Reviews

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CLINICALLY SIGNIFICANT MOLECULAR ALTERATIONS OF MITOCHONDRIA IN CARCINOGENESIS AND AGE-RELATED DISEASES: PART 1. DISEASE SUSCEPTIBILITY AND DIAGNOSIC SIGNIFICANCE

Mitochondrial dysfunction is associated with the hallmarks of cancer, aging, and age-related diseases. In recent years, numerous mitochondrial molecular alterations have been identified at the DNA, RNA, and protein levels, as well as metabolic shifts and metabolic reprogramming in various types of cancer and age-related diseases. The review analyzes a number of clinically significant parameters of mitochondrial disorders, including susceptibility to disease development, diagnosis, prognosis, and the course of these pathologies. The manifestations of mitochondrial dysfunction at the molecular level are constantly being refined and revised, so in the future, we can expect the emergence of new clinically significant signs of these disorders in cancer and age-related diseases.

Keywords: *mitochondria, somatic and germline genetic alterations, metabolic reprogramming, cancer, age-related diseases, clinical-significant alterations.*

Introduction

Mitochondria are cellular organelles that not only provide cells with ATP energy through oxidative phosphorylation (OXPHOS), but also play an important role in cellular homeostasis, survival, differentiation, cell death, and response to stress factors [1]. These factors have been shown to have a profound impact on both the prevalence and management of treatment of diseases.

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Mitochondrial dysfunction has been associated with the hallmarks of cancer [2, 3] and aging, as well as with many age-related diseases [4, 5]. Conversely, the active mitochondrial function and the capacity for recovery following periods of stress are indicative of optimal health [6]. Mitochondrial alterations and dysfunctions have been demonstrated to exert different effects and possess varying significances in various carcinogenesis theories, particularly the mutational and metabolic theories of cancer [3, 7, 8]. The prevailing theories of aging posit divergent interpretations of mitochondrial dysfunction, including the mitochondrial free radical theory [9], the hyperfunctional theory [10], and the epigenetic theory of aging [11]. Consequently, these theories adopt disparate approaches to the diagnosis, prognosis, and treatment of these diseases. However, mitochondrial alterations and dysfunction constitute an integral feature of carcinogenesis and age-related diseases across all of these theories.

In recent years, a number of studies have been conducted on molecular abnormalities of mitochondria at the DNA, RNA, and protein levels, as well as metabolic dysfunctions in various types of cancer and age-related diseases. A number of effects of these disorders on clinically significant parameters have been identified, including susceptibility to disease development, diagnosis, prognosis, course, and therapeutic responses to these pathologies. This review will analyze a number of these alterations in relation to their identified or potential clinical significance.

Key structural and functional specific features of human mitochondria

The human mitochondrial proteome comprises over 1,000 proteins that play a crucial role in the functioning of these organelles. In conjunction with tissue-specific mitochondrial proteins, their quantity can reach up to 1,500 [12]. However, it has been determined that only 13 proteins of the oxidative phosphorylation (OXPHOS) electron transport chain are encoded by mitochondrial DNA (mtDNA). Furthermore, mtDNA encodes a total of 37 genes, including 22 tRNAs and 2 rRNAs. mtDNA itself is 16,569 base pairs (bp) in size and is a double-stranded ring molecule that is not protected from damage, particularly by histones, in contrast to nuclear DNA [13]. mtDNA is susceptible to numerous genetic disturbances under the influence of endogenous and exogenous reactive oxygen species (ROS), stress, inflammation, high glucose levels and hormonal resistance among other factors [14]. While each mitochondrion contains numerous copies of mtDNA in every cell, genetic abnormalities in only a subset of these copies may be sufficient to trigger pathological processes [15]. The presence of normal mtDNA alongside mutated copies gives rise to the phenomenon of heteroplasmy. This phenomeno has been demonstrated to influence the appearance of precancerous cells in certain tissues, as well as senescent cells with impaired metabolism. In certain conditions, these cells can trigger the development of diseases [14, 15, 16, 17].

Mitochondrial tRNAs exhibit structural differences compared to cytoplasmic tRNAs, suggesting that mitochondria possess distinct aminoacyl-tRNA synthetases (aaRSs) that differ from those found in the cytoplasm. These aaRSs are encoded in the nucleus and subsequently transported to organelles. A total of 19 aminoacyl-tRNA synthetases have been identified as functioning in human mitochondria for all amino acids except Gln [18]. Of these, 17 aminoacyl-tRNA synthetases are specific to mitochondria, and two (GARS1 and KARS1) are isoforms of cytosolic enzymes [19].

The genetic code of mtDNA has slight differences from the nuclear code, particularly in the stop, tryptophan, and methionine codons [20]. The processes of replication, transcription, and translation in mitochondria are distinct from their nuclear counterparts. The human mitochondrial transcription initiation machinery contains two accessory factors, namely, transcription factors A and B2 (TFAM and TFB2M), and RNA polymerase (POLRMT) [21]. A distinctive feature of mitochondrial transcription

is its association with mtDNA replication, for which mitochondrial RNA polymerase is indispensable [22]. The processes of transcription elongation and termination are controlled by TEFM and MTERF1, respectively. The process of transcription results in the formation of polycistronic RNA from the heavy or light chain, which is then subjected to processing through two distinct pathways [23]. Disruption of the regulation of these factors directly leads to impaired mtDNA expression in tumor cells, mitochondrial dysfunction, and cellular metabolic reprogramming [24].

The import system of nuclear-encoded mitochondrial proteins plays a pivotal role in mitochondrial biogenesis [25]. The process of translocation through the outer and inner mitochondrial membranes is facilitated by the TIM-TOM complex translocases [26]. These processes necessitate precise nuclear-mitochondrial interaction, which is disrupted at various levels during the development of pathological processes, particularly cancer and age-related diseases [1, 4].

Another significant feature of mitochondria is the structure of the inner membrane, which forms cristae. These structures facilitate the formation of enzyme supercomplexes, which consist of rows of ATP synthase dimers that delineate the edges of lamellar cristae, MICOS subunits (mitochondrial contact site and cristae organizing system) that function as transport hubs, optic atrophy 1 (OPA1) isoforms, and specific tissue-specific features [27]. Furthermore, a specific phospholipid, cardiolipin, is present in the structure of the lipid bilayer of the inner membrane of mitochondria. It is synthesized by mitochondria and participates in the formation of cristae and the functioning of enzyme supercomplexes, protein translocation, and contacts with the endoplasmic reticulum [28].

The dynamics of mitochondria are an integral part of their functioning. These factors encompass transport, fission, fusion, and morphological changes of mitochondria, influenced by both endogenous and exogenous factors within physiological and pathological contexts [29]. Mitochondrial dynamics are closely related to the endoplasmic reticulum and mitochondria-associated membrane (MAM). Their dysfunction has been reported to be associated with the progression of hyperlipidemia, insulin resistance, hypertension, and other pathologies [30]. Metabolons and enzyme supercomplexes facilitate substrate channeling, which is critical for the effective functioning and normal metabolism of mitochondria. Disruptions in this process underpin carcinogenesis and age-related pathologies [31, 32].

mtDNA and nuclear encoded genes of mitochondrial proteins alterations for diagnostic and prognostic applications in cancer and age-related diseases

It has been established that mtDNA exposes a multitude of molecular characteristics and abnormalities, which have the potential to influence the development of cancer and age-related diseases. These abnormalities play different roles in these processes [33]. These characteristics can be either congenital, reflecting both population characteristics and relating to a specific haplotype, or they can be a feature of familial inheritance [34, 35]. It is important to note that mtDNA is transmitted exclusively through the maternal lineage. It has been posited that germline characteristics can function as adapters for pathological processes [33]. Somatic mtDNA disorders are acquired during life and may be associated with the influence of exogenous factors, lifestyle, and the development of pathological processes, in particular infections and chronic inflammation. These somatic alterations have been demonstrated to act as inducers of cancer and age-related diseases [15, 36].

Germinal alterations of mtDNA and nuclear-encoded genes of mitochondrial proteins in cancer and age-related diseases

Germinal types of mtDNA disorders have a high degree of correlation with various forms of cancer.

For instance, in Brazilian patients diagnosed with stomach cancer, the most prevalent disorders were identified in the following regions: MT-RNR1, MT-ND5, MT-ND4, MT-ND2, MT-DLOOP1, and MT-CO1 as being associated with haplogroup C (Native American ancestry) in this type of cancer [37]. Patients with mtDNA haplogroup M D5 exhibited an elevated risk of developing breast cancer, while those with haplogroup M D4a demonstrated an augmented risk of thyroid cancer. However, no discernible association was observed with respect to colorectal cancer [38].

In the context of age-related diseases, particularly dementia, mitochondrial haplogroups have been demonstrated to affect the risk of developing dementia. Furthermore, genetic variants in the nuclear and mitochondrial genomes interact to influence the age of onset of dementia [39].

Haplogroup characteristics have been demonstrated to influence a degree of protection against certain types of cancer. For instance, haplogroup K has been identified as an independent genetic factor associated with a reduced risk of neuroblastoma in populations of European descent [40]. Haplogroup N9a and its diagnostic SNP, m.16257C>A, negatively correlated with the incidence and progression of hepatocellular carcinoma in northern China [41]. Haplogroup D4a is a marker for extreme longevity in Japan [42].

Ghezzi (2005) found an association between haplogroup K and a reduced risk of developing Parkinson's disease in the Italian population [43]. A recent meta-analysis of European and Asian samples of patients with Parkinson's disease demonstrated a close relationship between mitochondrial haplotypes, mitochondrial dysfunction, and genomic instability of mtDNA at this disease [44].

Hereditary alterations in mitochondrial energy generation, otherwise known as mitochondrial diseases, are the causative agents of a clinically and genetically heterogeneous array of diseases, including those affecting the brain, skeletal muscle, eyes, and heart. The minimum prevalence of this condition is estimated to be 1 in 5,000 live births. In recent decades, mutations that underlie these disorders have been identified in nearly 290 genes [45]. The most prominent syndromes associated with m.3243A>G (MT-TL1) mutations are MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes). As indicated by Al-Gadi [46], the condition is associated with age-related complications, including di abetes and deafness. This mutation has been demonstrated to impact insulin secretion and resistance in individuals diagnosed with diabetes [47].

The inherited mutation m.8344A>G (MT-TK) is linked to MERRF (Myoclonic Epilepsy with Ragged-Red Fibers) syndrome, which is characterized by the developing of diabetes, thyroid/calcium disorders, and constitutes a component of age-related target organ damage [48]. The MT-ATP6 mutation (m.8993T>G/C) has been identified in NARP syndrome (Neuropathy, Ataxia, and Retinitis Pigmentosa) and leads to systemic damage with age [49].

The impact of these mutations on cancer remains to be substantiated; however, Pearson syndrome, an mtDNA deletion-based condition, are linked to an increased susceptibility to leukemia and age-related multisystemic lesions [50]. The collective effect of pathogenic mtDNA variants on health outcomes was a subject of considerable research interest. A body of evidence suggests a possible association between these variants and an increased risk of cancer [51] as well as elevated mortality rates from cancer [52].

The majority of clinically significant germline mutations have been identified in non-mitochondrial genes and proteins associated with human cancers [53—55]. Hereditary DNA mutations in mitochondrial proteins, encoded in the nucleus, are uncommon and manifest exclusively in specific types of cancer. For instance, rare germline mutations in isocitrate dehydrogenase 1 or 2 (IDH1/2), a pivotal enzyme in the citric acid cycle, have been identified in patients with gliomas, which have been shown to adversely impact survival outcomes in this disease [56]. Germline mutations in the succinate dehydrogenase subunit D gene (SDHD-G12S,

SDHD-H50R) (mitochondrial protein) and in the tumor suppressor gene *PTEN* have been identified as risk factors for a subgroup of Cowden syndrome, with the concurrence of these mutations resulting in an elevated probability of developing breast, thyroid, and other cancers [57, 58]. Two DNA repair genes that have mitochondrial isoforms (*MUTYH* and *NTHL1*) have been linked to cancer predisposition syndromes. Some germline mutations in *NTHL1* are associated with a syndrome that increases the risk of colorectal and other cancers (NTHL1-associated polyposis) [59]. The presence of germline pathogenic variants of *MUTYH* has been detected in sporadic gastric cancer, secretory carcinoma of the salivary glands, and adenocarcinoma of the pancreatic ducts. A subset of these variants are associated with alterations in sensitivity to chemotherapy [60]. On an annual basis, novel data appear concerning the germline variants associated with mitochondria disfunctions, a consequence of advancements in modern sequencing methodologies. These new data necessitate systematic analysis and the subsequent determination of the function in carcinogenesis and age-related diseases.

Somatic alterations of mtDNA and mitochondrial proteins in cancer and age-related diseases

Approximately fifteen years ago, a role of mtDNA mutations in carcinogenesis was the subject of extensive study, employing a variety of approaches. However, the conclusions regarding pathogenicity and impact on carcinogenesis remained controversial [61]. Furthermore, it has been established that somatic mutations accumulate in the mitochondrial genome of normal cells of various tissues and organs, as well as in stem cells, with age [62]. Therefore, it is necessary to separate the influence of various factors and determine their synergistic or antagonistic effects on the development of multifactorial pathologies, such as cancer and age-related diseases.

The advent of contemporary sequencing technologies over the past decade facilitated the identification and characterization of numerous genetic variants in mtDNA and nuclear-encoded mitochondrial proteins, both germline and somatic, that play a pivotal role in the onset of various diseases. These variants were thoroughly examined and evaluated with respect to their clinical significance. Additionally, significant genetic variants in mtDNA and mitochondrial proteins encoded in the nucleus, both germline and somatic, were identified as contributing factors to the development of various types of cancer and age-related pathologies. As a result of international collaboration, the whole-genome sequencing data from 2,658 cancers of 38 tumor types were analyzed, and the characteristics of mitochondrial genome mutations and mitochondrial protein transcriptomes were characterized [63]. These data are collected in The Cancer Mitochondrial Atlas (TCMA) in four modules: somatic mutations, mtDNA copy number, nuclear transfer, and gene expression in tumors. The study showed that, in contrast to nuclear DNA mutations, mtDNA mutations in tumors exhibit a high degree of similarity in their mutation signatures, independent of the origin of the cancerous tissue. These signatures predominantly consist of G > A and T > C substitutions on the L-strand [63, 64].

A multitude of somatic mutations, including synonymous, non-synonymous, and indels, were identified and thoroughly examined in the D-loop region of various cancerous specimens, extending to bladder, lung, stomach, ovarian, prostate, and colorectal cancers, among others [65]. Another study demonstrated that somatic mtDNA mutations in the D-loop and in the MT-ND1 and MT-ND5 genes affect mitochondrial function and are widely found in various types of cancer [66].

In the context of breast cancer, a number of potentially pathogenic mutations have been identified in mitochondrial tRNAs, including Val, Ile, Ser, Glu, and Thr, located in conservative positions capable of affecting tRNA transcription and modification during protein synthesis [76]. This may have implications for mitochondrial protein synthesis in tumors and mitochondrial metabolic function.

Conversely, pathogenic mtDNA mutations can have a deleterious effect on cancer cells, impeding their proliferation, migration, and metastasis. This phenomenon has been observed in melanoma cells [68].

Specific somatic mutations and mutation signatures of mtDNA in aging and age-related diseases in different cell and tissue types were identified using modern sequencing methods [69, 70]. Furthermore, clock-like mutation signatures were recognized as indicators of aging, environmental impact, and the activity of DNA repair and metabolism processes [71, 72].

The mtDNA mutation rate or burden has a significant impact on various indicators of clinical importance in the context of cancer and age-related diseases. It has been established that numerous malignant tumors exhibit elevated levels of somatic mtDNA mutations, which may generate a driver effect on carcinogenesis [73]. As indicated in the MITOMAP database, the non-coding region, designated as the D-loop, have the highest number of mtDNA mutations. They were demonstrated to regulate a multitude of mtDNA processes, with a particular emphasis on transcription and replication. Furthermore, the pathogenic mutations were identified in the coding regions of specific genes, MT-CO1 and MT-ND4L, among others. Furthermore, numerous mutations with unknown functions (VUS) were found. These mutations may have diagnostic and therapeutic potential for precision oncology [74, 75].

The topic of mitochondrial genes encoded in the nucleus has recently attracted significant attention due to the presence of somatic mutations in the numerous genes of this type in various cancerous tissues. A number of genes have been identified as clinically significant in the context of carcinogenesis, and the impact of the mutations in these genes have been demonstrated (Tier 1-Tier 2). This group include *IDH1, IDH2, FH,* the *SDHx* gene family, the *POLG, SDHAF2, SDHAF2, MPC1* genes, and others [76—79]. For the multitude of identified mtDNA mutations in cancer, their clinical significance remains to be validated, similar to the numerous somatic mutations of nuclear DNA in tumors [15]. In the context of age-related diseases, the elevated levels of somatic mtDNA mutations have been identified as biomarker, prognostic and therapeutic indicators of metabolic dysfunction in the human body with age [80, 81].

In addition to specific mtDNA sequence alterations, the changes in mtDNA copy number and the transfer of mtDNA sequences to the nucleus (NUMTs) may contribute to the development of certain types of cancer [33, 66]. The changes in mtDNA copy number have been identified as a diagnostic and prognostic indicator, as well as a risk factor for various types of cancer and some age-related diseases [82, 83]. For the patients with glioblastoma, a decrease in the mtDNA copy number was identified as an age-dependent prognostic marker [84]. Furthermore, the mtDNA copy number serves as a valuable indicator in combination with epigenetic age determination and the interplay between mitochondrial dysfunction and epigenetic abnormalities in the context of aging and age-related diseases [85].

Various types of mtDNA abnormalities, including point mutations and deletions in different regions, as well as a decrease in the mtDNA copy number, have been detected in the brains and blood of patients with neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis [86].

Mitochondrial haplogroups may have a population-specific, tissue-specific, and stage-specific role in cancer development and aging [38, 87]. Somatic mtDNA mutations have been shown to directly impact metabolic homeostasis in cancer cells, suggesting a need for further investigation using high-resolution sequencing methods and in-depth analysis of heteroplasmic disorders [73]. The heterogeneity of somatic and germline mtDNA mutations, as well as the disruption of its homeostasis, are pivotal factors in the progression of cancer and age-related diseases [88].

Metabolic alterations and mitochondrial dynamics changes in carcinogenesis and age-related diseases

Mitochondrial metabolic dysfunction is a hallmark of the aging process, contributing to the development of various age-related pathologies, including cardiovascular disease, metabolic syndrome, endocrine disorders, neurodegenerative diseases, and cancer [89, 90].

Mitochondrial dysfunction can be caused by molecular disorders at various levels, ranging from replication, transcription, and translation processes in mitochondria in cancer and age-related diseases to mitochondrial dynamics, disruption of apoptosis mechanisms and mitochondrial-nuclear interactions. For instance, TFAM and POLG have been identified as playing a role in mtDNA replication. The gene variants have been recognized that affect the functioning of these proteins in head and neck cancers and are associated with the patient survival in these diseases [91]. In the early stages of carcinogenesis and certain types of tumors, a decrease in mtDNA copy number is observed, which is directly related to the replication process [63, 92]. Conversely, as cancer progresses, an increase in this indicator may be observed as a result of an increase on the level of mtDNA transcription [93, 94]. A correlation between low mtDNA copy number and increased chemoresistance in esophageal squamous cell carcinoma has been demonstrated in recent studies [95]. However, for certain other types of cancer, this indicator is not associated with clinical manifestations [92]. On the contrary, the tumors exhibiting elevated replication/copy number may be amenable to pharmacological mitochondrial inhibition [93]. A potential explanation for the elevated mtDNA copy number observed in tumors may be alterations in the activity of the oncogenes, particularly KRAS and MYC [93, 94]. For *KRAS*, it has been demonstrated that the KRASG12D mutation can result in elevated mtDNA replication and mitochondrial respiration, thereby promoting the progression of lung adenocarcinoma [94].

In addition to impaired mitochondrial replication/copy number, many tumors have been found to have dysregulated transcription factors POLRMT, TFB2M, TFAM, and MTERF, leading to reprogramming of mitochondrial gene expression. This, in turn, affects the metabolism and proliferation of tumor cells and is associated with cancer prognosis [24, 96].

Disruptions in mitochondrial translation processes have also been observed during the process of carcinogenesis. Detected mutations in mt-tRNA has been shown to affect the process of aminoacylation and lead to defective mitochondrial translation [97]. Mutations in mt-tRNA genes in patients with breast cancer have functional consequences, including significantly lower levels of mtDNA copy numbers and ATP levels in tumors compared to the control group [67].

Cytoplasmic aminoacyl-tRNA synthetases have been widely described as participating in the carcinogenesis of various types of cancer [98]. Meanwhile, the mutations in mitochondrial aminoacyl-tRNA synthetases are associated with specific syndromes that affect the central nervous system [99] and many mitochondrial diseases [18, 100]. To date, the extant research has been limited in scope and has focused on the impact of changes in the expression of mitochondrial aminoacyl-tRNA synthetases on the carcinogenic process. For instance, mitochondrial AARS2 has been identified as overexpressed in numerous cancerous cell types through pan-cancer studies, a finding that is associated with the activity of oncogenic pathways. Conversely, its deficiency has been observed to inhibit cell proliferation and migration in hepatocellular carcinoma [101]. Furthermore, these studies substantiate the function of AARS2 as a novel biomarker for cancer prognosis. Given the significant role of mitochondrial aminoacyl-tRNA synthetases in mitochondrial function, it can be hypothesized that mutations in these genes and their expression disorders during the process of carcinogenesis and age-related diseases may intensify mitochondrial dysfunction in these pathologies. Further research is necessary to investigate this hypothesis [102, 103].

It has been revealed that defects in oxidative phosphorylation (OXPHOS) caused by somatic mtDNA mutations, which increase with age and during carcinogenesis, result in metabolic reprogramming in cells. This may functionally contribute to the accelerated development of various types of human cancer [104, 105]. It has been demonstrated that effective OXPHOS is essential for maintaining the differentiated state of somatic cells [106]. Therefore, researchers who support the metabolic theory of cancer consider chronic OXPHOS deficiency to be a pathophysiological mechanism associated with malignant transformation. This phenomenon is associated with an increase in glycolysis and glutaminolysis in transformed cells. Therefore, the pathophysiological phenotype common to all major cancer types is a greater dependence on phosphorylation at the substrate level than on OXPHOS for energy production [7, 107].

Numerous disturbances in the tricarboxylic acid cycle (TCA cycle), which is closely related to OXPHOS, have also been identified in carcinogenesis and age-related diseases. The disruption of this process can be attributed to mutations or shifts in the expression of enzymes such as isocitrate dehydrogenase (IDH), fumarate hydratase (FH), and succinate dehydrogenase (SDH). These alterations can lead to the production of various oncometabolites, including succinate, fumarate, itaconate, α-ketoglutarate, and others [108]. These factors have been demonstrated to significantly impact tumor progression, epigenetic regulation, and immune response evasion. Oncometabolites represent a class of target molecules for the development of various types of therapy [109]. In certain types of cancer, such as gastrointestinal stromal tumors, pheochromocytomas, and paragangliomas, a deficiency of the TCA cycle enzyme succinate dehydrogenase has been identified. This deficiency leads to the accumulation of the oncometabolite succinate, promoting tumor progression. The development of specific treatment strategies for this type of tumor is actively underway [77]. In age-related diseases, mitochondrial stress and TCA (tricarboxylic acid) abnormalities have been demonstrated to reduce acetyl-CoA levels. This phenomenon has been shown to contribute to mitochondrial dysfunction, which, in turn, is linked to a decline in histone acetylation and an increase in chromatin remodeling. This, in turn, is associated with an increased risk of age-related diseases [110].

The coenzyme NAD+, which participates in the OXPHOS and TCA cycles, plays a pivotal role in maintaining mitochondrial function. Its decline is associated with general aging and chronic disorders, which manifest themselves through the dysfunction of homeostatic components such as mitophagy and the disruption of mitochondrial antioxidant systems in age-related diseases [111]. NAD+ metabolism in carcinogenesis plays a dual role in cancer cells and the tumor microenvironment and is a target for targeted cancer therapy and restoration of immune functions in the tumor microenvironment [112, 113].

The decrease in mitochondrial intermembrane potential, impaired apoptosis, and increased mitochondrial ROS observed in cancer and age-related diseases are closely related to the metabolic activity of mitochondria and their dynamics. These phenomena have a number of clinical implications.

In aged tissues, a reduction in mitochondrial potential and an increase in mtROS, which are produced endogenously, promote cellular senescence and a senescence-associated secretory phenotype [114]. These effects are associated with the multimorbidity characteristic of age-related diseases, ranging from cardiovascular to neurodegenerative pathologies [115]. Moreover, this effect results in mtDNA damage and genomic instability in cancer cells. ROS levels in cancer cells have been demonstrated to function as a signaling driver of growth and invasion [116]. These phenomena, in turn, increase the likelihood of cancer recurrence and create tolerance to therapy. However, stabilizing mitochondrial dynamics (fusion) has been shown to reduce these effects [117].

It has been well established that mitochondria are the origin of diverse programmed cell death

pathways that regulate both apoptotic and non-apoptotic cell death [118]. Disruption of programmed cell death processes, particularly apoptosis, is a hallmark of carcinogenesis and age-related diseases, typically manifesting in opposite directions. For instance, cancer cells inhibit mitochondrial apoptosis through a variety of mechanisms. Specifically, anti-apoptotic proteins, including BCL-2, BCL-XL, and MCL-1, are activated, and mitochondrial pores (MOMP) are closed. This shift in the BH3 balance, within the BCL-2 protein family, has been identified as a critical factor in the immortality of cancer cells and the development of resistance to treatment [119, 120]. Conversely, in age-related diseases, mitochondrial apoptosis is observed to be activated and dysregulated in various organs (e.g., brain, heart, muscles), resulting in cell death, atrophy, fibrosis, and deterioration of organ function [9, 121].

It has been demonstrated that the size, shape, and configuration of cristae within mitochondria exhibit characteristic patterns that vary according to distinct metabolic states, physiological conditions, and pathological processes [122]. Disrupted cristae are a manifestation of increased ROS production and a reflection of mitochondrial dysfunction in cancer and age-related diseases [27]. Tumor cells actively remodel cristae through OPA1 and MICOS components, which are promising targets for cancer therapy [123]. Another significant component of cristae is cardiolipin. It plays a structural role in the formation of the internal structure of mitochondria and undergoes significant changes in age-related diseases in the form of pathological remodeling/oxidation, which clinically manifests itself in the progression of heart failure and muscle weakness [124]. A modification in the composition or oxidation of cardiolipin has been demonstrated to induce alterations in the apoptotic competence and metabolic plasticity of tumor cells. Simultaneously, the tumor-specific heterogeneity of cardiolipin levels is observed in different types of tumors [125]. The targeting of cardiolipin has emerged as a promising clinical therapeutic strategy for cardiovascular diseases and cancer [124, 126].

The importance of mitochondrial disorders, with an emphasis on dynamics in neurodevelopmental disorders, has been demonstrated by clinical studies [127].

It has been established that the accumulation of mtDNA mutations in neurodegenerative diseases leads not only to its incorrect replication and a highly oxidative environment, but also to defective mitophagy after division. This process involves a number of proteins, including ATAD3A, TFAM, and OPA1, among others [86].

The imbalance between mitochondrial quality control and mitochondrial biogenesis in cancer and ageing also has significant clinical implications. It has been established that the sensitivity of cancer cells to radiotherapy depends on mitophagy processes and has a double-edged effect. Furthermore, a relationship is identified between the time and dose of radiotherapy and the state of mitochondria in tumour cells [128]. Several studies have demonstrated an inverse relationship between cancer and neurodegenerative diseases. One of the underlying mechanisms is the dysregulation of mitophagy and mitochondrial dynamics in opposite directions [129]. While cancer is associated with PINK1/Parkin downregulation, BNIP3/NIX-mediated mitophagy increases for survival under hypoxia by preventing mitochondrial degradation through the downregulation of Mfn1/Mfn2. In neurodegenerative diseases, however, these processes have the opposite effect [129, 130].

PGC-1α is an important regulator of mitochondrial processes, recovery and the ROS stress response in normal cells [131].

In age-related diseases, there is a decrease in PGC-1α expression, which is associated with mitochondrial biogenesis deficiency, oxidative stress and neurodegenerative processes [132]. In tumours, this factor can have different effects on carcinogenesis. For example, increased PGC-1α plays a decisive role in maintaining the malignant phenotype of glioma cells [133]. In breast cancer, there

is a strong correlation between PGC-1α expression and tumour metastasis [134].

Among the key regulators of aging and age-related diseases are mitochondrial sirtuins, in particular SIRT3-5. Their dysfunction, particularly the reduction in expression and activity, results in impaired mtDNA stability, decreased biogenesis and quality control of mitochondria, and impaired mitophagy. Additionally, there is an increase in ROS production and impaired nuclear-mitochondrial interactions [135]. This statement applies to nearly the entire family of sirtuins (*SIRT1-7*), which function in both mitochondria and the nucleus and, under certain conditions, can be used as therapeutic targets for age-related diseases [136].

A number of paradoxes have been identified in the functioning of mitochondria. In particular, the prevailing notion that oxidative stress and apoptosis accelerate aging may not always be valid [137]. As many of the mechanisms of mitochondrial dysfunction are constantly being refined and clarified at a molecular level, we can expect new, clinically significant signs of these disorders to emerge in cancer and age-related diseases in the future.

Conclusion

Therefore, even minor alterations in the mitochondrial genotype and mitochondrial proteins encoded in the nucleus can have significant effects on nuclear-mitochondrial interactions, cellular metabolism, as well as carcinogenesis and age-related diseases. The mechanisms underlying these effects and their clinical significance for a variety of molecular mitochondrial dysfunctions have yet to be thoroughly delineated, particularly in different cell types and in the context of diverse factors and pathologies.

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КЛІНІЧНО-ЗНАЧУЩІ МОЛЕКУЛЯРНІ ПОРУШЕННЯ МІТОХОНДРІЙ ПРИ КАНЦЕРОГЕНЕЗІ ТА ВІКОВИХ ЗАХВОРЮВАННЯХ: СУЧАСНИЙ СТАН І ПЕРСПЕКТИВИ: ЧАСТИНА 1. СХИЛЬНІСТЬ ДО ЗАХВОРЮВАНЬ ТА ДІАГНОСТИЧНЕ ЗНАЧЕННЯ

Порушення функціонування мітохондрій пов'язано з ознаками раку, старіння та вікових хвороб. За останні роки виявлені численні молекулярні порушення мітохондрій на рівні ДНК, РНК, білків, метаболічних зсувів та перепрограмування метаболізму при різних видах раку та вікових хворобах. У огляді проаналізовано низку клінічно-значущих параметрів мітохондріальних порушень, зокрема схильність до розвитку хвороб, діагностика, прогноз та перебіг означених патологій. Прояви мітохондріальної дисфункції на молекулярному рівні постійно уточнюються та доопрацьовуються, тому у перспективі можна очікувати появу нових клінічно-значущих ознак цих порушень при раку та вікових хворобах.

***Ключові слова*:** мітохондрія, соматичні та термінальні генетичні порушення, метаболічне перепрограмування, рак, вікові захворювання, клінічно-значущі порушення.