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Unraveling the roles and mechanisms of mitochondrial translation in normal and malignant hematopoiesis

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Abstract

Due to spatial and genomic independence, mitochondria possess a translational mechanism distinct from that of cytoplasmic translation. Several regulators participate in the modulation of mitochondrial translation. Mitochondrial translation is coordinated with cytoplasmic translation through stress responses. Importantly, the inhibition of mitochondrial translation leads to the inhibition of cytoplasmic translation and metabolic disruption. Therefore, defects in mitochondrial translation are closely related to the functions of hematopoietic cells and various immune cells. Finally, the inhibition of mitochondrial translation is a potential therapeutic target for treating multiple hematologic malignancies. Collectively, more in-depth insights into mitochondrial translation not only facilitate our understanding of its functions in hematopoiesis, but also provide a basis for the discovery of new treatments for hematological malignancies and the modulation of immune cell function.

Keywords Mitochondrial translation, Hematopoiesis, HSC, Immune cell, T cell, Hematologic malignancy

Background

Mitochondria have retained their genomes throughout evolution to synthesize 13 core components of oxidative phosphorylation complexes (Table 1). Through this process, mitochondria generate a protein translation system that differs distinctly from that in the cytoplasm. Previous studies of mitochondrial translation have focused mainly on genetic diseases caused by mitochondrial mutations [1], and mitochondrial translation has been applied as a common antibiotic target [2]. In addition, recent studies emerge that mitochondrial translation is extremely likely to play a central role in hematopoiesis.

Hematopoiesis is the process of blood cell formation that occurs primarily in the bone marrow, which involves the differentiation of hematopoietic stem cells (HSCs) into various types of blood cells, including erythrocytes, leukocytes, and platelets. Recent evidence increasingly highlights the importance of mitochondrial translation in normal hematopoiesis. For example, the disruption of mitochondrial translation results in the impaired erythroid differentiation of HSCs [3, 4]. Additionally, mitochondrial translation regulates the functions of various types of blood cells, especially lymphoid cells. Deficiencies in mitochondrial translation have been closely linked to impaired T-cell effector function, yet the precise

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Table 1 Mitochondria-encoded proteins and factors coordinating OXPHOS complex assembly

13 Mitochondria-encoded proteins	
NADH dehydrogenase	ND1, ND2, ND3, ND4, ND4L, ND5, ND6
Cytochrome reductase	Cytb
Cytochrome c oxidase	CO1, CO2, CO3
ATP synthase	ATP6, ATP8
Factors coordinating OXPHOS complex assembly	
Translation regulator	TACO1
OXPHOS assembly factor	C12ORF62, MITRAC12
miRNAs	miR-1, miR-499-5p, miR-101

mechanisms involved remain unclear [5–7]. Malignant hematopoiesis, which underlies multiple hematological malignancies and is characterized by the uncontrolled growth and accumulation of abnormal blood cells, is also regulated by mitochondrial translation. Inhibiting mitochondrial translation has shown potential for suppressing the progression of various hematologic diseases, making it a promising target for therapeutic intervention [8, 9]. However, the mechanisms by which mitochondrial translation regulates normal and malignant hematopoiesis remain largely unknown.

In this review, we summarize the process of human mitochondrial translation and delineate its upstream and downstream regulatory mechanisms. Importantly, we provide a comprehensive overview of the impacts of mitochondrial translation on normal and malignant hematopoiesis. Furthermore, this review outlines the current technical approaches for studying mitochondrial translation to provide a detailed understanding of the role of mitochondrial translation in future research.

Specific Translation Machinery in Mitochondria

Originating from proteobacteria, mitochondria have retained their own genomes and specific machinery required for mitochondrial protein synthesis [10]. In order to meet the requirements for synthesizing mitochondrial membrane proteins, the translation systems in mitochondria, including ribosomes and translation factors, is apart from translation systems in the cytoplasm. In this section, we will introduce the process of mitochondrial translation and discuss its differences from cytoplasmic translation. Additionally, in recent studies, many components in mitochondrial translation system have been found to affect hematopoiesis, which will be discussed in this section as well.

Mitochondrial ribosome structure

In all organisms, ribosomes consist of two distinct subunits: a small subunit (SSU), which binds to messenger RNAs (mRNAs), and a large subunit (LSU). In mammals, mitochondrial ribosomes exist as 55 S particles, each composed of a 39 S LSU and a 28 S SSU rather than the 80 S ribosomes found in the cytoplasm. A mitochondrial LSU is composed of 16 S RNA, a tRNA, and 52 mitochondrial ribosomal proteins (MRPs). A mitochondrial SSU consists of a 12 S RNA and 30 MRPs. All RNA components are encoded by mitochondrial DNA (mtDNA) [11]. Compared to cytoplasmic ribosomes, mitochondrial ribosomes have a more streamlined composition of proteins and RNAs. And many MRPs contribute to the functional specialization of mitochondrial ribosomes. For example, some MRPs form a specialized tunnel to insert nascent peptide chains into the inner mitochondrial membrane (IMM) [12]. Additionally, MRPs such as CRIF1 and MRPL45 also participate in this process [12, 13].

Notably, the expression of MRPs is altered in various tumor cells and has long been recognized as closely associated with tumorigenesis and metastasis [14]. In recent years, numerous MRPs have been found to impact both normal and malignant hematopoiesis. Firstly, some MRPs are identified as biological markers for hematologic malignancies. For example, MRPL22 forms a fusion gene with LARP1, and is recurrently expressed in B-cell non-Hodgkin lymphoma (B-NHL), where it is believed to have lymphomagenic functions [15]. MRPL38 has been found to be overexpressed in precursor T-cell lymphoblastic lymphoma/leukemia (pre-T LBL) and is identified as a marker for oncogenic pathways and prognosis [16]. Moreover, the expression of MRPL21 and MRPS37 is elevated in acute myeloid leukemia (AML) cells with first relapse, and these proteins are considered markers of relapsed AML cells [17]. Secondly, some MRPs are considered potential therapeutic targets. For instance, MRPL15 is believed to be a target of the tumor-suppressing microRNA, miR-26b-5p, and its deletion can inhibit the proliferation of Burkitt lymphoma [18]. Thirdly, certain MRPs have prognostic value. For example, elevated expression of MRPL33 indicates poor prognosis in AML [19], while high levels of MRPS31 suggest a favorable prognosis in multiple myeloma (MM) [20]. Lastly, some MRPs play roles in normal hematopoietic cells. MRPL3, MRPL13, and MRPL47 have been found to promote macrophage polarization towards the M2 phenotype [21].

Among these MRPs, CR6-interacting factor 1 (CRIF1), a component of the mitochondrial LSU, shows diverse functions in hematopoiesis. As a tumor suppressor, CRIF1 induces cell cycle arrest in leukemia cells by inhibiting CDK2, while its deletion enhances the survival of leukemic T cells [22, 23]. Additionally, CRIF1 can be inhibited by lymphocyte-specific protein tyrosine kinase (Lck), a key factor in leukemia development, thus further promoting leukemic cell survival [23]. Recent studies have also demonstrated involvement of CRIF1 in lymphocyte functional modulation. CRIF1-deficient $CD4^+$ T cells show increased interleukin-17 (IL-17) production

and reduced regulatory T cell differentiation [24]. In another study, the deletion of CRIF1 was shown to cause mitochondrial dysfunction and upregulate glutaminolysis, leading to the generation of inflammatory non-suppressive regulatory T cells characterized by diminished suppressive capacity [25]. CRIF1-deficient B cells were found to enhance IL-17 and IL-6 production and more effectively promote the development of follicular helper T cells [26]. Furthermore, the deletion of CRIF1 promotes the polarization of macrophages towards the M1 phenotype [27].

Assembly of mitochondrial ribosomes

All mitochondrial ribosomal RNAs are encoded by mtDNA, whereas the proteins that compose the mitochondrial ribosome are encoded by nuclear DNA. These components, originating from different cellular compartments, are assembled into mitochondrial ribosomes through the actions of various biogenesis factors, including nucleases, RNA-modifying enzymes, DEAD-box helicases, GTPases, and other associated proteins [28]. Several mitochondrial ribosome assembly factors have been found to play a role in immune cells and malignant hematopoiesis. C1qbp, a factor that binds unassembled LSU proteins and facilitates their incorporation into the ribosome, promotes the differentiation of effector $CD8^+$ T cells via epigenetic pathways [29]. Additionally, NSUN4, an SSU assembly factor, is considered a biomarker for pediatric acute lymphoblastic leukemia (ALL) [30].

Notably, the import of mitochondrial ribosomal proteins into the mitochondrial matrix occurs in excess rather than in stoichiometric amounts matching those of the ribosomal RNAs (rRNAs). Overexpression of mitochondrial ribosomal proteins provides ample materials for mitochondrial ribosome assembly. However, the accessibility of the proper proteins from the large MRP pool may increase the time of mitochondrial ribosome biogenesis; this process lasts 2–3 h in total [31]. MRPs that are not involved in the assembly are degraded, which is essential to avoid excessive MRP accumulation [31]. However, whether specific degradation mechanisms are involved remains to be explored.

The mitochondrial translation cycle

Mitochondrial protein synthesis is performed by 55 S ribosomes with the help of many specific translation factors. Translation comprises four major steps: initiation, elongation, termination, and ribosome recycling (Fig. 1). In this section, we provide a comprehensive introduction to the translation factors required for protein synthesis in mitochondria and summarize the processes of each phase of mitochondrial translation.

Initiation

During the initiation phase of translation, mRNAs bind to the SSU, and initiation codons are recognized by initial transfer RNAs (tRNAs), thereby initiating the translation cycle. Notably, mammalian mitochondrial mRNAs are leaderless. They lack 5' UTRs, and most lack 3' UTRs [32]. In mitochondrial translation, the initiation tRNAs differ from their cytoplasmic counterparts in that they usually carry a formylated methionine (fMet-$tRNA^{Met}$) instead of an unmodified amino acid methionine (Met-$tRNA^{Met}$) [33]. Generally, mitochondrial open reading frames start with an AUG codon, which can also be an AUA or an AUU in humans [34]. In mammals, a single type of mitochondrial $tRNA^{Met}$ is used to initiate all these codons, and this versatility is achieved by modifying the wobble base to a formyl cytosine [35–37].

In the cytoplasm, translation initiation is facilitated by numerous translation factors, such as eIF1, eIF2, and eIF3, whereas mitochondrial translation relies on only two factors: mtIF2 and mtIF3. mtIF2, through a specific domain insertion, compensates for the absence of eIF1 and prevents tRNA from binding to the ribosomal A site, thus ensuring proper initiation [38–40]. The precise role of mtIF3 in translation initiation is still not fully understood. mtIF3 can either promote or inhibit the binding of the initiating tRNA, depending on the presence or absence of the mRNA, respectively [41–44]. Researchers have hypothesized that mtIF3 coordinates the initiation process by first facilitating the binding of mRNA to the SSU, as confirmed by cryo-electron microscopy results [45]. Notably, deletion of mtIF3 in megakaryocytes leads to increased megakaryocyte polyploidy, elevated circulating reticulated platelets and thrombocytopenia, indicating mtIF3 plays a role in the maturity of megakaryocytes [46].

Elongation

The elongation phase of translation consists of three steps: selection of an aminoacyl-tRNA corresponding to the mRNA codon, peptide bond formation, and translocation of the mRNA–tRNA complex. This program is conserved across all ribosomes. The selection and delivery of the corresponding tRNA are achieved by two elongation factors named mtEFTu and mtEFTs. Aminoacyl-tRNA is transported to the elongation complex by mtEFTu through GTP hydrolysis within the mitochondria. Once transported, mtEFTs, a guanine binding factor, binds mtEFTu with GTP to transport the next aminoacyl-tRNA [47–50].

As the nascent peptide chain extends during the elongation process, the ribosome must translocate the mRNA and tRNA to decode the next codon. This process is conducted by mtEFG1, a GTPase in mitochondria [51–53]. mtEF4 (also known as GUF1) functions in the

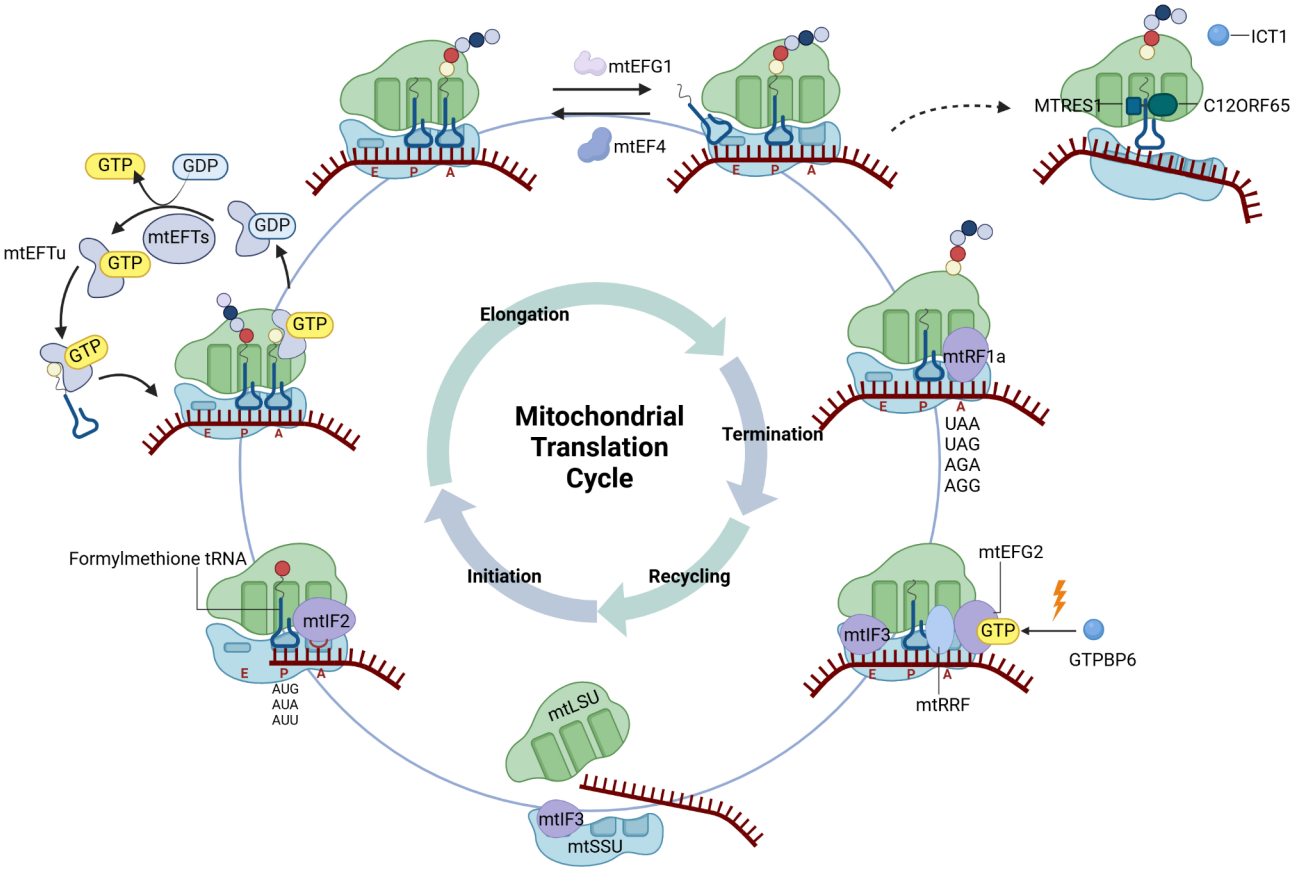

Fig. 1 The human mitochondrial translation cycle

Protein synthesis consists of four distinct steps: initiation, elongation, termination, and recycling. Mitochondria employ a simplified set of translation factors to perform the translation process. During initiation, mtIF2 and mtIF3 play crucial roles. mtIF2 prevents tRNA binding to the ribosomal A site through a specific structural domain, while mtIF3 is speculated to coordinate the initiation process by ensuring that mRNA first binds to mtSSU. In the elongation phase, mtEFTu facilitates the delivery of aminoacylated tRNA to the ribosome by hydrolyzing GTP. After delivery, mtEFTu replenishes GTP and binds to the next aminoacylated tRNA under the influence of mtEFTs. During elongation, mtEFG1 catalyzes mRNA–tRNA translocation by hydrolyzing GTP. Furthermore, mtEF4 enables reverse mRNA–tRNA translocation by hydrolyzing GTP, which allows for error correction during protein synthesis. When translation errors occur, C12ORF65 and MTRES1 work in concert to rescue stalled ribosomes by releasing nascent chains and tRNAs. ICT1 is likely involved in the process of releasing the nascent peptide chain. The termination of the translation process is dominated by mtRF1a, which reads the stop codon and possesses peptidyl tRNA hydrolase (PTH) activity. Following the release of the nascent peptide chain, the mitochondrial ribosome recycling factors mtRRF2 and mtEFG2 collaborate to dissociate ribosomal subunits for subsequent translation. Under stress conditions, GTPBP6 provides an additional pathway for ribosomal subunit dissociation

back-transport of posttranslocational ribosomes [54]. It can recognize defective ribosomes involved in the translocation process and induce their reverse translocation toward the 5' end of the mRNA, which is known as backward translocation. This action provides a second opportunity to facilitate proper tRNA translocation. It is worth noting that the expression of mtEF4 is increased in various tumor cells, and further research indicates that the overexpression of mtEF4 may promote tumorigenesis by facilitating the formation of respiratory chain complexes [55]. This suggests that mtEF4 has the potential to serve as a therapeutic target for cancer treatment.

Termination

When the ribosome reaches the end of an open reading frame, translation is terminated by the binding of the ribosome release factor to the stop codon. This binding triggers the hydrolysis of the ester bond between the tRNA at the P site and the nascent peptide chain. In cytoplasmic systems, stop codons typically include UAA, UAG, and UGA. Among them, UAA and UAG are still conserved and used in mitochondria. However, in mitochondrial translation, the stop codons exhibit notable differences from those in cytoplasmic translation. For example, in human mitochondria, UGA encodes tryptophan instead of a stop codon [56]. Additionally, two mitochondrial mRNAs encoding CO1 and ND6 include

the stop codons AGA and AGG, respectively, which normally encode arginine in the cytoplasm [57].

Four translation termination factors have been identified and characterized in mitochondria: mtRF1, mtRF1a, ICT1, and C12ORF65. mtRF1a recognizes UAG and UAA stop codons while also possessing peptidyl-tRNA hydrolase (PTH) activity, which is thought to carry the most tasks of termination [58, 59]. In particular, the translation termination of CO1 and ND6 is accomplished by mtRF1 [60]. As a component of the LSU [12], ICT1 lacks PTH activity when it is integrated into ribosomes. However, when it exists as a soluble form outside the ribosome, ICT1 can exhibit PTH activity to release the nascent peptide and rescue stalled ribosomes [61]. Moreover, ICT1 also participates in atypical stop codon (AGG and AGA) termination [61]. It is also found that ICT1 is related to various hematological malignancies. Its deletion leads to cell cycle arrest and apoptosis in leukemia cells, while its overexpression promotes the proliferation of diffuse large B-cell lymphoma (DLBCL) [62, 63]. C12ORF65 plays a role in rescuing stalled ribosomes within mitochondria, working in cooperation with the RNA-binding protein (RBP) MTRES1 to release the nascent peptide chain and tRNA from stalled ribosomes [64, 65].

Table 2 Differences between cytoplasmic and mitochondrial translation

		Cytoplasmic Translation	Mitochondrial Translation
Product		Multiple proteins operate in both the mitochondria and other compartments	13 components of the electron transport chain (ETC)
Ribosome Composition		80 S, consists of a 60 S LSU, a 40 S SSU and 4 rRNAs	55 S, consists of a 39 S LSU, a 28 S SSU and 3 rRNAs
rRNA Modification		More than 200 are known	Only 10 are known
Translation Factors	Initiation Factors	eIF1, eIF1A, eIF2, eIF2B, eIF3, eIF4A, eIF4B, eIF4E, eIF4F, eIF4G, eIF4H, Eif5, eIF5B,	mtIF2, mtIF3
	Elongation Factors	eEF1A, eEF2, eIF5A, eEF3	mtEFTu, mtEFTs, mtEFG1, mtEF4
	Termination	eRF1, eRF3	mtRFIa, mtRF1, ICT1, C12ORF65
	Recycling	ABCE1, eIF2D	mtRRF2, mtEFG2, GTPBP6
Initiation tRNA		Met-tRNA^{Met}	fMet-tRNA^{Met}
mRNA		Lower than mitochondrial mRNAs in yield, abundance, and degradation rate	All lack a 5′ UTR, and most lack a 3′ UTR
Stop Codons		UAA, UAG, UGA	UAA, UAG, AGA, AGG

Ribosome recycling

After the nascent peptide chain is released from the mitochondrial ribosome, the ribosomal subunit undergoes splitting for subsequent translation. This splitting is achieved through the synergistic action of the mitochondrial ribosomal recycling factors mtRRF and mtEFG2 [66]. Once the nascent chain is released, mtRRF binds to the vacant A site of the ribosome and recruits mtEFG2 [67]. However, the mechanism by which mtEFG2 separates ribosomal subunits is not fully understood. GTP-binding protein 6 (GTPBP6) can also facilitate ribosomal subunit splitting, particularly under stress conditions [68, 69]. Furthermore, mtIF3 has been suggested to actively split ribosomal subunits [70].

In summary, notable differences in mitochondrial translation have been observed compared with translation in the cytoplasm. The detailed content has been discussed earlier and summarized in Table 2. (1) First, mitochondrial ribosomes exhibit lower sedimentation rates and simplified protein compositions than cytoplasmic ribosomes. (2) Mitochondria rely on a simplified set of translation factors to perform the translation process. According to recent studies, 8–10 translation factors are sufficient to drive mitochondrial translation, whereas cytoplasmic ribosomes require at least 25 translation factors, some of which are complex multiprotein assemblies [71]. (3) In addition, differences have been identified between mitochondria and the cytoplasm in terms of details such as the initiation of tRNAs and stop codons, which have been described previously. In addition, many MRPs and other components of the mitochondrial translation system have been found to play a role in both normal and malignant hematopoiesis. We have presented these components and their specific functions in Table 3.

Regulatory mechanisms and functions of mitochondrial translation

Mitochondrial translation, a crucial biosynthetic process, plays diverse roles within cells. In existing researches, mitochondrial translation is regulated by a series of upstream regulators and exerts downstream effects on the regulation of cytoplasmic translation and cellular metabolism. Additionally, mitochondrial translation interacts with cytoplasmic translation through various stress responses. In this section, we discuss the specific upstream and downstream functions of mitochondrial translation.

Upstream regulators of mitochondrial translation

Multiple upstream factors regulate mitochondrial translation. The abundances of functional mRNAs, which are essential substrates for translation, significantly impact mitochondrial translation. Furthermore, nuclear-encoded protein factors also play a regulatory role in

Table 3 Components of mitochondrial translation system associated with hematopoiesis

Classification	Component	Impact	Reference
Mitochondrial ribosomal proteins	MRPL3	Promotes macrophage polarization to M2 subtype	[21]
	MRPL13	Promotes macrophage polarization to M2 subtype	[21]
	MRPL15	Loss affects survival of Burkitt lymphoma	[18]
	MRPL21	Expression increases in first relapse of AML	[17]
	MRPL22	Forms fusion gene with LARP1, recurrently expressed in B-NHL	[15]
	MRPL33	Associated with receptor tyrosine kinase expression in AML, with prognostic value	[19]
	MRPL38	Indicator for oncogenic pathways and prognostic marker in pre-T LBL	[16]
	MRPL47	Promotes macrophage polarization to M2 subtype	[21]
	CRIF1	Its deficiency promotes the generation of inflammatory non-suppressive regulatory T cells via increased glutaminolysis	[25]
		CRIF1-deficient B cells show increased IL-17 and IL-6 production and promote the development of follicular helper T cells	[26]
		CRIF1-deficient CD4 + T cells exhibit increased IL-17 production and reduced regulatory T cell differentiation	[24]
		Interacts with CDK2 to induce cell cycle arrest in AML cells	[22]
		Binds to and is inhibited by Lck, promoting human leukemia T-cell survival	[23]
		Its loss induces macrophage M1 polarization	[27]
	MRPS31	Potential marker for good prognosis in MM	[20]
	MRPS37	Expression increases in first relapse of AML	[17]
Assembly factors of mitochondrial ribosome	C1qbp	Promotes differentiation of effector CD8 + T cells through epigenetic pathways	[29]
	NSUN4	NSUN4 variants increase the risk of pediatric ALL, potential biomarker	[30]
Mitochondrial translation factors	mtIF3	Loss leads to increased megakaryocyte polyploidy and elevated circulating reticulated platelets and thrombocytopenia	[46]
	ICT1	Its deficiency promotes leukemia cell proliferation, S-phase arrest, and apoptosis	[62]
		Promotes DLBCL proliferation, potential marker for poor prognosis in DLBCL	[63]
Mitochondrial mRNA binding proteins	FASTK	Its deletion decreases leukemia cell activity and diminishes leukemogenic potential	[83]
	FASTKD1	Indicator of poor prognosis in ALL	[86]
	FASTKD1	RNA-binding protein biomarker of B cells for MM prognosis	[85]
	FASTKD5	Binds to NLRX1 to promote mitochondrial respiratory complex component expression in CD4 + T cells	[87]
	GRSF1	Involved in erythrocyte differentiation and proliferation	[89]

AML: Acute Myeloid Leukemia; ALL: Acute Lymphoblastic Leukemia; B-NHL: B-cell Non-Hodgkin Lymphoma; DLBCL: Diffuse Large B-cell Lymphoma; pre-T LBL: Precursor T-cell Lymphoblastic Lymphoma; MM: Multiple Myeloma; RBP: RNA-binding Protein; IL: Interleukin; CDK: Cyclin-dependent Kinase; Lck: Lymphocyte-specific Protein Tyrosine Kinase; NLRX1: NLR Family Member X1

mitochondrial translation. These factors ensure the seamless assembly of oxidative phosphorylation (OXPHOS) subunits by matching the mitochondria-encoded OXPHOS components with their nuclear-encoded counterparts. The precise functions of these upstream regulators will be elucidated in subsequent sections. Notably, some microRNAs (miRNAs) also regulate mitochondrial OXPHOS gene expression. For example, miR-1, miR-499-5p, and miR-101 have been shown to increase the synthesis of various mitochondria-encoded proteins, including CYTB, COX3, ATP8, ND4L, and ND1 [72].

The mRNA supplies regulate mitochondrial translation

Mitochondrial mRNA is encoded within polycistronic precursors transcribed from mtDNA. By cleaving tRNAs dispersed between mRNAs and rRNAs in precursors, 11 types of functional mRNAs are released [73, 74]. Theoretically, all mitochondrial mRNAs originate from the same precursor, and the quantities of different mRNAs should be roughly the same. However, the abundances of different mRNAs are disparate [75, 76]. The differences in mitochondrial mRNA abundances are attributed to the degradation function of the degradosome (also known as mtEXO) [77, 78]. The mitochondrial degradosome interacts with different RBPs to regulate the abundances of the corresponding mRNA types. These RBPs include the leucine-rich PPR motif-containing protein–SRA stem loop-interacting RNA-binding protein (LRPPRC-SLIRP) complex, members of the metazoan-specific Fas-activated serine/threonine kinase (FASTK) family of RBPs and G-rich sequence factor 1 (GRSF1). All of these genes are encoded by nuclear DNA.

The LRPPRC-SLIRP complex is an mRNA-binding protein complex that binds to mRNA coding sequences to prevent the formation of RNA secondary structures [79]. Research has demonstrated that this complex

inhibits mRNA degradation by the degradosome, thereby increasing mRNA stability [77, 80]. The FASTK protein family, comprising six members (FASTK and FASTKD1-FASTKD5), binds to different mitochondrial mRNAs and influences the expression of corresponding proteins [81]. Moreover, this family influences the hematopoietic system. FASTK expression protects ND6 mRNA from degradation by the degradosome [82], while its knockout decreases leukemia cell activity and diminishes leukemogenic potential [83]. FASTKD1 expression reduces ND3 mRNA stability [84] and is considered a prognostic factor for multiple myeloma (MM) and ALL [85, 86]. Moreover, FASTKD5 can promote the expression of respiratory chain complexes in $CD4^+$ T cells by interacting with NLRX1 [87]. Another RBP that impacts mitochondrial mRNA degradation is GRSF1. Knockdown of GRSF1 expression leads to decreased abundances of most mitochondrial mRNAs and a widespread impairment of translation [88]. Additionally, GRSF1 is linked to erythrocyte differentiation and proliferation, with its inhibition suppressing erythrocyte proliferation [89].

Factors that coordinate OXPHOS-related gene expression to regulate mitochondrial translation

In OXPHOS complex assembly, nuclear-encoded subunits are imported into the mitochondria and assembled with their corresponding mitochondria-encoded counterparts. In human mitochondria, an excess import of nuclear-encoded subunits seems to occur, suggesting that mitochondrial translation is a rate-limiting step in OXPHOS complex assembly [90]. Compared with nuclear mRNAs, mt-mRNAs are 1,100-fold greater in yield, have a 7-fold faster degradation rate, and are 160-fold greater in abundance [91]. Although mitochondrial mRNAs have faster degradation rates, they are not sufficient to maintain homeostasis between the mitochondrial and nuclear transcriptomes. A slow mitochondrial translation rate is thought to be the main reason for the balance of OXPHOS synthesis. According to previous studies, the mitochondrial translation rate needs to be more than 100 times slower than the cytoplasmic translation rate [91]. Therefore, matching mitochondrial translation with cytoplasmic translation is crucial. Multiple factors contribute to the coordination of mitochondrial and nuclear OXPHOS-related gene expression (Table 1). The mechanisms of action of these potential coordinating factors are listed below.

In yeast, the translation of each mitochondrial transcript is regulated by specific nuclear-encoded translation regulators, which are also called translation regulators [92]. These translation regulators, along with cytoplasmic translation products, are simultaneously imported into mitochondria. They monitor the efficiency of OXPHOS complex assembly and use this information to regulate the translation efficiency of mitochondrial ribosomes, ensuring that the synthesis of mitochondria adapts to cytoplasmic translation [92]. For example, the translation of cytochrome oxidase subunits in yeast is regulated by a series of translation regulators, including Pet309, Mss51, and Pet111 [92]. Currently, the only known human translation regulator is TACO1 (a translation activator of CO1), which binds to mitochondrial ribosomes and interacts with multiple sites in the CO1 mRNA. Mutations in TACO1 lead to specific CO1 synthesis defects and late-onset Leigh syndrome [93, 94].

Although mitochondria lack translational regulators, they achieve the coordination of mitochondrial and cytoplasmic translation through a series of assembly factors [95, 96]. These assembly factors directly modulate mitochondrial translation efficiency by sensing the availability of nuclear-encoded OXPHOS subunits [95–98]. Several assembly factors have been identified in mammalian mitochondria. In humans, the assembly of CO1 requires the early mitochondrial OXPHOS system assembly factors C12ORF62 (also known as cytochrome c oxidase assembly protein COX14) and MITRAC12 (mitochondrial translation regulation assembly intermediate of cytochrome c oxidase 12; also known as cytochrome c oxidase assembly factor 3 homolog). C12ORF62, an upstream factor of MITRAC, binds to the nascent CO1 peptide chain and recruits MITRAC12 for assembly in the presence of the nuclear-encoded complex IV CO4 subunit. The translation of CO1 is blocked when the CO4 subunit is not expressed [95]. When CO4 is available, CO1 translation then resumes.

Functions of mitochondrial translation

Recent research has shown that mitochondrial translation is essential for maintaining cellular hemostasis. A disruption of mitochondrial translation usually leads to cellular dysfunction. Mitochondrial translation affects cellular function through two major downstream effects: cytoplasmic translation and cellular metabolism. Here, we discuss these potential downstream effects in detail (Fig. 2).

Mitochondrial translation efficiency controls cytoplasmic protein homeostasis

Cellular proteostasis is maintained via coordinated protein synthesis in the cytoplasm and mitochondria. Abnormal mitochondrial translation can disrupt cytoplasmic protein homeostasis and induce cellular dysfunction. In general, a disruption of mitochondrial translation can result in a global decrease in cytoplasmic translation [99–101]. Cytoplasmic translation inhibition may trigger cellular dysfunction through multiple pathways. First, in many cells, robust protein synthesis is essential for proliferation and differentiation. For example, increased

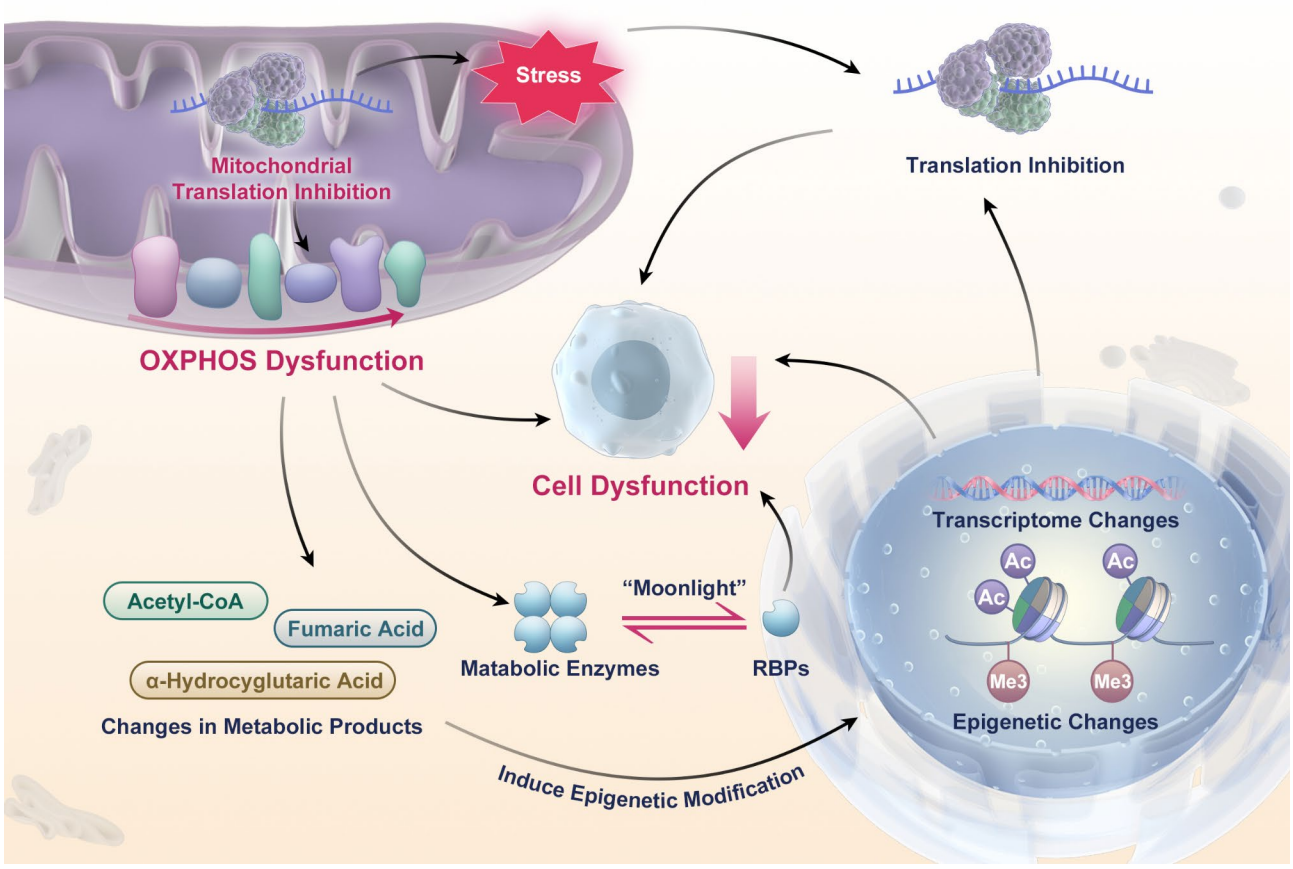

Fig. 2 Physiological consequences of the inhibition of mitochondrial translation
Mitochondrial translation can directly initiate the mitochondrial stress response, which in turn leads to the significant inhibition of cytoplasmic translation, thereby affecting cell function through signaling pathways such as the ISR (integrated stress response) and mTOR (mechanistic target of rapamycin). A key feature of mitochondrial translation inhibition is the impairment of OXPHOS function. Studies have shown that the inhibition of OXPHOS can result in an insufficient energy supply for multiple cell types, thereby inhibiting their proliferation and growth. An impairment of OXPHOS also induces changes in the abundances of metabolites, including acetyl coenzyme A. Many of these metabolites are involved in regulating epigenetic features. Alterations in their abundances can lead to epigenetic modifications dominated by histone acetylation and DNA methylation, potentially influencing cell differentiation and function. Furthermore, research has revealed that metabolic enzymes with RNA-binding capabilities, also known as "moonlighting" phenomena, may affect the expression of T-cell-associated effectors. These secondary effects of metabolic enzymes are likely linked to aberrant OXPHOS function

protein synthesis is required to accomplish proteomic reprogramming during T-cell activation [102]. Cytoplasmic translation inhibition caused by impaired mitochondrial translation may result in an inadequate supply of proteins, leading to disorders in proliferation and differentiation processes. Additionally, the effector functions of many cells rely on protein synthesis. For example, the cytotoxic function of $CD8^+$ T cells largely depends on the synthesis of effector factors such as TNF-α and IFN-γ. Cytoplasmic translation inhibition induced by mitochondrial translation disorders may affect cellular functions by suppressing the synthesis of these effector factors [5–7, 103].

Mitochondrial translation modulates metabolic fitness

Given that the products of mitochondrial translation constitute the electron transport chain (ETC), we hypothesize that the effects of mitochondrial translation on cellular function are likely achieved by influencing cellular metabolism.

Mitochondrial translation is essential for normal OXPHOS function. Inhibition of mitochondrial translation typically impairs OXPHOS, leading to an insufficient energy supply [5–7]. This change can lead to cellular dysfunction in terms of proliferation and growth, especially in cells that prefer OXPHOS metabolism, such as leukemia stem cells, OXPHOS-dependent diffuse large B-cell lymphoma, glioblastoma stem cells (GSCs), breast cancer cells, and hepatocellular carcinoma (HCC) cells [8, 104–106].

The inhibition of mitochondrial translation can result in cellular epigenetic changes, which are mediated by an imbalance in cellular metabolite levels. For example, researchers have induced mitochondrial translation

disorders in $CD8^+$ T cells by knocking out the expression of C1qbp, resulting in a decreased abundance of the metabolic product acetyl-coenzyme A and increased abundances of fumaric acid and 2-hydroxyglutarate [29]. These changes in metabolite abundance influence cellular epigenetic and transcriptional programs, leading to differentiation disorders in effector T cells [29]. Additionally, in HSCs, abnormal abundances of metabolites induced by abnormal mitochondrial gene expression can similarly affect HSC erythroid differentiation through cellular epigenetic pathways [107].

Numerous metabolic enzymes can translocate into the cytoplasm, where they function as RBPs for specific mRNAs, thereby modulating their expression [108]. This phenomenon is known as "moonlighting" and may also be one of the downstream pathways of a disruption in mitochondrial translation. Altered expression levels of metabolic enzymes that act as RBPs were observed in $CD8^+$ T cells with inhibited mitochondrial translation, which supports this hypothesis [5]. Many metabolic enzymes can "moonlight" as RBPs to regulate cellular translation [108]. Some "moonlighting" RBPs can regulate the expression of specific cytokines, such as granzyme B, TNF-α, and IFN-γ [109–111]. For example, GAPDH can bind to the 5' UTR of the IFN-γ mRNA and inhibit its translation in OXPHOS-dependent T cells [110].

Reactive oxygen species (ROS), metabolic byproducts that play diverse roles in cells [112–115], primarily depend on the ETC. Thus, a disruption of mitochondrial translation triggers a reduction in ROS levels, which may lead to cellular dysfunction. For example, in $CD8^+$ T cells in which mitochondrial translation is inhibited, reduced synthesis of effector factors such as IL-2, IFN-γ, and TNF-α is observed [116].

Dysfunction of mitochondrial translation induces mitochondrial transfer

Recent studies have revealed a process known as mitochondrial transfer, in which cells can transport their mitochondria to other recipient cells through various mechanisms, including cell connections and vesicles [117]. Mitochondrial transfer primarily affects the metabolic characteristics of recipient cells, typically resulting in an increase in the mitochondrial content and elevated mitochondrial metabolic levels [117]. Upon acute stress, cells tend to rapidly increase their mitochondrial quantity by receiving external mitochondria to meet the metabolic demands, followed by an increase in mitochondrial translation levels to promote endogenous mitochondrial biogenesis [118]. Furthermore, impaired mitochondrial translation is often accompanied by the production of ROS and other superoxides, which are believed to be key factors in initiating the acceptance of external mitochondria by recipient cells [118, 119]. Therefore, we hypothesize that mitochondrial transfer may serve as a compensatory mechanism for impaired mitochondrial translation. When mitochondrial translation is impaired, the superoxides produced may trigger the formation of intercellular connection channels, allowing recipient cells to accept external mitochondria to quickly increase their metabolic capacity, thereby compensating for the metabolic dysfunction caused by impaired mitochondrial translation. However, currently, research directly exploring the relationship between mitochondrial transfer and translation is lacking, and we hope that future studies will better elucidate this relationship.

In this section, we summarize the downstream effects of mitochondrial translation. First, a mitochondrial translation impairment can initiate a decrease in global cellular translation levels, which hinders normal proliferation and differentiation. The inhibition of cytoplasmic translation also disrupts cellular function by decreasing the expression of specific effector factors. The inhibition of mitochondrial translation leads to a metabolic disruption characterized by impaired OXPHOS. Dysregulated mitochondrial metabolism can also affect cell functions through downstream pathways, including the metabolic–epigenetic axis, RBPs, and ROS. Mitochondrial transfer may compensate for impaired translation. However, current research on the downstream effects of mitochondrial translation is limited. What mechanisms underlie the impacts of mitochondrial translation disorders on these pathways? Are known or unknown signaling cascade pathways involved in these processes? Does mitochondrial translation also influence other cellular functions? These questions remain unanswered. Notably, the relationship between mitochondrial and cytoplasmic translation has been extensively studied in the past, as discussed in the next section.

The Mitochondria-induced stress response links mitochondrial and cytoplasmic translation

Despite diverse upstream and downstream regulatory mechanisms, mitochondrial translation also has complicated interactions with cytoplasmic translation. Impediments to mitochondrial translation can affect the level of cytoplasmic translation through various signaling pathways represented by the stress response. Since numerous mitochondrial proteins are encoded in the nucleus and are then translated in the cytoplasm, disruptions in cytoplasmic translation levels can affect mitochondrial translation by altering mitochondrial protein expression, thereby alleviating stress and coordinating cytoplasmic and mitochondrial translation. The stress response plays a central role in coordinating mitochondrial and cytoplasmic translation.

The stress response represents a crucial class of signaling pathways that helps cells adapt to stressful environments and maintain homeostasis. It triggers widespread inhibition of cellular protein synthesis and the selective expression of specific stress genes. In the context of mitochondrial dysfunction, two stress responses have been identified: the integrated stress response (ISR) and the mitochondrial unfolded protein response (mtUPR). Additionally, the mammalian target of rapamycin protein complex 1 (mTORC1) plays a significant role in regulating mitochondrial translation and cytoplasmic translation under physiological or stress conditions.

Integrated Stress Response (ISR)

The ISR is a broad stress response that can be activated by various stress conditions, including mitochondrial dysfunction. The phosphorylation of eukaryotic translation initiation factor 2 subunit alpha (eIF2α) is a key step in the ISR [120]. Multiple eIF2α kinases have been implicated in the mitochondrial stress-induced ISR. Heme-regulated inhibitor (HRI), an eIF2α kinase, is activated by death ligand signal enhancer (DELE) released from mitochondria under mitochondrial stress, thereby triggering the ISR and impairing cytoplasmic translation [121, 122]. Moreover, the mitochondrial translation inhibitor doxycycline was found to induce the ISR through the eIF2α kinase GCN2 [123].

Phosphorylation of eIF2α leads to the widespread downregulation of cytoplasmic protein synthesis and preferential translation of specific mRNAs containing upstream open reading frames in the 5' UTR, including the transcription factor ATF4 [124]. ATF4, a stress-responsive transcription factor, plays roles in various cellular processes, such as the antioxidant response, cell apoptosis, energy homeostasis, and autophagy [125]. When stress cannot be relieved, ATF4 regulates the cellular apoptosis program to eliminate damaged cells [125]. In the context of mitochondrial stress-induced ISR, the ATF4 pathway is activated to promote processes such as serine biosynthesis, lipid synthesis, and other metabolic processes to maintain cellular function [99]. In addition, a previous study showed that the inhibition of mitochondrial translation can coordinate with cytoplasmic translation by activating ATF4 [100].

Mitochondrial unfolded protein response (mtUPR)

Mitochondria have a relatively independent protein quality control system that maintains the folding and integrity of mitochondria-synthesized and imported proteins. The accumulation of misfolded proteins in the mitochondrial matrix or an imbalance in the import of nuclear-encoded proteins triggers the mitochondrial unfolded protein response (mtUPR), a proteostasis control system activated by various mitochondrial perturbations, such as inhibited mitochondrial translation, the deletion of ribosomal components, or the inhibition of aspartate-tRNA synthetase or LON protease [126–130].

Upon activation, the mtUPR restores mitochondrial function through various mechanisms, such as inducing the expression of nuclear-encoded mitochondrial chaperone proteins and proteases, including Hsp60 (HSPD1), Hsp10 (HSPE1), mtDNAJ, mtHsp70 (HspA9), LONP1, and CLPP [127]; restricting the expression of nuclear-encoded metabolic enzymes and OXPHOS subunits [127]; and reducing the efficiency of nuclear-encoded mitochondrial protein import [131]. In addition, the mtUPR downregulates the expression of and degrades the RNase P subunit MRPP3 that lead to abnormalities at the 3' ends of mitochondrial mRNAs, thereby triggering a reduction in mitochondrial translation [127].

In *C. elegans*, several transcription factors associated with mtUPR activation have been identified. Activating transcription factor associated with stress-1 (ATFS-1) is a crucial transcription factor for mtUPR activation in *C. elegans* [132]. ATFS-1 possesses both a nuclear localization sequence (NLS) and a mitochondrial localization sequence (MLS). Under normal mitochondrial conditions, the MLS is dominant, and ATFS-1 is imported into mitochondria and degraded by the matrix-localized LON protease. However, when mitochondria are damaged, the NLS directs ATFS-1 to the nucleus to activate the mtUPR [133]. In mammals, the functional ATFS-1 homolog, ATF-5, possesses similar functions [134]. In addition to ATF-5, two other transcription factors, ATF-4 and C/EBP homologous protein (CHOP), are involved in the activation of the mammalian mtUPR. The exact interplay between these three transcription factors is not yet clear. Notably, CHOP, ATF-4, and ATF-5 are also associated with the ISR, and their expression is dependent on eIF2α phosphorylation [135, 136]. Although the mtUPR is associated with the ISR, the activation of the ISR does not always involve the mtUPR, as the induction of the expression of mitochondrial chaperone proteins and proteases is not consistently observed during mitochondrial stress [99, 121–123].

mTORC1 as a stress sensor

mTORC1 is a protein complex that regulates eukaryotic cell growth in response to progrowth signals such as nutrients, oxygen, and hormones to maintain normal growth and organismal homeostasis [137]. mTORC1 plays an important role in regulating translation. Upon receiving progrowth signals, mTORC1 promotes protein synthesis primarily through the phosphorylation of two key effectors: p70s6 protein kinase 1 (S6K1) and eIF4E-binding protein (4EBP) [137]. The phosphorylation of S6K1 activates eIF4B, a positive regulator of the eIF4F complex, and promotes the degradation of PDCD4, an

inhibitor of eIF4B, to facilitate translation initiation [138, 139]. S6K1 also enhances translation efficiency by binding to SKAR, a component of the binding region complex [140]. 4EBP inhibits translation initiation by binding to eIF4E, and mTORC1 phosphorylates 4EBP to release it from eIF4E, enabling cap-dependent translation initiation [141, 142]. mTORC1 also plays a crucial role as a stress sensor. Under conditions of mitochondrial stress, the mTORC1 signaling pathway is inhibited. This inhibition includes a reduction in the level of S6K phosphorylation, which may lead to a decrease in cytoplasmic translation [143].

mTORC1 regulates mitochondrial function by modulating cytoplasmic translation under physiological conditions or in response to mitochondrial DNA damage [144–147]. Upon 4EBP phosphorylation, mTORC1 promotes the translation of nuclear-encoded mRNAs encoding proteins involved in the OXPHOS complex, OXPHOS assembly factors, and TFAM (mitochondrial transcription factor A) [145–148]. TFAM, a DNA-binding high mobility group box protein, facilitates the packaging of the mitochondrial genome into nucleoids and is critical for the separation and initiation of mitochondrial DNA transcription [73, 149]. It is indispensable for both mitochondrial DNA replication and transcription processes. Recent research has shown that the absence of TFAM inhibits mitochondrial translation, an effect not seemingly linked to impaired mitochondrial transcription [150]. This conclusion is supported by observations that treatment with mitochondrial translation inhibitors does not exacerbate suppression, suggesting that TFAM deficiency leads to mitochondrial translation defects.

ATF4 is involved in both the ISR and the mtUPR. Notably, the anabolic response mediated by mTORC1 partly depends on the stress-responsive transcription factor ATF4 [100, 144, 146–148]. However, mTORC1 activates ATF4 independently of eIF2α phosphorylation; thus, the mTORC1-mediated ATF4 transcriptional program activates only a subset of genes activated by the ISR. These genes promote cytoplasmic tRNA aminoacylation, amino acid biosynthesis and uptake, *de novo* purine synthesis, one-carbon metabolism, and an increase in the abundance of the antioxidant glutathione, potentially counteracting oxidative stress resulting from increased respiratory activity [146–148].

In summary, cells maintain proteostasis between the cytoplasm and mitochondria through a series of signaling pathways, as described above. Under conditions of mitochondrial stress, both cytoplasmic and mitochondrial translation are globally suppressed to reduce the protein load (Fig. 3). Specific transcription factors are selectively expressed to induce the synthesis of mitochondrial chaperone proteins and proteases, which help eliminate misfolded proteins and restore mitochondrial function. However, several questions regarding these processes remain unanswered, such as the relationships among the mtUPR, ISR, and other mitochondrial stress responses, as well as the precise pathways, functions, and interrelationships of the associated transcription factors. Further research is needed to elucidate these mechanisms and improve our understanding of how cells adapt to mitochondrial dysfunction and maintain protein homeostasis.

Mitochondrial translation regulates normal hematopoiesis

The process of hematopoiesis, occurring primarily within the bone marrow, involves the differentiation of hematopoietic stem cells (HSCs) into diverse lineages. The differentiation of HSCs is a stepwise process from multipotent progenitor cells, which have the potential to produce multiple lineages, to oligopotent progenitor cells, which are restricted to certain lineages, and then to unipotent progenitor cells, which produce only a single lineage, culminating in mature blood cells. Researchers have depicted the hematopoietic hierarchy as a tree-like branching roadmap (Fig. 4). In the classical model of hematopoiesis, HSCs first differentiate into multipotent progenitor cells (MPPs). The downstream developmental pathways of MPPs are further classified into common lymphoid progenitors (CLPs), which have lymphoid-restricted differentiation potential, and common myeloid progenitors (CMPs), which can differentiate into megakaryocyte/erythroid progenitors (MEPs) and granulocyte/macrophage progenitors (GMPs) [151]. Studies regarding the role of mitochondrial translation in normal hematopoiesis have emerged in recent years. In this section, we provide a detailed overview of the roles of mitochondrial translation in HSCs and different cell lineages.

Hematopoietic stem cells (HSCs)

HSCs exhibit two basic features: the ability to self-renew and the sustained generation of all blood cell lineages, which are indispensable for maintaining normal hematopoiesis. Recent investigations have revealed the involvement of mitochondrial translation in HSC proliferation and differentiation, especially in erythroid differentiation. Upon erythropoietin (EPO) stimulation, the expression of eukaryotic translation initiation factor 5 A (eIF5A) in HSCs increases, which promotes the translation of diverse nuclear-encoded mitochondrial proteins. The suppression of eIF5A expression leads to decreases in mitochondrial translation levels and OXPHOS levels, thereby inhibiting erythroid differentiation [3]. Direct inhibition of mitochondrial translation in HSCs by chloramphenicol yields a similar inhibitory effect on erythroid differentiation [3]. In another study, mitochondrial translational repression triggered by decreased levels of mitochondrial tRNA pseudouridylation similarly

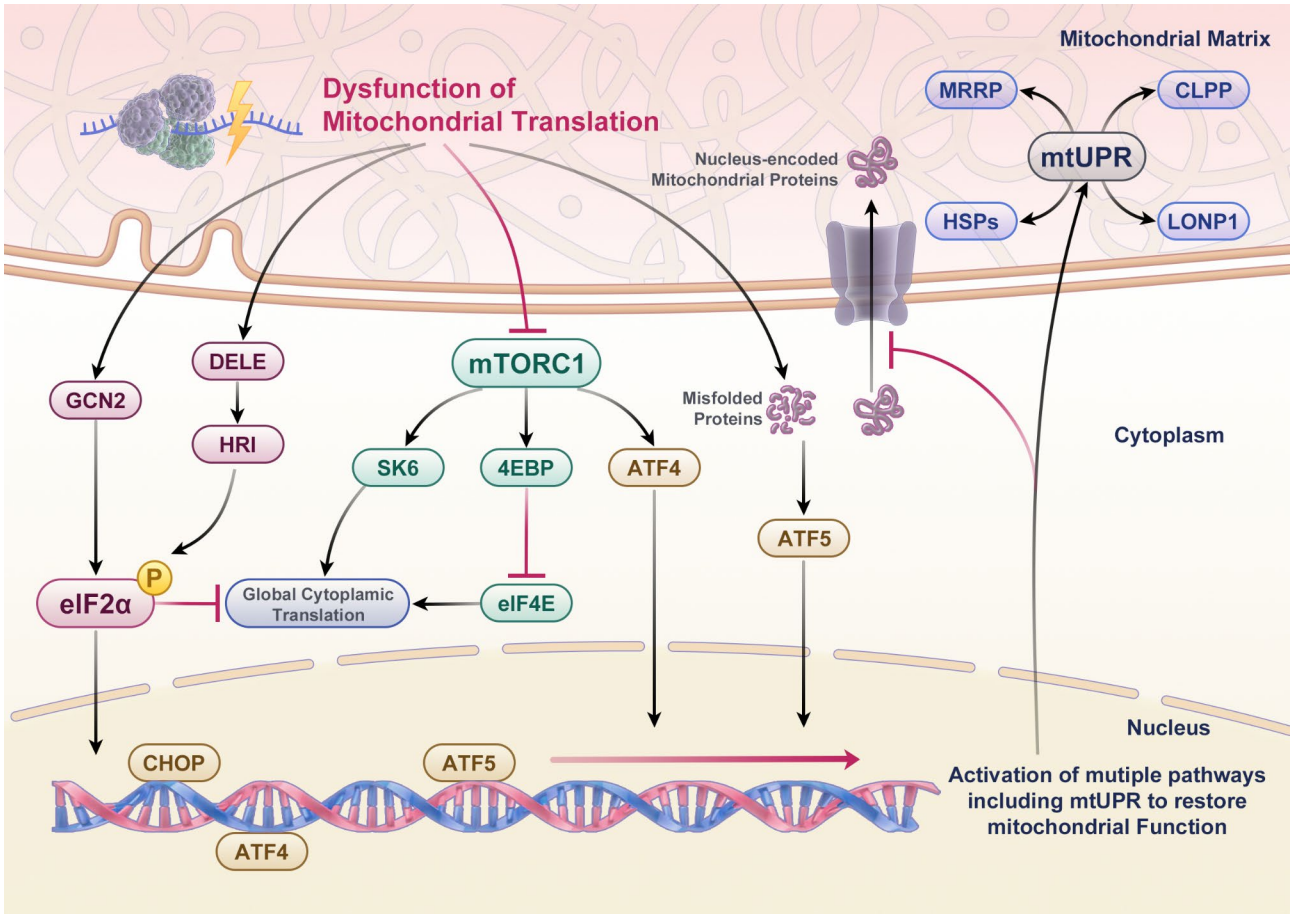

Fig. 3 Correlations between mitochondrial and cytoplasmic translation

Mitochondrial translation is interconnected with cytoplasmic translation through a series of stress response pathways. Under mitochondrial stress, mitochondria release DELE, which binds to HRI, an eIF2α kinase, leading to the phosphorylation of the translation initiation factor eIF2α. Another eIF2α kinase, GCN2, is also speculated to be involved in this process. Phosphorylation of eIF2α triggers widespread translational repression in the cytoplasm and the selective translation of mRNAs containing upstream open reading frames (uORFs), including ATF4, ATF5, and CHOP. When misfolded proteins accumulate in the mitochondrial matrix, cells activate a homeostatic protein control system known as the mitochondrial unfolded protein response (mtUPR). In mammals, ATF5 has been identified as a transcription factor that mediates the mtUPR. ATF5 possesses both a nuclear localization sequence (NLS) and a mitochondrial targeting sequence (MLS). In the event of mitochondrial damage, ATF5 translocates to the nucleus and cooperates with ATF4, CHOP, and other transcription factors to activate the mtUPR. The mtUPR induces the expression of HSPs, LONP1, CLPP, and other nuclear-encoded mitochondrial chaperone proteins and proteases to restore mitochondrial function. It also directly reduces mitochondrial translation by downregulating and degrading the RNase P subunit MRPP3. Furthermore, to alleviate mitochondrial stress, the translation and import of nuclear-encoded OXPHOS subunits and mitochondrial proteins are inhibited. Under physiological conditions, mTORC1 promotes cytoplasmic translation by activating S6K and preventing the binding of 4EBP to eIF4E. However, during mitochondrial stress, the induction of cytoplasmic translation is hindered

caused impaired mitochondrial metabolism and blocked erythroid differentiation in HSCs [4]. Moreover, another study revealed that a deficiency of TFAM, the core regulatory factor in mitochondrial genome transcription, results in mitochondrial metabolic dysfunction, culminating in aberrant abundances of metabolites, including β-hydroxybutyrate (βOHB). Through increased histone acetylation, these metabolites contribute to compromised erythroid gene expression and differentiation [107]. Collectively, these findings suggest that aberrant mitochondrial translation may disrupt HSC differentiation via perturbations in mitochondrial metabolism and epigenetic mechanisms.

As a downstream pathway of mitochondrial translational disorders, the mtUPR plays a unique role in HSC self-renewal. A downstream branch pathway exists in the mtUPR. This branch is mediated by the interaction of SIRT7 and NRF1, and its activation triggers the inhibition of mitochondrial translation and respiration [152]. Deactivation of SIRT7 triggers an increase in the folding pressure of mitochondrial proteins, and the regenerative capacity of HSCs is thus impaired [152]. Moreover, SIRT7 expression is reduced in aged HSCs, and the upregulation of SIRT7 expression improves the regenerative capacity of aged HSCs. These results suggest that the activation of the mtUPR is closely linked to the aging and self-renewal

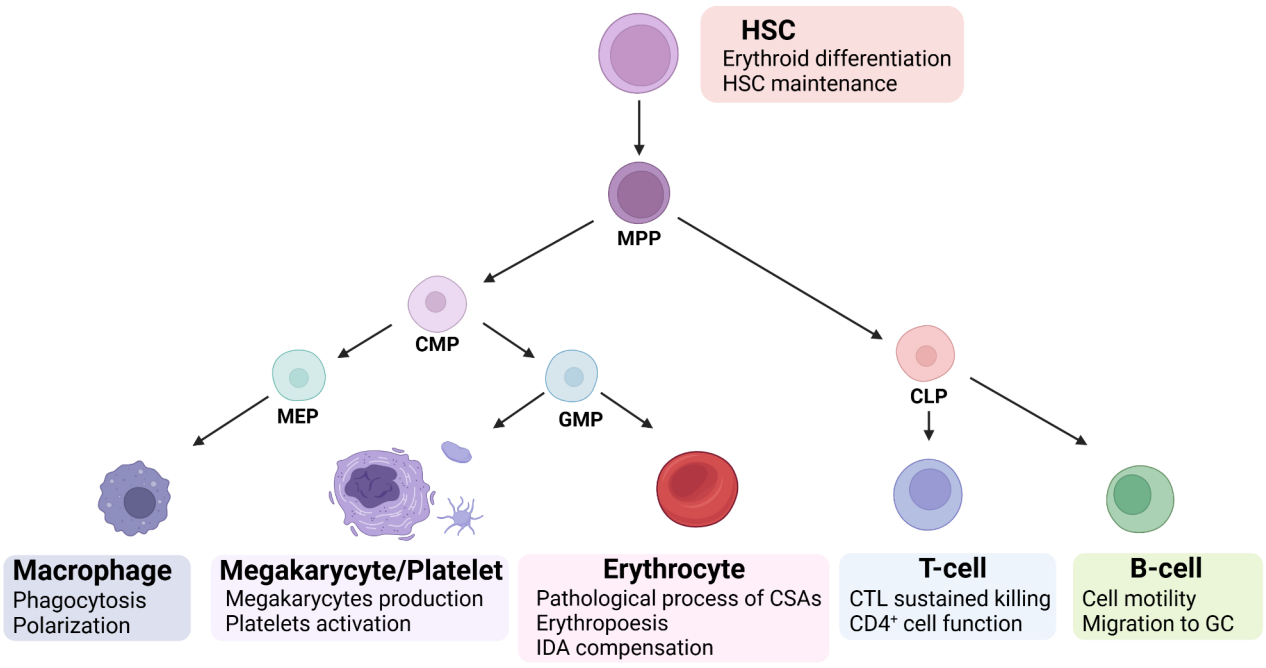

Fig. 4 Mitochondrial translation in normal hematopoiesis
Hematopoiesis is the process by which hematopoietic stem cells (HSCs) differentiate into various types of mature blood cells. According to the classical hematopoietic hierarchy model, HSCs first differentiate into multipotent progenitor cells (MPPs). MPPs can follow two differentiation pathways: One leads to the lymphoid lineage, forming common lymphoid progenitors (CLPs), which further differentiate into mature blood cells, including T cells, B cells, and NK cells. The second pathway leads to the myeloid lineage, forming common myeloid progenitors (CMPs). CMPs can differentiate into megakaryocyte/erythroid progenitors (MEPs) and granulocyte/macrophage progenitors (GMPs). MEPs further differentiate into mature blood cells, such as macrophages, platelets, and erythrocytes, whereas GMPs differentiate into neutrophils, basophils, eosinophils, and macrophages. Based on current research, we annotated the cellular processes influenced by mitochondrial translation in different cells, as detailed in the main text. Importantly, certain blood cells, such as NK cells and granulocytes, which have not been fully studied, are not depicted in this figure

capacity of HSCs. In addition, mtUPR activation is also observed during the shift of HSCs from a resting state to a proliferative state [153]. Taken together, these findings indicate that the mtUPR may play an important role in HSC maintenance. Dysregulation of mitochondrial translation, the main cause of mtUPR activation, may lead to an impairment of the self-renewal capacity of HSCs. However, studies related to the relationship between mitochondrial translation and HSCs are still lacking, and answers to related questions still require further research.

Lymphoid lineage

Common lymphoid progenitors (CLPs) can differentiate into various mature blood cells, including T cells, B cells, and natural killer (NK) cells. Currently, research on mitochondrial translation in lymphoid cells has focused mainly on T cells and B cells, whereas studies on NK cells are limited.

T cells

In recent years, research interest in the role of mitochondrial translation in maintaining T-cell function has increased. Knockout of USP30, a deubiquitinating enzyme that prevents mitochondrial autophagy and peroxisomal autophagy, leads to significant decreases in the mitochondrial quantity and OXPHOS levels in T cells, as well as a marked attenuation of mitochondrial translation [5, 154]. Intriguingly, USP30-deficient T cells initially retain their killing function, but they cannot sustain serial killing over time [5]. Researchers have attributed this decline to impaired *de novo* synthesis of cytolytic proteins. While the cells can initially perform their killing functions with prestored cytolytic proteins, the inability to synthesize these proteins *de novo* prevents the replenishment of lytic granules, thus failing to maintain a sustained cytotoxic function. Moreover, researchers have used doxycycline or chloramphenicol to inhibit mitochondrial translation, which leads to a similar defect in T-cell killing ability, suggesting the involvement of mitochondrial translation in the regulation of the sustained killing ability of cytotoxic T lymphocytes (CTLs) [5].

Another study revealed that exposing CTLs to a temperature of 39 °C improved mitochondrial quality and antitumor function. This increase in CTL function depended on the facilitation of mitochondrial translation [7]. Upon the use of tetracycline or the knockout

of MRPL39 (mitochondrial ribosomal subunit 39) or OXA1L (mitochondrial ribosome-associated insertion enzyme) expression, the opposite effect was observed [7]. Similar conclusions have been drawn from studies of $CD4^+$ T cells. Inhibition of mitochondrial translation either by linezolid, an antibiotic that specifically targets bacterial protein synthesis, or by knockout of the expression of the mitochondrial elongation factor GFM1 leads to impaired production of effector cytokines in $CD4^+$ T cells and reduced autoimmunity in a mouse model of multiple sclerosis [6].

Overall, multiple studies have indicated that impaired mitochondrial translation leads to T-cell dysfunction. However, the precise mechanisms underlying this phenomenon have yet to be fully elucidated. Through a literature review, we identified several relevant clues. Cytoplasmic translation inhibition and the metabolic imbalance triggered by the inhibition of mitochondrial translation may play roles in this process. The underlying mechanisms may involve epigenetic changes caused by abnormal abundances of metabolites, metabolic enzymes moonlighting as RBPs, and decreased levels of ROS. These aspects have been extensively discussed in the preceding sections.

B cells

Mitochondrial translation also contributes to the activation of normal B cells and their migration into the germinal center (GC). In activated B cells and GC B cells, the levels of mitochondrial transcription and translation are significantly increased. During the process of B-cell activation and entry into the GC, the expression levels of TFAM are elevated, thereby regulating the motility of B cells by increasing mitochondrial transcription and translation levels and promoting their migration to the GC [150]. Mitochondrial translation also influences the occurrence of B-cell malignancies, which are discussed in a later section.

Myeloid lineage

The differentiation of common myeloid progenitors (CMPs) occurs in two directions: megakaryocyte/erythroid progenitors (MEPs) and granulocyte/macrophage progenitors (GMPs). Megakaryocyte/erythroid progenitors (MEPs) differentiate into megakaryocytes, which produce platelets, and erythrocytes, whereas granulocyte/macrophage progenitors (GMPs) differentiate into mature blood cells, including neutrophils, basophils, and eosinophils. Mitochondrial translation plays a crucial role in megakaryocytes/platelets, erythrocytes, and macrophages, as described in existing studies, which will be discussed in detail below. However, research on mitochondrial translation in granulocytes remains limited.

Macrophages

Macrophage function is regulated by mitochondrial translation. 7-Ketocholesterol directly inhibits tumor necrosis factor signaling in tumor-associated macrophages (TAMs) by inhibiting mitochondrial translation, thereby inducing dysfunctional phagocytosis in TAMs [155]. This study documented the existence of the mitochondrial translation/TNF signaling axis in macrophages. In another study, the expression of the plasticity factor ZEB1 was found to prompt macrophages to shift from an inflammatory phenotype to an immunosuppressive state by inhibiting mitochondrial translation [156]. This study revealed a role for mitochondrial translation in regulating macrophage function. In addition, mitochondrial translation is associated with macrophage polarization. Studies have shown that metabolic reprogramming toward M2 polarization depends on the translation of the elongator complex subunit Elp3 and the mitochondrial ribosomal large subunit proteins MRPL3, MRPL13, and MRPL47 [21].

Erythrocytes

Erythrocytes are blood cells that carry oxygen throughout the body. Mitochondria gradually disappear in erythrocytes during differentiation to increase the efficiency of oxygen transport. Nevertheless, mitochondrial translation still participates in erythroid differentiation, as mentioned earlier. Moreover, mitochondrial translation is associated with anemia pathogenesis.

Congenital sideroblastic anemias (CSAs), a class of anemias characterized by the pathological deposition of iron in the mitochondria of erythroid precursors, can be induced by abnormal mitochondrial translation [157]. For example, Pearson marrow–pancreas syndrome (PMPS), a subtype of CSA characterized by bone marrow and exocrine pancreatic dysfunction, is characterized by the deletion of mitochondrial genome fragments. The deletion results in the defective translation of mitochondria-encoded proteins, thereby leading to impaired erythropoiesis [158]. Abnormal mitochondrial translation is also associated with mitochondrial myopathy with lactic acidosis and sideroblastic anemia (MLASA), another subtype of CSA. MLASA is the result of mutations in genes encoding either pseudouridine synthase (PUS1) or mitochondrial tyrosyl-tRNA synthetase (YARS2) [157]. Mutation of PUS1 leads to the loss of pseudouridine in mitochondrial tRNA, resulting in abnormal mitochondrial translation and thereby inhibiting erythropoiesis [4].

In addition to CSAs, mitochondrial translation also participates in the pathological process of iron deficiency anemia. In the presence of iron deficiency, one of the eIF2α kinases, HRI, is activated and restores mitochondrial function by inhibiting mitochondrial translation

and activating ATF4, thereby promoting erythropoiesis [159].

Megakaryocytes/Platelets

Platelets are small, anucleate cells produced by megakaryocytes that play crucial roles in blood coagulation, wound healing, and inflammatory responses [160]. Recent studies indicate that mitochondrial translation is essential for both the generation of the megakaryocyte lineage and the maintenance of its normal functions.

Defects in mitochondrial translation hinder the production of the megakaryocyte lineage. Researchers developed a mouse model with platelet-specific mitochondrial translation defects by selectively knocking out the gene encoding mitochondrial translation initiation factor 3 (mtIF3) in megakaryocytes. The findings revealed that mitochondrial translation defects resulted in reduced megakaryocyte production, leading to thrombocytopenia and prolonged bleeding times [46]. Transcriptomic and proteomic analyses revealed that megakaryocytes with mitochondrial translation defects presented downregulated expression of genes involved in platelet production, megakaryocyte development, hemostasis, and coagulation [46]. Additionally, mtIF3-deficient mice exhibited decreased levels of cytoplasmic proteins released by platelets (TLN1, WDR1, CAP1, and TUBA4A) [46]. These factors may collectively contribute to impaired megakaryocyte lineage generation.

Furthermore, defects in mitochondrial translation can impair platelet functionality. Platelets with mitochondrial translation defects exhibit compromised activation processes and increased apoptosis [46] that are possibly linked to metabolic dysfunction. As metabolically active cells, platelets have a high ATP turnover rate, with OXPHOS providing approximately 30–40% of their ATP supply [161]. During platelet activation, the OXPHOS rate must increase to meet the metabolic demands [162]. Conversely, the inhibition of mitochondrial respiration reduces platelet activation [163, 164]. In this study, platelets with mitochondrial translation defects presented a diminished mitochondrial content [46], potentially impairing platelet function by reducing the mitochondrial respiration capacity. However, the metabolic characteristics of platelets with mitochondrial translation defects remain poorly characterized, and a direct connection between mitochondrial translation and metabolic dysfunction has yet to be established.

Mitochondrial translation is a therapeutic target for hematologic malignancy treatment

Hematologic malignancies are the main outcomes of malignant hematopoiesis. Based on their origin, hematologic malignancies can be divided into myeloid and lymphoid types. In preclinical studies of various hematologic malignancies, mitochondrial inhibition has surprisingly produced selective toxicity toward malignant cells. However, its toxicity to normal hematopoietic cells is much less effective, confirming a potential therapeutic window. This selective effect is widely attributed to the increased sensitivity of malignant cells to mitochondrial inhibitors due to their reliance on mitochondrial metabolism [8, 9, 165–167]. A strong dependence on metabolism is a unique metabolic characteristic of certain hematologic malignancies. The majority of cancer cells undergo metabolic reprogramming known as the Warburg effect, in which cancer cells exhibit high glucose consumption and lactate production even under normoxic conditions, accompanied by the upregulation of glycolysis and a hypothesized decrease in OXPHOS levels in cancer cells. However, OXPHOS is upregulated in certain hematological malignancies, overriding the traditional Warburg effect; therefore, mitochondrial translational inhibition may reduce tumor viability by affecting OXPHOS activity to disrupt metabolism. Therefore, the inhibition of mitochondrial translation is considered a potential treatment for hematologic malignancies, but its mechanism of action and feasible therapeutic approaches remain to be explored.

Myeloid malignancies

Acute myeloid leukemia (AML) is the most common myeloid malignancy and is related to two cell populations: myeloblasts and leukemia stem cells (LSCs). Myeloblasts proliferate rapidly and exhibit glycolysis-dependent metabolic characteristics [168–170]. LSCs proliferate slowly and are more dependent on oxidative phosphorylation for energy. However, LSCs are thought to be responsible for AML relapse as reservoirs for myeloblasts [171, 172].

Based on this difference, targeting OXPHOS may be an effective therapy for AML. The inhibition of mitochondrial translation is considered a viable approach. In existing cases, the inhibition of mitochondrial translation in AML cells through the application of tigecycline and genetic depletion of the mitochondrial translation factor EF-Tu can selectively kill LSCs, inhibit leukemia cell proliferation, and induce apoptosis [8]. The proliferation and function of normal hematopoietic cells are not affected, which is attributed to the increased mitochondrial biogenesis rate of AML cells [8].

In addition, high OXPHOS levels have been implicated in the development of drug resistance in AML because AML cell populations resistant to cytarabine are enriched in cells with an increased mitochondrial mass, membrane potential, and OXPHOS. Therefore, inhibiting OXPHOS can increase the sensitivity of AML cells to cytarabine [173]. Furthermore, inhibiting mitochondrial translation has been found to be an effective approach for

overcoming AML resistance to venetoclax [174]. Venetoclax has been shown to inhibit mitochondrial complex I and can hinder the glycolytic capacity of AML cells in combination with mitochondrial translation inhibitors by activating the ISR, leading to adenosine triphosphate depletion and subsequent cell death [174].

In addition to AML, mitochondrial translation is also considered a potential treatment target for other myeloid malignancies. For example, in chronic myeloid leukemia (CML), the use of the mitochondrial translation inhibitor tigecycline combined with imatinib can specifically eliminate CML cells. This selective toxicity is believed to result from their dependence on mitochondrial metabolism [165].

Lymphoid malignancies

Lymphoma is a malignancy of lymphocytes. Diffuse large B-cell lymphoma (DLBCL), the most common form of lymphoma, can be divided into two metabolic subtypes: OXPHOS-DLBCL and B-cell receptor (BCR)-dependent DLBCL [175, 176]. BCR-DLBCL relies on glycolytic metabolism, whereas OXPHOS-DLBCL depends more on mitochondrial metabolism to provide energy, thus providing survival benefits beyond BCR signaling. Mitochondrial proteomic and gene expression analyses revealed that the expression of ETC components, particularly subunits of complexes I and IV, was upregulated in the OXPHOS-DLBCL subgroup [177]. Studies have shown that the mitochondrial translation pathway is necessary for increased mitochondrial energy reserves and ETC activity in OXPHOS-DLBCL cells [178]. Eradication of OXPHOS-DLBCL cell lines and primary tumors can be achieved by treatment with tigecycline or knockdown of the expression of mitochondrial translation-related proteins [178].

Myc is a hallmark oncogenic transcription factor that induces the progression of Burkitt lymphoma and is also an essential factor in AML development. Increased Myc expression corresponds to increased mitochondrial function, oxygen consumption, and mitochondrial mass. Studies have shown that inhibiting mitochondrial translation through antibiotic treatment [9], inhibiting human mitochondrial peptide deformylase (HsPDF) [166], or knocking down TFAM expression [150] can induce apoptosis in Myc-positive Burkitt lymphoma cells and prolong the survival time of tumor-bearing mice. The mechanisms may involve decreased activity of the ETC [9] and activation of the mtUPR [166], which result from impaired mitochondrial translation. Notably, some normal B-cell functions are affected, such as mobility and migration [150]. Furthermore, global upregulation of OXPHOS has also been observed in classic Hodgkin's lymphoma, accompanied by increased OXPHOS-related gene expression, increased mitochondrial mass, increased ETC protein expression, an increased oxygen consumption rate, and reduced lactate production promoted by NF-κB [179]. The inhibition of mitochondrial translation may also have a killing effect, given the enhanced OXPHOS.

The inhibition of mitochondrial translation has the potential to eradicate other lymphoid malignancies. The inhibition of mitochondrial translation by ICT1 knockdown can block the growth of ALL cells in S and sub-G1 phases and inhibit their proliferation [62]. Moreover, tigecycline treatment can selectively inhibit mitochondrial respiration and induce apoptosis in ALL cells [167]. Increased OXPHOS is also observed in primary CLL cells resistant to dasatinib, and this increase is mediated by AKT [180]. This phenomenon may reveal the possibility of treating CLL through the inhibition of mitochondrial translation.

Mitochondrial translation is thought to contribute to the pathogenesis of multiple myeloma (MM). Research indicates that MM cells exhibit a greater mitochondrial content and elevated expression of mitochondrial biogenesis-related genes, including the mitochondrial translation factors mtEFTu and TFAM, than normal plasma cells [181]. These findings suggest a potential role for mitochondrial translation in the malignant transformation of monoclonal gammopathy. A mitochondrial translation inhibitor effectively reduces mitochondrial activity and suppresses the proliferation of MM cells while significantly prolonging the survival of MM-transplanted mice in vivo [182]. These findings highlight the therapeutic potential of targeting mitochondrial translation in the treatment of MM.

These studies suggest that mitochondrial translation is a potential therapeutic target for treating hematological malignancies. Due to the similarities between mitochondrial and prokaryotic ribosomes, ribosome-targeting antibiotics are among the most commonly used candidates for modifying mitochondrial translation. Moreover, these antibiotics do not cause serious adverse reactions, such as hematological toxicity, in oncology patients [183–186], which lays a good foundation for their clinical application. Tigecycline, an FDA-approved drug for treating infections, was first observed to inhibit AML cell mitochondrial translation and selectively kill LSCs. In subsequent studies, it was found to have pharmacological functions in inhibiting mitochondrial translation in a variety of tumor cells, including AML, CML, DLBCL, Myc-driven lymphoma [8, 9, 165, 166, 178], and solid tumors such as renal cell carcinoma and ovarian cancer [187, 188]. However, in a phase I clinical trial of intravenous tigecycline treatment for patients with refractory AML, no clinical response was observed, possibly due to the short half-life of the drug in AML patients [189]. Therefore, identifying a stable and long-lasting method to

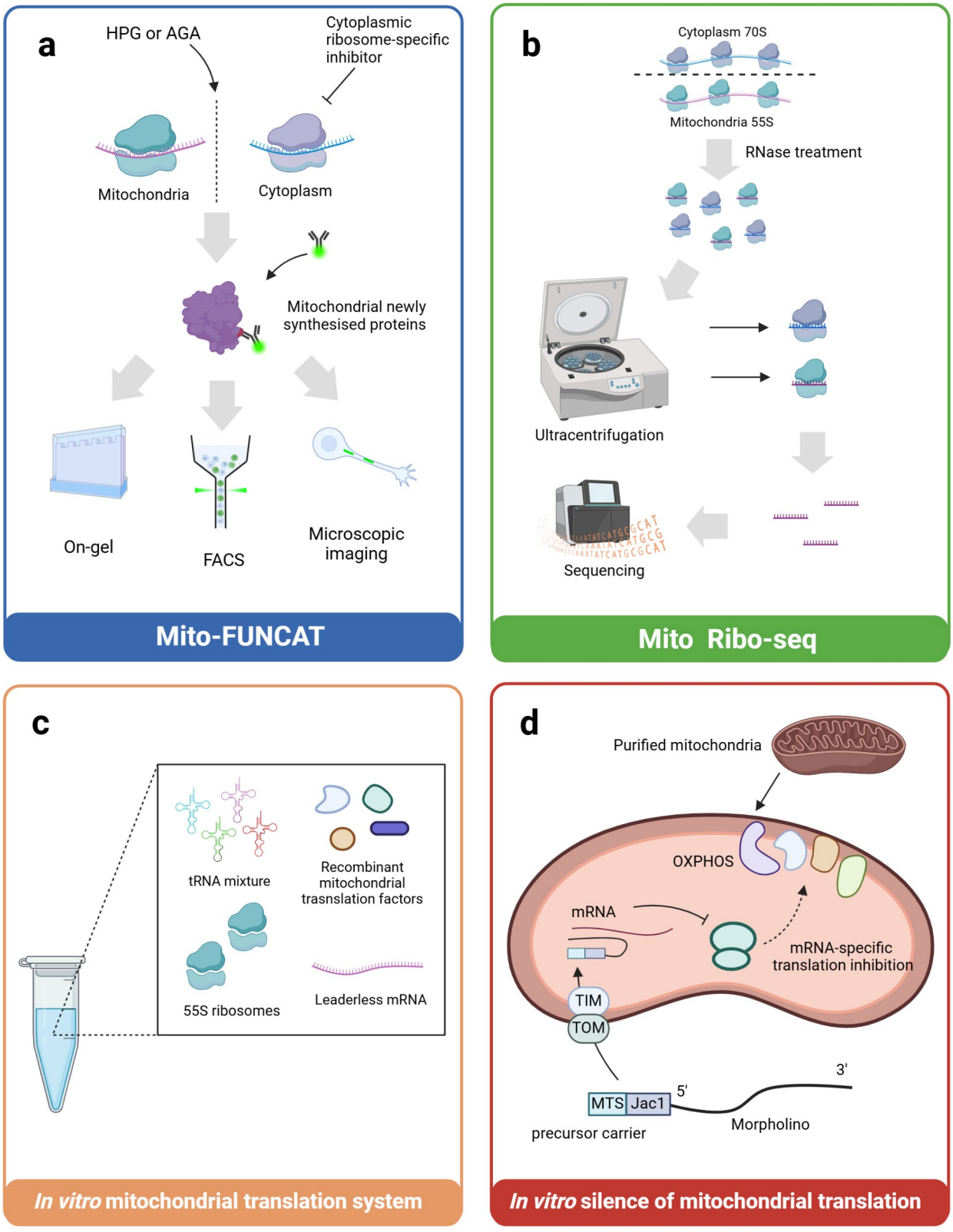

Fig. 5 (See legend on next page.)

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Fig. 5 Current methods for studying mitochondrial translation

(a) Fluorescence noncanonical amino acid tagging in mitochondria (mito-FUNCAT) allows the incorporation of bioorthogonal amino acids containing click-responsive alkynes or azides into newly synthesized mitochondrial proteins in the presence of cytoplasmic translational inhibition. Mitochondrial translation is subsequently assessed by on-gel detection, in situ microscopy or FACS. **(b)** Mitochondrial ribosome profiling (Mito Ribo-seq). Mammalian mitochondrial ribosomes are separated by size from cellular ribosomes by sucrose density gradient ultracentrifugation after RNase treatment, and mRNA fragments protected by mitochondrial ribosomes are analyzed using in-depth sequencing. **(c)** The addition of a mixture of recombinant mitochondrial factors, 55 S mitochondrial ribosomes, and tRNA to a single reaction allows the synthesis of mitochondrial and model proteins from leaderless mRNAs in a cell-free environment. **(d)** Morpholino–Jac1 chimeras can be introduced into purified mitochondria for mRNA-specific translational silencing via the TOM/TIM23 complex

inhibit mitochondrial translation in tumor cells may be a key breakthrough in achieving targeted mitochondrial translational therapy in the future.

Methods for studying mitochondrial translation

As mentioned above, mitochondrial translation plays an important role in various cells. However, the lack of relevant research techniques has made the study of mitochondrial translation mechanisms and mitochondrial gene function challenging. With the continuous advancement of related research, the development of many related technologies has increased. In the past, measuring mitochondrial translation has posed challenges due to the spatial autonomy of mitochondria. However, recent advancements have led to the emergence of numerous novel techniques for studying mitochondrial translation, thereby providing a solid technical foundation (Fig. 5).

Labeling of newly synthesized mitochondrial proteins

Treating cells with radionuclide- or fluorescence-labeled amino acids could aid in the detection of newly synthesized proteins. This method is commonly used to study cellular translation processes. After eliminating cytoplasmic translation disturbances using cytoplasmic ribosome-specific inhibitors, this method can be specifically applied to mitochondrial translation. Based on this hypothesis, scientists have developed mitochondrial fluorescence noncanonical amino acid tagging (mito-FUNCAT) methods. By treating cells with L-homopropargylglycine (HPG) or L-azidohomoalanine (AHA), mito-FUNCAT can be used to label newly synthesized mitochondrial proteins with fluorescence markers, thus allowing the quantification of mitochondrial translation levels [190–192]. For example, the synthesis rates of 13 mitochondria-encoded proteins can be assessed via an on-gel analysis of labeled proteins [191, 192].

In conjunction with confocal microscopy, mito-FUNCAT allows the visualization of mitochondrial translation at the subcellular level. Using in situ mito-FUNCAT, researchers have shown that mitochondrial protein synthesis is significantly active in the presynaptic compartment of neuronal axons and in the postsynaptic compartment of dendrites [191]. In addition, in conjunction with superresolution-stimulated emission depletion (STED) nanoscopy, mito-FUNCAT was used to visualize mitochondria even at the single-organelle level. Using this approach, scientists confirmed that the cristae membrane (CM) of the mitochondrial invagination site has the highest mitochondrial translational activity and that the active site of mitochondrial translation is colocalized with TACO1 expression [192]. Mito-FUNCAT in conjunction with fluorescence-activated cell sorting (FACS) enable high-throughput measurements of mitochondrial protein synthesis [193]. Mito-FUNCAT–FACS can reveal the heterogeneity of mitochondrial translation between cellular subpopulations [193].

Mitochondrial ribosomal profiling

The development of ribosomal profiling, also known as Ribo-seq, has significantly advanced the field of mRNA translational research. This technique involves the use of nucleases to degrade mRNA, facilitating the sequencing of ribosome-protected fragments (RPFs) that are actively undergoing translation. The sequencing results reveal the precise positions of ribosomes along the entire transcriptome at single-codon resolution, referred to as ribosomal footprints [194]. Based on the same principle, mitochondrial ribosome profiling, also known as Mito Ribo-seq, has emerged. Unlike ribosome profiling, Mito Ribo-seq first requires the isolation and purification of mitochondrial ribosomes, which is achieved by sucrose gradient centrifugation [195, 196].

The emergence of Mito Ribo-seq has greatly promoted research in the field of mitochondrial translation. According to the conventional perspective, excess input into the nuclear-encoded OXPHOS components occurs during the assembly of OXPHOS [90]. However, using Mito Ribo-seq, researchers have shown that the average synthesis level of OXPHOS components in mitochondria corresponds to the average synthesis level in the cytoplasm [197], indicating that the components of OXPHOS may be synthesized proportionally to one another, challenging previous viewpoints. In addition, researchers have discovered a short ORF in the MT-ND5 3' UTR that encodes a short peptide chain consisting of four amino acids [197]. The mitochondrial ribosome density of this ORF is comparable to that of other OXPHOS ORFs, suggesting that it may be translated and play a cellular role. However, due to the limited application of gene editing in mitochondria, its function has not yet been determined.

These functional noncanonical mitochondrial ORFs have also been described in other studies, indicating that the coding potential of the mitochondrial genome may have been underestimated [198].

In Vitro Construction of the mitochondrial translation system

Despite providing valuable approaches for monitoring intracellular mitochondrial translation, the aforementioned methods have limitations in investigating complex molecular mechanisms. A recombinant system for mammalian mitochondrial translation has been developed to overcome this challenge. This system involves a combination of purified recombinant mitochondrial factors, 55 S mitochondrial ribosomes, and leaderless mRNAs and tRNAs derived from yeast or *E. coli*. It enables the synthesis of model proteins, such as bacterial dihydrofolate reductase and nanoluciferase, as well as three mitochondria-encoded proteins (ATP8, ND3, and ND4L) [199].

Through various improvements, this technique has assisted scientists in obtaining a deeper understanding of the mitochondrial translation initiation system. Unlike cytoplasmic translation, leaderless mRNAs preferentially bind to assembled 55 S ribosomes rather than to small subunits [200]. mtIF2 was also found to be essential for translation initiation. In contrast, mtIF3 is dispensable and only required for the translation of ATP6 [200].

Mitochondrial gene editing

A technique has been developed to inhibit the translation of specific mitochondrial mRNAs in vitro, thereby interfering with the expression of specific mitochondrial transcripts. Using this technique, researchers constructed a precursor–morpholino chimera composed of Jac1 and a morpholino, in which the morpholino can impair RNA maturation and translation through an antisense mechanism of action. The precursor–morpholino chimera is imported into purified mitochondria through the TOM/TIM23 complex. Once inside the mitochondria, the chimera binds to the target mRNA, blocking its interaction with the mitochondrial ribosome [201]. This innovative technology addresses the question of the mechanism by which double cis-trans mRNAs, such as ATP8/ATP6 and ND4L/ND4, are translated. The translation of these two ORFs is not an independent ribosome association event. Protein synthesis from downstream ORFs requires translation initiation from upstream ORFs [201]. Furthermore, this technique facilitates the immunoseparation of individual mitochondrial transcripts during active translation. This process enables the identification of RNA-binding proteins through mass spectrometry. In recent studies, the use of this approach led to the identification of IGF2BP1 and DHX30 as activators of mitochondrial translation [201]. Overall, this technique provides valuable insights into the regulation and mechanisms of mitochondrial translation at the molecular level.

Gene editing technology for mtDNA has emerged as a prominent research focus in the field of mitochondrial biology. While CRISPR gene editing systems have revolutionized genetic editing, their direct applicability to mtDNA is hindered by the absence of a viable method for delivering guide RNA to the mitochondria. Inspiringly, the recent identification of DddAtox, a novel cytidine deaminase that targets double-stranded DNA (dsDNA), has paved the way for mitochondrial base editing through the development of DddA-derived cytosine base editors (DdCBEs) [202]. By leveraging DddA and its homologs, researchers have successfully manipulated site-specific mutations within mtDNA, providing innovative paths for disease modeling and the treatment of mitochondrial disorders [203–205]. Despite significant advances, mitochondrial gene editing technology needs further development in the future to address the challenges of efficiency and specificity [206].

Conclusions and perspectives

Mitochondria exhibit notable differences in protein translation processes compared to those of cytoplasmic translation, mainly due to the presence of distinct genomic and protein synthesis systems. Mitochondrial translation is regulated by the expression of RNAs and factors that coordinate OXPHOS complex assembly. Additionally, mitochondrial translation influences cytoplasmic translation through various signaling pathways, including the ISR, and the nucleus also regulates mitochondrial translation through selective protein expression. Recent studies have revealed the significant role of mitochondrial translation in normal and malignant hematopoiesis (Table 4). A disruption of mitochondrial translation leads to impaired normal hematopoiesis, such as hindered HSC erythroid differentiation and decreased T-cell cytotoxic function. Moreover, mitochondrial translation plays a crucial role in malignant hematopoiesis. It is regarded as a potential therapeutic target for various hematologic malignancies. Mitochondrial translation inhibition may affect both normal and malignant hematopoiesis through downstream effects on inhibiting cytoplasmic translation and disrupting metabolism. However, the exact underlying mechanisms remain unclear, and epigenetic changes, RBPs, and ROS may play potential roles in this process. Research techniques specifically focused on mitochondrial translation must be developed. Monitoring and studying mitochondrial translation using techniques such as mitochondrial ribosomal profiling may represent a promising direction for future research.

Despite significant advances in understanding the relationship between mitochondrial translation and hematopoiesis, unresolved issues remain in this field, which

Table 4 Methods and biological phenotypes of mitochondrial translation-mediated inhibition of normal and malignant hematopoiesis

Classification	Cell Type	Methods to Inhibit Mitochondrial Translation	Main Biological Phenotypes	Reference
Malignant hematopoiesis	AML	Tigecycline, chloramphenicol, and linezolid Knockdown of mtEFTu	Reduced growth and viability Decreased mitochondrial membrane potential and oxygen consumption in tumors	[8]
	ALL	Knockdown of ICT1	Suppression of proliferation The cell cycle is arrested at S and sub-G1 phases Promotion of apoptosis	[180]
	AML	Tedizolid Doxycycline	Inhibition of complex I Synergistic activation of the integrative stress response with venetoclax, thereby overcoming venetoclax resistance	[174]
	DCBCLs	Tigecycline Knockdown of mtEFG1, mtEFTu, or MRPS7	Selectively toxic to OXPHOS-DLBCL cell lines and primary tumors	[178]
	Myc-driven lymphoma	Tigecycline Inhibition of HsPDF; knockdown of TFAM	Inhibit myc-driven lymphoma proliferation Promotion of apoptosis	[9, 150, 166]
	CML	Tigecycline	Impairment of OXPHOS, glycolysis, and primary CML proliferation	[165]
	ALL	Tigecycline	Promotion of apoptosis Enhancement of chemotherapeutic sensitivity	[167]
	MM	Tigecycline	Reduction in mitochondrial activity Inhibition of cancer cell growth	[183]
Normal hematopoiesis	$CD8^+$ T cells	Doxycycline Chloramphenicol	Impairment in the *de novo* synthesis of cytolytic proteins Higher expression levels of metabolic enzymes and RBPs	[5]
	$CD8^+$ T cells	Knockdown of MRPL39 or OXA1L expression Tigecycline	Impairment of cellular oxygen consumption and an antitumor capacity during fever	[7]
	Th17 cells	Linezolid Knockdown of mEFG1 expression	Deficient OXPHOS Decreased NAD+/NADH ratio Impairing cytokine production	[6]
	$CD8^+$ T cells	Azithromycin	Diminished mtROS-dependent IL-2 production Decreased IL-2-dependent TNF, IFN-γ, perforin, and granzyme B production	[116]
	B cells	Knockdown of TFAM expression	Damage to the actin cytoskeleton Impaired the motility of GC B cells in response to chemokine signaling	[178]
	Macrophages	7-Ketocholesterol Doxycycline	Inhibition of tumor necrosis factor signaling, resulting in dysfunctional phagocytosis	[155]
	Megakaryocytes, Platelets	Knockdown of mtIF3	Inhibition of megakaryocyte production and platelet activation	[46]

ALL: acute lymphoblastic leukemia; DLBCLs: diffuse large B-cell lymphomas; AML: acute myeloid leukemia; CML: chronic myeloid leukemia; EF-Tu: mitochondrial elongation factor Tu; ICT1: immature colon carcinoma transcript 1; GFM1: G elongation factor, mitochondrial, 1; MRPS7: mitochondrial ribosomal protein, S7; HsPDF: human mitochondrial peptide deformylase; TFAM: transcription factor A, mitochondrial; MRPL39: mitochondrial ribosomal protein, L39; OXA1L: mitochondrial ribosome-associated insertase; mEF-G1: mitochondrial elongation factor G1; mtIF3: mitochondrial translation initiation factor 3; MM: multiple myeloma

are listed below. (1) Current studies have identified several potential downstream pathways of mitochondrial translation, but the specific mechanisms and possible signaling cascades involved have not been fully explored. Furthermore, determining whether these pathways are cell type specific is essential. For example, in T cells and HSCs, mitochondrial translation has been shown to affect cell function through epigenetic effects, RBPs, and ROS. However, whether these pathways are exclusive to specific cell types remains uncertain. (2) Research on mitochondrial translation needs to broaden its scope. While most hematopoietic cells have been studied, limited research has been conducted on NK cells and granulocytes. Additionally, the role of mitochondrial translation in other cells, such as fibroblasts, remains unknown, and its elaboration can improve our understanding of the whole tumor microenvironment. Cellular processes that may be influenced by mitochondrial translation, such as mitochondrial transfer, need to be investigated as well. (3) Inhibiting mitochondrial translation is considered a potential strategy for treating various hematological malignancies, but effective clinical studies are still lacking. The challenge of efficiently inhibiting mitochondrial translation in malignant cells in vivo remains

a significant barrier to clinical application. The development of novel mitochondrial inhibitors or gene editing technologies may represent promising approaches for future therapeutic interventions. Additionally, our recent studies confirmed the role of mitochondrial metabolism in enhancing the function of chimeric antigen receptor T cells [207–209]. Given the influence of mitochondrial translation on the metabolism of immune cells, mitochondrial translation could effectively enhance the efficacy of immunotherapies, which requires further investigation.

Abbreviations

HSC	hematopoietic stem cell
mRNA	messenger RNA
SSU	small subunit
LSU	large subunit
MRP	mitochondrial ribosomal protein
CRIF1	CR6-interacting factor 1
Lck	lymphocyte-specific protein tyrosine kinase
IL	interleukin
rRNA	ribosomal RNA
mtDNA	mitochondrial DNA
IMM	inner mitochondrial membrane
tRNA	transfer RNA
OXPHOS	oxidative phosphorylation
PTH	peptidyl-tRNA hydrolase
RBP	RNA binding protein
GTPBP6	GTP-binding protein 6
miRNA	microRNA
LRPPRC-SLIRP	leucine-rich PPR motif-containing protein–SRA stem loop-interacting RNA-binding protein
FASTK	Fas-activated serine/threonine kinase
GRSF1	G-rich sequence factor 1
mtPAP	mitochondrial poly(A) polymerase
TRNT1	tRNA nucleotidyltransferase 1
PDE12	2′,5′-phosphodiesterase
TACO1	translation activator of CO1
MITRAC12	mitochondrial translation regulation assembly intermediate of cytochrome c oxidase 12
TIM	inner membrane translocase
ETC	electron transport chain
GSC	glioblastoma stem cells
HCC	hepatocellular carcinoma
ROS	reactive oxygen species
ISR	integrated stress response
mTORC1	mammalian target of rapamycin protein complex 1
eIF2α	eukaryotic translation initiation factor 2 subunit alpha
HRI	heme-regulated inhibitor
DELE	death ligand signal enhancer
mtUPR	mitochondrial unfolded protein response
ATFS-1	activating transcription factor associated with stress-1
NLS	nuclear localization sequence
MLS	mitochondrial localization sequence
CHOP	C/EBP homologous protein
S6K1	p70s6 protein kinase 1
4EBP	eIF4E-binding protein
TFAM	mitochondrial transcription factor A
EPO	erythropoietin
βOHB	β-hydroxybutyrate
MRPL39	mitochondrial ribosomal subunit 39
OXA1L	mitochondrial ribosome-associated insertion enzyme
MPP	multipotent progenitor
CLP	common lymphoid progenitor
CMP	common myeloid progenitor
MEP	megakaryocyte/erythroid progenitor
GMP	granulocyte/macrophage progenitor
CTL	cytotoxic T lymphocyte
GC	germinal center
TAM	tumor-associated macrophage
CSA	congenital sideroblastic anemia
PMPS	Pearson marrow–pancreas syndrome
MLASA	mitochondrial myopathy with lactic acidosis and sideroblastic anemia
PUS1	pseudouridine synthase
TARS2	mitochondrial tyrosyl-tRNA synthetase
AML	acute myeloid leukemia
LSC	leukemia stem cell
CML	chronic myeloid leukemia
DLBCL	diffuse large B-cell lymphoma
HsPDF	human mitochondrial peptide deformylase
MM	multiple myeloma
mito-FUNCAT	mitochondrial fluorescence noncanonical amino acid tagging
STED	superresolution-stimulated emission depletion
CM	cristae membrane
FACS	fluorescence-activated cell sorting
RPF	ribosome-protected fragment
ORF	open reading frame
dsDNA	double-stranded DNA
DdCBEs	DddA-derived cytosine base editors

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

Declarations

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Boczonadi V, Horvath R. Mitochondria: impaired mitochondrial translation in human disease. Int J Biochem Cell Biol. 2014;48(100):77–84.
2. Zhang L, Ging NC, Komoda T, Hanada T, Suzuki T, Watanabe K. Antibiotic susceptibility of mammalian mitochondrial translation. FEBS Lett. 2005;579(28):6423–7.

3. Gonzalez-Menendez P, Phadke I, Olive ME, Joly A, Papoin J, Yan H, et al. Arginine metabolism regulates human erythroid differentiation through hypusination of eIF5A. Blood. 2023;141(20):2520–36.
4. Wang B, Shi D, Yang S, Lian Y, Li H, Cao M et al. Mitochondrial tRNA pseudouridylation governs erythropoiesis. Blood. 2024;blood.2023022004.
5. Lisci M, Barton PR, Randzavola LO, Ma CY, Marchingo JM, Cantrell DA, et al. Mitochondrial translation is required for sustained killing by cytotoxic T cells. Science. 2021;374(6565):eabe9977.
6. Almeida L, Dhillon-LaBrooy A, Castro CN, Adossa N, Carriche GM, Guderian M, et al. Ribosome-targeting antibiotics impair T cell effector function and ameliorate autoimmunity by blocking mitochondrial protein synthesis. Immunity. 2021;54(1):68–e836.
7. O'Sullivan D, Stanczak MA, Villa M, Uhl FM, Corrado M, Klein Geltink RI, et al. Fever supports CD8 $^{+}$ effector T cell responses by promoting mitochondrial translation. Proc Natl Acad Sci USA. 2021;118(25):e2023752118.
8. Skrtić M, Sriskanthadevan S, Jhas B, Gebbia M, Wang X, Wang Z, et al. Inhibition of mitochondrial translation as a therapeutic strategy for human acute myeloid leukemia. Cancer Cell. 2011;20(5):674–88.
9. D'Andrea A, Gritti I, Nicoli P, Giorgio M, Doni M, Conti A, et al. The mitochondrial translation machinery as a therapeutic target in myc-driven lymphomas. Oncotarget. 2016;7(45):72415–30.
10. Martijn J, Vosseberg J, Guy L, Offre P, Ettema TJG. Deep mitochondrial origin outside the sampled alphaproteobacteria. Nature. 2018;557(7703):101–5.
11. Greber BJ, Bieri P, Leibundgut M, Leitner A, Aebersold R, Boehringer D, et al. Ribosome. The complete structure of the 55S mammalian mitochondrial ribosome. Science. 2015;348(6232):303–8.
12. Greber BJ, Boehringer D, Leitner A, Bieri P, Voigts-Hoffmann F, Erzberger JP, et al. Architecture of the large subunit of the mammalian mitochondrial ribosome. Nature. 2014;505(7484):515–9.
13. Kim SJ, Kwon M, chul, Ryu MJ, Chung HK, Tadi S, Kim YK, et al. CRIF1 is essential for the synthesis and insertion of oxidative phosphorylation polypeptides in the mammalian mitochondrial membrane. Cell Metab. 2012;16(2):274–83.
14. Kim HJ, Maiti P, Barrientos A. Mitochondrial ribosomes in cancer. Semin Cancer Biol. 2017;47:67–81.
15. Matsumoto Y, Tsukamoto T, Chinen Y, Shimura Y, Sasaki N, Nagoshi H, et al. Detection of novel and recurrent conjoined genes in non-hodgkin B-cell lymphoma. J Clin Exp Hematop. 2021;61(2):71–7.
16. Lin YW, Aplan PD. Gene expression profiling of precursor T-cell lymphoblastic leukemia/lymphoma identifies oncogenic pathways that are potential therapeutic targets. Leukemia. 2007;21(6):1276–84.
17. Aasebø E, Berven FS, Hovland R, Døskeland SO, Bruserud Ø, Selheim F, et al. The progression of Acute myeloid leukemia from first diagnosis to Chemoresistant Relapse: a comparison of proteomic and phosphoproteomic profiles. Cancers (Basel). 2020;12(6):1466.
18. Niu F, Kazimierska M, Nolte IM, Terpstra MM, de Jong D, Koerts J, et al. The miR-26b-5p/KPNA2 Axis is an important Regulator of Burkitt Lymphoma Cell Growth. Cancers (Basel). 2020;12(6):1464.
19. Lebedev TD, Vagapova ER, Popenko VI, Leonova OG, Spirin PV, Prassolov VS. Two receptors, Two Isoforms, two cancers: comprehensive analysis of KIT and TrkA expression in Neuroblastoma and Acute Myeloid Leukemia. Front Oncol. 2019;9:1046.
20. Wang W, Xu SW, Zhu XY, Guo QY, Zhu M, Mao XL, et al. Identification and validation of a novel RNA-Binding protein-related gene-based prognostic model for multiple myeloma. Front Genet. 2021;12:665173.
21. Chen D, Nemazanyy I, Peulen O, Shostak K, Xu X, Tang SC, et al. Elp3-mediated codon-dependent translation promotes mTORC2 activation and regulates macrophage polarization. EMBO J. 2022;41(18):e109353.
22. Ran Q, Hao P, Xiao Y, Xiang L, Ye X, Deng X, et al. CRIF1 interacting with CDK2 regulates bone marrow microenvironment-induced G0/G1 arrest of leukemia cells. PLoS ONE. 2014;9(2):e85328.
23. Vahedi S, Chueh FY, Dutta S, Chandran B, Yu CL. Nuclear lymphocyte-specific protein tyrosine kinase and its interaction with CR6-interacting factor 1 promote the survival of human leukemic T cells. Oncol Rep. 2015;34(1):43–50.
24. Park JS, Choi SY, Hwang SH, Kim SM, Choi J, Jung KA, et al. CR6-interacting factor 1 controls autoimmune arthritis by regulation of signal transducer and activator of transcription 3 pathway and T helper type 17 cells. Immunology. 2019;156(4):413–21.
25. Lee S, Song SG, Kim G, Kim S, Yoo HJ, Koh J, et al. CRIF1 deficiency induces FOXP3LOW inflammatory non-suppressive regulatory T cells, thereby promoting antitumor immunity. Sci Adv. 2024;10(13):eadj9600.
26. Park JS, Yang S, Hwang SH, Choi J, Kwok SK, Kong YY, et al. B cell-specific deletion of CR6-Interacting factor 1 drives lupus-like autoimmunity by activation of Interleukin-17, Interleukin-6, and Pathogenic Follicular Helper T Cells in a mouse model. Arthritis Rheumatol. 2022;74(7):1211–22.
27. Jung SB, Choi MJ, Ryu D, Yi HS, Lee SE, Chang JY, et al. Reduced oxidative capacity in macrophages results in systemic insulin resistance. Nat Commun. 2018;9(1):1551.
28. Kummer E, Ban N. Mechanisms and regulation of protein synthesis in mitochondria. Nat Rev Mol Cell Biol. 2021;22(5):307–25.
29. Zhai X, Liu K, Fang H, Zhang Q, Gao X, Liu F, et al. Mitochondrial C1qbp promotes differentiation of effector CD8 + T cells via metabolic-epigenetic reprogramming. Sci Adv. 2021;7(49):eabk0490.
30. Wang X, Deng D, Yan Y, Cai M, Liu X, Luo A, et al. Genetic variants in m5C modification core genes are associated with the risk of Chinese pediatric acute lymphoblastic leukemia: a five-center case-control study. Front Oncol. 2022;12:1082525.
31. Bogenhagen DF, Ostermeyer-Fay AG, Haley JD, Garcia-Diaz M. Kinetics and mechanism of mammalian mitochondrial ribosome assembly. Cell Rep. 2018;22(7):1935–44.
32. Temperley RJ, Wydro M, Lightowlers RN, Chrzanowska-Lightowlers ZM. Human mitochondrial mRNAs–like members of all families, similar but different. Biochim Biophys Acta. 2010;1797(6–7):1081–5.
33. Spencer AC, Spremulli LL. Interaction of mitochondrial initiation factor 2 with mitochondrial fMet-tRNA. Nucleic Acids Res. 2004;32(18):5464–70.
34. Montoya J, Ojala D, Attardi G. Distinctive features of the 5'-terminal sequences of the human mitochondrial mRNAs. Nature. 1981;290(5806):465–70.
35. Nakano S, Suzuki T, Kawarada L, Iwata H, Asano K, Suzuki T. NSUN3 methylase initiates 5-formylcytidine biogenesis in human mitochondrial tRNA(Met). Nat Chem Biol. 2016;12(7):546–51.
36. Haag S, Sloan KE, Ranjan N, Warda AS, Kretschmer J, Blessing C, et al. NSUN3 and ABH1 modify the wobble position of mt-tRNAMet to expand codon recognition in mitochondrial translation. EMBO J. 2016;35(19):2104–19.
37. Van Haute L, Dietmann S, Kremer L, Hussain S, Pearce SF, Powell CA, et al. Deficient methylation and formylation of mt-tRNA(Met) wobble cytosine in a patient carrying mutations in NSUN3. Nat Commun. 2016;7:12039.
38. Hussain T, Llácer JL, Fernández IS, Munoz A, Martin-Marcos P, Savva CG, et al. Structural changes enable start codon recognition by the eukaryotic translation initiation complex. Cell. 2014;159(3):597–607.
39. Yassin AS, Haque ME, Datta PP, Elmore K, Banavali NK, Spremulli LL, et al. Insertion domain within mammalian mitochondrial translation initiation factor 2 serves the role of eubacterial initiation factor 1. Proc Natl Acad Sci U S A. 2011;108(10):3918–23.
40. Kummer E, Leibundgut M, Rackham O, Lee RG, Boehringer D, Filipovska A, et al. Unique features of mammalian mitochondrial translation initiation revealed by cryo-EM. Nature. 2018;560(7717):263–7.
41. Christian BE, Spremulli LL. Preferential selection of the 5'-terminal start codon on leaderless mRNAs by mammalian mitochondrial ribosomes. J Biol Chem. 2010;285(36):28379–86.
42. Ayyub SA, Dobriyal SLA, Aluri D, Spremulli S, Varshney LL. Fidelity of translation in the presence of mammalian mitochondrial initiation factor 3. Mitochondrion. 2018;39:1–8.
43. Haque ME, Spremulli LL. Roles of the N- and C-terminal domains of mammalian mitochondrial initiation factor 3 in protein biosynthesis. J Mol Biol. 2008;384(4):929–40.
44. Rudler DL, Hughes LA, Perks KL, Richman TR, Kuznetsova I, Ermer JA, et al. Fidelity of translation initiation is required for coordinated respiratory complex assembly. Sci Adv. 2019;5(12):eaay2118.
45. Itoh Y, Khawaja A, Laptev I, Cipullo M, Atanassov I, Sergiev P, et al. Mechanism of mitoribosomal small subunit biogenesis and preinitiation. Nature. 2022;606(7914):603–8.
46. Richman TR, Ermer JA, Baker J, Siira SJ, Kile BT, Linden MD, et al. Mitochondrial gene expression is required for platelet function and blood clotting. Cell Rep. 2023;42(11):113312.
47. Schwartzbach CJ, Spremulli LL. Bovine mitochondrial protein synthesis elongation factors. Identification and initial characterization of an elongation factor Tu-elongation factor Ts complex. J Biol Chem. 1989;264(32):19125–31.
48. Woriax VL, Bullard JM, Ma L, Yokogawa T, Spremulli LL. Mechanistic studies of the translational elongation cycle in mammalian mitochondria. Biochim Biophys Acta. 1997;1352(1):91–101.
49. Cai YC, Bullard JM, Thompson NL, Spremulli LL. Interaction of mitochondrial elongation factor Tu with aminoacyl-tRNA and elongation factor ts. J Biol Chem. 2000;275(27):20308–14.

50. Jeppesen MG, Navratil T, Spremulli LL, Nyborg J. Crystal structure of the bovine mitochondrial elongation factor Tu.Ts complex. J Biol Chem. 2005;280(6):5071–81.
51. Bhargava K, Templeton P, Spremulli LL. Expression and characterization of isoform 1 of human mitochondrial elongation factor G. Protein Expr Purif. 2004;37(2):368–76.
52. Chung HK, Spremulli LL. Purification and characterization of elongation factor G from bovine liver mitochondria. J Biol Chem. 1990;265(34):21000–4.
53. Eberly SL, Locklear V, Spremulli LL. Bovine mitochondrial ribosomes. Elongation factor specificity. J Biol Chem. 1985;260(15):8721–5.
54. Bauerschmitt H, Funes S, Herrmann JM. The membrane-bound GTPase Guf1 promotes mitochondrial protein synthesis under suboptimal conditions. J Biol Chem. 2008;283(25):17139–46.
55. Zhu P, Liu Y, Zhang F, Bai X, Chen Z, Shangguan F, et al. Human elongation factor 4 regulates Cancer Bioenergetics by acting as a mitochondrial translation switch. Cancer Res. 2018;78(11):2813–24.
56. Barrell BG, Bankier AT, Drouin J. A different genetic code in human mitochondria. Nature. 1979;282(5735):189–94.
57. Anderson S, Bankier AT, Barrell BG, de Bruijn MH, Coulson AR, Drouin J, et al. Sequence and organization of the human mitochondrial genome. Nature. 1981;290(5806):457–65.
58. Nozaki Y, Matsunaga N, Ishizawa T, Ueda T, Takeuchi N. HMRF1L is a human mitochondrial translation release factor involved in the decoding of the termination codons UAA and UAG. Genes Cells. 2008;13(5):429–38.
59. Soleimanpour-Lichaei HR, Kühl I, Gaisne M, Passos JF, Wydro M, Rorbach J, et al. mtRF1a is a human mitochondrial translation release factor decoding the major termination codons UAA and UAG. Mol Cell. 2007;27(5):745–57.
60. Nadler F, Lavdovskaia E, Krempler A, Cruz-Zaragoza LD, Dennerlein S, Richter-Dennerlein R. Human mtRF1 terminates COX1 translation and its ablation induces mitochondrial ribosome-associated quality control. Nat Commun. 2022;13(1):6406.
61. Akabane S, Ueda T, Nierhaus KH, Takeuchi N. Ribosome rescue and translation termination at non-standard stop codons by ICT1 in mammalian mitochondria. PLoS Genet. 2014;10(9):e1004616.
62. Li GY, Liu JZ, Zhang L, Liu GZ, Li SJ, Xiao TW, et al. Knockdown of immature colon carcinoma transcript 1 induces suppression of proliferation, S-phase arrest and apoptosis in leukemia cells. Oncol Rep. 2018;39(3):1269–75.
63. Xie W, Wu M, Fu T, Li X, Wang Z, Hu Y, et al. ICT1 predicts a poor survival and correlated with cell proliferation in diffuse large B-cell lymphoma. Gene. 2017;627:255–62.
64. Pearce SF, Rorbach J, Van Haute L, D'Souza AR, Rebelo-Guiomar P, Powell CA, et al. Maturation of selected human mitochondrial tRNAs requires deadenylation. Elife. 2017;6:e27596.
65. Gopalakrishna S, Pearce SF, Dinan AM, Schober FA, Cipullo M, Spåhr H, et al. C6orf203 is an RNA-binding protein involved in mitochondrial protein synthesis. Nucleic Acids Res. 2019;47(17):9386–99.
66. Tsuboi M, Morita H, Nozaki Y, Akama K, Ueda T, Ito K, et al. EF-G2mt is an exclusive recycling factor in mammalian mitochondrial protein synthesis. Mol Cell. 2009;35(4):502–10.
67. Kummer E, Schubert KN, Schoenhut T, Scaiola A, Ban N. Structural basis of translation termination, rescue, and recycling in mammalian mitochondria. Mol Cell. 2021;81(12):2566–e25826.
68. Lavdovskaia E, Denks K, Nadler F, Steube E, Linden A, Urlaub H, et al. Dual function of GTPBP6 in biogenesis and recycling of human mitochondrial ribosomes. Nucleic Acids Res. 2020;48(22):12929–42.
69. Zhang Y, Mandava CS, Cao W, Li X, Zhang D, Li N, et al. HflX is a ribosome-splitting factor rescuing stalled ribosomes under stress conditions. Nat Struct Mol Biol. 2015;22(11):906–13.
70. Christian BE, Spremulli LL. Evidence for an active role of IF3mt in the initiation of translation in mammalian mitochondria. Biochemistry. 2009;48(15):3269–78.
71. Weisser M, Ban N, Extensions. Extra factors, and Extreme Complexity: ribosomal structures provide insights into eukaryotic translation. Cold Spring Harb Perspect Biol. 2019;11(9):a032367.
72. Zhang X, Zuo X, Yang B, Li Z, Xue Y, Zhou Y, et al. MicroRNA directly enhances mitochondrial translation during muscle differentiation. Cell. 2014;158(3):607–19.
73. Hillen HS, Temiakov D, Cramer P. Structural basis of mitochondrial transcription. Nat Struct Mol Biol. 2018;25(9):754–65.
74. Barchiesi A, Vascotto C. Transcription, Processing, and decay of mitochondrial RNA in Health and Disease. Int J Mol Sci. 2019;20(9):2221.
75. Mercer TR, Neph S, Dinger ME, Crawford J, Smith MA, Shearwood AMJ, et al. The human mitochondrial transcriptome. Cell. 2011;146(4):645–58.
76. Ali AT, Boehme L, Carbajosa G, Seitan VC, Small KS, Hodgkinson A. Nuclear genetic regulation of the human mitochondrial transcriptome. Elife. 2019;8:e41927.
77. Chujo T, Ohira T, Sakaguchi Y, Goshima N, Nomura N, Nagao A, et al. LRPPRC/SLIRP suppresses PNPase-mediated mRNA decay and promotes polyadenylation in human mitochondria. Nucleic Acids Res. 2012;40(16):8033–47.
78. Borowski LS, Dziembowski A, Hejnowicz MS, Stepien PP, Szczesny RJ. Human mitochondrial RNA decay mediated by PNPase-hSuv3 complex takes place in distinct foci. Nucleic Acids Res. 2013;41(2):1223–40.
79. Sasarman F, Brunel-Guitton C, Antonicka H, Wai T, Shoubridge EA, LSFC Consortium. LRPPRC and SLIRP interact in a ribonucleoprotein complex that regulates posttranscriptional gene expression in mitochondria. Mol Biol Cell. 2010;21(8):1315–23.
80. Ruzzenente B, Metodiev MD, Wredenberg A, Bratic A, Park CB, Cámara Y, et al. LRPPRC is necessary for polyadenylation and coordination of translation of mitochondrial mRNAs. EMBO J. 2012;31(2):443–56.
81. Jourdain AA, Popow J, de la Fuente MA, Martinou JC, Anderson P, Simarro M. The FASTK family of proteins: emerging regulators of mitochondrial RNA biology. Nucleic Acids Res. 2017;45(19):10941–7.
82. Jourdain AA, Koppen M, Rodley CD, Maundrell K, Gueguen N, Reynier P, et al. A mitochondria-specific isoform of FASTK is present in mitochondrial RNA granules and regulates gene expression and function. Cell Rep. 2015;10(7):1110–21.
83. Sellin M, Mack R, Rhodes MC, Zhang L, Berg S, Joshi K, et al. Molecular mechanisms by which splice modulator GEX1A inhibits leukaemia development and progression. Br J Cancer. 2022;127(2):223–36.
84. Boehm E, Zaganelli S, Maundrell K, Jourdain AA, Thore S, Martinou JC. FASTKD1 and FASTKD4 have opposite effects on expression of specific mitochondrial RNAs, depending upon their endonuclease-like RAP domain. Nucleic Acids Res. 2017;45(10):6135–46.
85. Zhang J, He P, Wang X, Wei S, Ma L, Zhao J. A Novel Model of Tumor-infiltrating B lymphocyte specific RNA-Binding protein-related genes with potential prognostic value and therapeutic targets in multiple myeloma. Front Genet. 2021;12:778715.
86. Wang J, Mi JQ, Debernardi A, Vitte AL, Emadali A, Meyer JA, et al. A six gene expression signature defines aggressive subtypes and predicts outcome in childhood and adult acute lymphoblastic leukemia. Oncotarget. 2015;6(18):16527–42.
87. Guo H, Wang Q, Ghneim K, Wang L, Rampanelli E, Holley-Guthrie E, et al. Multi-omics analyses reveal that HIV-1 alters CD4 + T cell immunometabolism to fuel virus replication. Nat Immunol. 2021;22(4):423–33.
88. Antonicka H, Sasarman F, Nishimura T, Paupe V, Shoubridge EA. The mitochondrial RNA-binding protein GRSF1 localizes to RNA granules and is required for posttranscriptional mitochondrial gene expression. Cell Metab. 2013;17(3):386–98.
89. Nieradka A, Ufer C, Thiadens K, Grech G, Horos R, van Coevorden-Hameete M, et al. Grsf1-induced translation of the SNARE protein Use1 is required for expansion of the erythroid compartment. PLoS ONE. 2014;9(9):e104631.
90. Bogenhagen DF, Haley JD. Pulse-chase SILAC-based analyses reveal selective oversynthesis and rapid turnover of mitochondrial protein components of respiratory complexes. J Biol Chem. 2020;295(9):2544–54.
91. McShane E, Couvillion M, Ietswaart R, Prakash G, Smalec BM, Soto I, et al. A kinetic dichotomy between mitochondrial and nuclear gene expression processes. Mol Cell. 2024;84(8):1541–e155511.
92. Herrmann JM, Woellhaf MW, Bonnefoy N. Control of protein synthesis in yeast mitochondria: the concept of translational activators. Biochim Biophys Acta. 2013;1833(2):286–94.
93. Richman TR, Spåhr H, Ermer JA, Davies SMK, Viola HM, Bates KA, et al. Loss of the RNA-binding protein TACO1 causes late-onset mitochondrial dysfunction in mice. Nat Commun. 2016;7:11884.
94. Weraarpachai W, Antonicka H, Sasarman F, Seeger J, Schrank B, Kolesar JE, et al. Mutation in TACO1, encoding a translational activator of COX I, results in cytochrome c oxidase deficiency and late-onset Leigh syndrome. Nat Genet. 2009;41(7):833–7.
95. Richter-Dennerlein R, Oeljeklaus S, Lorenzi I, Ronsör C, Bareth B, Schendzielorz AB, et al. Mitochondrial protein synthesis adapts to influx of Nuclear-Encoded protein. Cell. 2016;167(2):471–e48310.
96. Wang C, Richter-Dennerlein R, Pacheu-Grau D, Liu F, Zhu Y, Dennerlein S, et al. MITRAC15/COA1 promotes mitochondrial translation in a ND2 ribosome-nascent chain complex. EMBO Rep. 2020;21(1):e48833.

97. Mick DU, Dennerlein S, Wiese H, Reinhold R, Pacheu-Grau D, Lorenzi I, et al. MITRAC links mitochondrial protein translocation to respiratory-chain assembly and translational regulation. Cell. 2012;151(7):1528–41.
98. Weraarpachai W, Sasarman F, Nishimura T, Antonicka H, Auré K, Rötig A, et al. Mutations in C12orf62, a factor that couples COX I synthesis with cytochrome c oxidase assembly, cause fatal neonatal lactic acidosis. Am J Hum Genet. 2012;90(1):142–51.
99. Quirós PM, Prado MA, Zamboni N, D'Amico D, Williams RW, Finley D, et al. Multi-omics analysis identifies ATF4 as a key regulator of the mitochondrial stress response in mammals. J Cell Biol. 2017;216(7):2027–45.
100. Molenaars M, Janssens GE, Williams EG, Jongejan A, Lan J, Rabot S, et al. A conserved mito-cytosolic translational balance links two longevity pathways. Cell Metabol. 2020;31(3):549–e5637.
101. Sasaki K, Uchiumi T, Toshima T, Yagi M, Do Y, Hirai H, et al. Mitochondrial translation inhibition triggers ATF4 activation, leading to integrated stress response but not to mitochondrial unfolded protein response. Biosci Rep. 2020;40(11):BSR20201289.
102. Marchingo JM, Cantrell DA. Protein synthesis, degradation, and energy metabolism in T cell immunity. Cell Mol Immunol. 2022;19(3):303–15.
103. Riesenberg BP, Hunt EG, Tennant MD, Hurst KE, Andrews AM, Leddy LR, et al. Stress-mediated attenuation of translation undermines T-cell activity in Cancer. Cancer Res. 2022;82(23):4386–99.
104. Yu M, Li R, Zhang J. Repositioning of antibiotic levofloxacin as a mitochondrial biogenesis inhibitor to target breast cancer. Biochem Biophys Res Commun. 2016;471(4):639–45.
105. Tan J, Song M, Zhou M, Hu Y. Antibiotic tigecycline enhances cisplatin activity against human hepatocellular carcinoma through inducing mitochondrial dysfunction and oxidative damage. Biochem Biophys Res Commun. 2017;483(1):17–23.
106. Sighel D, Notarangelo M, Aibara S, Re A, Ricci G, Guida M, et al. Inhibition of mitochondrial translation suppresses glioblastoma stem cell growth. Cell Rep. 2021;35(4):109024.
107. Liu X, Zhang Y, Ni M, Cao H, Signer RAJ, Li D, et al. Regulation of mitochondrial biogenesis in erythropoiesis by mTORC1-mediated protein translation. Nat Cell Biol. 2017;19(6):626–38.
108. Castello A, Hentze MW, Preiss T. Metabolic enzymes enjoying new partnerships as RNA-Binding proteins. Trends Endocrinol Metab. 2015;26(12):746–57.
109. Turner M, Díaz-Muñoz MD. RNA-binding proteins control gene expression and cell fate in the immune system. Nat Immunol. 2018;19(2):120–9.
110. Salerno F, Turner M, Wolkers MC. Dynamic post-transcriptional events governing CD8+T cell homeostasis and effector function. Trends Immunol. 2020;41(3):240–54.
111. Chang CH, Curtis JD, Maggi LB, Faubert B, Villarino AV, O'Sullivan D, et al. Post-transcriptional control of T cell effector function by Aerobic Glycolysis. Cell. 2013;153(6):1239–51.
112. DNA Damage Response and Mitochondrial Translation Mediate ROS Response. Cancer Discov. 2023;OF1.
113. Franchina DG, Dostert C, Brenner D. Reactive oxygen species: involvement in T cell signaling and metabolism. Trends Immunol. 2018;39(6):489–502.
114. Chávez MD, Tse HM. Targeting mitochondrial-derived reactive oxygen species in T cell-mediated Autoimmune diseases. Front Immunol. 2021;12:703972.
115. Peng HY, Lucavs J, Ballard D, Das JK, Kumar A, Wang L, et al. Metabolic reprogramming and reactive oxygen species in T cell immunity. Front Immunol. 2021;12:652687.
116. Fischer M, Bantug GR, Dimeloe S, Gubser PM, Burgener AV, Grählert J, et al. Early effector maturation of naïve human CD8+T cells requires mitochondrial biogenesis. Eur J Immunol. 2018;48(10):1632–43.
117. Borcherding N, Brestoff JR. The power and potential of mitochondria transfer. Nature. 2023;623(7986):283–91.
118. Mistry JJ, Marlein CR, Moore JA, Hellmich C, Wojtowicz EE, Smith JGW, et al. ROS-mediated PI3K activation drives mitochondrial transfer from stromal cells to hematopoietic stem cells in response to infection. Proc Natl Acad Sci U S A. 2019;116(49):24610–9.
119. Marlein CR, Zaitseva L, Piddock RE, Robinson SD, Edwards DR, Shafat MS, et al. NADPH oxidase-2 derived superoxide drives mitochondrial transfer from bone marrow stromal cells to leukemic blasts. Blood. 2017;130(14):1649–60.
120. Costa-Mattioli M, Walter P. The integrated stress response: from mechanism to disease. Science. 2020;368(6489):eaat5314.
121. Guo X, Aviles G, Liu Y, Tian R, Unger BA, Lin YHT, et al. Mitochondrial stress is relayed to the cytosol by an OMA1–DELE1–HRI pathway. Nature. 2020;579(7799):427–32.
122. Fessler E, Eckl EM, Schmitt S, Mancilla IA, Meyer-Bender MF, Hanf M, et al. A pathway coordinated by DELE1 relays mitochondrial stress to the cytosol. Nature. 2020;579(7799):433–7.
123. Michel S, Canonne M, Arnould T, Renard P. Inhibition of mitochondrial genome expression triggers the activation of CHOP-10 by a cell signaling dependent on the integrated stress response but not the mitochondrial unfolded protein response. Mitochondrion. 2015;21:58–68.
124. Harding HP, Novoa I, Zhang Y, Zeng H, Wek R, Schapira M, et al. Regulated translation initiation controls stress-induced gene expression in mammalian cells. Mol Cell. 2000;6(5):1099–108.
125. Tian X, Zhang S, Zhou L, Seyhan AA, Hernandez Borrero L, Zhang Y, et al. Targeting the Integrated stress response in Cancer Therapy. Front Pharmacol. 2021;12:747837.
126. Dogan SA, Pujol C, Maiti P, Kukat A, Wang S, Hermans S, et al. Tissue-specific loss of DARS2 activates stress responses independently of respiratory chain deficiency in the heart. Cell Metab. 2014;19(3):458–69.
127. Münch C, Harper JW. Mitochondrial unfolded protein response controls matrix pre-RNA processing and translation. Nature. 2016;534(7609):710–3.
128. Houtkooper RH, Mouchiroud L, Ryu D, Moullan N, Katsyuba E, Knott G, et al. Mitonuclear protein imbalance as a conserved longevity mechanism. Nature. 2013;497(7450):451–7.
129. Yoneda T, Benedetti C, Urano F, Clark SG, Harding HP, Ron D. Compartment-specific perturbation of protein handling activates genes encoding mitochondrial chaperones. J Cell Sci. 2004;117(Pt 18):4055–66.
130. Chung HK, Ryu D, Kim KS, Chang JY, Kim YK, Yi HS, et al. Growth differentiation factor 15 is a myomitokine governing systemic energy homeostasis. J Cell Biol. 2017;216(1):149–65.
131. Rainbolt TK, Atanassova N, Genereux JC, Wiseman RL. Stress-regulated translational attenuation adapts mitochondrial protein import through Tim17A degradation. Cell Metab. 2013;18(6):908–19.
132. Haynes CM, Yang Y, Blais SP, Neubert TA, Ron D. The matrix peptide exporter HAF-1 signals a mitochondrial UPR by activating the transcription factor ZC376.7 in C. Elegans. Mol Cell. 2010;37(4):529–40.
133. Nargund AM, Pellegrino MW, Fiorese CJ, Baker BM, Haynes CM. Mitochondrial import efficiency of ATFS-1 regulates mitochondrial UPR activation. Science. 2012;337(6094):587–90.
134. Fiorese CJ, Schulz AM, Lin YF, Rosin N, Pellegrino MW, Haynes CM. The transcription factor ATF5 mediates a mammalian mitochondrial UPR. Curr Biol. 2016;26(15):2037–43.
135. Teske BF, Fusakio ME, Zhou D, Shan J, McClintick JN, Kilberg MS, et al. CHOP induces activating transcription factor 5 (ATF5) to trigger apoptosis in response to perturbations in protein homeostasis. Mol Biol Cell. 2013;24(15):2477–90.
136. Zhou D, Palam LR, Jiang L, Narasimhan J, Staschke KA, Wek RC. Phosphorylation of eIF2 directs ATF5 translational control in response to diverse stress conditions. J Biol Chem. 2008;283(11):7064–73.
137. Saxton RA, Sabatini DM. mTOR Signaling in Growth, Metabolism, and Disease. Cell. 2017;168(6):960–76.
138. Dorrello NV, Peschiaroli A, Guardavaccaro D, Colburn NH, Sherman NE, Pagano M. S6K1- and ßTRCP-Mediated degradation of PDCD4 promotes protein translation and cell growth. Science. 2006;314(5798):467–71.
139. Holz MK, Ballif BA, Gygi SP, Blenis J, mTOR. S6K1 Mediate Assembly of the translation preinitiation complex through dynamic protein interchange and ordered phosphorylation events. Cell. 2005;123(4):569–80.
140. Ma XM, Yoon SO, Richardson CJ, Jülich K, Blenis J. SKAR links Pre-mRNA splicing to mTOR/S6K1-Mediated enhanced translation efficiency of spliced mRNAs. Cell. 2008;133(2):303–13.
141. Brunn GJ, Hudson CC, Sekulić A, Williams JM, Hosoi H, Houghton PJ, et al. Phosphorylation of the translational repressor PHAS-I by the mammalian target of rapamycin. Science. 1997;277(5322):99–101.
142. Gingras AC, Gygi SP, Raught B, Polakiewicz RD, Abraham RT, Hoekstra MF, et al. Regulation of 4E-BP1 phosphorylation: a novel two-step mechanism. Genes Dev. 1999;13(11):1422–37.
143. Condon KJ, Orozco JM, Adelmann CH, Spinelli JB, van der Helm PW, Roberts JM, et al. Genome-wide CRISPR screens reveal multitiered mechanisms through which mTORC1 senses mitochondrial dysfunction. Proc Natl Acad Sci. 2021;118(4):e2022120118.
144. Khan NA, Nikkanen J, Yatsuga S, Jackson C, Wang L, Pradhan S, et al. mTORC1 regulates mitochondrial Integrated stress response and mitochondrial myopathy progression. Cell Metabol. 2017;26(2):419–e4285.

145. Morita M, Gravel SP, Chénard V, Sikström K, Zheng L, Alain T, et al. mTORC1 controls mitochondrial activity and Biogenesis through 4E-BP-Dependent translational regulation. Cell Metabol. 2013;18(5):698–711.
146. Torrence ME, MacArthur MR, Hosios AM, Valvezan AJ, Asara JM, Mitchell JR, et al. The mTORC1-mediated activation of ATF4 promotes protein and glutathione synthesis downstream of growth signals. Elife. 2021;10:e63326.
147. Ben-Sahra I, Hoxhaj G, Ricoult SJH, Asara JM, Manning BD. mTORC1 induces purine synthesis through control of the mitochondrial tetrahydrofolate cycle. Science. 2016;351(6274):728–33.
148. Park Y, Reyna-Neyra A, Philippe L, Thoreen CC. mTORC1 balances Cellular amino acid supply with demand for protein synthesis through post-transcriptional control of ATF4. Cell Rep. 2017;19(6):1083–90.
149. Kaufman BA, Durisic N, Mativetsky JM, Costantino S, Hancock MA, Grutter P, et al. The mitochondrial transcription factor TFAM coordinates the assembly of multiple DNA molecules into nucleoid-like structures. Mol Biol Cell. 2007;18(9):3225–36.
150. Yazicioglu YF, Marin E, Sandhu C, Galiani S, Raza IGA, Ali M, et al. Dynamic mitochondrial transcription and translation in B cells control germinal center entry and lymphomagenesis. Nat Immunol. 2023;24(6):991–1006.
151. Zhang Y, Gao S, Xia J, Liu F. Hematopoietic hierarchy – an updated Roadmap. Trends Cell Biol. 2018;28(12):976–86.
152. Mohrin M, Shin J, Liu Y, Brown K, Luo H, Xi Y, et al. Stem cell aging. A mitochondrial UPR-mediated metabolic checkpoint regulates hematopoietic stem cell aging. Science. 2015;347(6228):1374–7.
153. Mohrin M, Widjaja A, Liu Y, Luo H, Chen D. The mitochondrial unfolded protein response is activated upon hematopoietic stem cell exit from quiescence. Aging Cell. 2018;17(3):e12756.
154. Marcassa E, Kallinos A, Jardine J, Rusilowicz-Jones EV, Martinez A, Kuehl S et al. Dual role of USP30 in controlling basal pexophagy and mitophagy. EMBO Rep. 2018;19(7).
155. Wang S, Yan W, Kong L, Zuo S, Wu J, Zhu C, et al. Oncolytic viruses engineered to enforce cholesterol efflux restore tumor-associated macrophage phagocytosis and anti-tumor immunity in glioblastoma. Nat Commun. 2023;14(1):4367.
156. Cortés M, Brischetto A, Martinez-Campanario MC, Ninfali C, Domínguez V, Fernández S, et al. Inflammatory macrophages reprogram to immunosuppression by reducing mitochondrial translation. Nat Commun. 2023;14(1):7471.
157. Fleming MD. Congenital sideroblastic anemias: iron and heme lost in mitochondrial translation. Hematol Am Soc Hematol Educ Program. 2011;2011:525–31.
158. Rötig A, Bourgeron T, Chretien D, Rustin P, Munnich A. Spectrum of mitochondrial DNA rearrangements in the Pearson marrow-pancreas syndrome. Hum Mol Genet. 1995;4(8):1327–30.
159. Zhang S, Macias-Garcia A, Ulirsch JC, Velazquez J, Butty VL, Levine SS, et al. HRI coordinates translation necessary for protein homeostasis and mitochondrial function in erythropoiesis. Elife. 2019;8:e46976.
160. van der Meijden PEJ, Heemskerk JWM. Platelet biology and functions: new concepts and clinical perspectives. Nat Rev Cardiol. 2019;16(3):166–79.
161. Melchinger H, Jain K, Tyagi T, Hwa J. Role of platelet mitochondria: life in a nucleus-free zone. Front Cardiovasc Med. 2019;6:153.
162. Wang L, Wu Q, Fan Z, Xie R, Wang Z, Lu Y. Platelet mitochondrial dysfunction and the correlation with human diseases. Biochem Soc Trans. 2017;45(6):1213–23.
163. Flierl U, Fraccarollo D, Widder JD, Micka J, Neuser J, Bauersachs J, et al. The nitric oxide donor pentaerythritol tetranitrate reduces platelet activation in congestive heart failure. PLoS ONE. 2015;10(4):e0123621.
164. Wang Z, Cai F, Chen X, Luo M, Hu L, Lu Y. The role of mitochondria-derived reactive oxygen species in hyperthermia-induced platelet apoptosis. PLoS ONE. 2013;8(9):e75044.
165. Kuntz EM, Baquero P, Michie AM, Dunn K, Tardito S, Holyoake TL, et al. Targeting mitochondrial oxidative phosphorylation eradicates therapy-resistant chronic myeloid leukemia stem cells. Nat Med. 2017;23(10):1234–40.
166. Sheth A, Escobar-Alvarez S, Gardner J, Ran L, Heaney ML, Scheinberg DA. Inhibition of human mitochondrial peptide deformylase causes apoptosis in c-myc-overexpressing hematopoietic cancers. Cell Death Dis. 2014;5(3):e1152.
167. Fu X, Liu W, Huang Q, Wang Y, Li H, Xiong Y. Targeting mitochondrial respiration selectively sensitizes pediatric acute lymphoblastic leukemia cell lines and patient samples to standard chemotherapy. Am J Cancer Res. 2017;7(12):2395–405.
168. Pereira O, Teixeira A, Sampaio-Marques B, Castro I, Girão H, Ludovico P. Signalling mechanisms that regulate metabolic profile and autophagy of acute myeloid leukaemia cells. J Cell Mol Medi. 2018;22(10):4807–17.
169. Castro I, Sampaio-Marques B, Ludovico P. Targeting metabolic reprogramming in Acute myeloid leukemia. Cells. 2019;8(9):967.
170. Poulain L, Sujobert P, Zylbersztejn F, Barreau S, Stuani L, Lambert M, et al. High mTORC1 activity drives glycolysis addiction and sensitivity to G6PD inhibition in acute myeloid leukemia cells. Leukemia. 2017;31(11):2326–35.
171. Hanekamp D, Cloos J, Schuurhuis GJ. Leukemic stem cells: identification and clinical application. Int J Hematol. 2017;105(5):549–57.
172. Lapidot T, Sirard C, Vormoor J, Murdoch B, Hoang T, Caceres-Cortes J, et al. A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature. 1994;367(6464):645–8.
173. Farge T, Saland E, De Toni F, Aroua N, Hosseini M, Perry R, et al. Chemotherapy-resistant human acute myeloid leukemia cells are not enriched for leukemic stem cells but require oxidative metabolism. Cancer Discov. 2017;7(7):716–35.
174. Sharon D, Cathelin S, Mirali S, Di Trani JM, Yanofsky DJ, Keon KA, et al. Inhibition of mitochondrial translation overcomes venetoclax resistance in AML through activation of the integrated stress response. Sci Transl Med. 2019;11(516):eaax2863.
175. Monti S, Savage KJ, Kutok JL, Feuerhake F, Kurtin P, Mihm M, et al. Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflammatory response. Blood. 2005;105(5):1851–61.
176. Monti S, Chapuy B, Takeyama K, Rodig SJ, Hao Y, Yeda KT, et al. Integrative analysis reveals an outcome-associated and targetable pattern of p53 and cell cycle deregulation in diffuse large B cell lymphoma. Cancer Cell. 2012;22(3):359–72.
177. Caro P, Kishan AU, Norberg E, Stanley IA, Chapuy B, Ficarro SB, et al. Metabolic signatures uncover distinct targets in molecular subsets of diffuse large B cell lymphoma. Cancer Cell. 2012;22(4):547–60.
178. Norberg E, Lako A, Chen PH, Stanley IA, Zhou F, Ficarro SB, et al. Differential contribution of the mitochondrial translation pathway to the survival of diffuse large B-cell lymphoma subsets. Cell Death Differ. 2017;24(2):251–62.
179. Birkenmeier K, Dröse S, Wittig I, Winkelmann R, Käfer V, Döring C, et al. Hodgkin and Reed-Sternberg cells of classical Hodgkin lymphoma are highly dependent on oxidative phosphorylation: specific bioenergetic adaptation of classical Hodgkin's lymphoma cells. Int J Cancer. 2016;138(9):2231–46.
180. Martinez Marignac VL, Smith S, Toban N, Bazile M, Aloyz R. Resistance to Dasatinib in primary chronic lymphocytic leukemia lymphocytes involves AMPK-mediated energetic re-programming. Oncotarget. 2013;4(12):2550–66.
181. Ruiz-Heredia Y, Ortiz-Ruiz A, Samur MK, Garrido V, Rufian L, Sanchez R, et al. Pathogenetic and prognostic implications of increased mitochondrial content in multiple myeloma. Cancers. 2021;13(13):3189.
182. Ortiz-Ruiz A, Ruiz-Heredia Y, Morales ML, Aguilar-Garrido P, García-Ortiz A, Valeri A, et al. Myc-related mitochondrial activity as a Novel Target for multiple myeloma. Cancers. 2021;13(7):1662.
183. Zhou XP, Ye XJ, Shen JP, Lan JP, Jiang HF, Zhang J, et al. Salvage tigecycline in high risk febrile neutropenic patients with hematological malignancies: a prospective multicenter study. Leuk Lymphoma. 2018;59(11):2679–85.
184. Sloan B, Scheinfeld N. The use and safety of doxycycline hyclate and other second-generation tetracyclines. Expert Opin Drug Saf. 2008;7(5):571–7.
185. Jaksic B, Martinelli G, Perez-Oteyza J, Hartman CS, Leonard LB, Tack KJ. Efficacy and safety of linezolid compared with Vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. Clin Infect Dis. 2006;42(5):597–607.
186. Ramírez-Daffós P, Jiménez-Orozco E, Bolaños M, González Astorga B, Rubiales S, Ceballos-Barbancho E, et al. A phase 2 study for evaluating doxycycline 50 mg once daily and 100 mg once daily as preemptive treatment for skin toxicity in patients with metastatic colorectal cancer treated with an anti-EGFR and chemotherapy. Support Care Cancer. 2022;30(10):8081–8.
187. Wang B, Ao J, Yu D, Rao T, Ruan Y, Yao X. Inhibition of mitochondrial translation effectively sensitizes renal cell carcinoma to chemotherapy. Biochem Biophys Res Commun. 2017;490(3):767–73.
188. Hu B, Guo Y. Inhibition of mitochondrial translation as a therapeutic strategy for human ovarian cancer to overcome chemoresistance. Biochem Biophys Res Commun. 2019;509(2):373–8.
189. Reed GA, Schiller GJ, Kambhampati S, Tallman MS, Douer D, Minden MD, et al. A phase 1 study of intravenous infusions of tigecycline in patients with acute myeloid leukemia. Cancer Med. 2016;5(11):3031–40.

190. Estell C, Stamatidou E, El-Messeiry S, Hamilton A. In situ imaging of mitochondrial translation shows weak correlation with nucleoid DNA intensity and no suppression during mitosis. J Cell Sci. 2017;130(24):4193–9.
191. Yousefi R, Fornasiero EF, Cyganek L, Montoya J, Jakobs S, Rizzoli SO, et al. Monitoring mitochondrial translation in living cells. EMBO Rep. 2021;22(4):e51635.
192. Zorkau M, Albus CA, Berlinguer-Palmini R, Chrzanowska-Lightowlers ZMA, Lightowlers RN. High-resolution imaging reveals compartmentalization of mitochondrial protein synthesis in cultured human cells. Proc Natl Acad Sci U S A. 2021;118(6):e2008778118.
193. Kimura Y, Saito H, Osaki T, Ikegami Y, Wakigawa T, Ikeuchi Y, et al. Mito-FUNCAT-FACS reveals cellular heterogeneity in mitochondrial translation. RNA. 2022;28(6):895–904.
194. Brar GA, Weissman JS. Ribosome profiling reveals the what, when, where and how of protein synthesis. Nat Rev Mol Cell Biol. 2015;16(11):651–64.
195. Rooijers K, Loayza-Puch F, Nijtmans LG, Agami R. Ribosome profiling reveals features of normal and disease-associated mitochondrial translation. Nat Commun. 2013;4:2886.
196. Li SHJ, Nofal M, Parsons LR, Rabinowitz JD, Gitai Z. Monitoring mammalian mitochondrial translation with MitoRiboSeq. Nat Protoc. 2021;16(6):2802–25.
197. Soto I, Couvillion M, Hansen KG, McShane E, Moran JC, Barrientos A, et al. Balanced mitochondrial and cytosolic translatomes underlie the biogenesis of human respiratory complexes. Genome Biol. 2022;23(1):170.
198. Kienzle L, Bettinazzi S, Choquette T, Brunet M, Khorami HH, Jacques JF, et al. A small protein coded within the mitochondrial canonical gene nd4 regulates mitochondrial bioenergetics. BMC Biol. 2023;21(1):111.
199. Lee M, Matsunaga N, Akabane S, Yasuda I, Ueda T, Takeuchi-Tomita N. Reconstitution of mammalian mitochondrial translation system capable of correct initiation and long polypeptide synthesis from leaderless mRNA. Nucleic Acids Res. 2021;49(1):371–82.
200. Remes C, Khawaja A, Pearce SF, Dinan AM, Gopalakrishna S, Cipullo M, et al. Translation initiation of leaderless and polycistronic transcripts in mammalian mitochondria. Nucleic Acids Res. 2023;51(2):891–907.
201. Cruz-Zaragoza LD, Dennerlein S, Linden A, Yousefi R, Lavdovskaia E, Aich A, et al. An in vitro system to silence mitochondrial gene expression. Cell. 2021;184(23):5824–e583715.
202. Mok BY, de Moraes MH, Zeng J, Bosch DE, Kotrys AV, Raguram A, et al. A bacterial cytidine deaminase toxin enables CRISPR-free mitochondrial base editing. Nature. 2020;583(7817):631–7.
203. Mok BY, Kotrys AV, Raguram A, Huang TP, Mootha VK, Liu DR. CRISPR-free base editors with enhanced activity and expanded targeting scope in mitochondrial and nuclear DNA. Nat Biotechnol. 2022;40(9):1378–87.
204. Cho SI, Lee S, Mok YG, Lim K, Lee J, Lee JM, et al. Targeted A-to-G base editing in human mitochondrial DNA with programmable deaminases. Cell. 2022;185(10):1764–e177612.
205. Wei Y, Jin M, Huang S, Yao F, Ren N, Xu K, et al. Enhanced C-To-T and A-To-G base editing in mitochondrial DNA with Engineered DdCBE and TALED. Adv Sci (Weinh). 2024;11(3):e2304113.
206. Lim K. Mitochondrial genome editing: strategies, challenges, and applications. BMB Rep. 2024;57(1):19–29.
207. Huang Y, Si X, Shao M, Teng X, Xiao G, Huang H. Rewiring mitochondrial metabolism to counteract exhaustion of CAR-T cells. J Hematol Oncol. 2022;15(1):38.
208. Si X, Shao M, Teng X, Huang Y, Meng Y, Wu L, et al. Mitochondrial isocitrate dehydrogenase impedes CAR T cell function by restraining antioxidant metabolism and histone acetylation. Cell Metab. 2024;36(1):176–e19210.
209. Huang Y, Shao M, Teng X, Si X, Wu L, Jiang P, et al. Inhibition of CD38 enzymatic activity enhances CAR-T cell immune-therapeutic efficacy by repressing glycolytic metabolism. Cell Rep Med. 2024;5(2):101400.

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