DIMT1 and Ribosomal Function: How Ribosomal Biogenesis Influences Lifespan and Energy Homeostasis

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ABSTRACT

Ribosomes are essential molecular machines responsible for synthesizing proteins, a process vital for cellular growth, repair, and overall homeostasis. Central to ribosomal function is ribosomal RNA (rRNA), which not only provides the structural framework of the ribosome but also catalyzes peptide bond formation during translation. Recent research has highlighted the significant role of ribosomal biogenesis in cellular aging and disease, emphasizing the impact of abnormalities in ribosome production and function. This review focuses on the complicated mechanisms underlying ribosome assembly, with particular emphasis on the role of rRNA and the novel involvement of the dimethyladenosine transferase 1 (DIMT1) gene. DIMT1 is responsible for specific methylation modifications of rRNA during ribosome maturation, contributing to the proper structure and functionality of ribosomes. Additionally, it is involved in regulating mitochondrial function, which is the cell's energy generation core. Recent evidence suggests that DIMT1 may play a crucial part in aging and longevity by increasing mitochondrial efficiency and altering cellular responses to metabolic stress. The gene's conservation across species highlights its potential as a therapeutic target for interventions to delay the development of age-related diseases and extend a healthy lifespan.

Keywords: Dimt1, Ribosomal biogenesis, Gene therapy, Longevity, Lifespan-extension therapy

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Additional material is published online only. To view please visit the journal online.

Cite this as: Svanishvili G. DIMT1 and Ribosomal Function: How Ribosomal Biogenesis Influences Lifespan and Energy Homeostasis. Premier Journal of Science 2024;3:100027

DOI: https://doi.org/10.70389/PJS.100027

Received: 3 October 2024
Revised: 21 October 2024
Accepted: 24 October 2024
Published: 1 November 2024

Ethical approval: N/a
Consent: N/a
Funding: No industry funding
Conflicts of interest: N/a
Author contribution: Giorgi Svanishvili – Conceptualization, Visualization, Writing – original draft, Writing – review & editing
Guarantor: Giorgi Svanishvili
Provenance and peer-review: Commissioned and externally peer-reviewed
Data availability statement: N/a

Introduction

Given the complexity and importance of protein synthesis, understanding the structure and function of ribosomes and ribosomal RNA (rRNA) has significant consequences for both basic biology and biomedical research. Ribosomal malfunction has been linked to a wide range of diseases, including cancer and ribosomopathies, making it a promising therapy.[1,8] This review will look at the molecular complexities of ribosome construction and function, with a focus on the role of rRNA in the translation process. In prokaryotes, these subunits are smaller, consisting of the 50S and 30S subunits, but they perform the same critical function of catalyzing peptide bond formation.[2–4]

The central role of rRNA in ribosome structure and function cannot be overstated. Initially believed to be only a structural scaffold, rRNA is now known for its catalytic role in peptide bond formation as well as its complicated involvement in ribosomal assembly, function, and interaction with other protein synthesis machinery components.[5,6] rRNA serves as a framework for ribosomal proteins and aids in ensuring the correct arrangement of messenger RNA (mRNA) and tRNA during translation.[7]

Given the complexity and importance of protein synthesis, understanding the structure and function of ribosomes and rRNA has significant consequences for both basic biology and biomedical research. Ribosomal malfunction has been linked to a wide range of diseases, including cancer and ribosomopathies, making it a promising therapy.[8] This review will look at the molecular complexities of ribosome construction and function, with a focus on the role of rRNA in the translation process.

Ribosomes Structure and Function, rRNA

Ribosomes are the molecular machines responsible for protein synthesis in all living cells. They are composed of rRNA and proteins, which together form two distinct subunits: the large subunit (LSU) and the small subunit (SSU). The LSU catalyzes peptide bond formation, while the SSU ensures accurate decoding of mRNA (Figure 1). The essential role of ribosomes in translating genetic information into proteins places them at the center of cellular function and survival.[9]

rRNA, a form of non-coding RNA, is the primary component of the ribosome. It plays a dual role as both a structural and catalytic element, making it essential for ribosome function. rRNA acts as a ribozyme, facilitating the critical chemical reactions that drive protein synthesis. The integration of rRNA into ribosomes begins with transcription from ribosomal DNA (rDNA), followed by modification, processing, and assembly with ribosomal proteins.[10] This assembly takes place in the cytoplasm in prokaryotes and within the nucleolus in eukaryotes.[11]

Ribosomes possess well-defined primary and secondary structures.[9] The large rRNA molecules form intricate secondary structures that have been highly conserved across evolutionary lineages, highlighting their essential role in both the structure and function of ribosomal particles. These conserved secondary elements are not only involved in maintaining ribosomal architecture but are also critical in forming the catalytic sites responsible for translation.[12]

In prokaryotes, the assembly of rRNA into ribosomes occurs in the cytoplasm due to the lack of membrane-bound organelles. By contrast, in eukaryotes, the process begins in the nucleolus, where pre-rRNA is synthesized and processed. rRNA then interacts with ribosomal proteins to form the LSU and SSU.[13]

During protein synthesis, rRNA serves as a physical and mechanical framework that ensures proper alignment of tRNA and mRNA, enabling accurate translation. The ribosome has three key binding sites for tRNA: the A (aminoacyl) site, P (peptidyl) site, and E (exit) site.[14]

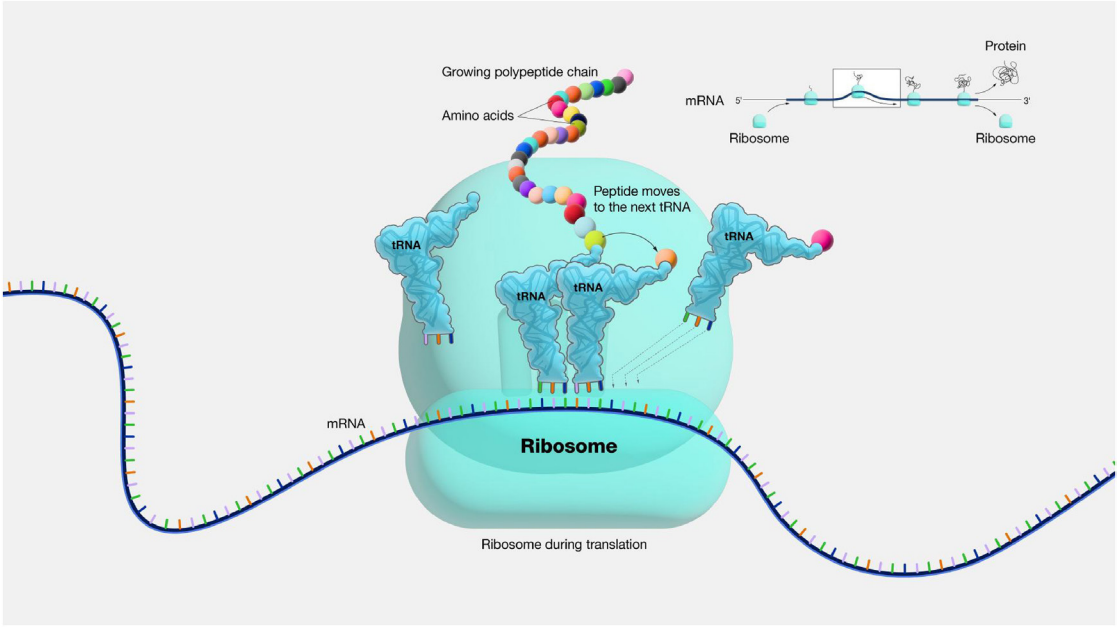

Fig 1 | Ribosome structure and its role in translation

The A site binds an aminoacyl-tRNA, which carries the next amino acid to be added to the growing peptide chain. The P site holds the tRNA with the nascent peptide chain, allowing the formation of a peptide bond between the amino acids. The E site contains the tRNA that has been discharged and is ready to exit the ribosome after its amino acid has been incorporated.[15]

The catalytic activity of rRNA in forming peptide bonds occurs in the peptidyl transferase center, a region located within the LSU. Here, the rRNA catalyzes the transfer of the peptide chain from the tRNA in the P site to the amino acid carried by the tRNA in the A site, a critical step in protein synthesis.[16]

rRNA is not only crucial for protein synthesis but also plays a role in maintaining genomic stability. The rDNA region, which encodes rRNA, is highly repetitive and susceptible to recombination. This fragility makes rDNA one of the most vulnerable regions of the eukaryotic genome.[17] When rDNA repeats are damaged, they may be repaired by recombination with other copies, but this can lead to a loss of rDNA copies.[18] Such instability in the rDNA region is linked to various cellular dysfunctions, including aging and senescence.[17]

The relationship between rDNA and cellular lifespan has been studied extensively. A landmark discovery by Guarente's group at MIT demonstrated that extra-chromosomal rDNA circles (ERCs), which are formed through recombination in rDNA, accumulate in mother cells as they age. This accumulation leads to cellular senescence, suggesting that rDNA instability contributes to aging.[19] ERCs act as molecular by-products that disrupt the balance of key factors required for maintaining cellular youthfulness. These findings have profound implications for understanding the molecular mechanisms underlying aging and the potential for interventions targeting rDNA stability.[20]

Ribosomal proteins account for roughly 50% of the total mass of ribosomes, while rRNA constitutes approximately 80% of the total RNA in a yeast cell.[21] The interaction between ribosomal proteins and rRNA is essential for the proper folding and functioning of ribosomes. The repetitive nature of rDNA regions contributes to their instability, and the continuous recombination and repair of rDNA have far-reaching consequences for cellular function and lifespan.

Process of Methylation, Oxidative Phosphorylation (OXPHOS), and Connection to Longevity

The cellular processes of methylation, phosphorylation, and OXPHOS are essential biochemical mechanisms that not only regulate energy production but also influence aging and longevity. These processes are tightly connected to genetic and environmental factors, allowing cells to adapt and respond to internal and external signals. They play critical roles in cellular metabolism, gene expression regulation, and the maintenance of mitochondrial and nuclear genome coordination, all of which impact aging and longevity.

OXPHOS is the primary mechanism by which cells generate ATP, the universal energy currency.[22] This process takes place in the mitochondria, where the electron transport chain is located. The OXPHOS pathway involves five protein complexes that work together to generate ATP through the transfer of electrons from NADH and FADH2 to oxygen, coupled with the creation of a proton gradient across the inner mitochondrial membrane. The proton gradient drives ATP synthesis by ATP synthase, completing the process of OXPHOS.[23]

In humans, the mitochondrial genome encodes 13 of the essential proteins involved in OXPHOS, while approximately 70 nuclear genes encode the remaining

DOI: https://doi.org/10.70389/PJS.100027 | Premier Journal of Science 2024;3:100027

components.[24] The coordinated expression of mitochondrial and nuclear genomes is essential for proper OXPHOS function. Dysfunctions in OXPHOS genes, whether in the mitochondrial or nuclear genome, can lead to a variety of disorders, including neurodegenerative diseases such as Alzheimer's and Parkinson's, as well as aging-related diseases.[25–27] These dysfunctions impair ATP production, leading to oxidative stress, which accelerates cellular aging by damaging proteins, lipids, and DNA.[28]

Mitochondria are unique in that they contain their own genome, separate from the nuclear genome. Mitochondrial DNA (mtDNA) is present in multiple copies per cell, making it susceptible to mutations caused by oxidative stress (Figure 2). Mitochondrial injury and the resulting oxidative damage are hallmarks of aging and are implicated in several neurological disorders.[26–28] Dysfunctional mitochondria accumulate over time, leading to decreased efficiency in ATP production and increased production of reactive oxygen species (ROS). ROS, in turn, causes further oxidative damage to mtDNA, establishing a vicious cycle of mitochondrial decline and cellular aging.[28]

Methylation is a reversible post-translational modification that involves the addition of a methyl group to proteins or nucleic acids, typically affecting lysine and arginine residues on histones. Histone methylation plays a pivotal role in regulating chromatin structure and gene expression by either activating or repressing transcription.[29,30] In particular, methylation of histone H3 at lysine 9 (H3K9) is associated with transcriptional repression, while methylation at lysine 4 (H3K4) is linked to gene activation.[30]

DNA methylation, specifically at cytosine residues in CpG islands, is another mechanism that influences gene expression. Age-related changes in DNA methylation patterns, often referred to as the "epigenetic clock," have been identified as indicators of biological aging. The gradual loss of methylation in specific genomic regions, coupled with hypermethylation in others, leads to dysregulation of gene expression and contributes to cellular aging.[31]

Importantly, these methylation changes are reversible, making them attractive targets for anti-aging interventions. Modifying methylation patterns through epigenetic therapies could potentially slow down or even reverse age-related changes in gene expression, thereby extending lifespan.

Phosphorylation is another key post-translational modification involving the addition of phosphate groups to proteins, typically at serine, threonine, or tyrosine residues. This modification regulates a wide range of cellular processes, including cell growth, apoptosis, and circadian rhythm regulation.[32]

One of the best-known examples of phosphorylation's impact on longevity is the regulation of the FOXO transcription factors. Phosphorylation of FOXO proteins inhibits their activity, preventing them from entering the nucleus and activating genes involved in stress resistance and DNA repair. Conversely, when phosphorylation is reduced, FOXO proteins can promote longevity by enhancing the expression of genes

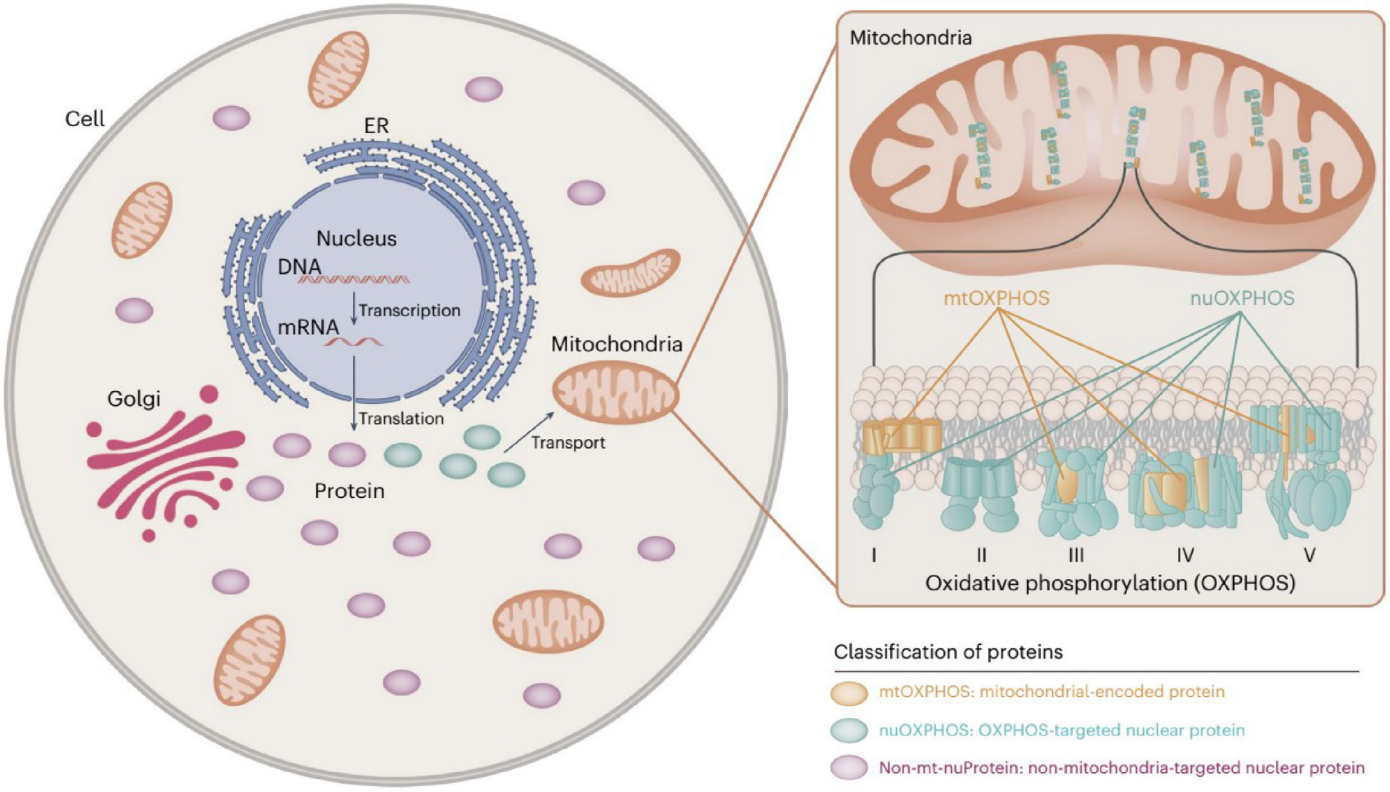

Fig 2 | OXPHOS system in nucleus and mitochondria

that protect against oxidative stress and promote cellular repair.[33]

Methylation and phosphorylation do not act in isolation; they often work together to regulate complex biological processes. For example, combinations of histone modifications, such as histone H3 lysine 9 methylation (H3K9me) and serine 10 phosphorylation (H3S10p), create a regulatory code that determines whether a gene is activated or repressed.[34] This intricate cross-talk between modifications allows for fine-tuned control of cellular signaling and gene expression.

New Longevity Gene: DMT1

Dimethyladenosine transferase 1 (DIMT1) has emerged as a crucial gene linked to cellular function, mitochondrial health, and lifespan regulation. This gene plays a significant role in ribosome biogenesis, ensuring proper protein synthesis, which is essential for cellular homeostasis and longevity. Recent research has uncovered DIMT1's evolutionary conservation across species and its potential impact on mitigating aging processes through its interplay with mitochondrial function.

In a large-scale study that examined the evolutionary rate covariation (ERC) between mitochondrial-encoded OXPHOS (mtOXPHOS) genes and nuclear-encoded OXPHOS genes across 472 insect species, a significant discovery was made regarding the gene CG11837. This gene, identified as an ortholog of human DIMT1, demonstrated one of the strongest ERC values ($r = 0.23$) with mtOXPHOS genes, suggesting a close evolutionary and functional connection between nuclear and mitochondrial genomes in supporting OXPHOS, the cell's primary energy production pathway.[35]

The OXPHOS pathway, vital for synthesizing ATP, requires coordinated expression of both mitochondrial and nuclear genes. Dysfunction in this pathway is linked to several disorders, including neurodegenerative diseases, metabolic conditions, and age-related declines.[25–27] The study identified 75 non-mitochondria-targeted nuclear genes, including CG11837, that exhibit strong ERC signals with mtOXPHOS genes. These genes are involved in essential processes such as ribosome biogenesis, DNA replication, and telomere maintenance. CG11837 stood out due to its role in both mitochondrial function and longevity regulation.

The functional relevance of CG11837 in lifespan regulation was tested through gene knockdown experiments in *Drosophila melanogaster* (fruit flies). When CG11837 expression was reduced, the flies exhibited severe mitochondrial morphological defects and significantly shortened lifespans. In contrast, overexpression of CG11837 extended the median lifespan of male flies by 30–59% and female flies by 27–30%. Similar experiments in worms showed a 12% increase in lifespan compared to controls, indicating that this gene plays a conserved role in promoting longevity across species.[35]

Further research into the human ortholog, DIMT1 (Figure 3), revealed similar protective effects against cellular aging. In human skin fibroblast cells, DIMT1 overexpression led to reduced levels of senescence-associated β-galactosidase activity, a marker of cell aging, and enhanced cellular proliferation even under conditions of oxidative stress and DNA damage.[35] These findings suggest that DIMT1 acts as a critical regulator of cellular aging by maintaining ribosome integrity and supporting mitochondrial health.

DIMT1 plays a pivotal role in ribosome biogenesis by catalyzing the methylation of adenosine residues in rRNA.[36] This methylation is a critical step in ribosome assembly, ensuring the accurate translation of proteins, which is essential for cellular health. The fidelity of protein synthesis is particularly crucial in aging, as errors in translation can lead to the accumulation of damaged proteins, contributing to cellular senescence and age-related diseases.

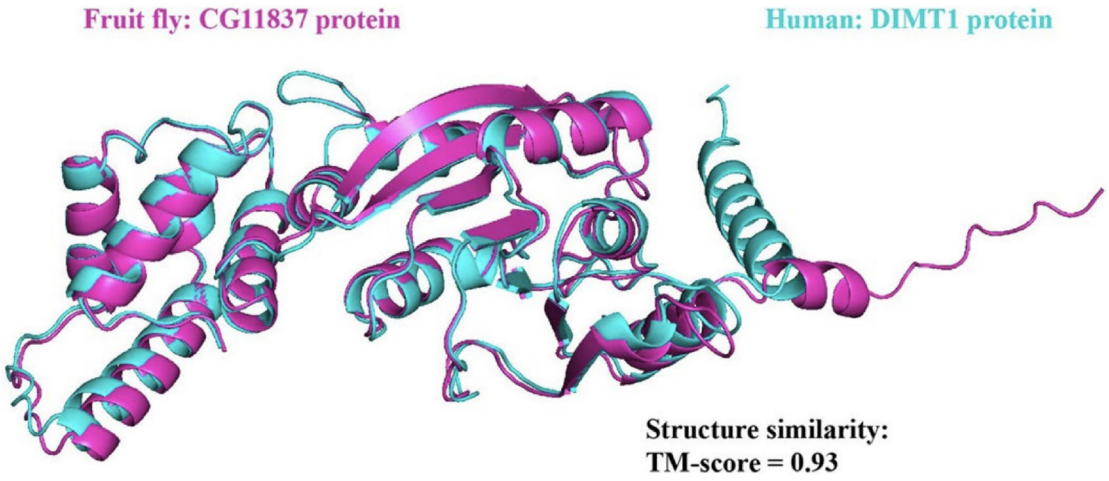

Fig 3 | Protein structures of fruit fly CG11837 and human DIMT1. Data were gathered from the Alphafold2 database (https://alphafold.ebi.ac.uk/). Template modeling score (TM-score) is 0.93

DOI: https://doi.org/10.70389/PJS.100027 | Premier Journal of Science 2024;3:100027

In addition to its role in ribosome biogenesis, DIMT1 influences mitochondrial function. Studies showed that overexpression of CG11837 led to the upregulation of nearly all OXPHOS genes, further underscoring its link to mitochondrial activity.[35] Mitochondria are central to cellular energy production, and their dysfunction is one of the key factors in aging and various diseases. By supporting proper mitochondrial function, DIMT1 indirectly contributes to cellular longevity and resilience to age-related damage.

One of the groundbreaking discoveries in this field involves the influence of parental environmental conditions, such as starvation, on the epigenetic makeup of their progeny. In *Caenorhabditis elegans* (*C. elegans*), researchers found that parental starvation leads to an increase in specific methylations on 18S rRNA. These methylations are transmitted across generations, influencing the offspring's stress resistance, fertility, and longevity even though the progeny are not directly exposed to starvation.[36]

BUD23 and DIMT1 share a common role as rRNA methyltransferases involved in the modification of rRNA, influencing ribosome function and translational regulation. Both enzymes add specific methyl marks on the rRNA: DIMT1 catalyzes the N6-dimethylation of adenosines 1735 and 1736, while BUD23 is responsible for the N7-methylation of guanosine 1531.[37,38] These modifications occur in the small ribosomal subunit and are critical for proper ribosome maturation and function. Importantly, their combined activity impacts the inheritance of traits related to longevity and stress response by altering ribosomal occupancy on particular mRNAs.

BUD23 (previously known as WBSCR22) is initially linked to tumor metastasis and inflammatory conditions.[39] Its functions include modifying cellular responses to glucocorticoids and influencing histone methylation. Despite these diverse roles, a common mechanism of action remained elusive for some time. Later studies, however, identified rRNA as the primary substrate of BUD23, which adds a methyl group to a specific guanosine residue in the small ribosomal subunit.[37,38] This modification is located at G1575 in yeast 18S rRNA and G1639 in human 18S rRNA, forming N7-methylguanosine.

BUD23's function is highly conserved across evolution, yet its physiological role in mammals remains underexplored. It is notably one of the genes deleted in Williams-Beuren syndrome, a complex condition characterized by neurological and metabolic abnormalities.[40] Its role in ribosome maturation suggests a significant function in regulating the translation of specific transcripts.

Recent findings have revealed an unexpected connection between BUD23 and mitochondrial function, particularly in maintaining OXPHOS capacity. Research also shows that during starvation, parents transmit altered 18S rRNA methylation patterns to their offspring, specifically increased N6,2A methylation (m6,2A) at adenosines 1735 and 1736 and N7-methylguanosine (m7G) at guanosine 1531.[36] DIMT1 is the enzyme responsible for adenosine methylation, while BUD23 is the methyltransferase for guanosine methylation. These methylation patterns influence ribosomal activity on specific mRNAs related to longevity, stress response, and reproduction in the next generation.[36]

Intriguingly, the roles of DIMT1 and BUD23 extend beyond general ribosome biogenesis. Their involvement is crucial for inheriting non-genetic traits, including improved resilience to environmental stress and enhanced longevity following parental starvation. This adaptive mechanism suggests that methylated rRNA carries non-genetic information across generations, potentially affecting ribosome heterogeneity rather than inducing a broad defect in ribosome formation. Thus, BUD23 and DIMT1 play a specialized role in shaping the translational landscape in response to environmental challenges, impacting longevity and stress adaptation in the progeny.[36]

Potential Therapies and Limitations

The involvement of DIMT1 in rRNA methylation and ribosome biogenesis suggests that modulating this gene could provide therapeutic benefits in several age-related and metabolic conditions. Enhancing DIMT1 activity could improve ribosomal efficiency, promoting protein synthesis and cellular repair mechanisms. This may be especially beneficial in conditions where ribosome dysfunction is implicated, such as neurodegenerative diseases or mitochondrial disorders, by preserving cellular energy production and reducing oxidative stress.

Additionally, DIMT1's role in regulating mitochondrial function through ribosomal activity makes it a promising target for therapies aimed at mitochondrial myopathies and metabolic syndromes. Targeted modulation of DIMT1 could help restore the balance between protein synthesis and mitochondrial energy output, potentially slowing the progression of age-related degeneration.

Furthermore, DIMT1 could be explored as a cancer therapy target. Given that ribosome biogenesis is often dysregulated in tumors, controlling DIMT1's activity could suppress aberrant protein synthesis in cancer cells, inhibiting tumor growth or enhancing the effectiveness of existing treatments.

On the other hand, there are significant challenges to targeting DIMT1 as a therapeutic strategy. Disrupting rRNA methylation poses risks, as this process is essential for proper ribosomal function. Over-activation or misregulation of DIMT1 could result in cytotoxic effects or impair vital cellular processes, leading to unintended consequences that may exacerbate disease states rather than improve them.

Target specificity is another critical issue. Since DIMT1 is expressed in various tissues, systemic interventions could cause off-target effects, impacting healthy tissues and disrupting normal cellular function. The development of precise delivery systems, such as gene-editing technologies (Figure 4) (e.g., CRISPR/Cas9) or RNA-based therapies, is necessary to ensure that therapies are targeted to affected cells without causing widespread disturbances in ribosome activity.

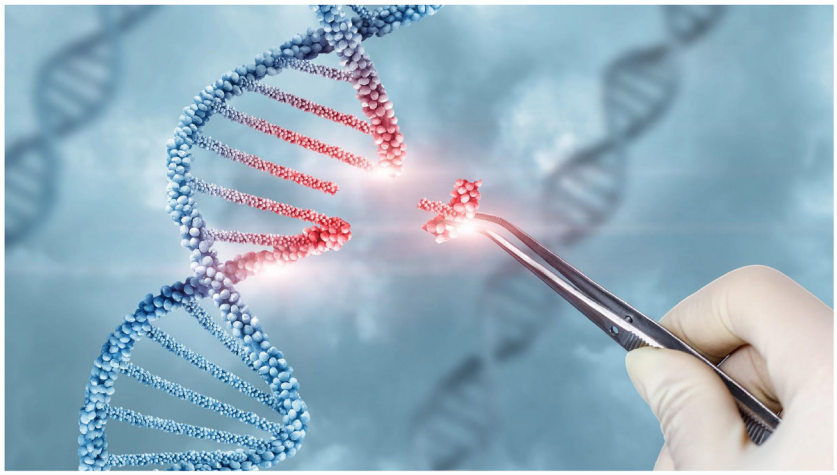

Fig 4 | Gene-editing methods provide precise DNA modifications at specified genomic locations, allowing targeted genetic alterations across diverse cell types and organisms

While there is potential for longevity therapies through enhancing DIMT1 function, the connection between ribosomal function and lifespan requires further exploration. Long-term studies are needed to confirm whether modulating DIMT1 can produce meaningful effects on aging or if the therapeutic benefits are restricted to specific pathologies.

Conclusion

The discovery of DIMT1's role in both ribosome biogenesis and mitochondrial function offers exciting possibilities for understanding the mechanisms of aging and developing interventions to extend healthy lifespan. As a gene that is conserved across species from insects to humans, DIMT1's influence on cellular energy metabolism and protein synthesis positions it as a promising target for therapies aimed at preventing age-related diseases and promoting longevity.

Additionally, the discovery of DIMT1's role in methylating rRNA and regulating epigenetic inheritance provides valuable insights into the molecular basis of longevity and stress resistance. By altering ribosome composition and function, DIMT1 allows cells to adapt to environmental stresses across generations, which has profound implications for our understanding of aging, fertility, and stress-related diseases.

While studies in model organisms like fruit flies and worms have provided valuable insights into the role of DIMT1, further research is required to fully understand its mechanisms in mammals, including humans. Preliminary findings in human cells suggest that DIMT1 may offer protection against cellular aging and enhance tissue regeneration, making it a potential candidate for future interventions in regenerative medicine and anti-aging therapies.

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