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REVIEW

The involvement of mitochondria in erythrocyte pathology and diseases: from mechanisms to therapeutic strategies

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Abstract

Erythrocytes, as the predominant cellular components within the bloodstream, are crucial for the maintenance of physiological health. Mitochondria, known as cellular powerhouses and metabolic regulators, play a critical role in the maturation of the erythroid lineage. The absence of mitochondria in red blood cells upon completing their maturation process is a defining characteristic of their development. Dysregulation of mitochondrial metabolism has been associated with the onset and progression of various diseases. Mitochondrial metabolic disorders, along with the involvement of mitochondria in the induction of oxidative stress and the activation of immune responses, significantly contribute to the pathogenesis of diverse hematologic disorders, particularly in sickle cell disease. This review offers a comprehensive overview of the role of mitochondria in disorders related to abnormal erythropoiesis, immune responses, and hemolysis, as well as evaluating potential therapeutic strategies that target mitochondria. Ultimately, we emphasize the necessity for future research to elucidate the involvement of mitochondria in red blood cell disorders, which may inform the development of novel diagnostic and therapeutic approaches.

Keywords Mitochondria · Red blood cell · Oxidative stress · Immune responses · Anemia

Introduction

Red blood cells (RBCs), recognized as the most prevalent cellular components within the bloodstream, are essential for the transport of oxygen and the removal of carbon dioxide. And their maturation is characterized by the selective loss of organelles, particularly mitochondria [1, 2]. Mitochondria serve essential and distinct functions during erythroid differentiation. Initially, they regulate hematopoietic stem cells by modulating energy metabolism and facilitating metabolic reprogramming, which aids the transition of early lineages from pluripotency to differentiation stages [3, 4]. In late-stage erythropoiesis, mitochondria are involved in iron metabolism, heme biosynthesis, and the maturation of reticulocytes [4, 5]. As erythroid maturation progresses, mitochondria undergo self-elimination through a process known as mitophagy, which is necessary for the production of fully mature RBCs [6, 7]. Mitophagy is a process that facilitates the degradation of mitochondria by encapsulating them within autophagosomes, which subsequently fuse with lysosomes [8]. While researchers have identified several proteins implicated in mitophagy during erythropoiesis, the complete mechanism remains to be fully elucidated.

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NIP3-like protein X (NIX) is recognized as a crucial regulatory protein for mitophagy during erythrocyte maturation, serving as a key mitochondrial protein that regulates the clearance of this organelle [6, 9, 10]. NIX is situated on the outer mitochondrial membrane (OMM), and its expression markedly increases during the terminal differentiation stage of erythrocytes [9]. ULK1 is identified as a critical regulatory factor for the clearance of both mitochondria and ribosomes during the final stages of erythrocyte maturation, with its expression level being directly correlated with the autophagic removal of these organelles during reticulocyte maturation [11]. Autophagy-related protein 7 (Atg7) also plays a significant role in regulating mitochondrial clearance in reticulocytes; the knockout of Atg7 results in anemia, a reduction in lymphocyte counts, and reticulocytosis in mice, accompanied by delayed mitochondrial depolarization and impaired clearance [12, 13]. Notably, in mouse models deficient in ULK1 and Atg7, mitochondrial clearance is only partially compromised, suggesting that additional pathways may be involved in this process [11, 12]. Furthermore, ubiquitin-dependent pathways contribute to erythrocyte maturation. In $\beta^{th3/+}$-thalassemic mice, the toxicity associated with excess α-globin is mitigated through ubiquitin-mediated proteolysis and autophagic processing within erythrocytes [14]. Additionally, the hypoxia-inducible factor (HIF)-mediated metabolic switch is responsible for activating the ubiquitin–proteasome system (UPS), which precedes the autophagic removal of mitochondria and is a prerequisite for this process. Deficiencies in this pathway result in the accumulation of RBCs containing mitochondria ($Mito^+$ RBC) in patients with systemic lupus erythematosus (SLE), and this accumulation is correlated with disease activity [15].

Mitochondrial dynamics are essential in the process of erythropoiesis. The fragmentation of mitochondria is necessary for this self-elimination process [16]. Research by González-Ibáñez et al. highlights that erythropoiesis, stimulated by erythropoietin, depends on a precise balance of these dynamics. Early stages are dominated by mitochondrial fusion, which supports the transition of progenitor cells into RBCs. In contrast, mitochondrial fission becomes prominent in later stages, inhibiting hemoglobin synthesis and disrupting RBC differentiation. Additionally, mitochondrial fusion and fission influence the mitochondrial permeability transition pore (mPTP), playing a critical role in metabolic reprogramming [16]. Consequently, any abnormalities in mitochondrial function or structure impair erythroid differentiation, potentially leading to anemia and other RBC disorders.

The retention of functional mitochondria in mature RBCs contributes to oxidative stress and immune activation, exacerbating the pathogenesis of various diseases [17]. Such retention can lead to anemia as well as complications like vascular obstruction, tissue damage, and immune dysfunction. Moreover, extracellular mitochondrial DNA (mtDNA) can bind to RBCs under specific pathological conditions, increasing RBC mortality and triggering inflammatory responses. The rapid advancements in cell biology and molecular medicine have heightened interest in the role of mitochondria within RBCs. Mitochondria play a crucial role in regulating numerous physiological processes in these cells, and their dysfunction is significantly linked to the onset and progression of various RBC disorders and diseases [17]. This review aims to examine the effects of mitochondrial dysfunction on the development of anemia, as well as the consequences of the retention of abnormal mitochondria in RBCs. Such retention may exacerbate pathological mechanisms and complicate therapeutic strategies by inducing inflammation and oxidative stress.

The role of mitochondria in anemia

Numerous research studies have indicated that targeting mitochondrial pathways may improve the management of certain anemic conditions. Mitochondrial oxidative phosphorylation (OXPHOS) is essential for the early differentiation of erythrocytes and the maturation of RBC [16, 18]. Inhibition of OXPHOS results in defects in the differentiation of erythroid progenitors, impairs ribosome biogenesis, and induces apoptosis, which are similar to the clinical manifestations observed in Diamond–Blackfan anemia (DBA) [18]. Analysis of bone marrow from DBA patients reveals significant inhibition of both the OXPHOS and ribosome biogenesis pathways, with approximately 10% of OXPHOS genes exhibiting frameshift and nonsense mutations. The OXPHOS activator CoQ10 has been shown to partially mitigate these defects and enhance the expression of the RanGAP1 protein [18]. Furthermore, the impaired enhancement of mitochondrial biogenesis during the early stages of erythropoiesis in DBA is a significant factor contributing to the pathology of the disease [19, 20]. Additionally, glutamine metabolism is upregulated during the early development of human RBCs, thereby enhancing OXPHOS through the production of α-ketoglutarate (αKG). Increased OXPHOS and reactive oxygen species (ROS) during the late stages of erythropoiesis hinder cell maturation and enucleation. The sustained production of late-stage RBCs is contingent upon reduced OXPHOS driven by αKG. The downregulation of isocitrate dehydrogenase 1 (IDH1) promotes the oxidation of αKG, leading to pathological erythrocyte differentiation, which can be mitigated by ROS scavengers such as vitamin C [16]. Mutations in IDH are prevalent in myeloid diseases, including acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) [21].

MDS are a heterogeneous group of clonal hematopoietic stem cell diseases, with anemia as the most common

symptom [22, 23]. Mitochondrial dysfunction plays a key role in the pathogenesis of anemia associated with MDS through early apoptosis and ineffective erythropoiesis, driven by impaired mitochondrial quality control and mtDNA mutations [24–26]. Congenital sideroblastic anemia (CSA) is a hereditary hematological disorder characterized by abnormalities in heme biosynthesis, defects in iron-sulfur (Fe-S) cluster biogenesis, or specific defects in mitochondrial protein synthesis associated with mitochondrial protein synthesis or OXPHOS [27, 28]. A review conducted by Ducamp et al. provides a comprehensive summary of the genes implicated in the various pathways that contribute to the pathogenesis of CSA; however, a significant number of CSA cases remain genetically unexplained [27]. Pseudouridylation in mitochondria is vital for erythrocyte production and is associated with mitochondrial myopathy, lactic acidosis, and sideroblastic anemia syndrome (MLASA) pathogenesis [29]. MLASA patient-derived inducible pluripotent stem cell line and mouse erythroblasts demonstrate compromised mitochondrial function and protein synthesis. Mechanistically, the deficiency of pseudouridine synthase 1 results in a loss of pseudouridylation, which in turn leads to decreased expression of mitochondrial tRNA and aberrant mitochondrial translation. Significantly, the mTOR inhibitor rapamycin effectively alleviates the anemia phenotype in these patients, suggesting a potential therapeutic option for related anemias [30]. During the terminal differentiation of erythrocytes in individuals with β-thalassemia, the disruption of mitophagy results in deficiencies in mitochondrial clearance and hinders the process of terminal erythropoiesis [31, 32].

In addition to hematological disorders, symptoms of anemia in a range of other diseases may be associated with mtDNA. For example, studies utilizing mouse models with mtDNA mutagenesis suggest that such mutations hinder mitochondrial removal during RBC development. This result leads to iron load, oxidative damage, alterations in membrane lipid structure, premature splenic capture, and a reduced lifespan of RBCs, ultimately contributing to the development of anemia [33]. This mechanism may be pertinent to mitochondrial diseases and anemia observed in the older adults [33]. In pathological conditions such as sepsis, pneumonia, and hematologic malignancies, research indicates that RBCs can interact with CpG-mtDNA through Toll-like receptor 9 (TLR9) present on their surface [34–36]. This interaction may facilitate the accelerated clearance of RBCs and activate the innate immune response, resulting in anemia and the secretion of pro-inflammatory cytokines [35, 36].

From the standpoint of mitochondrial research, the etiologies of anemia can be primarily categorized into two groups: disorders of erythropoiesis and excessive destruction of RBCs. Mitochondrial dysfunction is recognized as a significant pathological factor contributing to anemia in patients with various hematological disorders (Table 1). Genetic mutations and functional deficiencies in mitochondria are critical determinants influencing the differentiation and metabolism of RBCs. Moreover, advancements in mitochondrial research have the potential to introduce novel therapeutic strategies for anemia, which could diminish dependence on conventional blood products and enhance treatment efficacy as well as the quality of life for affected individuals. Presently, mitochondrial research predominantly resides within the preclinical experimental phase. Animal and cellular models offer substantial insights into specific hematological conditions, but their applicability is limited by the distinct pathological mechanisms of each disease.

Mitochondria induce immune regulation in RBCs

Despite the absence of mitochondria in healthy mature RBCs, recent studies have demonstrated the presence of mitochondria in the mature RBCs of patients with SCD, SLE, and Rett syndrome [37–40]. The retention of mitochondria could be caused by defects in mitophagy or the ubiquitin–proteasome system [37, 39, 41–43]. Individuals diagnosed with SCD and SLE exhibit an increased propensity for the generation of autoantibodies and are at a heightened risk of producing antibodies against RBC antigens following transfusion [44–46]. Mitochondria and their constituents may function as damage-associated molecular patterns (DAMPs), thereby initiating immune responses [47]. The role of mitochondria in RBC autoimmune and alloimmunization deserves further investigation.

Type I interferons (IFNs) enhance the allogeneic immune response of RBCs [48, 49]. Experiments have demonstrated that blocking IFN receptors can inhibit antibody formation, whereas injecting IFN-α stimulates its production [48, 49]. In nuclear-transfer derived embryonic stem cells, mismatched mitochondria can trigger adaptive immune responses, impair graft survival, and induce IFNγ responses [50]. In patients diagnosed with SCD, there is an observed higher frequencies mitochondrial components within reticulocytes and mature RBCs [39]. Mitochondria-containing RBCs induce robust expression of interferon-stimulated genes (ISGs) through cyclic GMP-AMP synthase (cGAS) activation. This process leads to the subsequent release of type I IFNs [38, 51, 52]. Furthermore, they stimulate innate immune cells to produce type I IFNs and various inflammatory mediators, which may contribute to the phenomenon of systemic inflammation [39, 53]. Type I IFNs gene signature is significantly upregulated in a range of autoimmune disorders [54–56]. This signature is associated with the production of autoantibodies and an increase in disease severity

Table 1 Targeted mitochondrial therapy for anemia in hematological disorders

Hematological disorders	Pathological mechanisms	Strategies to target mitochondrial pathway	References
DBA	The suppression of OXPHOS pathway	Activation of OXPHOS	[18]
	The translational efficiency of mitochondrial biogenesis factors is diminished, while mitochondrial turnover is enhanced through the process of mitophagy	Inhibition of NLK	[20]
CSA	The deficiency of heme biosynthesis, iron-sulfur cluster biogenesis, generalized mitochondrial protein synthesis, or the synthesis of specific mitochondrial proteins involved in oxidative phosphorylation	Treatment for specific gene mutations: ALAS2, HSPA9, HSCB, etc.	[27, 28]
β-thalassemia	The deficiency of mitophagy	Activation of the mTORC1-ULK1 pathway	[31]
SCD	The deficiency of mitophagy	Activation of mitophagy	[41, 43]
	The retention of mitochondria induces oxidative stress	Inhibition of LSD1, mTOR, and the clearance of mtROS	[41]
MDS	Mitophagy impairment, mtDNA mutation	The maintenance of Atg7 and mTOR	[25]
	Uncoupling abnormalities of CD71 shedding with mitochondrial clearance	the upregulation of IEX-1	[26]
hematologic malignancies	RBCs can interact with CpG-mtDNA via TLR9	mtDNA Clearance	[36]
myeloid diseases	IDH1 downregulation augments mitochondrial oxidation of αKG	mtROS Clearance	[16]
MLASA	The deficiency of pseudouridine in mt-tRNAs due to PUS1 mutation	Inhibition of mTOR	[30]

in patients diagnosed with SLE [57, 58]. The presence of functional mitochondria in mature RBCs may accelerate cell aging, increasing fragility and hemolysis [40, 59]. The rapid breakdown of sickle RBCs can result in the release of cell-free mitochondrial components into the plasma, potentially influencing immune responses and the progression of various diseases (Fig. 1) [60]. The association between mtDNA and autoimmune disorders has been found in other studies [61, 62]. In individuals diagnosed with SLE, platelet degranulation is associated with increased concentrations of the oxidized form of mtDNA (ox-mtDNA) in the bloodstream, which is highly immunogenic and may promote pathogenic type I interferon responses [63, 64]. mtDNA facilitates type I IFN responses through the activation of the cGAS-STING signaling pathway or by binding to TLR9, thereby initiating innate immune responses [65]. Although SLE does not rely on blood transfusion therapy, a strong IFNα/β signature may contribute to RBC alloimmunization following transfusion in lupus murine models and potentially increase the risk of RBC alloimmunization in patients with SLE [49, 52].

Inflammation is a known risk factor associated with heightened immune responses against RBCs [66]. Under physiological conditions, spleen macrophages primarily phagocytose aging or damaged RBCs without triggering immune responses, while other types of antigen-presenting cells (APCs) only consume RBCs in small amounts in the body [66, 67]. In a mouse model of HOD RBC transfusion, poly(I:C) induced inflammation can amplify a weak immune response into a strong one, significantly increasing RBC alloantibodies by promoting allogeneic T cell proliferation and modulating APC subtypes (CD8+ and CD11b+ dendritic cells) [67]. Patients with SCD and SLE have high circulating levels of pro-inflammatory cytokines and IFNs, which can affect the pattern of RBC consumption. Immunogenic APC subtypes may more effectively remove

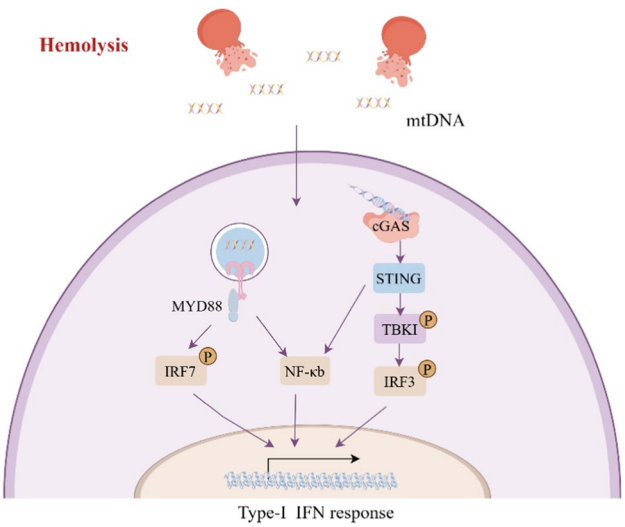

Fig. 1 During hemolysis, mtDNA released from ruptured RBCs that retain mitochondria has the capacity to stimulate innate immune cells to produce type I IFNs

aging RBCs, thereby initiating a humoral immune response that leads to the production of autoantibodies [39, 58, 68]. Further research is needed to identify the specific APC subtypes responsible for capturing Mito$^+$ RBCs. The increased frequency of reticulocytes in blood donors and the presence of mitochondria in recipient RBCs are key risk factors for alloimmune responses [39, 69]. In mouse models, mitochondrial proteins and metabolites rich in donor reticulocytes can trigger pro-inflammatory cytokines and enhance alloimmune responses independently of TLR-4. Splenic APCs clear RBCs, while splenic B cells preferentially consume reticulocytes [69]. Therefore, it is hypothesized that a potential method to mitigate adverse reactions associated with RBC transfusions is to lower reticulocyte counts in transfusion units. However, as significant levels of IFN-α and IFN-β were not detected in samples taken two hours after transfusion of units rich in reticulocytes in the mouse model, possibly due to sampling limitations or the immune response not being dependent on type I IFNs [39, 69].

In clinical studies, the presence of mitochondria in mature RBCs may augment the immune sensitivity of certain patient populations, making them suitable candidates for personalized transfusion strategies. The role of type I IFNs in RBC immune responses is well established. However, the complex role of type I interferon in modulating immune responses underscores the possible implications of diminishing its activity on other immune mechanisms [70]. The potential to prevent these reactions by downregulating type I IFNs expression or function lacks sufficient substantiation in current literature. Further empirical and clinical studies are required to validate this approach.

Mitochondrial in erythrocytes contributes to ROS-mediated hemolysis

Mature sickle Mito$^+$ RBCs demonstrate heightened oxidative stress and aging markers compared to healthy mature RBCs [40]. Sickle cell anemia (SCA) arises from mutations in the β-globin gene, which lead to the polymerization of hemoglobin S (HbS) and the subsequent formation of sickle-shaped cells under deoxygenated conditions [71]. The recurrent sickling process exacerbates the fragility of the RBC membrane, resulting in vaso-occlusive crisis and ischemia–reperfusion injury [72, 73]. As RBCs traverse venous capillaries, they encounter transient hypoxic conditions, during which mitochondrial metabolic activity in hypoxia generates ROS [74, 75]. The behavior of mature Mito$^+$ RBCs in SCD resembles that of reticulocytes, characterized by elevated fumarate levels within the cells [39]. Under hypoxia, ROS production may increase due to insufficient final electron acceptors, with fumarate serving as an alternative [76, 77]. The upregulation of NADPH oxidase catalytic subunits and the downregulation of superoxide dismutase 2 (SOD2) in SCD RBCs suggests the existence of oxidative environment that facilitates ROS production [78, 79]. Consequently, the abnormal accumulation of mitochondria in RBCs of individuals with SCD is correlated with increased ROS [40]. Elevated oxygen consumption has also been documented in reticulocytes and mature Mito$^+$ RBC in mouse models of SCD [59]. Changes in oxygen consumption may reduce the availability of oxygen in HbS, thereby facilitating HbS polymerization, promoting sickle cell formation, and perpetuating a detrimental cycle [40]. It is worth noting that there is ongoing debate regarding the functional status of mitochondria in the mature RBCs of SCD patients, with some studies positing that these mitochondria are nonfunctional [43]. Additionally, SCD RBCs exhibit a high level of oxidative stress due to other contributing factors [80]. Further investigation is warranted to elucidate the specific mechanisms and implications of mitochondrial ROS (mtROS) in SCA.

ROS can damage erythrocyte membranes, impairing fluidity and functionality, and promoting lysis [81]. The adhesion of abnormal RBCs to the vascular endothelium contributes to thrombin generation and thrombus formation, which accelerates hemolysis and enhances hypercoagulability. Oxidized RBCs facilitate thrombus formation, enlarge thrombus size, reduce permeability, and increase lysis susceptibility [81–83]. The connection between mitochondrial retention and hemolysis is gradually being established (Fig. 2). One study indicates that a higher proportion of mitochondria in mature RBCs from patients with SCA is associated with increased hemolytic activity, and these patients demonstrate

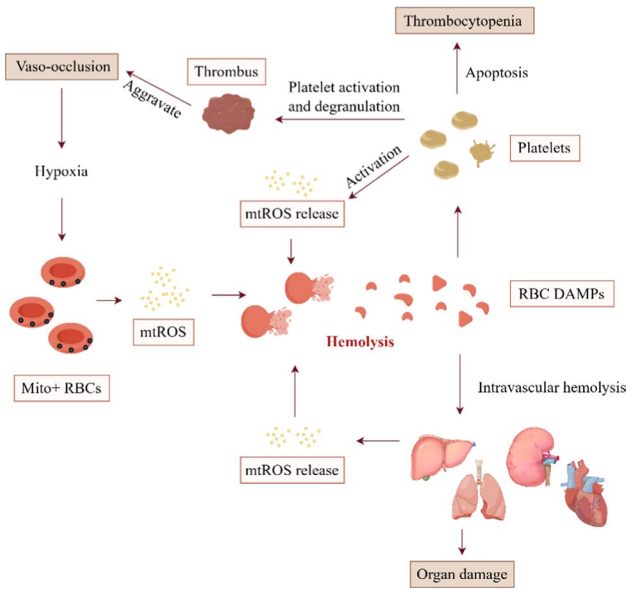

Fig. 2 The elevation of mtROS can initiate a cascade of oxidative stress, potentially exacerbating hemolysis in RBCs

elevated levels of reticulocytes and total bilirubin [40, 43]. Elevated rates of hemolysis may also disrupt erythropoiesis and the maturation of RBCs, leading to increased mitochondrial retention [40]. Under normal physiological conditions, 80–90% of RBCs are cleared via extravascular hemolysis without the release of hemoglobin, while the remainder are eliminated through intravascular hemolysis [84, 85]. Intravascular hemolysis can lead to disseminated intravascular coagulation, shock, hemoglobinuria, and acute kidney failure, conditions frequently observed in transfusion reactions, acquired hemolytic anemia, SCD, and beta-thalassemia [86, 87]. During intravascular hemolysis, hemoglobin is released into the plasma, where it oxidizes to form methemoglobin, which subsequently dissociates into heme and αβ dimers. Haptoglobin binds to all αβ-globin dimers to mitigate oxidation and pro-inflammatory effects [88, 89]. Additionally, hemopexin and albumin can help alleviate the detrimental effects of free hemoglobin [90]. Hemolysis results in the release of significant levels of DAMPs from RBCs, particularly heme, which can initiate inflammatory responses and inflict damage on blood vessels and adjacent tissues if not neutralized by innate protective mechanisms [86]. Heme and hemoglobin have the potential to disrupt mitochondrial function across various cell types, leading to damage to the respiratory chain and the generation of mtROS [91–93].

Mature RBCs that retain mitochondria demonstrate elevated intracellular calcium ion (Ca^{2+}) levels and increased externalized phosphatidylserine (PS) when compared to their counterparts that lack mitochondria [40]. The translocation of PS to the outer membrane serves as an early indicator of apoptosis [94]. Variations in Ca^{2+} concentration can significantly impact mitochondrial function, with calcium dysregulation potentially triggering both apoptosis and ferroptosis, as well as influencing mitochondrial dynamics [95–97]. While current research has primarily concentrated on the mechanisms underlying mitochondrial oxidative stress-related hemolysis in RBCs affected by SCD, further investigation is necessary to elucidate other mitochondrial pathways of cell death, including programmed cell death. Programmed cell death involves diverse pathways and mechanisms that may be closely linked to SCD pathophysiology. Future studies could investigate the roles of these pathways in SCD and assess their potential as therapeutic targets.

The review of mitochondrial retention in sickle RBCs is of paramount importance, as mitochondria produce ROS that can inflict damage on RBCs and expedite their removal from the circulatory system. By examining the oxidative stress present in RBCs affected by SCD, we can clarify the relationship between mitochondrial dysfunction, ROS production, and the progression of the disease. Current research primarily focuses on the potential role of platelet mitochondrial-targeted antioxidant therapy in relation to hemolysis and thrombosis associated with SCD (Fig. 2) [98, 99]. The efficacy of mtROS scavengers in preventing oxidative stress-induced hemolysis in mature RBCs that exhibit mitochondrial positivity, as well as their potential to alleviate hemolysis in patients, requires further validation. In conclusion, investigations into oxidative stress in SCD RBCs not only deepen our comprehension of SCD itself but also yield significant insights and prospective therapeutic approaches for other conditions characterized by mitochondrial retention in RBCs.

Conclusion

In conclusion, mitochondria play a crucial role in erythrocyte pathology and diseases. This review highlights the fundamental functions of mitochondria in the differentiation of RBCs and their significant contribution to the onset and advancement of various anemic disorders. Mitochondrial metabolic dysfunctions and responses to oxidative stress are critical factors that contribute to RBC impairment and increased rates of elimination. A comprehensive analysis of the existing literature suggests that mitochondrial-targeted therapeutic strategies, including the activation of the OXPHOS pathway, modulation of mitophagy, and inhibition of mtDNA release, have demonstrated considerable therapeutic efficacy in preclinical models. Furthermore, the role of mitochondria in RBC immune responses and the ROS-mediated hemolytic process provides novel insights and potential therapeutic targets for the management of hematological disorders, as well as new strategies to mitigate transfusion-related complications. Currently, most research concerning mitochondria remains in the preclinical stage. They face several limitations, including constraints on sample availability, potential biases in experimental design, and an incomplete understanding of mitochondrial functionality. Future investigations should clarify regulatory mechanisms of mitochondrial function and translate insights regarding mitochondria into effective clinical therapeutic strategies.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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