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REVIEW ARTICLE

The Ribosomopathy Paradox: Linking Impaired Ribosome Function to Developmental Defects and Malignancy

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ABSTRACT

Ribosomopathies are a group of disorders caused by mutations in ribosomal proteins or ribosome biogenesis factors. Despite the ubiquitous requirement for ribosomes in all cells, these disorders manifest as tissue-specific developmental abnormalities, bone marrow failure and an increased predisposition to cancer. A hallmark of ribosomopathies is the paradox of cellular hypo- to hyperproliferation, whereby defective ribosome biogenesis initially activates the p53-mediated stress response, leading to cell-cycle arrest, apoptosis, and impaired tissue growth but subsequently promotes the emergence of cells that bypass these checkpoints and undergo malignant transformation. This mini-review aims to summarize the current understanding of ribosomopathies. The first section provides an overview of ribosome structure, biogenesis, and function, followed by a discussion of the phenotypic spectrum of ribosomopathies and their underlying genetic mutations. The review then examines the paradox of cellular hypo- to hyperproliferation and the molecular mechanisms proposed to explain this phenomenon. Given the role of ribosomopathies in a wide spectrum of clinical diseases, a deeper knowledge of the major molecular pathways, genetic changes and pathogenic mechanisms would facilitate translational research and promote the development of tailored therapeutic approaches.

KEYWORDS

• Ribosomopathies • Diamond–Blackfan Anemia (DBA) • Ribosome biogenesis • Ribosomal proteins • TP53 • Hypoproliferation • Hyperproliferation • Bone marrow failure • Cancer predisposition • Translational regulation • Specialized ribosomes • Hematopoiesis • Outbreak

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INTRODUCTION

Ribosomopathies encompass a spectrum of inherited and acquired disorders characterized by impaired ribosome biogenesis and function resulting from mutations in ribosomal proteins or factors involved in ribosome assembly (Farley-Barnes *et al*., 2019). Although rare, with estimated incidences ranging from 1 in 50,000 to 1 in 200,000 live births, these disorders are associated with a broad spectrum of clinical manifestations, including hematopoietic defects such as anemia and cytopenias, craniofacial abnormalities, growth retardation, and developmental impairments (Kampen *et al*., 2020). The field of ribosomopathies emerged following the identification of mutations in the ribosomal protein gene *RPS19* in patients with Diamond–Blackfan anemia (Willig *et al*., 1999). Since then, advances in genomic studies have expanded understanding of disorders associated with ribosome dysfunction. More recently, the discovery of somatic mutations affecting ribosomal proteins and ribosome biogenesis factors in various cancers has challenged the traditional definition of ribosomopathies. Consequently, there is ongoing debate regarding whether the term should be restricted to inherited disorders caused by germline mutations or broadened to include diseases arising from acquired somatic alterations (De Keersmaecker *et al*., 2015). A widely accepted definition describes ribosomopathies as diseases caused by mutations in ribosomal proteins or ribosome biogenesis factors in which impaired ribosome biogenesis or function directly contributes to disease pathogenesis.

Phenotypes, genetics and Mutation

One of the most intriguing features of ribosomopathies is their pronounced tissue specificity. Although every cell in the body contains the same ribosomal defect, only selected tissues and developmental processes are affected, resulting in highly variable clinical phenotypes (Armistead and Triggs-Raine, 2014). Patients frequently present with bone marrow failure, craniofacial abnormalities, skeletal defects, and growth retardation, despite the ubiquitous requirement for ribosomes in cellular function (Da Costa & Warren, 2026). Paradoxically, many ribosomopathies are also associated with an increased predisposition to cancer. Patients with Diamond–Blackfan anemia, Shwachman–Diamond syndrome and 5q− syndrome exhibit significantly elevated risks of developing hematological malignancies and solid tumors, including acute myeloid leukemia, osteosarcoma and colorectal cancer (Da Costa *et al*., 2020; Venturi & Montanaro, 2020). This observation highlights the dual nature of ribosome dysfunction, which can lead to both impaired proliferation and oncogenic transformation. Additional disorders such as dyskeratosis congenita further expand the clinical spectrum of ribosomopathies (Valli & Penzo, 2023).

Traditionally, ribosomes were viewed as passive molecular machines responsible solely for protein synthesis. However, growing evidence suggests that ribosomes can regulate gene expression through selective mRNA translation. Early studies demonstrated that alterations in ribosomal structure affect translational fidelity and efficiency (Zaher and Green, 2009; Moine *et al*., 1997). More recent work has supported the concept of ribosome specialization, whereby specific ribosomal proteins influence the translation of distinct subsets of mRNAs (Park *et al*., 2026). A landmark study by Kondrashov *et al*. (2011) showed that mutations in Rpl38 selectively impaired translation of homeobox (Hox) mRNAs, leading to tissue-specific developmental abnormalities in mice. In addition to their ribosomal functions, several ribosomal proteins exert important extra ribosomal regulatory roles. For example, RPL26 enhances p53 translation by interacting with both the 5′ and 3′ untranslated regions of p53 mRNA, thereby linking ribosome biogenesis to cellular stress responses (Chen & Kastan, 2010). Such findings suggest that both ribosomal and extra ribosomal mechanisms contribute to the phenotypic diversity observed in ribosomopathies.

Diseases paradox and cellular mechanisms

In 1967, Dameshek posed a now-famous question, "What do aplastic anemia, paroxysmal nocturnal hemoglobinuria, and hypoplastic leukemia have in common?" (Dameshek, 1967). This observation highlighted a biological paradox in which disorders characterized initially by impaired cellular proliferation subsequently progress to hyperproliferative conditions, including leukemia and other malignancies. The ribosome composed of ribosomal RNA (rRNA), ribosomal proteins and small nucleolar RNAs (snoRNAs),

which together coordinate protein synthesis. Ribosome assembly begins in the nucleolus, where rRNA transcription and processing occur before ribosomal subunits are exported to the cytoplasm for translation (Moy and Silver, 1999). Mutations affecting ribosomal proteins or ribosome biogenesis factors disrupt this highly coordinated process and trigger cellular stress responses. Current models propose that ribosome biogenesis defects initially activate the p53 stress-surveillance pathway, leading to cell-cycle arrest, apoptosis, and impaired tissue growth (Hernández Borrero and El-Deiry, 2021). In some ribosomopathies, p53-independent mechanisms also contribute to disease pathology (Yadav *et al*., 2014). Consequently, affected tissues exhibit reduced proliferative capacity and bone marrow failure.

Despite these early hypoproliferative effects, defective ribosomes continue to be produced and may alter translational fidelity or selectively influence gene expression programs (Donati *et al*., 2012). Persistent proliferative stress creates strong selective pressure for the emergence of compensatory mutations that restore cellular fitness. These secondary genetic events may either repair the original defect or bypass ribosome biogenesis quality-control mechanisms (Sulima *et al*., 2014). As a result, cells regain proliferative capacity while retaining translational abnormalities that can promote oncogenic transformation (Ruggero and Shimamura, 2014). From an evolutionary perspective, chronic bone marrow failure places intense selective pressure on hematopoietic stem cells, favoring clones that acquire growth advantages (Kang *et al*., 2021). Over time, these clones may expand and accumulate additional mutations, ultimately leading to malignant transformation. This progression from cellular hypo- to hyperproliferation represents a defining hallmark of ribosomopathies and provides a compelling explanation for their strong association with cancer susceptibility.

Models to study Ribosomopathies

Experimental model systems have been indispensable for elucidating the molecular mechanisms underlying ribosomopathies and their progression from developmental disorders to malignancies. Among vertebrate models, zebrafish have emerged as a powerful platform for investigating the consequences of ribosomal protein deficiencies on hematopoiesis, development, and cancer susceptibility (Gore *et al*., 2018). Early studies demonstrated that ribosomal protein haploinsufficiency predisposes zebrafish to tumor development through impaired Tp53 translation and altered cellular stress responses (Yadav *et al*., 2014). These findings established zebrafish as a valuable model for exploring the relationship between ribosome dysfunction and oncogenesis. Mouse models have further revealed the impact of ribosomal defects on stem-cell biology and malignant transformation. Recent evidence indicates that ribosomal proteins influence hematopoietic stem cell fitness and metabolic regulation, thereby contributing to leukemogenesis. Harris *et al*. (2025) demonstrated that alterations in ribosomal protein function can drive hematopoietic stem-cell transformation through metabolic reprogramming, providing mechanistic insight into the transition from bone marrow failure to cancer.

Yeast remains one of the most informative systems for studying the molecular consequences of ribosomal mutations. The leukemia-associated RPL10/uL16 R98S mutation, originally identified in T-cell acute lymphoblastic leukemia (T-ALL), impairs ribosome biogenesis and cellular proliferation when expressed in yeast and mammalian cells, highlighting the paradoxical coexistence of hypoproliferative cellular phenotypes and hyperproliferative disease states (De Keersmaecker *et al*., 2015). Likewise, yeast models expressing disease-associated ribosomal mutations have revealed defects in translational fidelity and ribosome quality control, emphasizing the importance of translational accuracy in maintaining cellular homeostasis (Sulima *et al*., 2014).

Recent advances have expanded the repertoire of ribosomopathy models beyond classical genetic systems. Using cellular and biochemical approaches, Akers *et al*. (2025) identified ZNF574 as a quality-control factor that recognizes defective ribosome biogenesis intermediates, uncovering a previously unrecognized surveillance pathway that safeguards ribosome assembly. Furthermore, emerging studies on functional ribosome specialization have challenged the traditional view of ribosomes as uniform translational machines. Park *et al*. (2026) highlighted how ribosomal heterogeneity can selectively regulate subsets of mRNAs, providing a potential explanation for the tissue-

specific manifestations observed in many ribosomopathies. In addition, recent work has implicated phase-separation mechanisms in ribosome biogenesis and disease pathogenesis, suggesting that disruption of biomolecular condensates may contribute to both inherited and acquired ribosomopathies (Pan *et al*., 2025). Collectively, zebrafish, mouse, yeast and emerging cellular models continue to provide complementary insights into the genetic, molecular and translational mechanisms of ribosomopathies, thereby advancing our understanding of disease progression and identifying potential therapeutic targets.

DISCUSSION

The ribosome is one of the most complex and tightly regulated molecular machines in the cell, serving as the central apparatus for protein synthesis and playing a critical role in maintaining cellular homeostasis (Zaher & Green, 2009). Consequently, alterations in ribosomal proteins, ribosomal RNA processing factors, or other components involved in ribosome biogenesis can give rise to a diverse group of disorders collectively known as ribosomopathies (Farley-Barnes et al., 2019; Kampen et al., 2020). Over the past three decades, advances in genetic and genomic technologies have led to the identification of an expanding number of genes associated with both inherited and acquired ribosomopathies. Despite these discoveries, the molecular mechanisms linking ribosomal dysfunction to tissue-specific phenotypes, bone marrow failure, and cancer predisposition remain incompletely understood (Venturi and Montanaro, 2020; Valli and Penzo, 2023).

Although proteomic technologies have advanced considerably, comprehensive characterization of the entire cellular proteome remains technically challenging. Consequently, translatome-based approaches, including polysome-associated RNA sequencing and ribosome profiling, have emerged as powerful alternatives for examining translational regulation and identifying changes in protein synthesis associated with disease states (King and Gerber, 2016; Chasse et al., 2017). Ribosome profiling has become a valuable approach for investigating translational regulation by enabling the genome-wide identification of ribosome-protected mRNA fragments. Beyond measuring translation efficiency, this technique provides insights into alternative translation initiation, stop-codon read-through and translational dynamics, thereby facilitating a deeper understanding of how ribosomal defects alter gene expression programs (Choi et al., 2018). Detailed characterization of mutant ribosomes has also contributed to the concept that ribosomes may selectively regulate the translation of specific mRNAs, providing a potential explanation for the tissue-specific manifestations observed in many ribosomopathies (Kondrashov et al., 2011). In parallel, studies of ribosomal protein deficiencies and ribosome biogenesis defects have highlighted the importance of translational control in development and disease pathogenesis (Venturi and Montanaro, 2020). An alternative explanation for tissue-specific phenotypes involves the extraribosomal functions of ribosomal proteins. In addition to their roles in translation, several ribosomal proteins participate in transcriptional regulation, cell-cycle control, apoptosis and stress-response pathways (Donati et al., 2012; Chen and Kastan, 2010). Importantly, many mutations associated with ribosomopathies do not completely abolish ribosome biogenesis but instead generate partially functional ribosomes that support basal protein synthesis while inducing selective alterations in translation. These subtle translational defects are thought to underlie the developmental abnormalities, bone marrow failure, and cancer predisposition characteristic of ribosomopathies (Kampen et al., 2020; Farley-Barnes et al., 2019).

With the notable exception of 5q− syndrome, therapeutic approaches for most ribosomopathies remain largely supportive and are directed toward managing clinical manifestations rather than correcting the underlying molecular defect. Hematopoietic stem cell transplantation remains the definitive treatment option for patients with

severe bone marrow failure or progression to hematologic malignancies (Ruggero & Shimamura, 2014; Da Costa & Warren, 2026). Advances in our understanding of ribosome biology have prompted interest in novel therapeutic strategies targeting stress-response pathways, translational regulation, and ribosome biogenesis. Although modulation of the p53 pathway has been proposed as a potential therapeutic avenue, the complexity and heterogeneity of disease mechanisms suggest that treatment strategies will likely need to be tailored to specific molecular defects (Hernández Borrero & El-Deiry, 2021). Furthermore, emerging insights into ribosome quality control, specialized ribosomes, and phase separation-related mechanisms are expanding the range of potential therapeutic targets and providing new opportunities for translational research (Pan et al., 2025; Valli & Penzo, 2023). Continued integration of mechanistic and clinical studies will be essential for developing effective targeted therapies and improving outcomes for patients affected by these complex disorders.

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