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Ribosomal proteins' unforeseen impact on mitochondrial integrity.

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Abstract

Ribosome biogenesis and mitochondrial function are essential for cellular health, and dysregulation in ribosome production can lead to ribosomopathies. The authors investigated the effects of deficiencies in ribosomal proteins associated with ribosomopathy disorders, on mitochondrial function using *Caenorhabditis elegans* and human cells. They found that reduced ribosomal protein levels due to a single copy loss of function resulted in developmental delays, altered body sizes, and increased oxidative stress resistance in *C. elegans*. Conserved changes in translational efficiency and mitochondrial function across species were observed, indicating coordinated regulatory mechanisms. Mitochondrial impairments, including reduced electron transport chain components and compromised energy levels, were identified. In particular, mitochondrial activities were compromised in both *C. elegans rps-10* haploinsufficiency mutants and human *RPS10*-reduced leukemia cells. Finally, unbiased proportionality analysis of RNA and translation efficiency revealed extensive and significant coordinated regulation of ribosomal and mitochondrial genes in human cells. These findings offer insights into cellular resilience mechanisms and potential therapeutic avenues for ribosomopathies.

Keywords: Ribosomopathies, *Caenorhabditis elegans*, Human cells, Mitochondrial homeostasis

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About the Study

Ribosome biogenesis, a fundamental cellular process, requires significant energy expenditure and is intricately linked to mitochondrial function to maintain cellular energy equilibrium. Dysregulation in ribosome production gives rise to a spectrum of disorders known as ribosomopathies [1,2], underscoring the critical role of ribosomal proteins in cellular homeostasis. While the connection between ribosome biogenesis and mitochondrial function has been recognized [3-5], the precise mechanisms underlying this interplay, particularly in the context of ribosomal protein haploinsufficiency, remain elusive.

Surya *et al*. conducted a study investigating the impact of haploinsufficiency for four ribosomal protein genes implicated in ribosomopathy disorders, *rps-10, rpl-33, rps-23* and *rpl-5* using the model organism *C. elegans* [6,7]. A range of phenotypic defects associated with reduced ribosomal protein levels in the ribosomal protein haploinsufficiency mutants, including developmental delays, altered body sizes, and increased oxidative stress resistance mediated by SKN-1, which is a stress induced transcription factor and the ortholog of human NRF2 [8,9]. Additionally, alterations in translational efficiency across ribosomal protein haploinsufficient mutants were identified, with certain genes, such as ribosome components, showing decreased translation efficiency alongside RNA overexpression, suggesting compensatory responses to reduced translation levels. Interestingly, reductions in ribosomal proteins from either subunit led to RNA overexpression coupled with significant decrease in translational efficiency both in small and large subunit ribosomal protein genes in *C. elegans*, indicating a compensation mechanism to retain the stoichiometry of both subunits of the ribosome as a complex. Coordinated responses across both subunits at the RNA and translational efficiency levels were not observed in yeast [10], but were recapitulated in human hematopoietic cells [11], indicating a conserved regulatory mechanism across species.

Involvement of Nrf2 ortholog SKN-1, which is required for maintenance of mitochondrial homeostasis [12], and increased oxidative stress response of heterozygous ribosomal protein null animals, prompted authors to further investigate potential impairments in mitochondrial function due to ribosomal protein haploinsufficiency in *C. elegans*. This was evidenced by the upregulation of glutathione transferase activity, overexpression of stress response pathways, and reduced translation efficiency of mitochondrial-encoded electron transport chain components, indicating compromised mitochondrial integrity. Mitochondrial morphology quantification revealed a temperature and age dependent fragmentation

of mitochondria in all ribosomal protein haploinsufficient animals relative to their stage matched controls. In particular, single copy loss of *rps-10* specifically led to significantly reduced mitochondrial function assessed by MitoTracker staining, ADP/ATP ratio analysis, and oxygen consumption rate measurements. The specific reduction in mitochondrial function in response to approximately 50% reduction was likewise recapitulated in human leukemia cells, suggesting a key conserved role of *RPS10* gene in mitochondrial homeostasis [6].

Additionally, Surya *et al*. explored the impact of reduced levels of frequently mutated ribosomal proteins associated with Diamond-Blackfan anemia on RNA expression and translation efficiency in shRNA knockdown hematopoietic cells and *C. elegans* haploinsufficiency mutants. These findings revealed conserved alterations in RNA levels and translation efficiency of mitochondrial components across species, suggesting a potential conserved translational buffering mechanism for mitochondrial ribosomes and electron transport chain components in response to reduced ribosomal protein levels (Figure 1).

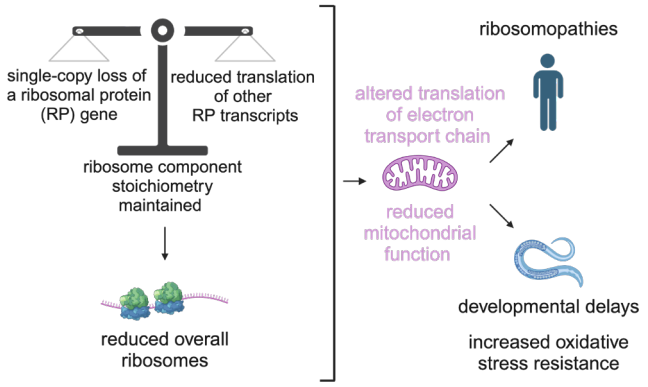

Figure 1. *Graphical representation of ribosomal protein gene developmental phases.*

Finally, unbiased composite proportionality analyses at the RNA and protein synthesis levels in healthy human lymphoblastoid cells from ~13 diverse genetic backgrounds [13], expose a striking proportionality between large amount of ribosomal genes and mitochondrial membrane genes, which is one of the most significantly correlated sets of gene categories observed with more than 1000 significant gene interactions between these two categories. This result overall suggests a tightly coordinated regulation of mitochondrial membrane components including the electron transport chain genes and ribosomes at both transcriptional and translational levels in humans [6].

Interestingly, a notable parallel has been observed between Diamond-Blackfan Anemia and Pearson syndrome. Pearson syndrome, resulting from large deletions in mitochondrial DNA, presents symptoms similar to Diamond-Blackfan Anemia, with approximately 5% of patients initially diagnosed with Diamond-Blackfan Anemia later found to have significant mitochondrial DNA loss, leading to reclassification as Pearson syndrome [14,15]. Similarly, expression analysis within a large family carrying a single-copy SNP variant in RPL11 displayed altered mitochondrial expression, indicating that coordination between mitochondria and ribosomes may be disrupted upon the single-copy loss of ribosomal protein genes [16].

Conclusion

These findings suggest that ribosomopathies such as Diamond-Blackfan Anemia and Pearson syndrome may share underlying metabolic dysfunctions, emphasizing the critical interplay between ribosomal proteins and mitochondrial function in the pathophysiology of these disorders.

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