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SLIRP at the Interface of Mitochondrial RNA Homeostasis and Translation

(SLIRP pada Antara Muka Homeostasis dan Translasi RNA Mitokondria)

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ABSTRACT

Mitochondrial gene expression relies on precise coordination between RNA metabolism and protein synthesis, yet how these processes are functionally coupled remains incompletely understood. Stem-loop interacting RNA-binding protein (SLIRP), a conserved component of the LRPPRC-containing ribonucleoprotein complex, has emerged as a key factor in this process. While initially characterized as a stabilizer of mitochondrial mRNAs, accumulating structural, biochemical, and genetic evidence indicates that SLIRP primarily functions to coordinate mitochondrial translation. Rather than being required for transcript production, SLIRP ensures the efficient and selective utilization of mitochondrial mRNAs by the mito-ribosome, thereby maintaining ordered and productive protein synthesis. Disruption of SLIRP results in selective translational defects, tissue-specific vulnerability, and mitochondrial disease phenotypes, despite the persistence of mitochondrial transcripts. We propose a conceptual framework in which SLIRP acts at the interface between RNA homeostasis and translational output, integrating mitochondrial gene expression across molecular, cellular, and organismal scales.

Keywords: LRPPRC; mitochondria; protein translation; RNA homeostasis; SLIRP

ABSTRAK

Ekspresi gen mitokondria bergantung pada penyelarasan yang tepat antara metabolisme RNA dan sintesis protein, namun bagaimana kedua-dua proses ini digandingkan secara fungsian masih belum difahami sepenuhnya. Gelung batang yang berinteraksi dengan protein pengikat RNA (SLIRP), iaitu komponen terpelihara dalam kompleks ribonukleoprotein yang mengandungi LRPPRC, telah muncul sebagai faktor utama dalam proses ini. Walaupun pada awalnya dicirikan sebagai penstabil mRNA mitokondria, bukti struktur, biokimia dan genetik yang semakin bertambah menunjukkan bahawa SLIRP berfungsi terutamanya untuk menyelaraskan translasi mitokondria. Berbanding berperanan dalam penghasilan transkrip, SLIRP memastikan penggunaan mRNA mitokondria yang cekap dan selektif oleh mitoribosom, sekali gus mengekalkan sintesis protein yang tersusun dan produktif. Gangguan terhadap SLIRP mengakibatkan kecacatan translasi yang selektif, kerentanan tisu yang khusus dan fenotip penyakit mitokondria, walaupun transkrip mitokondria masih wujud. Kami mencadangkan satu kerangka konseptual bahawa SLIRP bertindak pada antara muka antara homeostasis RNA dan output translasi, dengan mengintegrasikan ekspresi gen mitokondria merentasi skala molekul, sel dan organisma.

Kata kunci: Homeostasis RNA; LRPPRC; mitokondria; SLIRP; translasi protein

INTRODUCTION

Mitochondria are essential organelles that sustain cellular and organismal physiology by generating ATP through oxidative phosphorylation (OXPHOS) (Suomalainen & Nunnari 2024). Although the mitochondrial genome encodes only a limited number of proteins, their expression is indispensable and depends almost entirely on nuclear-encoded factors that govern mitochondrial transcription, RNA processing, and translation (Darfarin & Pluth 2025; McShane et al. 2024).

Stem-loop interacting RNA-binding protein (SLIRP) was originally identified as an RNA-dependent corepressor

of nuclear hormone receptors through its interaction with the long non-coding RNA steroid receptor RNA activator (SRA), positioning SLIRP initially within the context of nuclear transcriptional regulation (Hatchell et al. 2006). Subsequent studies, however, demonstrated that the predominant pool of endogenous SLIRP localizes to mitochondria, where it forms a stable ribonucleoprotein complex with the pentatricopeptide repeat protein LRPPRC (Lagouge et al. 2015; Spåhr et al. 2016). This finding fundamentally shifted the view of SLIRP biology and established SLIRP as a component of the mitochondrial gene expression machinery. Functional analyses across multiple systems have shown that disruption of the LRPPRC-SLIRP complex leads to defects in mitochondrial gene expression, with pronounced effects on the synthesis of mitochondrially encoded subunits of the respiratory chain (Pham et al. 2024; Xu et al. 2012). Notably, these defects cannot be fully explained by loss of mitochondrial transcripts alone, implicating SLIRP in the regulation of mitochondrial translation rather than transcription or RNA production per se (Lagouge et al. 2015; Rubalcava-Gracia et al. 2024; Singh et al. 2024). The physiological relevance of SLIRP-dependent regulation is supported by *in vivo* evidence from animal models and human genetics (Colley et al. 2013; Guo et al. 2021; Lagouge et al. 2015). While SLIRP deficiency can be compatible with organismal viability under basal conditions, it is associated with severe phenotypes in tissues with high energetic demand, including the nervous system and the germline, underscoring the importance of SLIRP for mitochondrial function *in vivo* (Cao et al. 2025).

In this review, we summarize current knowledge of SLIRP biology with a focus on its established role in mitochondrial RNA homeostasis and protein translation. We discuss the molecular architecture of the LRPPRC-SLIRP complex, its involvement in coordinating mitochondrial translation, and evidence from *in vivo* models linking SLIRP dysfunction to impaired mitochondrial gene expression. By integrating mechanistic and physiological data, we aim to clarify the functional role of SLIRP within mitochondrial gene expression without extending beyond conclusions supported by experimental evidence.

MOLECULAR ARCHITECTURE OF SLIRP AND THE LRPPRC-SLIRP COMPLEX

Structural features and tissue distribution of SLIRP

SLIRP is a small, evolutionarily conserved protein shared across human, rat, and mouse lineages (Figure 1). SLIRP is characterized at the primary sequence level by a single RNA recognition motif (RRM) containing the canonical Ribonucleoprotein motif1 (RNP1) and Ribonucleoprotein motif2 (RNP2) (Burd & Dreyfuss 1994). The RNA recognition motif (RRM), one of the most prevalent protein domains in eukaryotes, was originally characterized as a modular RNA-binding fold (Maris, Dominguez & Allain 2005). Subsequent structural and biochemical analyses have broadened this view, showing that RRMs can mediate diverse molecular interactions, including specific protein-protein interfaces and scaffolding functions within ribonucleoprotein assemblies (Muto & Yokoyama 2012). Collectively, these structural features suggest that SLIRP is optimized for incorporation into higher-order ribonucleoprotein complexes.

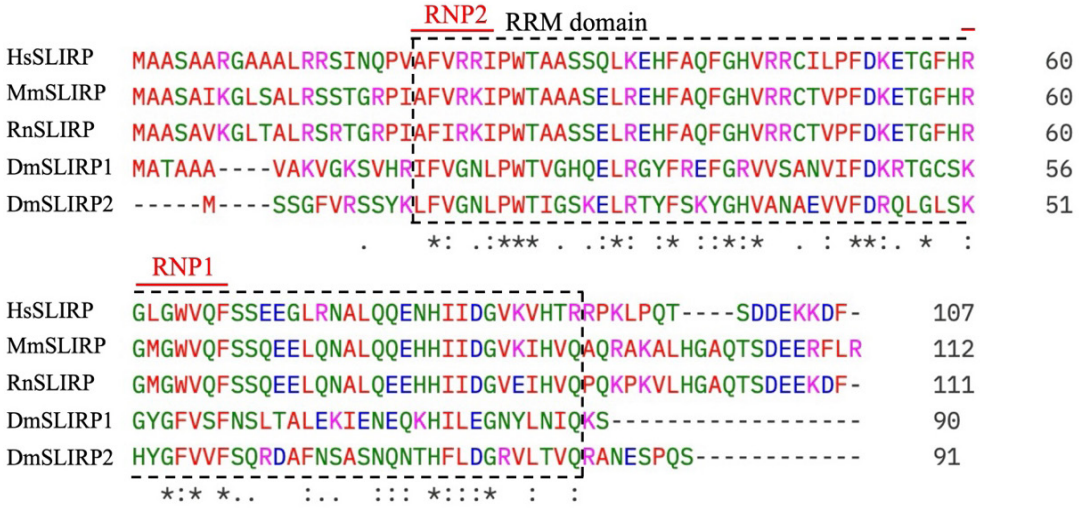


FIGURE 1. Sequence conservation and domain organization of the SLIRP protein family. Human (Hs), mouse (Mm), rat (Rn), and *Drosophila* (Dm) SLIRP proteins contain a conserved RNA recognition motif (RRM; black box). The canonical ribonucleoprotein 1 (RNP1) and ribonucleoprotein 2 (RNP2) consensus motifs are highlighted in red. Conservation of these residues supports potentially shared biological roles such as RNA binding

SLIRP mRNA is broadly expressed in human tissues, albeit at variable levels, with enriched expression in metabolically active tissues including heart, liver, skeletal muscle, and testis. At the cellular level, SLIRP protein is detectable across a wide range of cell lines, with higher expression observed in metabolically active or rapidly proliferating cells such as HeLa, Calu-6, and HepG2 (Hatchell et al. 2006). This expression profile supports a role for SLIRP in mitochondrial gene expression and oxidative phosphorylation, particularly in tissues and cell types with elevated energetic or biosynthetic demands.

Assembly and mutual stabilization of the LRPPRC-SLIRP complex

Biochemical and cellular studies demonstrate that SLIRP and LRPPRC assemble into a stable mitochondrial ribonucleoprotein complex (Lagouge et al. 2015; Spåhr et al. 2016; Trisciuoglio et al. 2016). Within this complex, LRPPRC is a large pentatricopeptide repeat (PPR) protein composed of tandem α-helical repeats, a structural organization that provides an extended surface for RNA binding (Barkan et al. 2012). In contrast, SLIRP does not exhibit strong RNA-binding activity on its own, consistent with a functional division of labor in which LRPPRC serves as the principal RNA-binding component. These observations are not necessarily mutually exclusive: SLIRP may have low intrinsic RNA affinity in isolation yet form productive RNA contacts when positioned by LRPPRC and the mito-ribosome. Conversely, a structural contact in a trapped ribosome-bound state does not by itself establish strong free-solution affinity or transcript specificity. Thus, the relative RNA-binding contributions of LRPPRC and SLIRP are likely state-dependent and remain an important topic for quantitative study.

At the structural level, SLIRP engages LRPPRC through interfaces that overlap with conserved surfaces of its RNA recognition motif (RRM) (Spåhr et al. 2016). This interaction effectively repurposes the RRM fold as a protein-protein interaction module, rather than a canonical RNA-binding domain (Maris, Dominguez & Allain 2005). Such an arrangement allows SLIRP to modulate the properties of the RNA-bound scaffold without directly conferring RNA specificity. A key feature of this interaction is mutual stabilization. LRPPRC is intrinsically unstable when not incorporated into a complex, and SLIRP contributes to maintaining its stability and functional integrity (Spåhr et al. 2016). Conversely, SLIRP protein levels are also dependent on LRPPRC, indicating that formation of the complex is required for the persistence of both components in mitochondria (Sasarman et al. 2010). Taken together, the molecular architecture of the LRPPRC-SLIRP complex supports a model in which SLIRP functions as a regulatory subunit that stabilizes the RNA-bound scaffold and facilitates the controlled utilization of mitochondrial transcripts.

SLIRP IN MITOCHONDRIAL RNA HOMEOSTASIS

Mitochondrial gene expression in metazoans is regulated predominantly at the post-transcriptional level, where RNA stability, processing, and utilization are tightly coordinated (Baughman et al. 2009; Sasarman et al. 2010; Siira et al. 2017). Early functional studies of the LRPPRC-SLIRP complex placed SLIRP within this regulatory landscape by demonstrating a global reduction in steady-state levels of mitochondrial mRNAs upon depletion of either component (Sasarman et al. 2010) (Figure 2). Importantly, these effects were selective for mRNAs, while mitochondrial rRNAs and tRNAs were largely preserved, indicating that the complex operates downstream of transcription initiation and RNA processing (Chujo et al. 2012). Mechanistically, the LRPPRC-SLIRP complex has been implicated in protecting mature mitochondrial mRNAs from degradation (Chujo et al. 2012). Mitochondrial transcripts are subject to turnover by the mitochondrial degradosome (mtEXO), composed of the RNA helicase SUV3 and the 3′-5′ exoribonuclease PNPase (Borowski et al. 2013). Loss of LRPPRC or SLIRP leads to reduced stability of mitochondrial mRNAs, consistent with a model in which the LRPPRC-SLIRP complex protects transcripts from degradation by the mitochondrial degradosome (Chujo et al. 2012; Sasarman et al. 2010). In this context, SLIRP contributes to RNA homeostasis indirectly, by stabilizing the LRPPRC-bound RNA pool rather than acting as a primary RNA-binding factor. These findings established a foundational role for SLIRP in maintaining mitochondrial mRNA abundance. However, they also raised an important conceptual issue: Reductions in mRNA levels alone are insufficient to explain the selective and context-dependent phenotypes observed upon SLIRP loss, suggesting that RNA stabilization represents only one facet of SLIRP-dependent regulation.

Mitochondrial mRNA stability is intimately linked to 3′ end metabolism. In mammalian mitochondria, polyadenylation serves dual functions: Completing stop codons for certain transcripts and marking RNAs for degradation (Rorbach & Minczuk 2012; Temperley et al. 2010) (Figure 3). The LRPPRC-SLIRP complex has been proposed to influence this balance by shielding mRNAs from excessive readenylation and subsequent decay. Notably, SLIRP deficiency does not lead to a uniform loss of mitochondrial poly(A) tails, and polyadenylation can be maintained *in vivo* despite reduced transcript stability (Chujo et al. 2012; Ruzzenente et al. 2012) (Figure 2). These observations suggest that SLIRP does not function as a global regulator of mitochondrial RNA maturation. Rather, it fine-tunes RNA homeostasis in a manner that reflects downstream functional requirements, foreshadowing a closer integration between RNA stability and translational control.

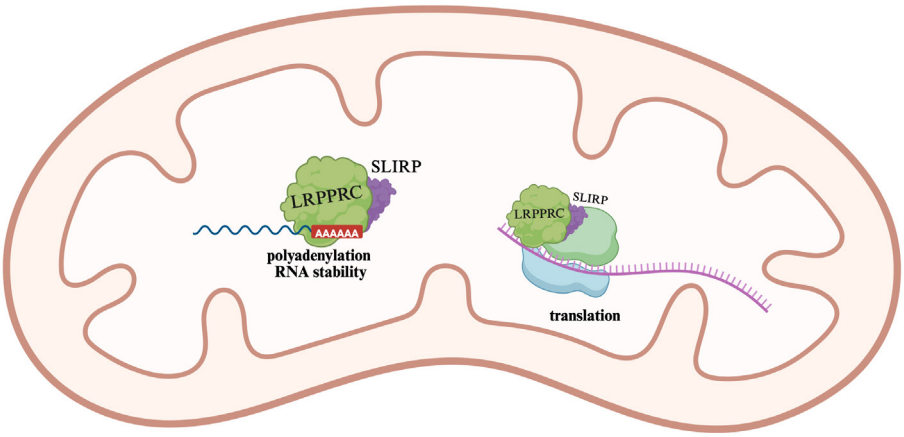


FIGURE 2. This diagram illustrates the hierarchical roles of SLIRP (as part of the LRPPRC-SLIRP complex) in the post-transcriptional control of mitochondrial mRNAs (mt-mRNAs). Following mtDNA transcription, SLIRP participates in the processing of polycistronic RNA precursors and facilitates polyadenylation of the released mature transcripts. By coating the mt-mRNAs, the SLIRP complex ensures their stability and protects them from exonucleolytic degradation. Subsequently, SLIRP acts as a delivery factor that physically transfers the stabilized mt-mRNAs to the mitochondrial ribosome (mitoribosome). Finally, it engages in the translation initiation/elongation process, thereby coupling mRNA maturation with protein synthesis to sustain mitochondrial oxidative phosphorylation

SLIRP AS A COORDINATOR OF ORDERLY MITOCHONDRIAL TRANSLATION

Initial studies of SLIRP-associated mitochondrial dysfunction emphasized its role in maintaining transcript abundance, with defects in protein synthesis generally interpreted as secondary to reduced mitochondrial mRNA levels (Chujo et al. 2012; Sasarman et al. 2010). However, this model has been challenged by multiple *in vivo* and biochemical observations demonstrating that mitochondrial mRNAs are not fully depleted in the absence of SLIRP, indicating that translational defects cannot be explained by transcript loss alone (Lagouge et al. 2015; Sasarman et al. 2010). Despite this apparent transcript surplus, mitochondrial protein synthesis is markedly impaired, indicating that SLIRP regulates translation through mechanisms beyond transcript stabilization (Li et al. 2019). Importantly, loss of SLIRP does not lead to a uniform reduction in mitochondrial translation; rather, synthesis of specific subsets of mitochondrially encoded proteins, particularly subunits of respiratory chain complexes I and IV, is preferentially impaired (Guo et al. 2021; Lagouge et al. 2015). This selective vulnerability argues against a simple rate-limiting model and instead suggests that SLIRP regulates qualitative aspects of mitochondrial translation, including coordination, timing, and ribosome engagement. In this context, SLIRP likely contributes to maintaining ordered and productive translation of these transcripts.

Mammalian mitochondrial translation occurs in a unique architectural and regulatory context. Mitochondrial mRNAs lack canonical untranslated regions and must be recognized and engaged by the mitoribosome through non-classical mechanisms (Ott, Amunts & Brown 2016) (Figure 3). Within this framework, the LRPPRC-SLIRP complex has emerged as a key factor linking mitochondrial mRNAs to the translational machinery. Structural and biochemical evidence indicates that LRPPRC-bound mRNAs are delivered to the mito-ribosome, where they form a transient assembly that promotes translation initiation (Rubalcava-Gracia et al. 2024; Singh et al. 2024). SLIRP, while not directly responsible for RNA binding, facilitates the association of mitochondrial mRNAs with the ribosome and supports efficient translation. In the absence of SLIRP, mRNA-ribosome association is impaired, leading to reduced synthesis of specific mitochondrial proteins (Lagouge et al. 2015; Singh et al. 2024). This model explains why ribosome occupancy and polysome profiles can appear abnormal in SLIRP-deficient mitochondria despite the presence of abundant mRNA. Rather than reflecting enhanced translational output, such ribosome accumulation likely represents stalled or uncoordinated translation attempts, underscoring the distinction between ribosome binding and productive translation.

In vivo FUNCTIONS AND DISEASE RELEVANCE OF SLIRP

In vivo studies of SLIRP

Genetic analyses across animal models indicate that SLIRP is not strictly required for mitochondrial gene expression under basal physiological conditions. In both mammalian and invertebrate systems, loss of SLIRP

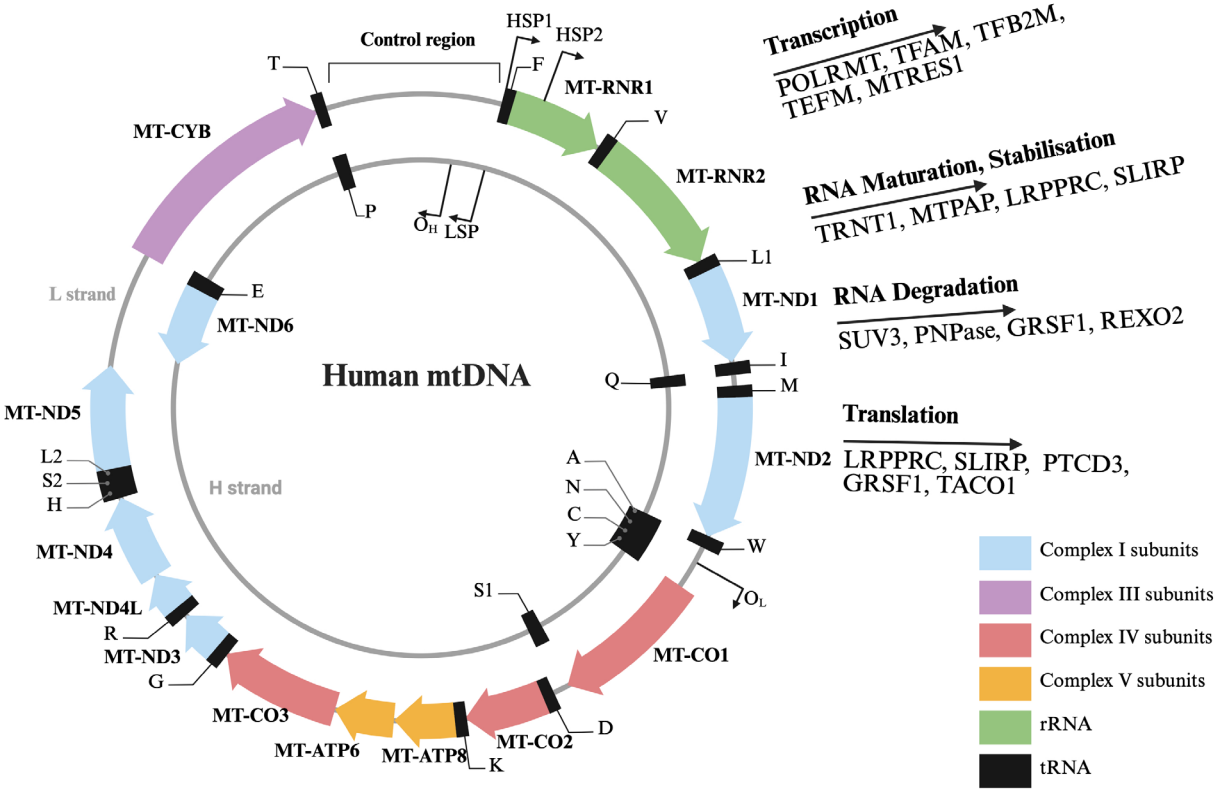


FIGURE 3. Organization of the human mitochondrial genome and key factors involved in mitochondrial gene expression. Schematic representation of the circular human mitochondrial genome, showing genes encoded by the heavy (H) and light (L) strands and the major regulatory elements within the control region. Transcription of the H strand is initiated from the heavy-strand promoters HSP1 and HSP2, whereas transcription of the L strand is initiated from the light-strand promoter (LSP), generating polycistronic precursor RNAs that are subsequently processed into mature mitochondrial mRNAs, rRNAs, and tRNAs. The mitochondrial genome encodes 13 oxidative phosphorylation (OXPHOS) subunits, including components of complex I, complex III, complex IV, and complex V, together with two rRNAs and 22 tRNAs. Selected nuclear-encoded factors involved in different steps of mitochondrial gene expression are indicated. Transcription is mediated or regulated by POLRMT, TFAM, TFB2M, TEFM, and MTERF1, RNA maturation and stabilization involve TRNT1, MTPAP, LRPPRC, and SLIRP, mitochondrial RNA degradation is controlled by SUV3, PNPase, GRSF1, and REXO2, and mitochondrial translation involves LRPPRC, SLIRP, PTCD3, GRSF1, and TACO1

does not abolish mitochondrial transcription or eliminate mitochondrial translation (Cao et al. 2025; Lagouge et al. 2015; Shan et al. 2020). Mitochondrial mRNAs remain detectable, and residual protein synthesis can be observed under basal conditions. Together, these observations indicate that SLIRP is not strictly required for mitochondrial translation per se (Cao et al. 2025; Lagouge et al. 2015). Metabolic labeling and biochemical analyses show selective and disproportionate impairment in the synthesis of mitochondrially encoded proteins, particularly subunits of respiratory chain complexes I and IV (Lagouge et al. 2015). Consistent with these observations, studies in *Drosophila* further demonstrate that loss of Slirp2 impairs mitochondrial protein translation *in vivo*, leading to reduced ATP production and defects in oxidative phosphorylation. These primary mitochondrial defects are accompanied by alterations in key metabolic signaling pathways, including reduced Akt and mTOR activity, as well as increased oxidative stress and apoptosis. At the organismal level, Slirp2 deficiency results in severe defects in oogenesis, culminating in female sterility (Cao et al. 2025). Notably, these phenotypes arise despite the persistence of mitochondrial transcripts, reinforcing the conclusion that impaired translation cannot be explained by transcript loss alone. A defining feature of SLIRP deficiency *in vivo* is the emergence of tissue-specific pathology rather than uniform mitochondrial failure. Tissues with high energetic demand, including the nervous system and skeletal muscle, appear particularly sensitive to SLIRP loss, and studies in *Drosophila* further suggest a critical role in the germline.

Human disease links defective translational coordination to pathology

Recent human genetic studies provide direct evidence linking SLIRP dysfunction to disease. Biallelic pathogenic variants in SLIRP cause mitochondrial encephalomyopathy characterized by combined deficiencies of respiratory chain complexes I and IV (Guo et al. 2021; Ku et al. 2024). Patient-derived cells retain mitochondrial transcripts yet exhibit impaired mitochondrial protein synthesis, supporting a model in which SLIRP is required for efficient utilization of mitochondrial mRNAs rather than their stability alone (Guo et al. 2021).

NUCLEAR AND NON-MITOCHONDRIAL FUNCTIONS OF SLIRP: SECONDARY OR CONTEXT-DEPENDENT ROLES

SRA-dependent regulation of nuclear receptors

SLIRP was originally identified as a nuclear factor through its interaction with the long non-coding RNA steroid receptor RNA activator (SRA), where it was reported to modulate transcriptional activity of nuclear hormone receptors, including estrogen, androgen, and glucocorticoid receptors (Dong et al. 2017; Hatchell et al. 2006). In this context, SLIRP was proposed to function as an RNA-dependent corepressor, associating with SRA-containing ribonucleoprotein complexes at hormone-responsive promoters. Mechanistically, SLIRP can bind structured regions of SRA RNA and influence receptor-mediated transcription in reporter assays and chromatin-based systems (Colley, Iyer & Leedman 2008; Hatchell et al. 2006). However, genetic disruption of SLIRP does not produce phenotypes classically associated with impaired nuclear receptor signaling, whereas mitochondrial defects are consistently observed across models (Cao et al. 2025; Colley et al. 2013; Shan et al. 2020). Together, these observations suggest that SRA-dependent nuclear functions of SLIRP represent a secondary or context-restricted activity rather than its dominant physiological role.

G-quadruplex binding and rRNA modification-associated activities

Beyond transcriptional regulation, SLIRP has been implicated in additional non-mitochondrial processes, including binding to G-quadruplex (G4) DNA structures and association with factors involved in ribosomal RNA modification (Williams et al. 2017). Biochemical and proteomic studies have reported interactions between SLIRP and RNA helicases or ribonucleoprotein complexes implicated in rRNA 2′-O-methylation, suggesting potential roles in ribosome biogenesis or translational regulation outside mitochondria (Li et al. 2019).

While these findings expand the repertoire of SLIRP-interacting partners, their functional relevance remains incompletely defined. In particular, direct causal links between SLIRP-dependent G4 binding or rRNA modification and specific cellular phenotypes are lacking. Moreover, these activities have not yet been integrated into a coherent mechanistic framework that explains the well-established mitochondrial phenotypes associated with SLIRP loss. A notable feature of these studies is that they often rely on overexpression systems, *in vitro* binding assays, or global proteomic associations. In contrast, *in vivo* genetic models consistently highlight mitochondrial translation defects as the primary and most penetrant consequence of SLIRP dysfunction.

LIMITATIONS OF THE CURRENT EVIDENCE AND OF THIS REVIEW

Several limitations constrain current models of SLIRP function. First, much of the mechanistic literature relies on acute knockdown, transformed cell lines, isolated mitochondria, or purified proteins. These systems fail to recapitulate the assembly and functional execution of these proteins under normal physiological conditions. Second, loss of SLIRP destabilizes LRPPRC, making it difficult to distinguish functions mediated directly by SLIRP from secondary consequences of reduced LRPPRC. Third, structural studies capture high-resolution but largely static states, whereas mRNA loading, handoff, initiation, and release are kinetic processes. Fourth, transcript-specific conclusions are based on a limited number of tissues and experimental conditions, and the small number of known patients limits clinical generalization. Finally, this review is a narrative synthesis rather than a systematic review or meta-analysis, and differences in experimental design across studies preclude quantitative comparison of effect sizes.

CONCLUSIONS AND FUTURE PERSPECTIVES

Accumulating evidence from structural, genetic, and *in vivo* studies necessitates a redefinition of SLIRP's biological function. Rather than acting as a generic mitochondrial RNA-binding protein or a simple stabilizer of mitochondrial transcripts, SLIRP emerges as a regulator operating at multiple hierarchical levels of mitochondrial gene expression. At the molecular level, SLIRP functions as an adaptor within the LRPPRC-SLIRP complex, stabilizing RNA-bound scaffolds and facilitating productive engagement of mitochondrial mRNAs with the mito-ribosome (Spåhr et al. 2016). At the translational level, SLIRP coordinates the orderly synthesis of mitochondrially encoded proteins, ensuring stoichiometric balance and assembly competence of respiratory chain complexes (Singh et al. 2024). At the systems level, SLIRP confers robustness to mitochondrial gene expression, buffering translational output against genetic, metabolic, and inflammatory stress. This hierarchical view reconciles seemingly disparate observations-preserved mitochondrial transcripts, selective translational defects, tissue-specific phenotypes, and disease-associated vulnerabilities-within a single

conceptual framework. SLIRP is therefore best understood not as a permissive factor for mitochondrial translation, but as a determinant of translational coordination and RNA fate. Despite significant progress, several fundamental questions remain unresolved.

Why SLIRP deficiency preferentially affects certain tissues remains incompletely understood. Neural tissues, skeletal muscle, and the germline repeatedly emerge as sites of vulnerability, yet the molecular determinants underlying this sensitivity are unclear. Differences in energetic demand, mitochondrial turnover, and translational load likely contribute, but systematic analysis of tissue- specific SLIRP dependency is lacking. Dissecting how SLIRP function is modulated across cell types will be essential for understanding phenotypic heterogeneity in both animal models and human disease.

Structural studies have begun to illuminate how the LRPPRC-SLIRP complex interfaces with the mito-ribosome, yet these snapshots provide limited insight into the dynamics of this interaction. How SLIRP regulates the timing, frequency, or stability of mRNA-ribosome engagement, and how these processes respond to metabolic or stress signals, remain open questions. Understanding these dynamics will be essential for defining how translational order is established and maintained *in vivo.*

Model organisms continue to play a central role in resolving these questions. In particular, *Drosophila* offers unique experimental advantages for dissecting SLIRP function at organismal, tissue-specific, and developmental scales. The ability to combine precise genetic manipulation with physiological and metabolic readouts has showed conserved roles of SLIRP in mitochondrial translation, while also uncovering systemic consequences-such as altered insulin/mTOR signaling and fertility defects-that are difficult to capture in mammalian systems alone. These strengths position *Drosophila* as a powerful platform for probing context-dependent functions of SLIRP and for testing mechanistic models derived from mammalian studies.

The emerging view of SLIRP as a regulator of mitochondrial RNA fate has important implications for disease research. In mitochondrial disorders, defective coordination of mitochondrial translation provides a mechanistic explanation for combined respiratory chain deficiencies and tissue-specific pathology, even in the presence of residual transcript pools. Recent findings have uncovered a previously unappreciated immunological dimension of SLIRP-dependent mitochondrial RNA dysregulation. Mechanistically, SLIRP stabilizes mitochondrial double-stranded RNAs (dsRNAs), promoting their accumulation in the cytosol and triggering a positive feedback loop that amplifies interferon signaling. This observation challenges the conventional view that mitochondrial defects are primarily pathological due to energy failure and instead points to aberrant innate immune activation as an equally critical downstream consequence. These mechanistic insights naturally translate into specific translational priorities. At the biomarker level, we propose that SLIRP/LRPPRC-associated molecular signatures including transcript-specific ribosome occupancy, respiratory-chain complex assembly patterns, and circulating or tissue-based indicators of mitochondrial stress, should be systematically evaluated for their diagnostic and prognostic potential. In parallel, therapeutic strategies should be mechanism-informed and cautiously designed: initial efforts may focus on stabilizing residual LRPPRC/SLIRP complex formation, enhancing compensatory mitochondrial translation capacity, or correcting pathogenic variants. However, a note of caution is warranted broad, non-selective stimulation of mitochondrial translation could prove detrimental if stoichiometric control of mitochondrial gene expression is disrupted, underscoring the need for precision in any future intervention.

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