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The Role of Mitochondrial Dysfunction in the Pathogenesis of Anemia

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ABSTRACT

Mitochondria play a pivotal role in erythropoiesis by regulating heme biosynthesis, iron-sulfur cluster formation, and cellular energy metabolism. Dysfunctional mitochondria contribute significantly to the pathogenesis of anemia, particularly in disorders such as sideroblastic anemia, myelodysplastic syndromes, and mitochondrial cytopathies. This review explores the mechanisms through which mitochondrial defects impair red blood cell (RBC) production and function, focusing on oxidative stress, defective iron metabolism, impaired ATP production, and apoptosis dysregulation. We also highlight potential therapeutic interventions, including antioxidants, mitochondrial-targeted therapies, and iron chelation strategies, which may alleviate anemia linked to mitochondrial dysfunction. Understanding these pathways may lead to novel treatment approaches for mitochondrial-related anemias.

Keywords: Mitochondrial dysfunction, anemia, erythropoiesis, oxidative stress, iron metabolism, mitochondrial cytopathies, therapeutic interventions.

INTRODUCTION

Anemia, a condition marked by a reduction in hemoglobin levels or red blood cell (RBC) count, remains a significant global health concern affecting millions of individuals across diverse populations[1–3]. Its etiology is multifaceted, encompassing nutritional deficiencies (such as iron, vitamin B12, and folate deficiencies), chronic inflammatory diseases, infections, and genetic disorders like sickle cell disease and thalassemia[4, 5]. While these well-established causes contribute to anemia's development, emerging evidence highlights the crucial role of mitochondrial dysfunction in its pathogenesis[5]. Mitochondria, often referred to as the powerhouse of the cell, are indispensable for erythropoiesis—the complex process of RBC production[6]. Their roles extend beyond ATP generation to include heme biosynthesis, iron-sulfur cluster assembly, and the regulation of oxidative stress, all of which are vital for maintaining erythrocyte integrity and function[7]. Dysfunctional mitochondria can disrupt these processes at various stages of RBC maturation, leading to impaired differentiation, ineffective erythropoiesis, and increased erythrocyte destruction[8]. Additionally, mitochondrial abnormalities contribute to conditions such as sideroblastic anemia, myelodysplastic syndromes, and anemia associated with mitochondrial myopathies, underscoring their significance in hematopoiesis [8]. Despite the growing recognition of mitochondrial involvement in anemia, the underlying molecular mechanisms remain incompletely understood[9]. Recent advances in bioenergetics, metabolomics, and transcriptomics have shed light on key pathways linking mitochondrial dysfunction to anemia, including disruptions in iron homeostasis, excessive reactive oxygen species (ROS) production, and defective mitophagy. Understanding these mechanisms is critical for identifying novel therapeutic targets[10]. This review aims to comprehensively explore the interplay between mitochondrial dysfunction and anemia, dissecting the molecular underpinnings that drive impaired erythropoiesis and RBC dysfunction. Furthermore, it will discuss potential therapeutic strategies, including pharmacological interventions, gene therapies, and mitochondrial-targeted therapies, that could mitigate mitochondrial dysfunction and improve anemia outcomes. By integrating current research findings, this review seeks to provide a foundation for future studies and clinical advancements in the management of anemia linked to mitochondrial defects.

Mitochondrial Functions in Erythropoiesis

Mitochondria are indispensable for erythropoiesis due to their crucial roles in cellular metabolism, energy production, and biochemical pathways that sustain red blood cell (RBC) development[11]. Despite the fact that

mature erythrocytes lack mitochondria, these organelles are essential during erythroid progenitor differentiation and maturation. Mitochondria are primarily involved in heme biosynthesis, iron-sulfur (Fe-S) cluster formation, ATP production, and the regulation of apoptosis, all of which are fundamental for efficient erythropoiesis[12].

Heme Biosynthesis: Heme is an iron-containing porphyrin that serves as the functional core of hemoglobin, the oxygen-carrying protein in RBCs. Heme biosynthesis occurs through a series of enzymatic reactions that are partially carried out within the mitochondria. The process involves[**13**]:

Initial Step in Mitochondria: The first and rate-limiting step of heme biosynthesis is catalyzed by the enzyme aminolevulinic acid synthase (ALAS), which combines glycine and succinyl-CoA (a tricarboxylic acid cycle intermediate) to form aminolevulinic acid (ALA). This reaction takes place inside the mitochondria and is tightly regulated by cellular iron levels and heme availability[14].

Cytosolic Processing and Re-entry to Mitochondria: ALA is then transported into the cytosol, where it undergoes several transformations to produce protoporphyrin IX. This molecule is then imported back into the mitochondria for the final step of heme biosynthesis[15].

Final Step in Mitochondria: Ferrochelatase, a mitochondrial enzyme, catalyzes the insertion of ferrous iron (Fe^{2+}) into protoporphyrin IX to form heme. This step is essential for generating functional hemoglobin and other heme-containing proteins necessary for erythroid maturation. Defects in mitochondrial heme biosynthesis can lead to disorders such as sideroblastic anemia, where erythroid precursors accumulate iron-laden mitochondria due to impaired heme synthesis.[15]

Iron-Sulfur Cluster FormationL Iron-sulfur (Fe-S) clusters are inorganic cofactors composed of iron and sulfur atoms that play a vital role in electron transport, enzymatic activity, and redox homeostasis. Mitochondria serve as the primary site for Fe-S cluster assembly, which is crucial for erythropoiesis in the following ways[**15**]:

Iron Homeostasis: Fe-S clusters regulate iron metabolism by modulating iron import, storage, and utilization within erythroid progenitors. The mitochondrial iron-sulfur cluster assembly (ISC) system facilitates the formation of these clusters, which are then transferred to recipient proteins within the cell[16].

Erythropoiesis-Related Enzymes: Several key enzymes involved in erythropoiesis require Fe-S clusters for their function. For example, ferrochelatase, which catalyzes the final step of heme biosynthesis, contains an Fe-S cluster essential for its enzymatic activity[17].

Regulation of Iron Transporters: Fe-S clusters are crucial for the function of iron regulatory proteins (IRPs), which control the expression of transferrin receptors and ferritin, ensuring a balanced supply of iron for heme synthesis. Deficiencies in Fe-S cluster assembly can lead to severe anemias and mitochondrial disorders, as improper Fe-S cluster function disrupts iron homeostasis and RBC development[18].

ATP Production: Erythropoiesis is a highly energy-demanding process that requires substantial ATP production to support cell proliferation, differentiation, and hemoglobin synthesis. Mitochondria fulfill this requirement through oxidative phosphorylation (OXPHOS), which generates ATP via the electron transport chain (ETC). The key aspects of mitochondrial ATP production during erythropoiesis include[**19**]

Oxidative Metabolism in Early Erythroid Progenitors: During the early stages of erythroid differentiation, erythroblasts rely on mitochondrial respiration to meet their energy demands. ATP generated from oxidative phosphorylation supports the biosynthetic activities necessary for cell growth and hemoglobin synthesis[20].

Transition to Glycolysis: As erythroid cells mature, mitochondria gradually become less active, and the cells shift toward glycolysis for ATP production. However, before this metabolic shift occurs, mitochondrial ATP production is critical for enabling efficient RBC formation[21].

Maintenance of Redox Balance: The mitochondrial electron transport chain also helps maintain cellular redox balance by regulating reactive oxygen species (ROS) levels. Proper ROS levels are necessary for signaling processes involved in erythroid differentiation, but excessive ROS can induce oxidative stress and damage erythroid precursors. Mitochondrial dysfunction leading to impaired ATP production can result in ineffective erythropoiesis and anemia[21].

Regulation of Apoptosis: Mitochondria play a central role in regulating apoptosis (programmed cell death) during erythropoiesis. This regulation is necessary for ensuring proper maturation of erythroid progenitors and preventing the accumulation of defective or excess cells. Key mechanisms include[**22**]

Mitochondrial-Dependent Apoptotic Pathway: The mitochondrial pathway of apoptosis is governed by members of the Bcl-2 protein family. Pro-apoptotic proteins (e.g., Bax, Bak) and anti-apoptotic proteins (e.g., Bcl-2, Bcl-xL) regulate mitochondrial membrane permeability and cytochrome c release, which ultimately activates caspases to trigger apoptosis.

Erythroblast Survival and Differentiation: During erythroid differentiation, mitochondrial-mediated apoptosis helps eliminate defective progenitor cells and ensures that only fully functional erythrocytes are released into circulation.

Erythropoietin (EPO) Signaling: Erythropoietin, a hormone that stimulates RBC production, exerts its effects partly by modulating mitochondrial apoptosis pathways. EPO prevents excessive apoptosis in erythroid

progenitors by upregulating anti-apoptotic proteins, thereby promoting RBC maturation. Dysregulation of mitochondrial apoptosis in erythropoiesis can lead to bone marrow failure syndromes and ineffective RBC production. Mitochondria are integral to erythropoiesis, despite being absent in mature RBCs. Their roles in heme biosynthesis, Fe-S cluster formation, ATP production, and apoptosis regulation are critical for erythroid progenitor survival, differentiation, and maturation. Any dysfunction in mitochondrial processes can lead to hematological disorders, including anemia and ineffective erythropoiesis. Future research into mitochondrial metabolism and biogenesis in erythropoiesis may provide new insights into treating anemia and other blood-related disorders.

Mitochondrial Dysfunction and Anemia Pathogenesis

Oxidative Stress and ROS Accumulation

Mitochondria are the primary source of reactive oxygen species (ROS) in cells, and their dysfunction can lead to excessive ROS production[23]. This oxidative stress plays a pivotal role in the pathology of various hematological disorders, particularly those affecting erythropoiesis. In normal physiological conditions, ROS serve as secondary messengers in various signaling pathways, including those regulating erythroid differentiation and maturation[24]. However, when mitochondrial dysfunction occurs, an overproduction of ROS ensues, overwhelming the cell's antioxidant defense mechanisms and causing oxidative stress. Elevated ROS levels have detrimental effects on erythroid precursors.[24] These effects include lipid peroxidation, protein oxidation, and DNA damage, all of which compromise the integrity and function of erythroid cells. Oxidative stress directly affects heme biosynthesis, a crucial process in erythropoiesis. Heme is a vital component of hemoglobin, and its production requires functional mitochondria. Excessive ROS interfere with heme synthesis by oxidizing key enzymatic components, thereby impairing their function. This disruption results in the accumulation of toxic intermediates, leading to ineffective erythropoiesis and contributing to the pathogenesis of anemia[25].

Additionally, increased oxidative stress promotes premature apoptosis of erythroid progenitors[26]. The accumulation of ROS activates various pro-apoptotic signaling pathways, including the intrinsic mitochondrial apoptotic pathway. Cytochrome c release from damaged mitochondria triggers caspase activation, leading to programmed cell death[26]. This heightened apoptosis rate reduces the population of viable erythroid precursors, further exacerbating anemia. Moreover, oxidative stress impacts erythrocyte lifespan. Mature red blood cells (RBCs) lack nuclei and mitochondria, relying on antioxidant systems such as superoxide dismutase (SOD), catalase, and glutathione peroxidase to neutralize ROS. However, oxidative damage can still occur, leading to membrane instability, increased rigidity, and hemolysis. Hemolysis further depletes the RBC pool, intensifying the severity of anemia[27]. The compounding effects of ROS accumulation, heme biosynthesis impairment, and apoptosis contribute to anemia's complexity and severity, particularly in mitochondrial disorders and hematological diseases such as sideroblastic anemias and myelodysplastic syndromes[27].

Defective Iron Metabolism

Iron metabolism is tightly regulated in erythropoiesis, as iron is a critical component of hemoglobin and other essential cellular processes[28]. Mitochondria play a central role in iron-sulfur (Fe-S) cluster biogenesis, which is crucial for various enzymatic functions, including those involved in heme synthesis. Mitochondrial dysfunction disrupts Fe-S cluster formation, leading to defects in iron homeostasis. One of the primary consequences of impaired mitochondrial iron metabolism is ineffective erythropoiesis[28]. In conditions such as sideroblastic anemia, defective Fe-S cluster assembly leads to iron mismanagement, resulting in the accumulation of iron within erythroid precursors. This iron overload manifests as mitochondrial iron deposition, which can be observed histologically as ring sideroblasts—erythroblasts containing iron-laden mitochondria. The presence of these ring sideroblasts is a hallmark of sideroblastic anemias and certain myelodysplastic syndromes.[29]

Iron accumulation within mitochondria further exacerbates oxidative stress. The Fenton reaction, in which iron catalyzes the conversion of hydrogen peroxide into highly reactive hydroxyl radicals, leads to increased ROS production[29]. This further damages mitochondrial components, creating a vicious cycle of oxidative damage, iron accumulation, and ineffective erythropoiesis. Additionally, iron overload can lead to systemic complications such as secondary hemochromatosis, in which excess iron deposits in vital organs, including the liver, heart, and pancreas, contributing to multi-organ dysfunction[30]. Furthermore, mitochondrial dysfunction affects the regulation of iron transport proteins, including mitoferrin, which is responsible for iron import into mitochondria for heme and Fe-S cluster synthesis. Dysfunctional mitoferrin impairs iron availability for heme production, further compromising erythropoiesis. This disruption in iron metabolism is not limited to hereditary sideroblastic anemias but is also observed in acquired conditions such as myelodysplastic syndromes and certain forms of anemia of chronic disease[30].

Therapeutic interventions targeting mitochondrial iron metabolism have shown promise in managing these disorders. Agents such as deferiprone and deferasirox, which chelate excess iron, are used to alleviate iron overload and reduce oxidative stress[31]. Additionally, mitochondrial-targeted antioxidants and Fe-S cluster

stabilizers are being explored as potential therapeutic strategies to restore iron homeostasis and improve erythropoiesis.

ATP Deficiency and Erythropoiesis Impairment

ATP production is crucial for cellular energy homeostasis, and mitochondria serve as the primary ATP generators through oxidative phosphorylation. Erythropoiesis, the process of RBC formation, is highly energy-dependent, requiring sufficient ATP for cell proliferation, differentiation, and maturation[32]. Mitochondrial dysfunction leads to ATP depletion, which disrupts these critical processes and contributes to hypoproliferative anemias. During erythropoiesis, erythroid progenitors undergo rapid proliferation and differentiation, processes that require significant energy input[32]. ATP is necessary for chromatin remodeling, transcriptional regulation, and cytokine signaling—all of which are crucial for erythropoiesis. Energy deficits caused by mitochondrial dysfunction lead to impaired cell cycle progression and reduced survival of erythroid progenitors, resulting in insufficient RBC production.[33]. Moreover, ATP is required for the activity of various enzymes involved in heme biosynthesis and iron metabolism. Energy depletion impairs these enzymatic functions, leading to defective hemoglobin synthesis and exacerbating anemia. Additionally, ATP is necessary for membrane maintenance and ion transport in developing RBCs. ATP deficiency compromises the stability and deformability of RBC membranes, increasing their susceptibility to hemolysis[34]. Mitochondrial ATP deficiency is implicated in several hematological disorders, including Pearson syndrome, a mitochondrial disease characterized by sideroblastic anemia and bone marrow failure. Similar ATP-related deficiencies are observed in other mitochondrial cytopathies, underscoring the importance of mitochondrial energy metabolism in erythropoiesis[34]. Potential therapeutic approaches to mitigate ATP deficiency in erythroid cells include metabolic support strategies such as coenzyme Q10 supplementation, which enhances mitochondrial function and ATP production[34]. Additionally, agents targeting mitochondrial biogenesis, such as peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) activators, are being investigated as potential therapies to restore energy balance in erythroid progenitors.

Dysregulated Apoptosis

Apoptosis, or programmed cell death, is a tightly regulated process that ensures the proper turnover of erythroid progenitors[35,36,37,38,39,40]. Mitochondria play a central role in apoptotic signaling, particularly through the intrinsic apoptotic pathway[41,42,43,44,45]. Dysregulated apoptosis due to mitochondrial dysfunction contributes significantly to anemia by reducing the pool of viable erythroid precursors. The intrinsic apoptotic pathway is primarily mediated by the balance between pro-apoptotic and anti-apoptotic proteins of the Bcl-2 family. Under normal conditions, erythroid progenitors maintain a balance that allows for appropriate differentiation and survival [46,47,48,49,50]. However, mitochondrial dysfunction skews this balance toward excessive apoptosis. Increased mitochondrial permeability leads to the release of cytochrome c into the cytoplasm, where it activates caspase-9 and the downstream caspase cascade, ultimately leading to cell death.
Excessive apoptosis of erythroid progenitors results in bone marrow failure and ineffective erythropoiesis, characteristic of conditions such as refractory anemia and certain subtypes of myelodysplastic syndromes. Moreover, mitochondrial-mediated apoptosis is implicated in the pathophysiology of anemia associated with chronic inflammation and infections, where inflammatory cytokines exacerbate mitochondrial dysfunction and apoptotic signaling. Therapeutic strategies aimed at modulating apoptosis in erythropoiesis include the use of apoptosis inhibitors such as Bcl-2 mimetics and caspase inhibitors. Additionally, erythropoiesis-stimulating agents (ESAs) like erythropoietin (EPO) can counteract apoptotic signaling by promoting erythroid progenitor survival. Understanding the interplay between mitochondrial dysfunction and apoptosis regulation is crucial for developing targeted interventions for anemia management [51].

Mitochondrial Dysfunction-Associated Anemia Disorders

Mitochondria are essential for erythropoiesis, responsible for heme biosynthesis, iron-sulfur cluster formation, and energy metabolism.[37] Dysfunctional mitochondria can lead to impaired red blood cell (RBC) production and survival, contributing to various forms of anemia. Several hematologic conditions are directly associated with mitochondrial dysfunction, including sideroblastic anemia, myelodysplastic syndromes (MDS), and mitochondrial cytopathies. Sideroblastic anemia is characterized by defective mitochondrial iron utilization, leading to iron accumulation within erythroblasts and the formation of ringed sideroblasts[37]. This disorder can be congenital or acquired, and can result from mutations in genes involved in mitochondrial heme biosynthesis and iron-sulfur cluster formation. Myelodysplastic syndromes (MDS) are clonal hematopoietic disorders characterized by ineffective hematopoiesis and a risk of transformation to acute myeloid leukemia (AML). Mitochondrial dysfunction is increasingly recognized as a key contributor to MDS-related anemias, primarily through mitochondrial DNA (mtDNA) mutations, abnormal iron metabolism dysregulation, altered heme biosynthesis, and bone marrow failure. Mitochondrial cytopathies are inherited disorders caused by mutations in nuclear or mitochondrial genes encoding components of the oxidative phosphorylation system. Anemia in these disorders arises due to impaired ATP production, increased RBC apoptosis, and bone marrow failure. Commonly associated mitochondrial disorders include Pearson Syndrome, Kerns-Sayre Syndrome, and

Leigh Syndrome. Treatment of mitochondrial cytopathies remains supportive, focusing on managing anemia with transfusions, iron chelation, and experimental therapies targeting mitochondrial function. Understanding these pathways may pave the way for novel mitochondrial-targeted therapies in hematological disorders. Overall, mitochondrial dysfunction significantly impacts erythropoiesis by impairing iron metabolism, heme biosynthesis, and energy production, leading to anemia.

Potential Therapeutic Strategies

Antioxidant Therapy: Oxidative stress is a key contributor to mitochondrial dysfunction in mitochondrial-related anemias. Excessive reactive oxygen species (ROS) production impairs erythroid progenitor cell function and disrupts normal red blood cell (RBC) homeostasis. Antioxidants such as **N-acetylcysteine (NAC)** act as precursors to glutathione, one of the body's primary intracellular antioxidants, helping to neutralize ROS and maintain mitochondrial integrity[**38**]. Similarly, **coenzyme Q10 (CoQ10)**, an essential component of the mitochondrial electron transport chain, supports ATP production and reduces oxidative stress[**39**]. Other promising antioxidants, such as **vitamin E, alpha-lipoic acid, and melatonin**, have shown potential in mitigating mitochondrial damage and improving erythropoiesis in preclinical studies.

Mitochondrial-Targeted Therapies: Several mitochondrial-directed strategies aim to restore normal RBC production by enhancing mitochondrial quality control mechanisms. Mitophagy inducers, such as urolithin[40]. A and spermidine, help clear dysfunctional mitochondria, preventing the accumulation of defective organelles that contribute to ineffective erythropoiesis. Additionally, mitochondrial biogenesis enhancers, including peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) agonists**,** promote the formation of new mitochondria, counteracting mitochondrial depletion seen in certain anemias. Pharmacological agents like bezafibrate and resveratrol have been explored for their role in enhancing mitochondrial function and improving RBC production.[40]

Iron Chelation Therapy: Mitochondrial iron homeostasis is critical for heme biosynthesis and erythropoiesis. In conditions such as sideroblastic anemia, iron overload in mitochondria leads to the formation of toxic ROS, exacerbating mitochondrial dysfunction. Iron chelators such as deferiprone and deferasirox help mobilize excess iron, reducing oxidative damage and improving RBC production[41]. Additionally, mitochondria-specific iron chelators like TAT-MTSc (mitochondria-targeted salicylaldehyde isonicotinoyl hydrazone derivatives) are being investigated for their ability to selectively remove iron from mitochondria while preserving systemic iron homeostasis**.**

Gene Therapy: Gene therapy offers a promising long-term approach for addressing mitochondrial-related anemias, particularly those caused by mitochondrial DNA (mtDNA) mutations. Advances in mitochondrial gene editing techniques, including TALENs (transcription activator-like effector nucleases), zinc-finger nucleases (ZFNs), and CRISPR-based approaches, aim to correct mtDNA mutations responsible for defective mitochondrial function[42]. Additionally, allotopic expression, a technique that allows nuclear DNA-encoded proteins to compensate for defective mitochondrial proteins, is under investigation as a therapeutic strategy. While challenges remain in delivering therapeutic genes specifically to mitochondria, emerging RNA-based therapies and mitochondrial transfer techniques offer potential avenues for long-term correction of mitochondrial dysfunction in anemic disorders[**42**].

CONCLUSION

Mitochondrial dysfunction is a significant yet underrecognized contributor to anemia pathogenesis. By elucidating the underlying mechanisms and exploring targeted therapies, we can advance treatment strategies for mitochondrial-related anemias. Further research into mitochondrial biology in erythropoiesis may pave the way for novel therapeutic interventions.

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