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Key Aspects of Mitochondrial Dysfunction in Leukemia

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Abstract

A major factor in the etiology and development of leukemia is mitochondrial dysfunction. This review explores key aspects of mitochondrial abnormalities in leukemia, including mitochondrial DNA mutations, disrupted mitochondrial apoptosis and metabolic shifts. We discuss how impaired mitochondrial function contributes to the survival and proliferation of leukemic cells, facilitating disease progression and resistance to therapies. Additionally, we examine the potential of targeting mitochondrial pathways as a therapeutic strategy, highlighting recent advances in mitochondrial-targeted drugs and their implications for improving patient outcomes. Understanding the intricate link between mitochondrial dysfunction and leukemia offers new avenues for innovative treatment approaches and underscores the need for further research in this area.

Keywords: mitochondria; mutations; apoptosis; metabolic shifts; targeted therapies

Introduction

Uncontrolled neoplastic proliferation of undifferentiated or partially differentiated hematopoietic cells leads to the development of leukemia, a category of diverse hematological malignancies [1]. Leukemia cell incidence is tightly linked to genetic differences. But non-chromosomal mitochondrial genetic abnormalities also significantly contribute to the development of leukaemia, in addition to these nuclear genetic alterations [2-5].

A 16 kb double-stranded circular genome, mitochondrial DNA (mtDNA) contains 37 respiratory chain-related genes, including 22 transfer RNAs (tRNAs), 2 ribosomal RNAs (rRNAs), and 13 messenger ribonucleic acids (mRNAs), which are essential for mitochondrial protein synthesis [4]. Because the mitochondrial genome is composed solely of encoding genes and regulatory sequences and does not have an intron like the nuclear genome, one-point mutation may lead to changes to important structural genes that could change the expression or properties of the expressed proteins [6].

Additionally, the rate of mtDNA mutation is ten times higher than that of the nuclear genome. Because of this, even in healthy humans, mtDNA progressively accumulates unique, permanent genetic mutations that can be used to trace ancestors and are passed on to daughter cells [7-9]. The mtDNA variants include both mutations and changes in the mtDNA copy number. Mutations in mtDNA are the primary source of abnormalities in mitochondria [10]. By altering the generation of reactive oxygen species, the redox state, and mitochondrial intermediates that serve as substrates for chromatin-modifying enzymes, mtDNA mutations contribute to carcinogenesis. Furthermore, changes in mtDNA can affect mitochondrial metabolites, which in turn can affect nuclear DNA gene expression and the epigenome [11].

The number of copies of the mitochondrial genome in each nucleated cell is known as the mtDNA copy number. Finding the ratio of mtDNA copies to nDNA reads—two copies per cell—is the most used method for determining the number of mtDNA copies. [12] Changes in the copy number of mtDNA can affect energy metabolism and oxidative phosphorylation, which can lead to mitochondrial malfunction [13-14]. Remarkably, changes in the number of mitochondria per cell are linked to leukemia development via disrupting respiratory patterns [15]. With a focus on mtDNA mutations, copy number variations, mtDNA sequencing methods, and their application as prognostic markers and natural genetic barcodes, we aimed to provide a comprehensive examination of mitochondrial genetic abnormalities in leukemia in this review. It aims to facilitate the identification of potential therapeutic targets for the treatment of this hematological malignancy.

Both nuclear and mtDNA are responsible for the twofold genetic regulation of mitochondria. Mutations in mtDNA are essential for reprogramming mitochondrial metabolism.

According to studies, mtDNA plays a crucial role in carcinogenesis because disruptive mutations of the molecule are generally uncommon in healthy cells but experience positive selection in cancer tissues [16]. Since several mtDNA mutations are linked to leukemia, this observation has also been verified in this disease.

Penter and colleagues, for example, found that more than 50% of cells with chronic lymphocytic leukemia (CLL) have at least one mtDNA mutation and

are capable of accumulating multiple additional mutations. About 40% of patients had somatic mtDNA mutations, according to He et al. [17] with the A15296G mutation acting as a flag unique to leukemia. Furthermore, it was discovered that the platelets of leukemia patients had mutation frequencies of above 5% in two genes (ND6 and Cytb), which code for mitochondrial proteins. With a mutation frequency of 32.65%, the ND6 gene in particular showed the highest frequency. 11 Frequent changes in mtDNA D-Loop location T489C have been linked to a number of cancers [18-20].

The T489C position may be a hotspot for recurrent variations linked to relapse, according to Tyagi et al.'s [21] investigation of pediatric acute myeloid leukemia (AML) cases. These variations occur within the noncoding regions and seem functionally silent, but they may have an effect on respiratory chain polypeptide levels, change electron transport chain (ETC) activity, and affect cellular energy capacity. Both the diagnostic and remission samples had some somatic mutations, most likely as a result of the leukemia cells' continued presence [22].

The most common mtDNA sequence variations in AML cases were single nucleotide changes, which may have changed how well mtDNA bound to transcription factors, causing aberrant protein complex formation and changing typical expression patterns [23].

Changes in mtDNA mutations and chromatin accessibility may also coincide with changes in copy number variations [24]. Moreover, some research indicates that mtDNA and RNA changes in AML are consistent [25]. Rates of mitochondrial mutation are positively correlated with leukemia incidence [26]. The exact role that mtDNA mutations play in the pathophysiology of leukemia is yet unknown, though. It is still up for debate whether the accumulation of mutant mtDNA is the consequence of rapid cell division or if these mutations confer particular benefits to transformed cells that facilitate leukemia development and metastasis, such as changing mitochondrial metabolism in that cell lineage.

Tumor cells display metabolic alterations through modifications to mitochondrial metabolism, ETC complex activity, and mtDNA copy numbers [27]. Analysis of transcriptional profiles has revealed strong relationships between mtDNA copy numbers and the transcript levels of tricarboxylic acid cycle enzymes and ETC, fatty acid β-oxidation, and branched-chain amino acid catabolism pathways. The cumulative consequences of gene-environment interactions are reflected in variations in mitochondria copy number, which has been suggested as a possible biomarker for a number of malignancies [4,28,29].

Different tumor types have different alterations in the mtDNA copy number. According to studies, patients with AML had a mean mtDNA copy number that was around nine times higher than that of controls (P <.0001).

Patients with acute promyelocytic leukaemia (APL) treated with chemotherapy and all-trans retinoic acid who had leukemia cells with elevated mtDNA content had a noticeably reduced cumulative frequency of relapse, according to Pereira-Martins et al [30]. According to a different study, red blood cell-bound mtDNA had a negative correlation with patients' hemoglobin levels, while mtDNA copy number was linked to anemia in hematologic malignancies [31].

TFAM, POLG, and POLRMT are among the several mitochondrial biogenesis genes that regulate the quantity of mtDNA copies. Increased mitochondrial biogenesis is a notable cellular change in pediatric AML blasts that could impact the disease's biology and progression [32]. Recent research on adults with AML also revealed increased expression of TFAM and POLRMT, along with additional mitochondrial transcriptional factor genes like TFB1M and TFB2M, however these findings were not very significant for prognosis [23].

Further research is required to investigate the relationship between mtDNA copy number alterations and the pathophysiology and prognosis of leukemia. Variations in the quantity of mtDNA copies in certain cancers could be an adaptive response to mutations that provide certain tumor types an edge in growth. Furthermore, even within a class of tumors, differences in mtDNA content can be linked to the degree of malignancy [11]. Leukemia, however, has not yet been demonstrated to corroborate these conclusions.

MtDNA Variations as a Leukemia Prognostic Marker

Numerous studies have demonstrated that mitochondria have a functional role in leukemia by suggesting that mtDNA changes may serve as a prognostic marker. MtDNA mutations in AML patients were associated with a decreased disease-free survival rate. A larger [33 mtDNA copy number was often linked to worse disease aggressiveness and a lower survival rate in juvenile acute leukemia [4,27]. The prognosis of leukemia has also been linked to variations in mitochondrial heteroplasmic single nucleotides [34]. Mutations in mitochondrial genes encoding complexes I, III, and IV of the ETC have been linked to the worst outcomes in AML patients; these mutations could be candidates for therapeutic intervention [35,36].

The positive prognostic influence of acquired ND4 mutations in AML is suggested by the considerably longer OS (P =.021) and relapse-free survival (P =.017) of patients with somatically acquired ND4 mutations compared to those with ND4 (WT) [37]. A transmembrane component of the ETC respiratory complex I that is encoded by the mitochondria is nicotinamide adenine dinucleotide hydrogen dehydrogenase subunit 4 (ND4). Variations in one of the hypervariable regions in the D-Loop region (HV-1), specifically 16126T-->C (P =.05), 16224T-->C (P <.01), and 16311T-->C (P <.001), were significantly associated with the inferior encrypting file system in pediatric AML. [38]

Additionally, studies discovered a high correlation between mortality and deleterious heteroplasmic mitochondrial mutations [34].

More research should be done to investigate this matter, nevertheless, as some studies suggested that the effect of mtDNA copy number on outcomes in adult AML did not significantly correlate with survival [4].

Disrupted Mitochondrial Apoptosis Contributing to Leukemia

Mitochondrial apoptosis is essential for regulating cell death and survival, significantly influencing the progression of acute leukemia. Acute leukemia is a fast-progressing cancer that affects immature blood cells and is mainly classified into two types: ALL, more prevalent in children, and AML, primarily seen in adults. Both types involve complex genetic and epigenetic changes that result in uncontrolled cell growth and resistance to apoptosis [41,42,43].

In LL, malignant transformation typically occurs during various stages of lymphoid progenitor development, impacting either B- or T-cell lineages. In contrast, AML originates from myeloid progenitor cells, leading to an accumulation of immature myeloblasts in the bone marrow and peripheral blood, which disrupts normal blood cell formation and causes symptoms such as anemia, thrombocytopenia, and neutropenia [44,45].

The biology of acute leukemia involves mutations in genes that control the cell cycle, differentiation, and apoptosis, including **TP53**, **FLT3**, and **NPM1** in AML, as well as **NOTCH1** and **TEL-AML1** in ALL. These mutations lead to uncontrolled proliferation and contribute to the resistance of leukemia cells to programmed cell death [46,47]. For instance, TP53 mutations can impair mitochondrial permeability, crucial for apoptosis regulation, thereby allowing leukemic cells to survive even after damage [63].

Chromosomal translocations, such as the t(9;22) Philadelphia chromosome in ALL and t(15;17) in acute promyelocytic leukemia, are critical to the development of leukemia. Although advances in treatment have improved outcomes, adult AML still presents significant challenges, with lower long-term survival rates compared to pediatric ALL [48,49].

Mitochondria are crucial for the intrinsic pathway of apoptosis, which is vital for maintaining cellular balance. Apoptosis, or programmed cell death, is a tightly regulated process involving significant cellular changes including shrinkage and nuclear fragmentation. In acute leukemia, mitochondrial dysfunction results in altered energy production and unregulated cell death pathways, facilitating the survival of cancer cells [50,51].

In acute leukemia, mitochondrial disruptions can lead to several irregularities that promote disease progression, including:

Increased mt DNA Content: Higher levels of mitochondrial DNA are associated with increased metabolic activity in leukemic cells.

Reduced Mitophagy: Impaired removal of damaged mitochondria can result in the accumulation of dysfunctional organelles, enhancing cell survival.

Evasion of Apoptosis: Elevated levels of anti-apoptotic proteins prevent apoptosis, allowing leukemia cells to thrive [52,53].

The progression of acute leukemia depends on the interruption of mitochondrial apoptosis. High levels of anti-apoptotic proteins, such as Bcl-2 and Bcl-XL, inhibit mitochondrial outer membrane permeabilization (MOMP), preventing cytochrome c release and giving leukemia cells a survival advantage [54,55]. Anti-apoptotic protein overexpression enables these cells to resist apoptosis and continue proliferating [64,65].

Leukemic stem cells (LSCs) are a subpopulation of leukemia cells capable of self-renewal and sustaining leukemia clones. These cells exhibit resistance to standard therapies due to their quiescence and robust anti-apoptotic defenses. Mitochondrial pathways are crucial for LSC survival and maintenance, as they often show altered mitochondrial dynamics and metabolic functions that favor survival [66,67].

The production of ATP and the start of apoptosis depend on the mitochondrial membrane potential ($\Delta\psi m$). Particularly in leukemic cells, alterations in $\Delta\psi m$ can result in resistance to apoptosis. Increased $\Delta\psi m$ may raise the threshold for apoptotic signaling, making leukemia cells less prone to programmed cell death [58].

Leukemia cells often undergo metabolic reprogramming, shifting from oxidative phosphorylation to glycolysis, known as the Warburg effect. This shift reduces dependence on mitochondrial ATP production while still allowing leukemic cells to utilize functional mitochondria for essential metabolic processes and ROS regulation [59,60].

Fission, fusion, and mitophagy are examples of mitochondrial dynamics that are necessary to preserve mitochondrial function. In acute leukemia, evidence suggests that disrupted mitochondrial dynamics can lead to energy imbalances and difficulties in managing ROS levels. Proteins involved in these processes may be altered in leukemia cells, indicating potential therapeutic targets [61,62].

Targeting Mitochondrial Apoptosis in Therapy

Apoptotic priming measures a cell's sensitivity to apoptotic signals. When exposed to chemotherapy, myeloblasts in acute leukemia are more vulnerable to apoptotic priming than healthy hematopoietic stem cells. The link between drug response and apoptotic priming is stronger than the correlation with cell proliferation and pro-apoptotic protein expression [56,57]. This emphasizes the significance of mitochondrial pathways in determining treatment success.

The use of mitochondria-targeted treatments for acute leukemia is growing in significance. BH3 mimetics, particularly Venetoclax, have shown promise in restoring apoptotic mechanisms and overcoming resistance [72,73]. These therapies can be combined with traditional chemotherapy or novel agents to improve treatment efficacy and patient outcomes.

Numerous clinical trials have explored the efficacy of mitochondria-targeted therapies in acute leukemia, with significant findings from studies like the VIALE-A and VIALE-C trials. These trials have shown improved survival rates and remission outcomes when combining BH3 mimetics with standard treatments [74,75].

To enhance the effectiveness of mitochondria-targeted therapies, ongoing research focuses on developing dual inhibitors that target multiple anti-apoptotic proteins and optimizing existing Mcl-1 inhibitors. Additionally, expanding combinations with other targeted therapies and immunotherapies may help address various survival mechanisms in leukemia cells [76].

Drug resistance is a significant challenge in leukemia treatment. Resistance mechanisms often involve evasion of apoptosis through the intrinsic mitochondrial pathway. Leukemia cells achieve this by increasing anti-apoptotic protein levels, which block MOMP and cytochrome c release, thus preventing apoptosis [68,69].

Mitochondria play a central role in mediating drug resistance in leukemia. Functional changes, such as metabolic shifts and mitochondrial dynamics alterations, support cell survival during therapeutic stress. For example, a shift toward oxidative phosphorylation can enhance energy production and lower ROS levels, typically cytotoxic to cells [70,71].

Metabolic Shifts in Leukemia

One of the features of leukemia pathophysiology is its metabolic reprogramming, which is featured by a global restructuring of the process of biosynthesis and energy production in the cell. One of the most evident changes is the utilization of aerobic glycolysis, or Warburg effect, where leukemia cells prefer to metabolize glucose to lactate even in the presence of oxygen [77].

This reprogramming from oxidative phosphorylation (OXPHOS) to glycolysis is an intentional adaptation that bestows several advantages on cancer cells. Leukemia cells promote a continued uptake and quick metabolism of glucose by upregulating glucose transporters and glycolytic enzymes, typically controlled by oncogenes such as MYC and pathways such as PI3K/AKT.

Apart from being a quicker, albeit less efficient, source of ATP, this also provides important intermediates necessary for lipid synthesis, amino acid synthesis, and nucleotide synthesis, thereby supporting aggressive growth. Together with its oxygen and nutrient gradient, bone marrow's metabolic microenvironment also selectively promotes the growth of cells with high glycolytic flux, fueling the disease progression and the resistance to conventional treatments [78]. OXPHOS and mitochondria are still essential despite glycolysis predominance in certain leukemic subpopulations. Leukemia stem cells (LSCs) are shown to be more reliant on mitochondrial respiration compared to their differentiated counterparts and are believed to be responsible for initiation, maintenance, and relapse of the disease [79].

Apart from ATP generation, OXPHOS in these cells facilitates the generation of metabolites required for anabolic reactions and redox equilibrium. The metabolic plasticity of leukemia cells to both microenvironmental stressors and therapeutic insults is underscored by their dual dependency on glycolysis and OXPHOS. Importantly, reactive oxygen species (ROS), which can damage cellular constituents if uncontrolled, are associated with high mitochondrial activity. Therefore, leukemia cells acquire robust antioxidant mechanisms, including high glutathione levels and overexpression of antioxidant enzymes, to neutralize ROS and prevent oxidative damage, sustaining their capacity to survive under stress [80]. ROS play a dual role in leukemia biology.

As secondary messengers in a variety of carcinogenic processes, low levels of ROS are required for cell signaling, growth, and survival. Cell death can be caused by lipid peroxidation, protein oxidation, and DNA damage due to the over accumulation of ROS. Leukemia cells maintain their metabolism through the maintenance of ROS levels that favor proliferation over apoptosis. This is achieved by a fine balance between ROS production and antioxidant potential, which is primarily induced by mitochondrial OXPHOS. This equilibrium can tip towards cytotoxicity if this homeostasis is disrupted, either by overwhelming antioxidant mechanisms or by generating too much ROS. Because leukemia cells, especially those with elevated OXPHOS activity, can be induced to undergo apoptosis if ROS levels are selectively increased beyond a tolerance level that is acceptable, this trend has been of intense interest as a therapeutic target [81].

New therapeutic approaches to leukemia are based on the interplay between glycolysis, OXPHOS, and ROS control. Whereas mitochondrial inhibitors aim at OXPHOS-dependent leukemia stem cell survival, glycolytic inhibitors such as 2-deoxyglucose attempt to starve leukemia cells of glucose-derived energy and biosynthetic precursors. Therapies that modulate

ROS, either by increasing ROS production or by inhibiting antioxidant defenses, have also shown potential in preclinical models. For example, agents that inhibit thioredoxin reductase or deplete glutathione can sensitize leukemia cells to oxidative injury and cause cell death. However, since leukemia cells are metabolically flexible, inhibition of one pathway generally leads to compensatory mechanisms; inhibition of glycolysis can cause dependency on OXPHOS, and vice versa. In order to prevent resistance and kill both bulk tumor cells as well as normal stem cell populations, increasing attention is focused on combination therapies that simultaneously inhibit more than one metabolic pathway or combine metabolic inhibitors with traditional chemotherapeutics [82].

A second new direction of investigation involves tailoring therapy to the patient's own unique metabolic profile or leukemia subtype. Even in the same patient, metabolic phenotyping using the help of newer technologies such as metabolomics and single-cell RNA sequencing has revealed broad heterogeneity in the metabolic states of leukemia cells. Acute myeloid leukemia (AML) with IDH mutations is one such subtype that has different metabolic requirements that can be targeted. Furthermore, the stromal cells can secrete factors or provide metabolic substrates that affect leukemia metabolism and response to treatment, which adds yet another layer of complexity to the metabolic interaction between leukemia cells and the bone marrow microenvironment. Elucidating these interactions is key to the creation of long-term effective treatments.

Conclusion

The intricate relationship between mitochondrial dysfunction and leukemia highlights the essential role of mitochondrial genetics in the disease's pathogenesis and treatment. Mitochondrial DNA (mtDNA) mutations and changes in copy number are significantly linked to tumor development and the dynamics of clonal expansion, influencing how malignant cells respond to therapies, including those that may induce resistance [39, 40].

Moreover, disrupted mitochondrial apoptosis plays a critical role in acute leukemia, affecting cell survival and therapeutic outcomes. A deeper understanding of the mechanisms underlying mitochondrial dysfunction and the strategic targeting of these pathways presents a promising opportunity to enhance treatment efficacy for patients with acute leukemia. Continued research is vital to develop innovative therapies that can effectively address drug resistance and improve survival rates.

Elucidating the complexities of metabolic reprogramming in leukemia—including how oxidative phosphorylation (OXPHOS), reactive oxygen species (ROS), and glycolysis are altered—will be crucial for the rational design of future treatments. This knowledge could ultimately provide new hope for patients confronting this challenging disease.

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