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RESEARCH ARTICLE

RIBOSOME BIOGENESIS IN DISEASE AND THERAPEUTIC TARGETS

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ABSTRACT

RNA biogenesis is a highly coordinated and fundamental biological process that regulates the synthesis, processing, modification, maturation, transport and turnover of cellular RNA molecules. The coordinated production of wide range of RNAs and other non-coding RNAs is essential for maintaining gene expression, protein synthesis and cellular homeostasis. Ribosome quality control (RQC) provides an important protective mechanism by detecting defective or stalled ribosomes, resolving ribosome collisions, and eliminating abnormal nascent proteins and dysfunctional ribosomal components. RQC surveys incomplete nascent polypeptides produced by interrupted translation. Several protein players in RQC sense large ribosomal subunits obstructed with nascent chains and then promote nascent-chain proteolysis. Defects in RNA biogenesis and RNA-processing pathways have been increasingly associated with human diseases. Abnormal RNA splicing, RNA modification, RNA transport and RNA degradation are also implicated in diseases of CNS and cancers. The present review summarizes the RNA biogenesis, mechanisms through which RNA dysregulation contributes to human disease, using representative disease examples by providing background to basic concepts. We discuss individual category of diseases using representative diseases and the underlying genetic and cellular mechanisms. The application of ribosome biosynthesis in drug design against viral and antibiotic resistance and their applications in clinical medicine highlights their growing importance and roles in disease biology.

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INTRODUCTION

Protein homeostasis is necessary for many life processes to function properly. Proteins are vital components of nearly all organisms since they are the main executors in intracellular activities like growth, reproduction, and metabolism (Rodwell *et al*., 2018). Ribosomes are essential for maintaining protein homeostasis since they are the primary machinery of protein translation. However, a variety of external and internal stressors, including as gene mutations, errors in gene expression, chemical toxins, or the lack of an interacting partner, can result in the synthesis of abnormal proteins (Nelson *et al*., 2021). When abnormal proteins or shortened polypeptides build up over time, their detrimental effects on cells can result in cell death, which can contribute to the onset and progression of a number of human disorders. Because ribosomes are stable organelles with a half-life of several days, they have evolved mechanisms that allow them to degrade redundant or malfunctioning ribosomes and modify their numbers in response to environmental changes. In order to maintain the quantity and quality of intracellular ribosomes, cells evolve a number of ribosome quality control systems, including the ribosome quality control system (RQCS) (Filbeck *et al*., 2022).

Protein homeostasis and ribosome function are monitored throughout the entire process, from ribosome synthesis to destruction, rather than only during protein synthesis. In summary, RQCS is a self-defense mechanism that controls ribosome synthesis, transportation, and destruction in response to adverse internal or external stimuli (Rodwell *et al*., 2018). RQCS mainly concentrates on the quality control activities of the ribosome itself, rather than the ribosome-associated protein synthesis process. Autophagy maintains and restores intracellular homeostasis by engulfing and breaking down damaged or excessive organelles and intracellular components (Heras-García *et al*., 2023). They also have significant functions in ribosome life-cycle. Additionally, RQCS has the ability to deal with ribosomal dysfunction, such as misassembled ribosomes and improperly synthesized ribosomal proteins, by closely monitoring the entire process from ribosome biogenesis to its destruction. Significant dysfunction of ribosomes can lead to the creation of aberrant proteins, which can interfere with cellular response and cause a number of human illnesses. Diamond-Blackfan anemia, Schwachman-Diamond syndrome, Dyskeratosis Congenita, Cartilage and Treacher Collins syndrome are few disorders.

The majority of these represent congenital diseases characterized by haploinsufficiency of genes encoding ribosomal proteins (Nakhoul *et al*., 2014).

Components, synthesis, distribution and functions of ribosomes: The ribosome is a complex organelle made up of short nucleolar RNAs (snoRNA), ribosomal proteins (RPs), and ribosomal RNA (rRNA) (Nelson, 2021). While RPs optimize rRNA processing and maintaining the ribosomal structure, rRNA primarily serves as a scaffold that catalyses the creation of peptide bonds during protein synthesis (Rodwell *et al*., 2018; Catalanotto *et al*., 2023). snoRNAs mainly control ribosomal chemical changes (Huang *et al*., 2022). The 60S large subunit (LSU) and the 40S small subunit (SSU) make up the components of eukaryotic 80S ribosomes; the former is roughly twice as large as the latter. 18S rRNA and 33 distinct RPs make up the SSU of eukaryotes, whereas 5S rRNA, 5.8S rRNA, 25S-28S rRNA, and 46 (in yeast)/47 (in humans) RPs make up the LSU (Kumar *et al*., 2021). Functionally, SSU acts as the decoding center to bring together messenger RNAs (mRNAs) and aminoacyl-transfer RNAs (tRNAs) in order to translate the genetic code ribosomes, which are primarily located in the cytoplasm. Whereas, LSU primarily catalyses the formation of peptide bonds with the peptidyl transferase center (PTC) (Lewinska *et al*., 2019). Ribosomes are divided into two categories based on their subcellular location: free ribosomes and attached ribosomes. The former is the primary executor of translation. Ribosomes, also known as mitoribosomes are found in the mitochondrion in addition to the cytoplasm. Mitoribosomes are mostly found in the organelle matrix and are specialized in the synthesis of a few polypeptides that are necessary for aerobic ATP generation and oxidative phosphorylation (OXPHOS) (Sharma *et al*., 2019). Ribosomes are thought to be a platform and executors in the regulated process of translation. Translation can be separated into four stages: start, extension, termination, and ribosome recycling, based on the characteristics of various stages of translation (Nelson, 2021). At every stage of the translation process, ribosomes have distinct functions. Eukaryotic initiation factor 3 (EIF3) separates the LSU and SSU of eukaryotic ribosomes during the first stage of translation. This is followed by the development of a translation initiation complex that includes SSU along with mRNA and MettRNAi. Each aminoacyltRNA binds sequentially to the A, P, and E sites on the SSU to complete the entry, peptide band formation, and translocation during the elongation stage (Nelson, 2021). The peptidyl-tRNA bond is hydrolysed to release the developing peptide chain by the time the ribosome reaches a termination codon, and release factors enable separation of the mRNA from the ribosome (Rodwell *et al*., 2018).

Ribosome biogenesis: The process of putting the ribosome complex together is called ribosome biogenesis. The 18S, 5.8S, and 28S rRNA are produced by cleaving the 47S pre-rRNA, which is transcribed from rDNA within the nucleolus (Kumar, 2021). Following cytoplasmic synthesis, the RPs are brought into the nucleus to join the rRNAs. Following additional snoRNA modifications, the rRNAs leave the nucleolus (Baweja *et al*., 2021). The 40S ribosome subunit is created from the 18S rRNA, whereas the 60S ribosome subunit is created when the 5.8 LafontaineS and 28S rRNA are linked by the 5S rRNA in the nucleus and exported to the cytoplasm (Kyritsis *et al*., 2019). Ribosome precursor 60S (pre-60S) and precursor 40S (pre-40S) is produced in the nucleolus of eukaryotic cells by rRNA, RPs, short nucleolar RNAs, and other closely related proteins. When these molecules are transferred to the cytoplasm, the final ribosome assembly and maturation are finished (Kisly *et al*., 2023). This maturation is made possible by a sequence of chemical changes to precursor rRNAs, or pre-rRNAs. RNA polymerase III (Pol III) processes the transcription of 5S rRNA, while RNA polymerase I (Pol I) converts pre-47S transcripts into 5.8S, 18S, and 28S rRNA (Popov *et al*., 2013; Talyzina *et al*., 2023). Mature rRNA is formed more quickly when RPs are assembled into pre-rRNA transcripts.

Signalling: Mammalian target of rapamycin (mTOR), myelocytomatosis oncogene (Myc), and noncoding RNA (ncRNA) are key signalling pathways that control ribosome synthesis. RP expression, rRNA synthesis, and pre-rRNA transcription are all controlled by the mTORC1 pathway. By activating S6 kinase 1 (S6K1) and encouraging the production of ribosomal 40S subunits through *RPS6,* mTORC1 positively controls rDNA transcription (Rosario *et al*., 2020). These findings are supported by the inhibition of aberrant ribosome biogenesis by cancer treatments that block mTORC1/ribosomal protein S6 (*RPS6*) signalling (Mossmann *et al*., 2018). Through eIF4E and eIF2α, mTORC1 facilitates the start and elongation of mRNA (Rios-Fuller *et al*., 2020). By deactivating 4E-BPs, mTORC1 also causes translation initiation.

A downstream target of mTORC1 signalling is the RP assembly factor Urb1 (Wang *et al*., 2019). By preventing the binding of La-related protein 1 (LARP1) and Poly(A)-binding protein cytoplasmic 1 (*PABPC1)*, *mTORC1*facilitates the translation of mRNA (Iadevaia *et al*., 2014). mTORC1 signalling regulates ribosomal protein S6K1. Studies on zebrafish show that Urb1, an assembly factor of RPs, promotes the development of the digestive tracts by acting as a downstream target of mTORC1 signalling (He *et al*., 2017). Thus, tissue formation, growth, and regeneration depend on the mTORC1/S6K1/RPL26/RPS10 ribosome biogenesis pathway (Ghosh *et al*., 2017). Ribosomal translocation is mediated by the eukaryotic elongation factor 2 (eEF2) (Vasamsetti *et al*., 2019). Additionally, by lowering eEF2's phosphorylation, S6K1 can increase its activity (Santini *et al*., 2014). Moreover, protein synthesis is stimulated by the phosphorylation of eukaryotic initiation factor 4G (eIF4G).

According to Solsona *et al*. (2021), mTORC1/S6K1 increases the phosphorylation of eIF4G, which promotes protein synthesis during skeletal muscle regeneration. The RNA-binding protein LARP1 controls the synthesis of RP (Fonseca *et al*., 2018). A crucial translation initiation factor involved in metabolism, translation, and cell development downstream of mTORC1 is 4E-binding protein 1 (4E-BP1) (Gallagher *et al*., 2019). When 4E-BP1 is phosphorylated, it separates from eIF4E and associates with eIF4G (Sun *et al*., 2019). According to Brown *et al*. (2022), Myc signalling primarily controls ribosome biogenesis through RNA Pol I–III mediated rDNA transcription via upstream binding factor (UBF) and transcription and selectivity factor 1 (SL1), rRNA processing and transcription of RPS and RPL, and the transcription of 5S rRNA and tRNA.Myc recruits UBF and SL1 and increases their expression to boost rDNA transcription in an RNA Pol I-dependent manner (Van Riggelen *et al*., 2010). Myc interacts with the TATA binding factor (TBP)-associated factor, a part of the SL1 complex, to attract RNA Pol I to target promoters.

According to research, a tiny chemical inhibits RNA Pol I in neuroblastoma cells CX-5461, preventing the connection (Hald, 2019). RNA Pol I is activated and drawn to the ribosomal DNA promoter after binding to the initiating factor factor-IA (TIF-IA, also known as RRN3) (Li *et al*., 2022). enhanced expression of RNA Pol I-specific transcription initiation factor RRN3/TIF-IA is linked to enhanced rRNA synthesis in medulloblastoma cells with elevated Myc expression (Lewinska *et al*., 2019). 43% of the genes encoding RNA Pol III-specific subunits have their expression increased by Myc (Koh *et al*., 2016). In a variety of cell types, Myc improves the activity of RNA pol III and 5S rRNA (Li *et al*., 2013). In several cell types, the RNA Pol III specific transcription factor *TFIIIB/C* recruits Myc to Pol III target genes (Park *et al*., 2017). To encourage binding to *TFIIIB, TFIIIC* enlists Myc and the associated histone acetyltransferase (Basu, 2024). Thus, Myc interacts with RNA Pol III at the promoters of its target genes to control ribosome synthesis.

Recent research has demonstrated that ncRNAs, including circular RNAs (circRNAs), long noncoding RNAs (lncRNAs), and microRNAs (miRNAs), are involved in controlling ribosome synthesis (McCool *et al*., 2020). By specifically targeting the RNA Pol I pre-priming complex factors POLR1A and UBTF, miR-424-5p reduces the amounts of mature rRNA (Connolly *et al*., 2018). By suppressing Ncl expression, miR-20a, miR-194, and miR-206 influence the processing of 47S pre-RNA (Bose *et al*., 2016). On the other hand, miR-595 decreases RPL27A expression, which prevents the production of the mature 60S subunit (Alkhatabi *et al*., 2016). By altering rDNA chromatin and lowering pre-rRNA levels, lncRNA prevents translation (Karakas *et al*., 2021). The 40S ribosomal subunit is recruited by circRNA to aid in the start of protein synthesis. Deregulation of miRNAs in myelodysplastic syndrome (MDS) and Diamond-Blackfan anaemia (DBA) highlights the role of miRNAs in regulating mRNA stability (Wilkes *et al*., 2022). There is growing evidence that circRNA can initiate protein translation by engaging the 40S ribosomal subunit (Khan *et al*., 2022).

Synthesis, transport and degradation: At the nucleolus, where RPs are cotranscriptionally linked to pre-ribosome RNAs (pre-rRNA), ribosomal biogenesis begins (Klinge *et al*., 2019). The preribosomal particles transported from the nucleolus to the cytoplasm, where they eventually develop into translation-competent ribosomal subunits. Several signalling networks and specialised chaperones intricately control ribosome synthesis in response to elevated protein demand or ribosomal network recovery (Lafontaine *et al*., 2020). To guarantee the synthesis of functional ribosomes, the crucial biogenesis factors can track and promptly fix errors made during the assembly process including the ribosome protein gene transcriptional activator interacts with forkhead 1 (Ifh1), the rRNA processing factor U3 small nucleolar RNA-associated protein 22 (Utp22), U3 small nucleolar ribonucleoprotein particles (U3-snoRNP), U three-associated protein (UTP)-A, UTP-B, and UTP-C (Albert *et al*., 2016; Razi *et al*., 2017). The TRAMP complex and the exosome complex of exonucleases are two examples of complexes are involved in the surveillance and turnover of misassembled preribosomes in addition to the molecules discussed above (Ghosh *et al*., 2020). By polyadenylating the 3′ end of aberrant or less stable tRNA, *TRAMP* creates a single-stranded RNA extension long enough to allow the Mtr4 helicase to bind it (Puno *et al*., 2018). After ribosomal subunit precursors are synthesized in the nucleus, they pass through the nuclear pore into the cytoplasm before joining RPs to finish the maturation process. To guarantee the effective execution of this procedure, specialized chaperones exclusively mediate the trafficking of RPs. According to a study by Liang *et al*. (Liang *et al*., 2019), Puf6 and Loc1 are the specific chaperones of the ribosomal protein *Rpl43*, which create a ternary complex necessary for the synthesis of 60S LSU. *Rrb1, Sqt1, Acl4,* and *Bcp1* have long been shown to be the specific chaperones of the large ribosomal subunit *Rpl3, Rpl10, Rpl4*, and *Rpl23*, in addition to recently identified molecular chaperones (Stelter *et al*., 2015). While Yar1, Tsr2, and Fap7 are specific chaperones of the 40S subunit r-proteins *Rps3, Rps26,* and *Rps14*, respectively. The Syo1 functions as a chaperone that binds two 60S r-proteins *Rpl5* and *Rpl1* simultaneously (Kressler *et al*., 2012).

Ribosome stagnation can result from a number of physical and chemical stressors, such as two arginine CGA codons adjacent to one another, proline codons arranged in a row, chemical damage, endonuclease activity, and errors in gene expression. No-go decay (NGD) and RQC pathways break down mRNAs and aberrant proteins generated by ribosome standstill, respectively (Karamyshev *et al*., 2018). After being split into large and small subunits, collided ribosomes rejoin the translational process. The first stages of ribosome recycling include identifying colliding ribosomes and separating 40S and 60S subunits. According to research E3 ligase ZNF598 in mammalian cells (Hel2 in yeast) uses receptor for activated C kinase 1 (RACK1, Asc1 in yeast) to identify the interface of the 40S unit of colliding ribosome (Juszkiewicz *et al*., 2018). Following ubiquitin labelling, the ribosome subunits are separated using Dom34, Hbs1, Rli1 (PELO, HBSL1, and ABCE1 in higher eukaryotes), and RQC complexes. While the GTPase Hbs1 detects ribosome stalling in budding yeast and loads Dom34, Dom34 removes stalled ribosomes from truncated mRNAs and rescues ribosomes in 3'untranslated regions (Yip *et al*., 2021).

The 80S-like complexes made up of pre-40S and big (60S) subunits are broken up by the ATPase Rli1 (Kratzat *et al*., 2021). *NEMF* and *LTN1* handle the 60S subunit-incorporated peptidyl-tRNA further since they can polyubiquitinate the polypeptide (Lytvynenko *et al*., 2019). Furthermore, G3BP1-family-USP10 complexes shields ubiquitinated 40S subunits from lysosomal degradation. After escaping lysosomal degradation, ribosomal subunits reassemble and enter the ribosome recycling to perform translational tasks for proteins (Meyer *et al*., 2020). RPs and rRNA are assembled into ribosomes in an appropriate ratio. RPs may be produced disproportionately if thallium therapy or genetic mutations impair rRNA synthesis. In order to prevent proteotoxic stress, excess RPs must be broken down over time (Zencir *et al*., 2020). Suppression of the proteasome caused several endogenous ribosomal proteins to accumulate within insoluble aggregates, suggesting that overproduced RPs were quickly ubiquitinated and broken down in a proteasome-dependent manner Sung *et al*. (2016). Additionally, redundant RPs produced by transcriptional or translational imbalance are first ubiquitinated by an enzyme called Tom1 in yeast (Bianco *et al*., 2024) or HECT, UBA, and WWE domain containing E3 ubiquitin protein ligase 1 (HUWE1) in human (Giovannini *et al*., 2025). They then work with the E2 enzymes Ubc4 and Ubc5 before entering the proteasomal degradation process.

The ubiquitin-proteasome system primarily breaks down individual RP, which is susceptible to the excess ribosomal protein quality control (ERISQ), in contrast to autophagy, which can break down the entire ribosome (Qu *et al*., 2021). While superfluous ribosomal subunits produced during erythroid development are removed by the ubiquitin conjugating enzyme E2O (UBE2O), excess RPs produced from chromosomes can be immediately broken down by the proteasome (Maffeo *et al*., 2024). Excess or nonfunctional rRNAs must be removed; otherwise, their accumulation will impede translation (Li *et al*., 2025). Dim1p prevents the precursor rRNA from maturing in the absence of demethylation Lafontaine *et al*. (1998). Numerous pre-rRNA quality control routes have been identified, such as the TRAMP complex-mediated pathway and the nuclear exosome pathway in the degradation of nuclear-restricted rRNAs (Li *et al*., 2019). LaRiviere *et al*. 2006 identified a novel rRNA quality-control mechanism commonly known as nonfunctional rRNA decay (NRD). Unlike the above quality-control pathways for degradation of precursor rRNA, NRD can specifically target mature 18SrRNA and 25SrRNA (Kazibwe *et al*., 2019).

Autophagy: Autophagy functions as a significant mechanism for maintaining the homeostasis between ribosome biogenesis and degradation. When the *ATG5* gene was knocked off in starving mouse embryonic fibroblasts, proteomics study revealed that ribosome abundance remained unchanged (Sharma *et al*., 2019). The same conclusion was reached by quantitative study of fibroblasts, which showed that silencing the important autophagy-related genes, such as *ATG5* and *ATG7*, did not significantly change the half-life of the ribosomal protein RPL11 (Hao *et al*., 2022). These studies revealed an unexpected result: autophagic induction was not linked to the control of ribosome abundance during fasting. On the one hand, only a small portion of ribosomes are degraded by autophagy; on the other hand, autophagosomes are not the only factor influencing the intensity of Ribo-Keima flow (An *et al*., 2017). Therefore, any vesicular structure encasing the ribosomes for lysosomal breakdown may be responsible for the entire autophagy flow. In recent years, there has been growing evidence that autophagy is one of the important routes for limiting ribosome abundance, even though it contributes to the breakdown of a portion of ribosomes and is typically activated under cellular stress (López *et al*., 2023). According to Gnanasundram *et al*. (2018), ribosomes are abundantly built to satisfy the increased demand of protein translation, however proteins will be momentarily deficient when the cells are subjected to various challenges, such as starvation, drug toxicity, or other stimuli. Autophagy works as an RQC mechanism to break down of nonfunctional ribosomes because ribosomes may be misassembled or disproportionately over-generated during this process. In *Saccharomyces cerevisiae*, Kraft *et al*. (2008) first proposed the idea of ribosomal autophagy after discovering that mature ribosomes were broken down by both non-selective autophagy and a unique selective mechanism known as "ribophagy" in response to nutritional shortage. Wyant *et al*., 2018 discovered that Nuclear fragile X mental retardation-interacting protein 1 (NUFIP-1) is a receptor for famine-induced ribophagy in mammals, demonstrating the presence of selective autophagy that targets ribosomes and offering fresh perspectives on ribophagy research. Cdc48 and Ufd3 functioned as the primary executors of the ubiquitin proteasome system and were essential for the selective autophagy of mature ribosomes in *Saccharomyces cerevisiae* that was both starvation-induced and Ubp3-Bre5 dependent (Ossareh-Nazari *et al*., 2010). The synergy of the structure and function of various organelles is the prerequisites for intracellular homeostasis. As a key organelle for protein synthesis, ribosome is structurally and functionally correlated with other organelles, including endoplasmic reticulum and mitochondria (Schwarz *et al*., 2015). Recent studies have shown that there are intricate relationships across various organelles in the selective autophagy of organelles. An *et al*. (2018) report that a fraction of ribosomes could be packaged and degraded incidentally during the process of selective autophagy targeting other organelles. Although the ratio was relatively low, it revealed the potential relationship among disparate types of organelle specific autophagy, and pioneered the research on another pathway of ribosomal autophagy, in terms of “bystander” autophagy. Additionally, RNA is directly transported by autophagy to the lysosomes for destruction. Lysosome-associated membrane glycoprotein 2C (LAMP2C) functions as a particular receptor in this process, which needs ATP to supply energy (Sakai *et al*., 2025). Heat shock 70 kD protein 8 (HSPA8) has no discernible effect on the uptake of RNA into the sequestered lysosomes, in contrast to CMA. Furthermore, all RNA types can be bound by LAMP2C, and 10%–20% of the total RNA in live cells is degraded by RNautophagy (Ray *et al*., 2025).

Ribosome quality control (RQC): Ribosome quality control (RQC) is a co-translational quality control surveillance mechanism for degradation of nascent polypeptides in aberrantly stalled ribosomes during translation (Endo *et al*., 2023). This process protects cells from proteotoxic stress and preserves protein homeostasis. Persistent stalling promotes ribosome collision and activates quality-control pathways that identify the aberrant ribosomal complex, rescue and recycle ribosomal subunits, and eliminate incomplete nascent polypeptides. The ribosome-associated quality control (RQC) mechanism can be triggered by issues with the elongation or termination steps of translation, which can result in ribosome collision and ribosome stalling. A build-up of defective translation products that disrupt protein homeostasis (proteostasis) may result from inadequate RQC (Lu, 2022). As a result, RQC is a crucial part of the larger network of cellular protein quality control.

The RQC pathway involves multiple steps that are controlled by several factors The stalling of ribosomes on aberrant mRNAs, which can be caused by a variety of stresses like rare codon repetitions, excessive mRNA structure, the lack of a stop codon, and the presence of a poly(A) sequence, is a trigger for RQC. Hel2/ZNF598 initially detects these stalled ribosomes by binding to the 40S ribosome subunit and ubiquitinating the ribosomal proteins *Rps10* and *Rps20*. This causes the stalled 80S ribosome to split into 40S and 60S subunits through the Dom34/Pelota-Hbs1 (Sandaramoorthy *et al*., 2016; Garzia *et al*., 2017). The ASCC3 helicase subunit of the RQC trigger (RQT) complex is crucial for the splitting of the colliding ribosome in humans. The 60S subunit remains attached to a nascent peptidyl-tRNA conjugate while the 40S subunit is released for recycling. While the 40S subunit is released for recycling, the 60S subunit remains attached to a nascent peptidyl-tRNA conjugate. Then, nuclear export mediator factor (NEMF) binds to the 60S subunit and adds C-terminal alanine and threonine residues (CAT-tails) to nascent polypeptides (Kostova *et al*., 2017; Osuna *et al*., 2017).

Rqc2/NEMF detects these obstructed 60S subunits and then recruits LTN1/Listerin, an E3 ligase, for nascent peptide ubiquitination. This polyubiquitinates the nascent polypeptides with CAT-tails for further proteasomal degradation (Shao *et al*., 2015; Shen *et al*., 2015). The first known RQC component for nascent peptide ubiquitination is LTN1/Listerin. Another RQC complex subunit, Rqc1/TCF25, is necessary for the production of K48-linked ubiquitin chains. The ubiquitin signal recruits the VCP-Ufd1-Npl4 complex, which extracts and delivers the nascent chain to the 26S proteasome for degradation (Filbeck *et al*., 2022).

Apart from the RQC, co-translational quality control of nascent polypeptides in aberrantly stalled ribosomes is also regulated by a cellular pathway involving UFM1, a ubiquitin-like posttranslational modification covalently attached to a lysine residue of substrates (Wang *et al*., 2020; Wang *et al*., 2021). E1-like UBA5, E2-like UFC1, and E3-like UFL1 are involved in UFMylation, as is known for the ubiquitination pathway (Gerakis *et al*., 2019; Banerjee *et al*., 2020). DDRGK and CDK5RAP3, two essential components that mediate UFMylation of substrate proteins in the ER, form a complex with UFL1 (Wang *et al*., 2020; Wang *et al*., 2021).

RQC and human diseases: Ribosome stalling and collisions can occur due to several cellular mechanisms such as truncated ORFs, lack of stop codons, or early polyadenylation, which impact a sizable portion of mRNAs (Pelechano *et al*., 2013).The significance of RQC in maintaining cellular homeostasis is highlighted by the recognition that cells respond to ribosome collisions in a variety of ways, including interventions at the collision site, the translation of affected mRNAs, and broader impacts on general translation. Various human diseases have been linked to disruptions in the RQC pathway as well as dysregulated expression or mutations in key "RQC factors". Based on the detection of relevant phenotypes in genetically modified animal models, they encompass mutations or dysregulated expression of the RQC pathway components associated with the disease pathophysiology (McGirr *et al*., 2025). In the subsequent paragraph using few representative samples were describe the unique/salient features of few disorders in detail.

Neurodegeneration and neurological disorders: There is growing evidence linking RQC dysfunction to neurophysiological impairment and the development of neurological disorders (Tseng *et al*., 2023). For instance, the protein TDP-43, a hallmark of some neurodegenerative diseases, interacts with the activated ribosomal protein receptor, causing ribosome stalling and subsequent the formation of cytoplasmic vacuoles (Russo *et al*., 2017). Similarly, ribosome stalling caused by the mutant huntingtin protein hinders protein synthesis and lead to a loss of function (Eshraghi *et al*., 2021). The health and function of cells suffer significantly as a result of this disruption of regular cellular functions. Toxic protein aggregates may also build up as a result of mutations in other RQC pathway factors. These aggregates may exhibit a "gain-of-function" characteristic, which is frequently linked to degenerative diseases (Wang *et al*., 2025). Dysregulated proteostasis and build-up of protein aggregates are hallmarks of several neurological disorders (Tsoi *et al*., 2023; Wilson *et al*., 2023). Because of their long lifespan, limited potential for regeneration, intricate synaptic connections, and restricted immune clearance, neurons are especially susceptible to protein misfolding and aggregations. Accordingly, a dysfunctional RQC may have a disproportionate impact on neuronal growth and function, leading to neurological diseases (McGirr *et al*., 2025). In probands belonging to different families with neurological characteristics disruptive mutations in the *GTPBP2* gene have been reported (Jaberi *et al*., 2016; Bertoli-Avella *et al*., 2018).

Huntington's disease: Huntington's disease presents with psychological, cognitive, and movement impairments. The causative reason is the expansion of CAG trinucleotide repeats in exon 1 of the Huntingtin (*HTT*) gene (Ormsby *et al*., 2020), which leads to the development of a polyglutamine (polyQ) tract in the encoded protein. The *HTT* mRNA's CAG repeats change the dynamics of elongation and result in ribosome collisions. As a result, the mutant *HTT* (*mHTT*) protein contributes to the neurotoxic phenotype and is prone to intracellular aggregation (Sobti *et al*., 2023). Additionally, by sequestering the elongation factor eIF5A, translation of the *mHTT* mRNA increases ribotoxicity. Reduction in available eIF5A compromises co-translational proteostasis and stress responses and exacerbates ribosome stalling on eIF5A-dependent sites (usually proline-rich motifs) (Aviner *et al*., 2024). *HTT* is a multifunctional protein involved in essential cellular processes, including vesicular transport, synaptic transmission, and autophagy (Masi *et al*., 2022). However, the mutated form of *HTT* impairs its normal function and prevents protein synthesis by slowing ribosomal translocation. Interestingly, *mHTT* binds to ribosomes and specifically affects many target messenger RNAs' (mRNAs') and translocation (Eshraghi *et al*., 2021). This aberrant interaction causes ribosome stalling during translation elongation by hinders protein synthesis and interfering with ribosomal translocation. As a result, *mHTT* acts as a strong inhibitor of translation elongation rates, leading to persistent ribosome stalling that damages collisions and disrupted protein synthesis (Nithianantharajah *et al*., 2013).

Alzheimer's disease: AD is a chronic, long-term, progressive neurodegenerative condition characterized by deteriorating memory and cognitive function. It is the most common type of dementia in elderly individuals. The dysfunctional metabolism of the amyloid precursor protein (APP) mRNA translation leads to the formation of CAT-tailed protein that accelerate the β-amyloid (Aβ) plaques derived from $A\beta_{42}$cleavage products of APP that drive disease progression (Scheltens *et al*., 2021). During co-translational translocation of the APP C-terminal fragment (APP.C99), ribosomes stall at the ER membrane, resulting in truncated proteins with aggregation-prone CAT-tails. This accumulation leads to endolysosomal/autophagy defects, seeding Aβ peptide aggregation. Brain tissue from AD patients shows enrichment of mutations in *ZNF598, NEMF,* and *ANKZF1*gene coded proteins in the nuclei of amyloid plaques, consistent with the hypothesis that ribosome collision may contribute to the pathogenesis of AD (Rimal *et al*., 2021).

Parkinson's disease: Parkinson's disease (PD) is a neurodegenerative disorder that primarily affects the motor system and progresses over time. Movement and coordination are affected by dopamine deficiency and dopaminergic neuron loss. The model that PINK1-mediated mitophagy causes the buildup of defective mitochondria and PD pathogenesis was developed after *PINK1*gene mutations were found in familial PD (Jankovic *et al*., 2020). Notably, late-stage PD and *PARK11* familial PD have been shown to contain mutations in the *GIGYF2* gene, which maps to the *PARK11* locus

Table-1. A brief list of Human disorders associated with ribosome biosynthesis abnormalities

Disease	Dysfunction	Clinical manifestation	Therapeutic regimen	References
Dyskeratosis congenita	*DKC1* gene defect	The triad of oral leukoplakia, nail dystrophy, and reticular hyperpigmentation	Surveillance for associated complications; stem cell transplantation	Zhao *et al.,* 2023
Cartilage hair hypoplasia	*RMRP* gene defect	Short limbed short stature, hypoplastic hair, defective immunity and erythrogenesis.	Prevention of secondary complications.	
Congenital mental retardation	*NUFIP-1*	Severe distraction, poor memory, and speech ability.	None	
Stroke	Disturbance of ribophagy and ERS	Sudden weakness on one face, arm or leg, fainting, confusion, and severe headache.	Thrombolytic therapy; surgery	
Motor neuron disease	*NEMF* mutation	Motor neurons degeneration, neurogenic muscle atrophy, and movement disorders.	Respiratory support, nutritional support, symptomatic treatment, drug treatment	
Jabi-Elahi syndrome	*GTPBP2* mutation	Dystonia, motor and sensory neuropathy, ataxia, and cognitive impairment.	Symptomatic treatment, drug treatment	
Uterine cancer	*RPL23A* gene amplification and *RPSA* gene mutation	Painless hematuria, frequent urination, urgency and other urinary symptoms.	Surgery, chemotherapy, radiotherapy,	
Metastatic neuroblastoma	Mutations of *NUFIP-1*	Fever, general malaise, weight loss, bone pain, constipation or diarrhea.	Surgery, chemotherapy, radiotherapy	
Acute lymphoblastic leukemia Anemia,	Mutations of union gene *ETV6-NUFIP1*	Fever and infection, bleeding, and organ tissue infiltration.	Hematopoietic stem cell transplantation, induction therapy; post remission therapy; consolidation chemotherapy with a cytarabine-based regimen.	
Lupus-like syndrome	Ro protein	An autoimmune syndrome characterized by anti-ribosomal antibodies, anti-chromatin antibodies, and glomerulonephritis.	Promoting the expression of Ro protein, avoiding ultraviolet radiation, immunotherapy.	
Inflammatory bowel disease	Decline of ribosome biogenesis eIF5A	Abdominal pain, diarrhea, bloody stools, and weight loss.	Targeted regulation of ribosome biogenesis eIF5A.	
Hepatitis C	Disorder of interaction between ribosomal proteins and 18SrRNA	Nausea, decreased appetite, general weakness, and jaundice.	Targeting the interaction between ribosomal proteins and 18SrRNA.	
Severe sepsis	*Nucleophosmin*	Organ dysfunction, circulatory failure, and shock.	Acting as an alarmin to detect severe sepsis patients early.	

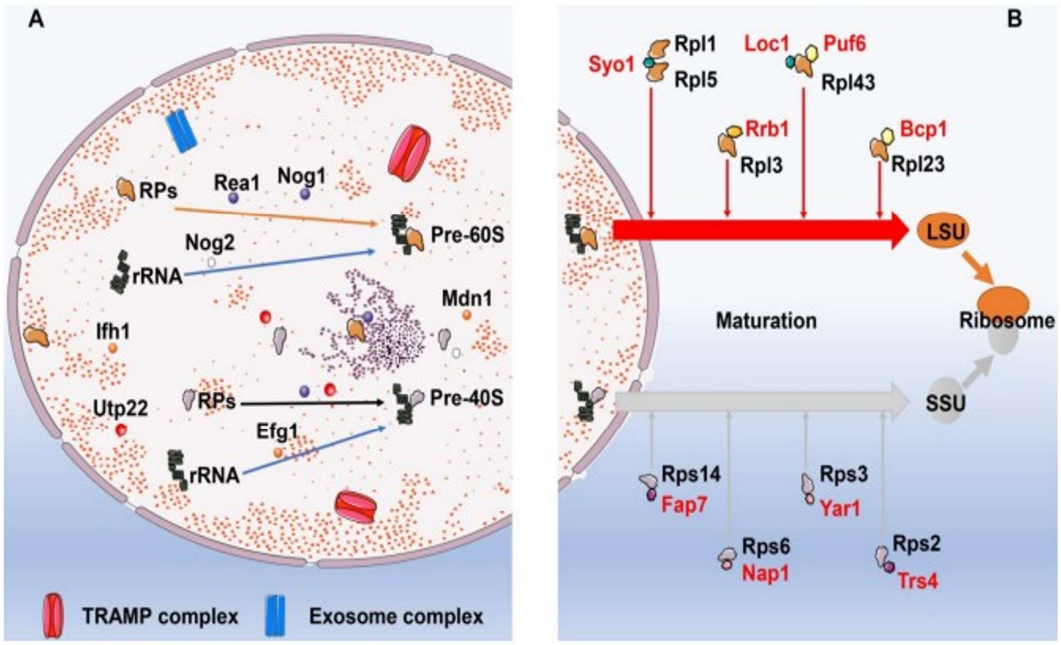

Figure 1. Mechanisms of Ribosome biogenesis and maturation and the components involved

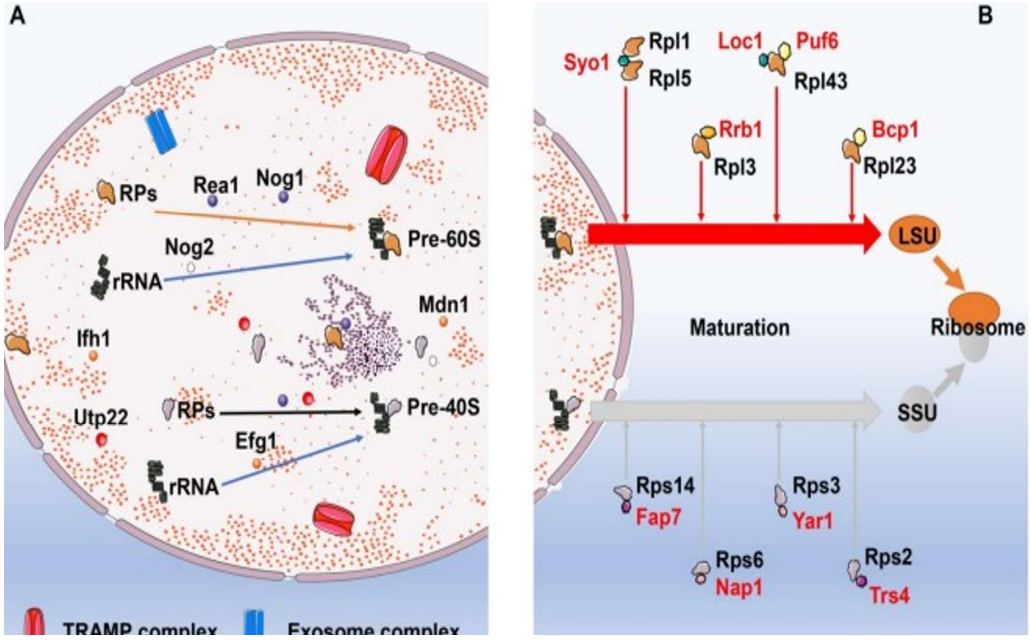

Figure 2. Ribosome recycling and the components (Abbreviation: RACK1: receptor for activated C kinase 1; RQC: ribosome quality control; NGD: no-go decay)

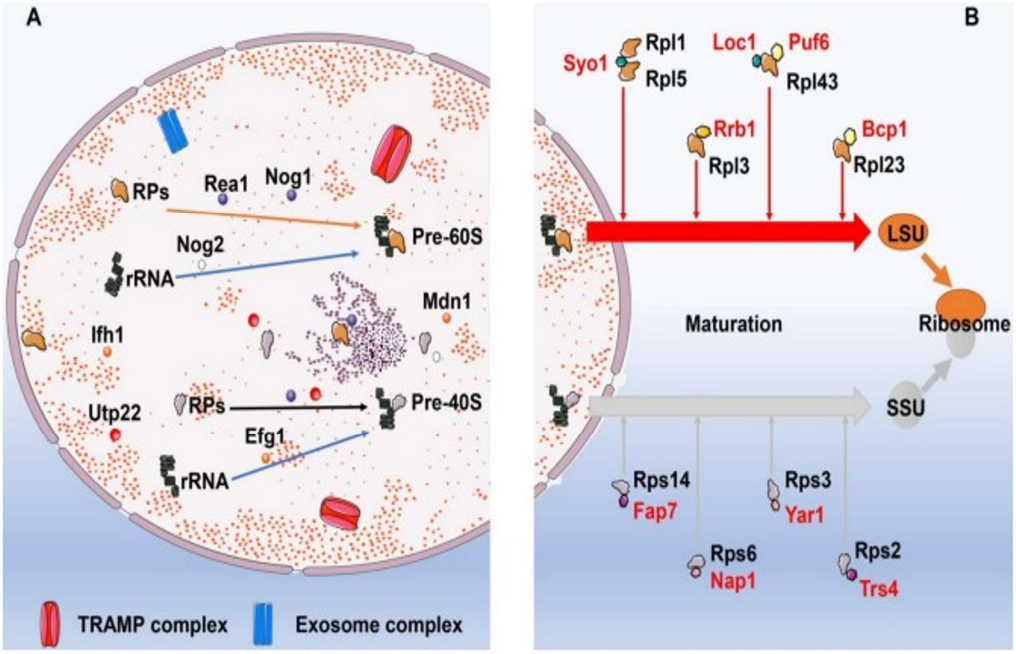

Figure 3. Abnormal ribosome biogenesis and its role in various human diseases

(chromosome 2q37)(Zhang *et al*., 2015; Lautier *et al*., 2008). These mutations have also been associated with an elevated risk for PD (Ruiz-Martinez *et al*., 2015). It has been suggested that *PINK1* protein activates mitophagy by triggering RQC on nuclear-encoded mRNAs that produce mitochondrial outer membrane proteins during mitochondrial damage. Ribosome stalling on these mRNAs causes NOT4 protein to ubiquitinate *ABCE1* in response to mitochondrial stress. The process of mitophagy is initiated when ubiquitinated *ABCE1* attracts autophagy receptors to the outer membrane of the mitochondria. *ABCE1* and *HBS1L* genes were significantly downregulated in brain tissue samples from PD patients when compared to healthy individuals, according to differential expression analysis (Wu *et al*., 2018). These results emphasize the critical role of the RQC process in the pathogenesis of PD (Wu *et al*., 2019).

Neuromuscular diseases: Amyotrophic lateral sclerosis (ALS) is a diverse heterogeneous neurodegenerative disease affects motor neurons. It causes progressive muscular weakness, respiratory failure in most cases (Mehta *et al*., 2022). The increase of the GGGGCC (G4C2) repeats in the Chromosome 9 open reading frame 72 (*C9ORF72*) gene is typically associated with ALS. One of the main causes of neurotoxicity in ALS patients is proteotoxicity resulting from arginine-containing dipeptide repeats obtained from mistranslated *C9ORF72* expansion transcripts (Feldman *et al*., 2022; Kriachkov *et al*., 2023). The most common genetic mutation reported in familial cases of ALS with frontotemporal lobar degeneration (ALS/FTD) is the expansion of intronic *G4C2* hexanucleotide repeats within *C9ORF72* (Renton *et al*., 2011). Dipeptide repeat (DPR) proteins aggregate as a result of the *G4C2* repeats tendency to

encode repeat amino acids and have the propensity to form complex secondary structures. Further, by inhibiting ribosomal elongation, which eventually initiates the RQC pathway, the *G4C2* repeat induces ribosome collisions (Liu *et al*., 2021). Increased DPR expression and aggregation may result from RQC pathway dysfunction, which ultimately stimulate cellular stress and toxicity. Despite initiating the RQC pathway, the RQC complexes *LISTERIN* and *NEMF* cannot effectively ubiquitinate these DPRs because they lack lysine residues (Viera Ortiz *et al*., 2023). Remarkably, repetitive RNA sequences can be used by the Pelota and ZNF598 RQC factors to modify translation dynamics (Latallo *et al*., 2023).

Research studies on neurons generated through re-differentiations of induced pluripotent stem cells (iPSCs) derived from *C9ORF72* ALS patients revealed an impaired RQC activity in these cells, as a result of lower expression of *ZNF598* (Park *et al*., 2021). Additionally, due to lack of lysine residues, these nascent peptides are resistant to LTN1-mediated ubiquitination and proteasomal degradation (Viera Ortiz *et al*., 2023). The positively charged amino acid sequences of the mitochondrial targeting sequence (MTS) in the N terminus of nuclear-encoded proteins are typically recognized by the translocase of the outer membrane (TOM) complex at the surface of mitochondria, which then facilitates their importation into mitochondria (Avendano-Monsalve *et al*., 2022).The *C9ORF72* expansion's arginine-rich region imitates the MTS and interacts with the TOM complex, leading to importation of the nascent protein into mitochondria, and causing further toxicity (Li *et al*., 2020). Notably, ribosome stalling is frequently caused by translation of mRNAs that encode mitochondrial proteins close to the outer mitochondrial membrane. To prevent the aggregation of these peptides, which otherwise could result in sequestering mitochondrial chaperones and toxicity, Vms1 binds to 60S ribosomes at the mitochondrial surface to prevent CAT-tailing of proteins already engaged with import machinery (Izawa *et al*., 2017).

Schizophrenia: Schizophrenia (SCZ) is a complex syndrome characterized with a wide range of clinical manifestations and positive and negative symptoms (Wang *et al*., 2025). SCZ has a complicated etiology that is influenced by both environmental and genetic variables. However, recent research findings indicate that dysregulation of translational control may contribute to the development of SCZ (Hui *et al*., 2019). A study identified a variant in the *LISTERIN* gene increased the risk of SCZ (Lencer *et al*., 2017) with lower levels of expression. These findings provide support to evidences for *LISTERIN* role in SCZ pathogenesis, potentially by impacting translation and consequently affecting neural activity (Farhang *et al*., 2022).

Developmental and congenital disorders: Developmental and neurodevelopmental deficits are linked to RQC deficiency as indicated by several research publications. Due to downregulation of *ABCE1*, accumulation of stalled ribosomes has also been seen during the terminal differentiation of platelets and erythroid cells (Mills *et al*., 2016). Rare biallelic loss of function mutations in *HBS1L* have been linked to range of phenotypes including developmental defects include global developmental delay, severe intrauterine growth restriction, microcephaly, submucous and cleft palate (Sankaran *et al*., 2013). Human hearing loss and aberrant limb development are linked to familial mutations in *ZAKα*'s sterile alpha motif (SAM) motif (Spielmann *et al*., 2016). These SAM domain mutants may acquire a constitutively active conformation according to research (Vind *et al*., 2020). There have also been reports of unique (tissue-specific) and temporal developmental defects due to deficiency of other "RQC factors." In prenatal cerebellar neurogenesis Pelo and *HBS1L* elimination have a major impact but it does not influence survival after development (Terrey *et al*., 2021).

Severe neurodevelopmental deficits result from RQC deficiency. In neurons with decreased *Ltn1* mRNA expression, the tetratricopeptide repeat domain 3 (*TTC3*) protein and the UFMylation signalling proteins UFM1, UFL1, and CDK5RAP3 are upregulated, leading to developmental abnormalities. This causes the ribosomal protein *RPL26* to become highly UFMylated. It is a ubiquitin-like posttranslational modification that facilitates the proteasome-mediated degradation of stalled polypeptides. Furthermore, by inhibiting translation initiation—a mechanism that may be facilitated by *RPS2* ubiquitination—*TTC3* reduces the build-up of translationally stalled products. On the other hand, aberrant *TTC3* protein accumulation during neuronal development causes dendritic abnormalities and decreased surface-localized $GABA_A$ receptors. In model organism study *TTC3* accumulation is consistently observed in *Ltn1*-deficient, leading to dendritic and synaptic abnormalities as well as behavioural deficits linked to cognitive problems (Endo *et al*., 2023).

Fragile X syndrome (FXS): Fragile X syndrome (FXS) is the most prevalent inherited form of intellectual disability, characterized childhood seizures, and autistic behaviours. One possible potential contributing factor to FXS pathobiology is excessive mRNA translation, especially of the highly abundant and efficiently translated mRNAs that encode ribosomal proteins (Seo *et al*., 2022). FXS is caused by loss of function of the Fragile X mental retardation protein (FMRP), which is necessary for synaptic plasticity and neuronal development. FMRP stalls ribosomes along the coding regions of mRNAs associated with autism, neuronal development, and synaptic function. Studies show that loss of FMRP relieves these stalled ribosomes (Anadolu *et al*., 2023; Das Sharma *et al*., 2019; Scarpitti *et al*., 2024). Potential interactions between FMRP and "RQC factors" including ZNF598 (Youn *et al*., 2018) and ZAKα were found by a high-throughput interactome analyses. These findings further suggest a cross-talk between FMRP-mediated stalling and the RQC pathway (Wu *et al*., 2018).

Metabolic stress and diseases: Numerous evidence highlights the complex interaction between RQC and metabolic stress, which is essential for maintaining cellular homeostasis and responding to stress. Through a various mechanism, metabolic imbalances can impede mRNA translation and result in ribosome stalling. These include stalling due to a limited availability of specific amino acids or the tRNAs that correspond to them (Darnell *et al*., 2018; Rubio *et al*., 2021). Also, the RQC can be triggered by oxidative and alkylating stressors that cause ribosome stalling. Both RNAs and components of the translation machinery may be directly impacted by such stresses. For example, changes in cellular redox levels induced by treatment with reactive oxygen species (ROS) and the lipid electrophile 4-hydroxy-2-nonenal (Topf *et al*., 2018) cause ribosomal proteins and translation factors to be oxidized, changing their functions (Chio *et al*., 2016). It has been demonstrated that excessive ROS

production damages translation factors and tRNAs and causes ribosome stalling and collision (Snieckute *et al*., 2023). Modifications of ribosomal proteins by oxidative stress may potentially interfere with translation elongation or termination and cause the translating ribosomes to stall. These modifications render difficulty in ribosomal coding which could result in ribosome stalling. Research implicates when oxidizing and alkylating agents or UV radiation are applied to adducts colliding ribosomes can be resolved by RQC (Yan *et al*., 2019; Stoneley *et al*., 2022). RNA-protein crosslinks due to treatment with aldehydes may cause ribosome stalling (Suryo Rahmanto *et al*., 2023). The resolution of colliding ribosomes resulting from aldehyde-induced RNA-protein crosslinks and the maintaining cellular fitness depend on the *GCN1/GCN2* and ZAKα-mediated RQC (Zhao *et al*., 2023). Significant impacts on metabolic fitness can arise from excessive ribosome collisions, which cause the activation of ISR mediated by *GCN1/GCN2* or RSR mediated by *ZAKα.*

Cancer: The accelerated cell proliferation in cancers needs significant substantial cellular resources, such as increased protein synthesis and higher ribosome content. Therefore, total translation activity and ribosome biogenesis are frequently increased during oncogenic transformation (Ebright *et al*., 2020), in part stimulated by *mTORC1*signaling pathways (Alboushi *et al*., 2021). This higher rate of translation may also augment the risk of ribosome collisions in cancer cells, given the increased likelihood of ribosome collisions on highly translated mRNAs (Park *et al*., 2019; Goldman *et al*., 2021). Elevated cancer risk is increased by ribosome stalling caused by chemical modifications to mRNAs, ribosomes, and translation factors. Further risk is contributed by metabolic stresses due to oxidative agents such as ROS and nitric oxide (Hayes *et al*., 2020), Excessive production of aberrant mRNAs, such as abnormally spliced (Zhang *et al*., 2021), polyadenylated mRNAs (Xiang *et al*., 2018), and dysregulated RNA modifications such as pseudouridination can further exacerbate the potential for ribosome stallingin cancer as evidenced through cell lines studies (Hu *et al*., 2023).

Several "RQC factors" have been found to have mutations or dysregulated expression in a variety of cancer types. For example, tumorigenesis is associated with increased expression of p97/VCP, and a number of inhibitors have shown promising anti-cancer effects thus providing evidence for the role of p97/VCP (Li *et al*., 2021). The interpretation of p97/VCP's participation in p97/VCP-dependent RQC in cancer is complicated by the fact that it is involved in pathways other than RQC, such as the Endoplasmic Reticulum-Associated Protein Degradation (ERAD) pathway. It's interesting to note that when p97/VCP is inhibited, activation of oncogenic HRAS or the AKT pathways, which result in increased mRNA translation, increases proteotoxic stress and cell death (Lee *et al*., 2024). Several genes involved in ribosome biogenesis have been implicated in Cancer. The *ZAK* Gene encodes two major kinase isoforms, with ZAKα acting as a crucial cellular sensor for ribotoxic stress and ribosome stalling. The epithelial-mesenchymal transition (EMT) and cell motility are linked to ZAKα's oncogenic activity in colorectal cancer (Li *et al*., 2018; Rey *et al*., 2016). Further, ZAKα expression shows a negative correlation with survival and substantially increased in several cancers gastric, colorectal, breast, and urinary cancers (Zhou *et al*., 2019; Li *et al*., 2018; Rey *et al*., 2016; Tang *et al*., 2019).

Blood diseases

Diamond-Blackfan anemia (DBA): Diamond-Blackfan anemia (DBA) is a bone marrow failure syndrome in which the number of erythroid precursor cells in the marrow of patients is markedly decreased or even disappears, which increases the risk of malignant transformation (Da Costa *et al*., 2020; Dorn *et al*., 2021). It is heterogeneous genetic disorder characterized by red blood cell aplasia in association with skeletal anomalies, craniofacial anomalies, thumb deformities and short stature (Lipto *et al*., 2009). Chronic macrocytic-normochromic anemia, low reticulocyte count, and decreased or totally absent erythroid precursors characterized by failure of erythropoiesis with normal production of leukocytes and platelets in the bone marrow, are the main hematological features of DBA (Ball *et al*., 2011).

Mutations and deletions in either the large or small ribosomal protein genes results in an imbalance between the biosynthesis of rRNA and ribosomal proteins, which ultimately activates the p53 oncogene. Both congenital and acquired bone marrow failure syndromes in humans are generally linked to abnormalities in bone marrow function in DBA (Engidaye *et al*., 2022). Recent advancements in genetic diagnostic technology have revealed that mutations in genes encoding ribosomal proteins, such as *RPS19, RPS24, RPS17, RPL35A, RPL5,* and *RPL11,* in DBA patients. However, the clinical manifestations resulting from different ribosomal gene mutations are quite varied. For instance, patients with *RPL11* mutations were more likely to acquire thumb abnormalities, and *RPL5* mutations were strongly associated with craniofacial malformations (Zhao *et al*., 2022).

Shwachman-Diamond syndrome (SDS): SDS the inherited ribosomopathy, is characterized by bone marrow failure and a high risk of myeloid malignancies at an early age. Shwachman Bodian Diamond Syndrome (SBDS) gene is the genetic cause for developing SDS (Kawashima *et al*., 2023). The protein serves as a cofactor for elongation factor-like GTPase1 (EFL1), which cleaves the large ribosomal subunit of eukaryotic translation initiation factor 6 (eIF6) enabling the 60S subunit to attach the 40S ribosomal subunit to form an active ribosome (Stepensky *et al*., 2017; Venturi *et al*., 2020). Specifically, eIF6 is removed from the 60S subunit along with SBDS due to mutations in *DNAJC21, EFL1, SRP54*, and other genes linked to SBDS (Stepensky *et al*., 2017; Carapito *et al*., 2017). SDS also results from a failure to release eIF6 (Tan *et al*., 2019). Coprecipitation and sucrose gradient studies implicate SBDS is attached to 28S rRNA as a part of the mature 60S ribosomal subunit and with pre-60S subunit (Ganapathi *et al*., 2007). Additionally, cell line studies demonstrate decreased expression of several ribosomal protein genes in SDS cells such as *RPS9, RPS20, RPL6, RPL15, RPL22, RPL23,* and *RPL29* involved in cell growth and survival. Also, in aberrant expression of numerous genes involved in rRNA and mRNA processing (Rujkijyanont *et al*., 2009; Jiao *et al*., 2023).

Cardiovascular diseases (CVDs)

Cardiac hypertrophy: Inflammatory cardiomyopathy, pressure or volume overload, and prolonged stimulation can all result in cardiac hypertrophy, an adaptive response that eventually causes heart failure (Packer, 2021; Gao *et al*., 2021).

According to recent research, ribosome biogenesis plays an important role in cardiac hypertrophy by promoting or inhibiting the pathological process (Liao *et al*., 2021; Gelinas *et al*., 2018). The degree of phosphorylation of RNA Pol I and the upstream binding factor (UBF) are positively correlated with the rate of rDNA transcription. Research has shown that by upsetting the UBF/SL1 complex, the hypophosphorylated form of UBF inhibits rDNA transcription (Theophanous *et al*., 2023). According to Zeitz *et al*. (2020), there is a correlation between the phosphorylation of UBF and the proliferation rate of cultured newborn cardiomyocytes. UBF hyperphosphorylation is linked to endothelin-1-induced cardiac hypertrophy (Jen *et al*., 2016). Furthermore, in conditions of α1 adrenergic receptor or stress-load-induced cardiac hypertrophy, elevated rDNA transcript levels are linked to elevated UBF protein levels (Jiao *et al*., 2023). In addition to acting as the primary scaffold for ribosomal subunits, rRNA is also the focal point of catalytic activity during ribosome biogenesis (Liu *et al*., 2021). The aberrant pre-rRNA processing results in ventricular hypertrophy, disturbs the balance of cardiac proteins, and damages ribosome structure and function (Nieto *et al*., 2021).

Myocardial infarction (MI): MI is caused by blockage of the coronary artery (Dagenais *et al*., 2020). Ribosome dysfunction has been shown in numerous studies to be a significant factor in MI (Tran *et al*., 2020) MI-induced ribosomal dysfunction is associated with downregulation of *Ncl, rRNA, RPL9,* and *RPL26* genes (Tong *et al*., 2019).

Atherosclerosis: Atherosclerosis is an inflammatory disorder caused by lipid accumulation in the artery wall intima and subsequent thickening (Fonseca *et al*., 2022; Xiang *et al*., 2022). Macrophages cells contribute to atherosclerosis by phagocytising lipid droplets to produce foam cells and hasten the disease's progression (Xiang *et al*., 2022). Further, aberrant vascular smooth muscle cell (VSMC) proliferation speeds up the atherosclerosis by encouraging artery intimal hyperplasia. Ribosome biogenesis regulates cell division and proliferation. Three essential processes are known to be involved in ribosome biogenesis: the synthesis of rRNA, the synthesis of ribosomal proteins (RPs), and their assembly into the mature ribosome (Zisi *et al*., 2022; Klinge *et al*., 2019). The PES-BOP1-WDR12 (PeBoW) complex, which binds to pre-rRNA and promotes 47S pre-rRNA into mature 28S and 5.8S rRNA, is closely associated to the maturation of rRNA during ribosome assembly. 28S and 5.8S rRNA is produced by the main regulator of the PeBoW complex (Jia *et al*., 2021). According to Jia *et al*. (2021), patients with atherosclerosis have elevated BOP1 in their coronary arteries accompanied by neointimal hyperplasia brought on by VSMC proliferation. Consequently, elevated BOP1 and PES1 expression stimulates ribosome biogenesis, which results in aberrant VSMC proliferation and atherosclerosis.

Innate immunity and response to viral infections: According to research evidence several "RQC factors" may also be involved in the regulation of the innate immune response. Depletion of *ASCC3* an interferon-stimulated gene (ISG) (Martineze *et al*., 2006), results in decreased replication of several positive-strand RNA viruses belonging to the Flaviviridae, Togaviridae, and Picornaviridae families (Li *et al*., 2013). Whereas, the increased expression of several other ISGs such as *IFI44, RSAD2*, and *IFIT2* decrease the replication Additionally evidence suggests a direct role for RQC in promoting infection and DNA viral replication. ISG activation of the cGAS/STING pathway, and relocation of cGAS from the nucleus to the cytosol are all consequences of RQC deficiency. Interestingly, when ribosome collisions are more frequent, cGAS exhibits a preference for binding to collided ribosomes (Wan *et al*., 2021). A unique 5′ UTR with an uninterrupted poly(A) sequence is present in poxviruses belonging to the family of double-stranded DNA viruses (Jha *et al*., 2017). The translation of viral mRNAs and reporter mRNAs with a poly(A) sequence in their 5′ UTRs are facilitated by the phosphorylation of RACK1 by the viral B1 kinase. Importantly, Vaccinia infection triggers the ubiquitination of tiny ribosomal proteins and efficient viral mRNA translation and infection depend on the presence of functional ZNF598 (DiGiuseppe *et al*., 2018; Sundaramoorthy *et al*., 2021).

Another ISG that prevents viral replication is viperin, which also causes broad-spectrum suppression of cellular and viral mRNA translation. This is accomplished by catalysing the conversion of cytidine triphosphate (CTP) into 3'deoxy-3′,4′-didehydro-CTP (ddhCTP), which randomly incorporates into RNAs and causes ribosome collision with activating ZAKα/GCN2-mediated ISR and translational repression (Hsu *et al*., 2022). In contrast, other evidence suggests that RQC might potentially contribute to repression of viral infection and increase immune response activation when viral infection is detected. By preventing the translation of the EBV Nuclear Antigen 1 (EBNA1) mRNA in infected cells, RQC may also block the Epstein-Barr virus (EBV). To overcome this, the ubiquitin residues on the 40S subunits and the nascent EBNA1 protein are removed by the virally encoded ubiquitin deconjugase (vDUB) BPLF1, which is catalyzed by ZNF598 and LTN1, respectively (McGirr *et al*., 2024). As a result, the entire protein is produced and the stalled ribosome on the viral mRNA is read through (Liu *et al*., 2023). By promoting the proteasomal degradation of the viral protein and improving its presentation on MHC class I, RQC also helps to activate the CD8+ T cell-mediated immune response to viral infection (Trentini *et al*., 2020).

Other disorders

X-linked dyskeratosis congenita (X-linked DC): Mutations in the *DKC1* gene, which codes for dyskerin, are connected to X-linked dyskeratosis congenita (X-linked DC) (Nguyen *et al*., 2020). The pseudouridylation of particular uridine residues in newly generated rRNAs is catalyzed by the enzyme dyskerin (Garus *et al*., 2021). When linked to small nucleolar RNAs (snoRNA), pseudouridines regulate ribosome and rRNA biosynthesis. X-linked DC patient cell lines show abnormalities in rRNA processing and altered snoRNA regulation (Venturi *et al*., 2020). Moreover, rRNA 2'-O-methylation is altered by *NPM1* mutations in DC patients (Nachmani *et al*., 2019).

Cartilage Hair Hypoplasia (CHH): The RNA component of the mitochondrial RNA processing endoribonuclease (*RMRP*) gene is mutated in Cartilage Hair Hypoplasia (CHH), an autosomal recessive condition (Welting *et al*., 2004). *RMRP* is a long noncoding RNA (lncRNA) that contributes to tRNA maturation and RNase-MRP complex formation. Classified as snoRNAs, *RMRP* in mitochondria encodes the RNA component of RNase-MRP and is involved in several steps of ribosomal RNA synthesis (Narla *et al*., 2010).

Ribosome biogenesis is shown to be reduced in CHH fibroblasts (Steinbusch *et al*., 2017; Jiao *et al*., 2023).

DISCUSSION

The capacity to convert genetic information into useful proteins is seen as a significant evolutionary milestone. Through selecting processes that have given each species a distinct fitness to their individual niches, nutrient availability, diet composition, and developmental programs have shaped the human beings (Tu *et al*., 2023). Numerous intrinsic and environmental factors have altered the complexity of life thus influencing the evolution of sophisticated biological mechanisms to respond to these stimuli (Duclos *et al*., 2019). Proliferating cells need a constant supply of structural and catalytic proteins to feed, develop, and divide, highlighting the significance of protein synthesis (Hoerter *et al.,* 2026). The multi-unit complex known as the ribosome is responsible for translating mRNA into protein. The process that produces ribosomes is known as ribosome biogenesis is crucial for cell division, proliferation, apoptosis, development, and transformation. Research has shown that the ribosome influences the pace of protein synthesis and is involved in cell division, proliferation, apoptosis, and transformation thus enabling cellular homeostasis. The process is regulated by the various signalling pathways, indicating the necessity of coordination, specificity, and diversity.

The main mediators that collaborate with RNA polymerases and ribosomal proteins to regulate ribosome biogenesis and protein synthesis are the mTORC1, Myc, and noncoding RNA signalling pathways. Pharmacologic drugs have been used as therapy interventions to target the pathways. mTOR signalling has been shown to be a successful method of controlling the growth of cancer (Gentilella *et al*., 2015), studies support MYC targeting in cancer treatment (Koh *et al*., 2016). Ribosome-related illnesses, including COVID-19 viral infection, bacterial resistance, cardiovascular diseases (CVD), blood disorders, neurological diseases, and cancer, can be caused by ribosome anomalies that significantly impact cell fate. The process of constructing the ribosome complex, known as ribosome biogenesis, is a highly coordinated process that is intimately linked to a number of important cellular functions was covered in the previous section of the review. From its synthesis to its breakdown, the ribosome, an essential organelle for the preservation of protein homeostasis, performs intricate translational tasks under the guidance of numerous quality control systems.

However, ribosomal dysfunction can result from dysregulation and impairment of ribosome compositions and functions due to exposure to internal or external adverse stimuli. As discussed in detail in the previous section deeper/in depth insights have accumulated over the last two decades on several aspects of ribosome biosynthesis. However, number of constraints necessitate in-depth investigations, such as the relationship between RQCS malfunction and the pathophysiology of human diseases. Deeper knowledge of the pathophysiological role of RQCS in human disorders appears to be hampered due to investigations in yeast, *in vitro* tests, and mammal-based studies which don't completely recapitulate the translational significance to humans. There is a lack of dynamic monitoring of ribosome function in diseased cells. Lastly, there are currently relatively few particular markers that represent the ribosome's functioning condition. Since the protein synthesis machinery is essential for both the immune response and viral proliferation, ribosomes play a vital role during infection (Sohier *et al*., 2026). Understanding the function of ribosomes in viral infections can be gained from studying the biology of viruses in human cells. This prospect enables basic studies such as gain understanding of the molecular and cellular processes involved in ribosome biogenesis and related processes. The importance of ribosome biogenesis in cellular processes and pathology has been highlighted by the coronavirus illness pandemic. Through a variety of mechanisms, SARS-CoV-2 controls ribosome biogenesis in host cells (Jiao *et al*., 2023). The SARS-CoV-2 virus uses Nsp1 to cleave host mRNAs while preventing their entry. It has been demonstrated that SARS-CoV-2 infection impacts ribosome biogenesis, resulting in viral replication and immune evasion. The ribosomes of the host cell are used by viruses to make proteins. For instance, coronaviruses exploit frameshift to create viral proteins by taking over the cell's translation process (Kelly *et al*., 2021). According to recent research, the ribosome is not a static structure but can experience dynamic variations in composition and function (ribosomal heterogeneity), which may have an impact on the equilibrium between host defence and viral proliferation. Drugs that target viral infections may be developed using this knowledge Pott *et al.,* 2026.

In the current situation, drug-resistant microorganisms are developing far more quickly than antibiotics. An appealing target for the creation of novel antibiotics is ribosome biosynthesis (Lin *et al*., 2018). Research is being conducted to produce antibiotics that target novel locations on the ribosome. Antibiotics that target bacterial ribosomal protein production can be produced with a thorough understanding of ribosome structure. In the area of structural and cell biology investigation into shape, structure, translocation, and ribosome "frameshift," stalling, and ribosome collision can all be precisely evaluated using a number of novel technologies, including polysome profiling, ribosomal sequencing, cryo-electron microscopy, and translating ribosome affinity purification. In addition, these technologies have significantly increased our knowledge of "ribosome diseases." Additionally, they have offered fresh goals for the accurate identification and management of many illnesses.

The understanding that cells react differently to ribosome collisions highlights the importance of RQC in preserving cellular homeostasis. Numerous tissues are impacted by the related human diseases as evidenced by the range of phenotypes discussed in the review and in literature. Thus, RQC has an impact on cell differentiation and development. Its role in maintenance of cellular homeostasis is highlighted by their involvement in stress and metabolism. Neurodegenerative illnesses have been associated with a range of mechanisms such as "gain-of-function", translation errors, protein aggregation, autophagy, deubiquitination, and mitophagy. Mutations and deletions and aberrations of elongation factor are reported in haematological disorders. Repeat domain alterations and posttranslational modifications along with mutations in genes is a common theme emerging from research. Furthermore, their significance in ribosome biogenesis is highlighted by mutations in a number of genes related to ribosome biosynthesis, accessory proteins, and ribosomal proteins. These observations highlight the diverse role of ribosome biogenesis in protein synthesis.

Although the underlying mechanisms of CX-3543, BMH-21, and CX-5461 differ, clinical trials have demonstrated their promise for ribosome-targeted treatment methods (Bywater *et al*., 2012; Gitareja *et al*., 2025). However, a crucial prerequisite is the right dosage of ribosome biogenesis-based treatment that is effective without producing serious side effects. To find novel treatment targets, a thorough examination of the mechanisms underlying drug resistance is also required. The identification of aberrantly expressed proteins in the plasma of patients with certain disorders has been made possible by ribosome-sequence technology in clinical medicine (Kunamneni *et al*., 2020). Ribosome-Halo technology allows for a thorough monitoring of ribosomal protein abundance. It is acknowledged that there is a critical need in oncology for methods to precisely inhibit cancer without impairing the function of normal cells by loading therapeutic medicines onto cancer-specific sites. According to Elhamamsy *et al*. (2025), ribosome biogenesis is facilitating precision medicine and creating a trend for the hierarchical care of many individuals with various illnesses, including the same ailment. Thus, RNA biogenesis represents a central molecular network connecting gene expression with human disease, making it an important area for future biomedical research.

CONCLUSION

This review explores the relationships between RQC and diverse human diseases highlighting the diverse cellular components and mechanisms involved. RNA biogenesis is a highly coordinated and essential cellular process that regulates the production, processing, modification, maturation, transport, and degradation of RNA molecules. Proper regulation of these processes is fundamental for maintaining several genomic and cellular functions such as gene expression, protein synthesis, cellular differentiation, and tissue homeostasis. Defects in RNA biogenesis have profound effects as evidenced by several human diseases. The diverse process affected include disruptions in ribosome biogenesis can lead to ribosomopathies.

RNA modification, RNA transport, and RNA degradation contribute to neurological disorders, developmental abnormalities, hematological diseases, and cancer. A deeper understanding of RQC and its downstream signaling pathways is envisaged to provide valuable insights into the pathogenesis of these disorders. Additionally, research is necessary to elucidate the specific mechanisms through which RQC dysfunction impacts the nervous system given the diversity of cells in the CNS.

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