will provide the foundation for the development of methods to prevent, diagnose, and effectively treat these diseases.

Biomarkers, associated with molecular alterations and metabolism of mitochondria in cancer and age-related diseases

The presence of mitochondrial dysfunction in age-related and oncological diseases can be ascertained at various levels, including genetic, transcriptomic, proteomic, and metabolic, by employing a range of modern methods [47, 48]. These techniques permit the evaluation of a variety of parameters, including but not limited to: cellular bioenergetics, mitochondrial DNA levels and genetic abnormalities, mitochondrial membrane potential, mitochondrial reactive oxygen species, mitochondrial enzyme levels, circulating extracellular mtDNA, levels of mitochondrial and oncometabolites, and others. The application of these techniques is integral to the assessment of patient condition, diagnosis of diseases, and selection of effective treatments [49—52].

In clinical practice, immuno-histochemical methods are most often used to visualize indicators of metabolic processes in tissues and biopsies, in particular SDHB, FH/2-SC [53, 54]. Positron emission tomography (PET) with various labeled substrates (tracers) is a widely utilized clinical modality for real-time assessment of metabolic processes in tumors [55].

Plasma lactate dehydrogenase (LDH) levels have been identified as a significant prognostic indicator of various types of cancer, exhibiting a correlation with systemic inflammatory response in advanced pancreatic cancer [56] and urothelial carcinoma [57]. The assessment of oncometabolite levels is a critical component of clinical practice, serving to facilitate diagnosis, classification, and ongoing monitoring of tumors [50]. The detection of elevated plasma 2-hydroxyglutarate levels in cancer patients has been found to correlate with reduced survival [58]. Abnormal changes in succinate concentration have been observed to be associated with pathological conditions, including chronic inflammation, ischemia/reperfusion, and cancer [59]. Accumulation of succinate is the hallmark of tumorigenesis in paraganglioma and pheochromocytoma [60] and may indicate increased cancer angiogenesis in tumors through an HIF-1α independent mechanism [61].

Elevated levels of the oncometabolite fumarate have been shown to be indicative of an increased risk for inherited cancer syndromes. Furthermore, these levels have been demonstrated to serve as a prognostic indicator, providing insights into the behavior of tumors and the status of the tumor microenvironment [62]. The ratio of succinate/fumarate oncometabolites is determined in order to detect asymptomatic germline pathogenic variants of the *SDHB* and *SDHD* genes, and to reclassify SDHx VUS variants [63].

The implementation of molecular markers in the diagnosis of mitochondrial disorders remains limited in clinical practice, though certain markers have been integrated into medical protocols. The gene sequencing or polymerase chain reaction (PCR) is performed to identify mutations in genes associated

with mitochondrial dysfunction, including *IDH1/IDH2, SDHx*, and *FH*. A number of mutations in these genes are clinically significant for the diagnosis and treatment of tumors [64, 65], in particular gliomas [66] and cholangiocarcinoma [67].

Biochemical and molecular biomarkers are currently being actively researched for inclusion in diagnostic and therapeutic protocols for the treatment of cancer and age-related diseases. The 13 metabolic biomarkers identified as the most clinically relevant include lactate, pyruvate, the lactate: pyruvate ratio, creatine kinase, creatine, amino acid profiles, glutathione, malondialdehyde, GDF-15, FGF-21, gelsolin, light chain neurofilament, and circulating extracellular mtDNA [68, 69]. Mitokines GDF-15, FGF-21, and humanin are all considered systemic signals of mitochondrial stress and metabolic reorganization. In the context of age-related and oncological diseases, these levels are known to be subject to disruption, and their potential as biomarkers for diagnosis has been well-documented [70].

Mitochondrial DNA (mtDNA) abnormalities, including mutations and copy number variations, have been identified as significant biomarkers for various cancer-related applications. These genetic alterations can be detected in both tumors and biological fluids, offering a comprehensive approach to cancer diagnosis, monitoring of metastasis, and evaluation of disease progression. Furthermore, these biomarkers play a crucial role in predicting treatment response and resistance across different cancer types, facilitating personalized treatment strategies. The detection of circulating cf-mtDNA in liquid biopsies has been identified as a promising tool for diagnosis in oncology [47].

The identification of potential biomarkers for the determination of risk factors associated with specific types of cancer and age-related diseases may be facilitated by germline characteristics of mtDNA, including mitochondrial haplogroups. These concepts were previously discussed in the first part of the review [1]. A number of somatic abnormalities of both mtDNA and mitochondrial proteins encoded by genomic DNA are also considered potential biomarkers for the diagnosis and prognosis of cancer and age-related diseases [71, 72].

At the level of the transcriptome, there are a number of studies of transcriptomic biomarkers that allow us to see the characteristics of the OXPHOS signature [48], *GLUT1* and *PKM2* expression [73]. These characteristics allow us to predict the effect of treatment, predict survival, and determine immune profiles in cancer patients. A total of 17 nuclear mitochondria-related genes were identified in bladder cancer. Differential expression of these genes was correlated with the overall survival of bladder cancer patients, and it also had potential therapeutic guidance [74].

The MitoScore indicator, based on the expression of six mitochondrial genes (*CYP27B1, DNA2, MTFR2(FAM54A), PIF1, POLQ,* and *RECQL4*), has revealed a potential framework for assessing the level of hypoxia, genomic instability, mitochondrial activity in tumors and normal tissues, and the presence of stromal and immune infiltration in tumors [75].

Dozens of nuclear non-coding RNAs, including *LncUCA1, PCGEM1, miR-210, miR-185, miR-342*, and others, have been shown to influence mitochondrial dynamics and metabolism in cancer and have potential roles as biomarkers and therapeutic targets for cancer diagnosis and treatment [76]. However, in addition to nuclear non-coding RNAs, recent years have demonstrated the significance of mitochondrial non-coding RNAs, particularly *t00043332, t00000434, t00000674*, and others, as novel potential biomarkers and targets for cancer therapy [77]. Transfer RNA-derived small RNAs (*tsRNA-FAM155B, tRF-21-FSXMSL73E, tRF-23-FSXMSL730H, etc.*) have been identified as new biomarkers and potential targets for breast cancer treatment [78].

Effective epigenetic biomarkers in many types of cancer may be methylation changes not only in mitochondrial gene promoters in nuclear DNA, but also in mtDNA. Changes in mtDNA methylation are associated with tumor progression and may contribute to tumor drug resistance [79]. Furthermore, mitochondrial dysfunction has been

demonstrated to induce epigenetic abnormalities, resulting from quantitative changes in substrates for genomic DNA methylation and post-translational modifications of histones, particularly acetyl-CoA, S-adenosylmethionine, α-ketoglutarate, NAD+, and O-linked beta-N-acetylglucosamine. These compounds are essential for the regulation of gene transcription and the determination of cell fate in oncogenesis and aging [80]. The role of RNA methylation, including mitochondrial tRNA, has received significantly less research attention despite its critical importance in tumor metastasis processes, which are considered potential markers and targets for therapy [81].

At the protein level and mitochondrial dynamics disruption, many different biomarkers have been studied for different types of cancer, in particular DRP1/OPA1 dysregulation associated with invasion, metastasis, and resistance to treatment [82]. The downregulated expression of TFAM, a pivotal regulator of mtDNA replication and transcription in cancer, was identified as a biomarker of tumor-associated macrophage infiltration. These cells constitute a component of the tumor microenvironment, which contributes to the proliferation and progression of tumors [83].

A pivotal role as cancer biomarkers linked to mitochondrial metabolic dysfunctions belongs to oncometabolites, in particular succinate, fumarate, itaconate, α-ketoglutarate, and others [49, 50]. It is imperative to acknowledge the significance of their detection in two distinct yet interconnected domains. Firstly, their detection is crucial for the evaluation of the tumor process's state. Secondly, their detection is essential for the selection of efficacious treatment modalities [84].

Mitochondrial biomarkers associated with age-related diseases exhibit a multi-level molecular complexity. These include mutations and mtDNA copy number as indicators of cardiovascular pathologies [85] and neurological pathologies, in particular Alzheimer's disease and Parkinson's disease [86]. The detection of mitochondrial-derived peptides, particularly MOTS-c, in plasma provides a means to evaluate the potential impact on cardiovascular disease, insulin resistance, and inflammation [87]. The mitochondrial proteins humanin and small humanin-like peptides have been identified as biomarkers of vascular disorders in age-related diseases and as targets for therapeutic intervention [88]. The cytokine GDF-15 has been linked to the aging process and the body's response to stress. This association supports its clinical value as a biomarker, which is a tool used to measure biological processes in medical research. Non-invasive detection is possible even in saliva [89]. The cGAS-STING pathway has been demonstrated to function not only as an indicator of aging associated with mitochondrial dysfunction, but also as a contributing factor to disease progression [8].

Mitochondrial pharmacological and pharmacogenetic markers constitute a separate group. As previously mentioned, these have been partially described above among various groups of biomarkers at the level of mtDNA, nuclear DNA, epigenetic changes, transcriptional abnormalities, changes in mitochondrial protein levels, metabolites, oncometabolites, *etc.* [47, 48, 50, 82]. The effectiveness of mitochondrial signature genes (*DTYMK, ABCB6, GOT2*, and *TOMM40L*) for prognostic stratification and prediction of response to immunotherapy in patients with hepatocellular carcinoma have been demonstrated [90]. Another expression signature based on the mitochondrial unfolded protein response (*HSPD1, LONP1, SSBP1, MRPS5, YME1L1, HDAC1*, and *HDAC2*) has been proposed. It has been demonstrated that this process not only contributes to the maintenance of mitochondrial integrity, but also plays a pivotal regulatory role in the progression of cancer and the development of drug resistance (Sorafenib) [91]. The research [6] has identified biomarkers of ovarian cancer chemoresistance through various processes underlying mitochondrial dysfunction, specifically targeting (ROS), metabolites, and reverse metabolic pathways. The mitochondrial state has the functional capacity to regulate and modulate tumour radioresistance, chemotherapy, and immunotherapeutic resistance by integrating multidimensional signalling networks, thereby coordinating cell survival

mechanisms under therapeutic stress [92]. Though targeting mitochondrial dysfunction is promising for defining therapeutic strategies, the high heterogeneity of mitochondria in tumour cells, tumour microenvironment cells, and adaptive resistance mechanisms complicate the determination, analysis, and interpretation of results and requires further in-depth research.

Therapeutic targets and treatment strategies associated with molecular alterations and metabolism of mitochondria in cancer and age-related diseases

Over the past decade, a large number of studies have been published and a number of therapeutic approaches to mitochondrial dysfunction in cancer and age-related diseases have been developed. The following discussion will concern the analysis of the pivotal therapeutic strategies that have been developed for the influence of mitochondrial status in the following pathologies. The initial observation to be made concerning cancer treatment strategies is that the target of therapy can be divided into three categories: firstly, tumour cells; secondly, the cancer microenvironment; and thirdly, systemic effects on the patient's body state [93].

The development of targeted pharmacological drugs that target various links in mitochondrial metabolism is an active area of research for the treatment of cancer [92, 93]. A significant number of molecular targeted drugs have been developed against mitochondrial dysfunction pathways, particularly in ovarian cancer. These include olive leaf extract, nilotinib, salinomycin, Sambucus nigra agglutinin, tigecycline, and eupatilin [7]. Furthermore, targeted mitochondrial drugs are also being developed to overcome tumor chemoresistance [94]. It is imperative to acknowledge the significance of mitochondrial dynamics in the therapeutic management of numerous types of cancer [95].

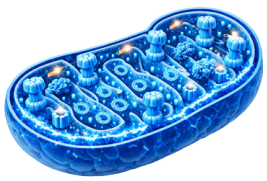
As a therapeutic modality targeting mitochondrial dysfunction in cancer, modern genetic technologies are undergoing active development, including targeted gene delivery in various systems, such as mLumiOpto [96], Fusion Gene Therapy [97], mitochondrial genetic editing of CRISPR/Cas9 [98], and re-engineering of mitochondrial genes [99]. A number of approaches to mitochondrial editing using mtDNA nucleases and base editors are also being developed for potential clinical use [100]. A series of studies on mitochondrial dysfunction are aimed at restoring the immune system and anti-cancer immunity in cancer patients [101] and inhibiting the tumor microenvironment to increase the efficiency of cancer immunotherapy [102]. The efficacy of pharmaceutical agents that target tumor-associated fibroblasts with the objective of reprogramming them, reducing tumor oncogenicity, and overcoming drug resistance has been demonstrated [103].

The therapeutic interventions devised for age-related diseases are principally focused on the restoration of energy and the biogenesis of mitochondria in diverse organs and systems of the body, as well as the body in its entirety [104, 105]. A distinct research domain encompasses the development of senolytics and senomorphics, which are designed to restore mitochondrial function to its normal state [106].

Another area of therapeutic strategies for cancer treatment is systemic metabolic interventions aimed at hormonally correcting the patient's metabolism. A considerable number of scientists and physicians subscribe to the perspective that cancer is a metabolic disease characterized by impaired energy production by mitochondria. These individuals contend that, in such instances, Lamarck's evolutionary theory provides a more adequate account of the progression of cancer. The hypothesis posits that cancer can be managed by inducing the body to prioritize ketone body metabolism over glucose and glutamine, a shift that can be facilitated through dietary modifications [107—109]. In recent years, the therapeutic effect of hypoxia and hyperoxia factors on mitochondrial metabolism in oncological and age-related diseases has been examined [110]. The temperature effects on the body, including hypo- and hyperthermia, have

Healthy active mitochondria: ↑ High ATP production, high intermembrane potential, highly organized cristae structure, intact mtDNA, high mtDNA copy number, active mt dynamics, strong mt-nucleus interaction, functioning of enzyme supercomplexes, active synthesis of tissue-specific substances and metabolites, ↓ low mtROS, strong regulated cell death

Highly active mitochondria

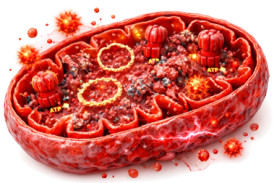


Endogenous and exogenous (Exposome) pathogenetic factors

Carcinogenesis	Age-related diseases
Genetic alterations (germline, somatic), carcinogenes, oncoviruses, chronic inflammation, immune escape, ageing, chronic metabolic disorders, sedentary lifestyle, chronic stress, microbiome alterations	Ageing: SASP, hormonal changes, metabolism inhibition, inflammaging, sarcopenia,: diabetes, metabolic syndrome, nutrient deficient, sedentary lifestyle, chronic stress, microbiome alterations

Mitochondrial dysfunction: ↓ Low ATP production, low intermembrane potential, altered cristae structure, mutated mtDNA, heteroplasmia, low mtDNA copy number, disrupted mt dynamics, low mt-nucleus interaction, programmed cell death alterations, disintegration of enzyme supercomplexes, metabolic reprogramming, altered programmed cell death, ↑ high mtROS

Destroyed, low active mitochondria



Biomarkers

Carcinogenesis	Age-related diseases
Genetic (germinal and somatic DNA alterations, mtDNA mutations, mtDNA copy number), epigenetic (DNA, RNA methylation, ncRNA and mt-ncRNA), transcriptomic (MitoScore, gene signatures), proteomic, metabolic, biochemical, immunohistochemical, pharmacogenomic, pharmacological	

Therapeutic strategies

Carcinogenesis	Age-related diseases
Targeting cancer cell mt: OXPHOS inhibitors/ modulator, HIF-, GLS-, oncometabolite inhibitors, PINK1-Parkin, BNIP3/NIX modulators, PGC-1α/ NRF1/TFAM inhibitors, apoptose/ ferroptose/ necroptose inducers, etc. **Targeting microenvironment mt:** imuno-metabolic reprogramming of T-cells, NK, TAM, DC, CAF, endotelial cells. **Systemic strategies**	**Targeting mt pathway:** PGC-1α/ NRF1/TFAM, SIRT1/3/5 activators, AMPK↑, mTOR↓, mitophage/ biogenesis indusers, urolithin A, spermidine, mt transfer, genotherapy, **Systemic strategies:** senolitics, senomorphics, mito-peptides, hormesis, microbiome correction

Repairing mitochondria

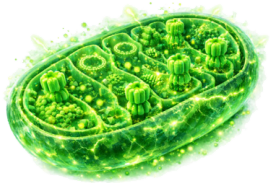


Fig. 2. Generalized scheme of mitochondrial states, factors, indicators of mitochondrial dysfunction and therapeutic strategies in cancer and age-related diseases (Abbreviations: ncRNA — noncoding RNA, mt — mitochondria, HIF-inhibitors — Hipoxia-indusible factors inhibitors, GLS-inhibitors — Glutaminase inhibitors, NK — Natural killer cells, TAM — Tumor-associated macrophages, DC — Dendritic cells, CAF — cancer-associated fibroblasts)

been investigated [111, 112]. The role of physical activity as a therapeutic component has been explored [113—115]. Light therapy has been studied [116 Al Balah OF, 2025]. The effects of fasting and intermittent fasting techniques have been reviewed [117].

A significant area of research in the field of cancer and age-related diseases pertains to the correction of the microbiome through mitochondria-microbiome crosstalk. This process operates through two distinct mechanisms: firstly, as a contributing factor to the development of pathologies in dysbiosis, and secondly, as a therapeutic approach to address pathologies by normalising the composition of the microbiome [45]. While pathogenic and conditionally pathogenic bacteria promote cancer development in dysbiosis, some other specific intestinal bacteria have been shown to suppress cancer development and progression, and to enhance the therapeutic effect on cancers [118]. In particular, for malignant melanomas, the role of the microbiome as a co-driver in melanoma immuno-oncology has been demonstrated [119]. Changes in the composition of microbiota influence host neuronal health through their metabolites on Alzheimer's disease progression [120]. In addition to strategies for treating age-related diseases, the microbiome-based therapies have been developed that are specifically adapted for older people, with the main goal of preventing disease and promoting health and longevity [121].

Summary

We propose a generalized scheme (Fig. 2) of significant clinical molecular and structural mitochondrial characteristics, factors influencing the manifestation of mitochondrial dysfunction, groups of biomarkers for detection, and therapeutic approaches for cancer and age-related diseases.

It is imperative to formulate a comprehensive description of healthy and active mitochondria as a point of departure for further investigation. Despite the fact that their structural and functional characteristics may vary between different cells and tissues, these organelles possess a number of shared properties. These include the synthesis of ATP, the generation of metabolites, a high intermembrane potential, low levels of ROS, the presence of a clearly defined structure of cristae and enzyme complexes, the capacity to respond to nuclear signals, and mitochondrial dynamics in response to alterations in the physiological state of the cell and potential stresses. The structural and functional characteristics of mitochondria may be subject to alteration over time due to the influence of pathogenic factors of the exposome, which may be prevalent and diversified in the development of oncological and age-related diseases. This results in mitochondrial dysfunction, manifesting as a range of signs and changes at all levels of mitochondrial metabolic activity. The identification of these features of dysfunction is facilitated by the existence of groups of biomarkers that allow for the determination of the level and depth of structural and functional disorders of mitochondria in these diseases. The most significant stage in the general scheme is therapeutic approaches. It is noteworthy that in recent years, new areas of therapeutic influence on mitochondrial metabolism in oncological and age-related diseases have emerged, while existing ones have been further developed.

It is important to acknowledge that all the points outlined in the generalized scheme, from the detection of molecular mitochondrial disorders to treatment strategies, are the subject of very intensive research. This is evidenced by the significant number of articles published over the past five years. Consequently, there is an expectation of forthcoming achievements and scientific breakthroughs in the near future in terms of the prevention, diagnosis and treatment of socially significant oncological and age-related diseases in humans.

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КЛІНІЧНО-ЗНАЧУЩІ МОЛЕКУЛЯРНІ ПОРУШЕННЯ МІТОХОНДРІЙ ПРИ КАНЦЕРОГЕНЕЗІ ТА ВІКОВИХ ЗАХВОРЮВАННЯХ: СУЧАСНИЙ СТАН І ПЕРСПЕКТИВИ: ЧАСТИНА 2. ФАКТОРИ ЕКСПОЗОМУ, БІОМАРКЕРИ ТА ТЕРАПЕВТИЧНІ СТРАТЕГІЇ

У другій частині огляду проаналізовано низку факторів експозому, що впливають на розвиток молекулярних порушень та метаболічних зсувів мітохондрій при раку та вікових хворобах. Розглянуто певні мітохондріальні біомаркери означених хвороб як біохімічні, генетичні та молекулярно-біологічні для діагностики, прогнозування, лікування раку та вікових хвороб. Проаналізовано певні напрямки терапії та нові сучасні терапевтичні підходи лікування раку та вікових хвороб в контексті патогенетичного впливу на мітохондріальні порушення в клітинах та органах людини для корекції патологічних станів та повернення до здорового довголіття.

***Ключові слова*:** мітохондріальна дисфункція, молекулярні порушення, рак, вікові захворювання, експосома, біомаркери, терапевтичні стратегії, гормезис.