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Illuminating ribosome biogenesis disorders through structural biology

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ABSTRACT

Ribosomes are essential nanomachines responsible for synthesizing all cellular proteins. Their production, known as ribosome biogenesis, is a highly complex and energy-intensive process that requires the coordinated action of hundreds of proteins and RNA-based *trans*-acting factors to assemble and mature the functional ribosomal components. Ribosome biogenesis is increasingly recognized as a key contributor to human disease: excessive ribosome production can fuel tumorigenesis, while insufficient or defective ribosome production is observed in a group of tissue-specific disorders known as ribosomopathies. Although the basis of this tissue specificity remains poorly understood, the most commonly affected systems are the blood, brain, and bones. Recent advances in structural biology have yielded high-resolution snapshots of precursor (pre-)ribosomes at various stages of maturation, offering new insights into how pathogenic variants of ribosomal proteins or assembly factors disrupt critical molecular interactions. In this review, we highlight selected examples where structural information is beginning to illuminate the molecular basis of ribosomopathies.

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Aberrant ribosome biogenesis is linked to pathologies

Ribosome biogenesis is an indispensable process in the life of a cell, driving protein synthesis and, consequently, cellular growth. Accordingly, cells devote substantial resources to ribosome production. This includes the synthesis of four ribosomal RNAs (rRNAs) and approximately 80 ribosomal proteins in human cells, as well as hundreds of assembly factors required for ribosome maturation – encompassing processing, modification, transport, and assembly – into two ribosomal subunits of unequal size with specialized functions in translation [1]. The process is highly sophisticated, involving hundreds of coordinated steps and the formation and maintenance of a prominent membraneless organelle – a biomolecular condensate – the nucleolus, where many of the early events take place [2]. Ribosome biogenesis is also tightly regulated, incorporating built-in fail-safe mechanisms and quality control pathways to ensure the continuous and accurate production of ribosomes [3].

Dysfunction in ribosome production has been increasingly implicated in human disease. These include rare genetic conditions affecting specific tissues – most notably the haematopoietic system, the brain, and the skeleton – collectively referred to as ribosomopathies [4,5]. A case affecting the gut has also recently been described [6]. Beyond these rare disorders, defects in ribosome biogenesis may contribute to more prevalent conditions, including cancer and neurodegeneration [7–9].

Given that ribosomes are present in every cell, understanding the tissue specificity of ribosomopathies remains a major challenge. One proposed explanation is that reduced ribosome production leads to the preferential translation of specific subsets of mRNAs at the expense of others [10], which may affect certain cell types disproportionally. Another possibility is that structurally or compositionally distinct ribosomes are generated in diseased cells [11], which may selectively translate particular transcripts. Identifying the

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precise molecular mechanisms underlying this tissue specificity is a key objective for the field and will be critical for the development of effective therapeutic interventions.

Here, we highlight selected cases in which structural biology reveals the molecular basis of ribosome biogenesis disorders and generates experimentally testable hypotheses.

Mapping disease-associated ribosomal proteins and assembly factors onto pre-ribosomes in space and time

Scores of ribosome assembly factors interact transiently with maturing precursor ribosomes, with some remaining associated for longer periods than others. Consequently, pre-ribosomes undergo continuous remodelling over time, both in their composition and in their resulting three-dimensional (3D) structure. To assess the prevalence and spatial distribution of assembly factors associated with pathogenic variants, we mapped them onto the 3D structures of maturing ribosomal subunit precursors (Figure 1).

We integrated recent experimental structural data on pre-ribosomes [12–17] and systematically cross-referenced all identified protein factors with disease associations listed in the UniProt database [18]. We then identified known pathogenic variants linked to these diseases using UniProt's Variant Viewer. This included both manually curated entries and automatically imported data from external sources such as dbSNP and ClinVar [19,20]. As this resource also encompasses a wide range of genomic variations, we focused exclusively on confirmed pathogenic variants, in keeping with the scope of this review (Supplementary Tables S1 and S2). Altogether, this analysis identified 226 mutations affecting 36 proteins. These included variants in 10 assembly factors, of which 8 are involved in small-subunit biogenesis and 2 are required for large-subunit production. In addition, variants were identified in 26 ribosomal proteins, including 12 small-subunit proteins and 14 large-subunit proteins. While we acknowledge that this list is not exhaustive of all ribosomopathies identified to date, we hope it provides a useful resource for linking genetic variation with structural biology data.

To infer which stages of ribosome biogenesis may be affected by pathogenic variants, we mapped the catalogued mutations onto the structures of a series of pre-ribosomes arranged in space and time according to their predicted assembly sequence (Figure 1). This approach provides both spatial and temporal insights into disease aetiology.

We observe that disease-associated factors are distributed throughout the assembly pathway, consistent with the idea that ribosome biogenesis is a highly druggable process [21,22]. Notably, many affected factors participate in early assembly steps (Figure 1, PDB codes 7MQ8 and 8FKP), suggesting that the initial stages of biogenesis may represent common targets in ribosomopathies. Interestingly, early ribosomal subunit precursors reveal three-dimensional clustering of disease-associated assembly factors, defining neighbourhoods that may be particularly sensitive to structural perturbations during assembly. In several instances, disease-associated assembly factors are located in close proximity to ribosomal proteins, suggesting disruption of local contacts and consequent effects on assembly (Figure 1 depicted in red and green, respectively). We also identified a case in which a perturbed interaction between a modification enzyme and its rRNA substrate may underlie disease (see below).

Altogether, we selected a few representative cases illustrating common features of ribosomopathies, including haematopoietic sensitivity, neurodevelopmental defects, and craniofacial abnormalities, for detailed description.

AROS, a putative Diamond-Blackfan anaemia gene

Diamond – Blackfan anaemia (DBA) is a bone marrow failure syndrome characterized by erythrocyte paucity, caused by mutations in ribosomal proteins (twenty-five out of eighty have been implicated in the disease to date) or assembly factors [23]. Ribosomal protein RPS19 alone accounts for ~25% of all cases in the Western world, and up to 35% in China [23].

The active regulator of SIRT1 protein **AROS** – also known as RPS19-binding protein 1 (RPS19BP1) – has been shown to bind directly to RPS19 (eS19) via its C-terminus [12,24]. The RPS19–AROS complex forms part of the SSU processome (Figure 2(a), 7MQA), where AROS engages RPS19 through a conserved C-terminal helix comprising residues 121–135 (Figure 2(b–d)). The amino acid sequence of AROS contains

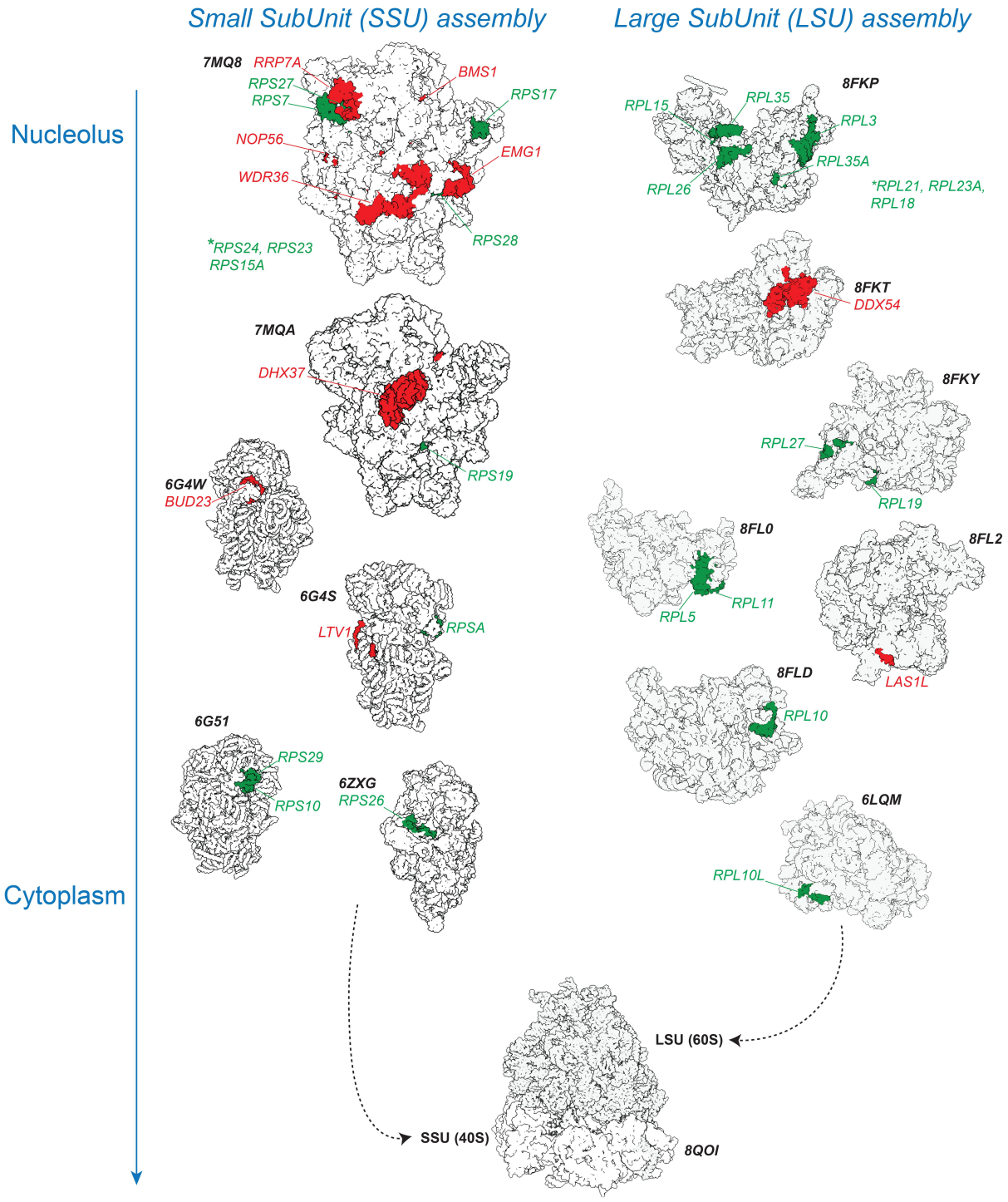

Figure 1. Mapping disease-associated factors and ribosomal proteins in space and time during human ribosomal subunit assembly. Pre-ribosome structures (atomic models) built using cryo-EM data are presented from top to bottom according to their predicted stage of assembly (early to late assembly steps), as well as their spatial distribution in cells, from the nucleolus to the cytoplasm. Structures can be identified via their PDB codes. SSU Processome: 7MQ8, 7MQA; Late Pre-40S: 6G4W, 6G4S, 6G51, 6ZXG; Pre-60S: 8FKP, 8FKT, 8FKY, 8FL0, 8FL2, 8FLD, 6LQM; Mature ribosome: 8QOI [12–17]. Factors implicated in ribosomopathies are listed adjacent to, as well mapped on each structure (Ribosome assembly factors: red, Ribosomal proteins: green). Diseases associated with each factor, along with pathogenic mutations, are listed in Supplementary Tables S1 and S2. Dashed arrows signify progress from late-stage pre-ribosomes to a functional, mature ribosome. Note: Factors are highlighted based on their earliest detection in the pathway, and not in subsequent structures where they continue to be present. Asterisks denote factors not visible due to the orientation of the structure.

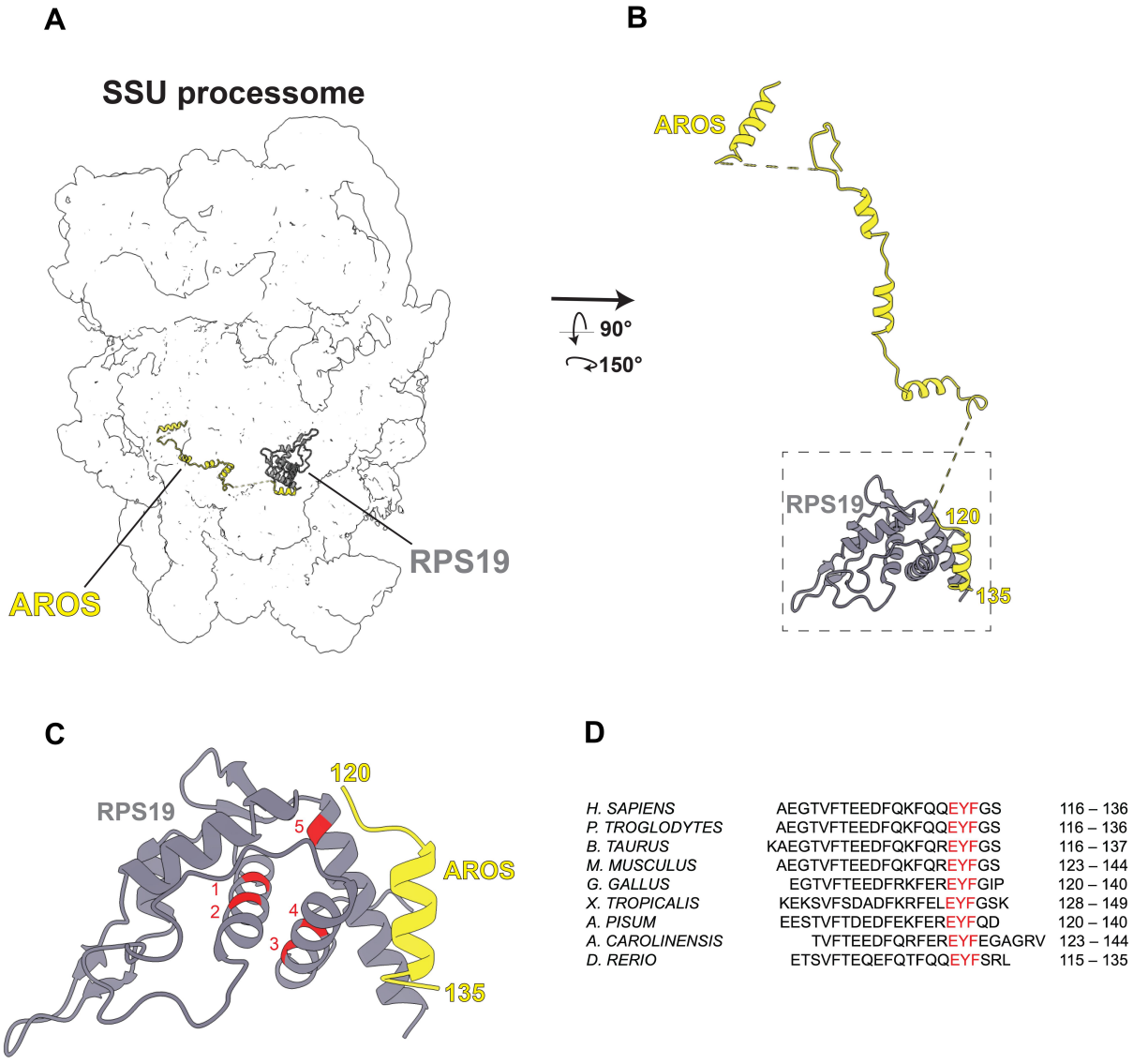

Figure 2. Diamond-Blackfan anemia and the RPS19-AROS interaction. AROS is a chaperone that specifically mediates RPS19 passage into the SSU processome. a) The structure of the AROS-RPS19 interaction as visualized within the SSU processome (PDB:7MQA). b) The C-terminus of AROS binds RPS19 to facilitate its integration into the SSU processome (region contained with dashed square). c) A zoomed-in view of the AROS-RPS19 binding. Mutations reported to abolish nucleolar localization of RPS19 [25] are highlighted in red (1: A61E, 2: A57P, 3: V15F, 4: L18P, 5: G127E). d) Sequence alignment (Clustal Omega [26]) of the AROS C-terminus from 9 species, with highly conserved residues highlighted in red.

both nuclear import and export signals, suggesting that the protein may shuttle between the cytoplasm, nucleus, and nucleolus, potentially acting as a chaperone for RPS19 and facilitating its positioning within the SSU processome. Its proposed role is reminiscent of that of HEATR3, a DBA-associated protein that chaperones the assembly of uL18 (RPL5) and likely uL5 (RPL11) into maturing pre-60S subunits [27] (see below, Figure 3). These structural observations therefore point to a broader role for AROS as a regulator of RPS19, whose impact on ribosome biogenesis and disease warrants further investigation.

Previous studies have identified a large number of RPS19 mutations in DBA patients, several of which abolish nucleolar localization of RPS19 [25]. Mapping these mutations onto the RPS19 structure within the SSU processome revealed that they cluster within or near the AROS-binding site (Figure 2(c)). We speculate that these mutations may disrupt the RPS19–AROS interaction in the cytoplasm, thereby preventing AROS-mediated localization of RPS19 to the nucleolus. This would lead to defects associated with RPS19 depletion, characterized by impaired pre-rRNA processing, including accumulation of 21S and 21S-C precursors of 18S rRNA (see https://www.ribosomalproteins.com/es19/ [28,29]). This relationship between AROS and

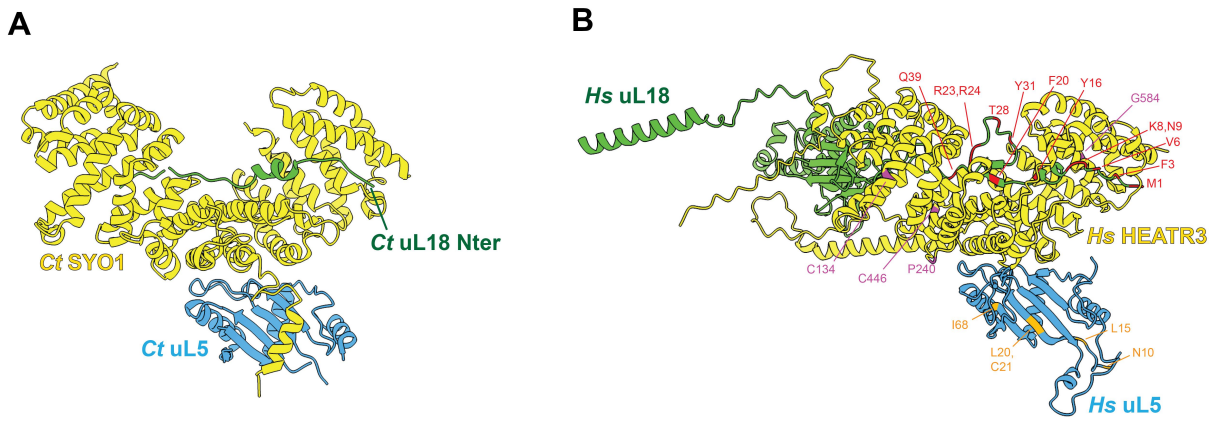

Figure 3. Diamond-Blackfan anemia and the uL5-HEATR3-uL18 complex. a) Experimentally determined structure of the uL5-Syo1-uL18 complex from *Chaetomium thermophilum (Ct)*(PDB: 5AFF). b) Structural model of the human (*Hs*) uL5-HEATR3-uL18 complex generated using AlphaFold3 and structural alignment. Highlighted residues correspond to pathogenic variants [27]; Supplementary Table S2). For clarity, only a subset of variants clustering at or near the interfaces between HEATR3 and its client ribosomal proteins is shown.

RPS19 is further supported by functional studies showing that siRNA-mediated knockdown of AROS phenocopies RPS19 loss, leading to accumulation of 21S pre-rRNA ([30] and Jing Chen and DLJL, unpublished). These findings suggest that AROS may represent a previously unrecognized factor contributing to DBA. Consistent with this idea, recent studies have demonstrated a crucial role for AROS in erythropoiesis, supporting its potential contribution to DBA pathophysiology [31]. In addition, AROS has also been shown to play an important role in heart development [32], an intriguing observation given the partially shared embryonic origin of the haematopoietic and cardiac lineages.

Although AROS has not yet been implicated in Diamond – Blackfan anaemia (DBA), several AROS missense variants have been reported in public variant repositories. These include several missense mutations (K115T, K115E, G135V) located at or near the C-terminal AROS helix (residues 120–135) that mediates RPS19 binding. However, the effects of these mutations on RPS19 binding, their broader impact on AROS function in ribosome biogenesis, and their potential implications for the aetiology of DBA, related syndromes remain to be determined.

Involvement of HEATR3 in Diamond–Blackfan anemia

Ribosomal proteins RPL5 (uL18) and RPL11 (uL5), together with 5S rRNA, form a trimeric complex (5S RNP) that is assembled during late maturation of the large ribosomal subunit and gives rise to the central protuberance [33,34]. Notably, evolution appears to have converged on these components: among the approximately 80 ribosomal proteins, they are the most critical for nucleolar structural maintenance [28], and they also play a central role in regulating homoeostasis of the tumour suppressor p53 [35,36]. After RPS19, RPL5 and RPL11 are the most frequently mutated genes in Diamond – Blackfan anaemia, with variants consistently associated with a higher prevalence of craniofacial and other congenital malformations than RPS19 mutations.

In yeast, RPL5 and RPL11 are co-imported into the nucleus by Syo1, which chaperones their assembly into nascent pre-60S particles [37]. The human homolog of Syo1, HEATR3, binds RPL5 (uL18) co-translationally, thereby facilitating its nuclear import and assembly into nascent pre-60S ribosomes [27]. HEATR3 has also been strongly associated with Diamond – Blackfan anaemia (DBA) [27]. However, it remains unclear whether, similar to its yeast counterpart, HEATR3 also promotes RPL11 (uL5) assembly, although it has clearly been reported to form a complex with both RPL5 and RPL11 [38].

To gain further insight into the conserved function of HEATR3, we used the experimentally determined structure of the uL5–SYO1–uL18 complex from *Chaetomium thermophilum* [39,40] (Figure 3(a)) to model the homologous human complex using AlphaFold3 and structural mapping (Figure 3(b)). All three components are predicted to be highly conserved at the structural level. Consistent with the *Chaetomium*

structure, the model predicts that the interaction interfaces between the three components are also highly conserved. The interaction between uL18 and HEATR3 involves the uL18 N terminus, which reaches into HEATR3, whereas the interaction between uL5 and HEATR3 is mediated by a conserved four-stranded antiparallel β-sheet (Figure 3(b)).

The human uL5–HEATR3–uL18 model further reveals that several pathogenic HEATR3 variants are located in close proximity to its client ribosomal proteins (Figure 3(b)). Mapping pathogenic variants of uL5 and uL18 onto the structure (Table 2) also shows that several cluster at or near the interaction interfaces, suggesting that they may destabilize the binding surfaces between HEATR3 and its client proteins. Remarkably, twelve uL18 variants localize to the N-terminal tail of the protein, which threads through HEATR3 and forms extensive contacts with it, whereas five uL5 variants localize directly to the HEATR3-binding interface (Figure 3(b)). Their striking enrichment at the interaction surfaces suggests that these mutations may disrupt HEATR3 binding. Together, these findings support a role for HEATR3 in the assembly of uL5 and uL18 and provide a plausible structural explanation for a subset of Diamond – Blackfan anaemia-associated variants affecting these proteins.

The primary microcephaly gene RRP7A

There is emerging evidence that brain size is constrained by ribosome biogenesis capacity during development [41,42]. Primary microcephaly (MCPH) is a neurodevelopmental disorder in which the brain fails to reach its normal size during foetal development, resulting in a markedly reduced head circumference at birth. It is typically caused by genetic defects affecting neural progenitor proliferation, leading to a reduced number of neurons and varying degrees of intellectual disability, often without major structural brain malformations.

Ribosomal RNA-processing protein 7 homolog A (*RRP7A*) is a ribosome biogenesis factor that forms part of the SSU processome (Figure 4) and is involved in the processing of early 18S rRNA intermediates [12,43]. A homozygous missense mutation in exon 5 of RRP7A (W155C) was recently reported in individuals diagnosed with MCPH [42]. Mutations in RRP7A were shown to impair neurogenesis, while nucleolar levels of mutant RRP7A-W155C were significantly reduced in patient-derived dermal fibroblasts, pointing to defects in ribosome biogenesis. Cells expressing mutant RRP7A also displayed reduced nucleolar levels of another ribosome biogenesis factor, NOL6. In addition, these cells exhibited defects in pre-rRNA processing, specifically an accumulation of the 30S pre-rRNA, an intermediate in the small subunit biogenesis pathway, whereas large subunit processing remained unaffected. These findings were supported by experiments in zebrafish embryos, in which knockout of RRP7A caused brain defects resembling MCPH, along with depletion of mature 18S rRNA and accumulation of early processing intermediates [42].

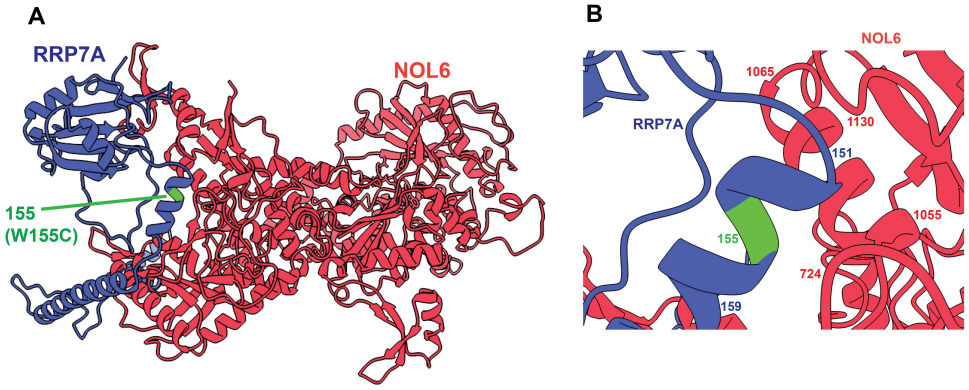

Figure 4. Primary microcephaly and RRP7A-NOL6. A RRP7A mutation (W155C) in primary microcephaly (MCPH) is expected to disrupt its interaction with NOL6 [43]. a) The structure of the RRP7A-NOL6 complex as observed within the structure of the human SSU processome (PDB:7MQ8). The location of the mutation (W155C) reported in MCPH patients is highlighted green. b) A zoomed-in view of the RRP7A-NOL6 interaction highlighting the segment of the RRP7A helix (151–159) that fits into a NOL6 binding pocket and makes close contact with a helix spanning residues 1055–1065.

Mapping the W155C mutation onto the structure of RRP7A in the human SSU-processome revealed an RRP7A-NOL6 interaction interface affected in MCPH (Figure 4(a)). This interface primarily involves an RRP7A helix (151–162) that fits into a NOL6 binding pocket and makes close contact with a helix spanning the NOL6 residues 1055–1065 (Figure 4(b)). We speculate that the W155C mutation destabilizes the RRP7A structure, thereby disrupting its interaction with NOL6. The reduced nucleolar levels of NOL6 in MCPH patient cells further suggest that RRP7A may act as a chaperone for NOL6, facilitating its delivery to the nucleolus. It is therefore interesting to consider whether mutations in NOL6 within this binding pocket might also lead to MCPH, or related neurodevelopmental disorders.

The critical role of ribosome biogenesis factors in brain development is further underscored by several recent studies identifying pathogenic variants in additional factors associated with neurodevelopmental disorders, including METTL5 [44], AIRIM/C1orf109 [41], and ACTL6B [45], among others. METTL5 is a S-adenosyl-L-methionine (SAM)-dependent methyltransferase that, together with its cofactor TRMT112, catalyzes the formation of N^6-methyladenosine (m^6A) at A1832 of the 18S rRNA, adjacent to the ribosomal decoding center [46]. Although METTL5 is dispensable for pre-rRNA processing [46], loss of this evolutionarily conserved rRNA modification causes a syndromic neurodevelopmental disorder characterized by developmental delay, intellectual disability of variable severity, gait abnormalities, and other neurological manifestations [44]. Notably, the locomotor defects associated with METTL5 deficiency have been successfully recapitulated in a *Drosophila* model [47]. Pathogenic variants in AIRIM/C1orf109, a factor required for recycling late cytoplasmic ribosome assembly factors to the nucleolus, impair brain development and have been modelled in human brain organoids. These studies suggest that the programmed reduction in ribosome biogenesis accompanying neuroepithelial cell differentiation renders these cells particularly vulnerable to defects in ribosome biogenesis production [41]. Likewise, ACTL6B, a nucleolar-associated factor required for efficient pre-rRNA processing, is mutated in a broad spectrum of severe neurodevelopmental disorders [45]. Together, these examples illustrate that neurological disorders arising from defects in ribosome biogenesis are not restricted to mutations in ribosomal proteins or core pre-rRNA processing factors but can also result from perturbations of rRNA modification and other components of the ribosome biogenesis machinery. As high-throughput sequencing technologies become increasingly accessible in clinical practice, additional links between ribosome biogenesis and neurodevelopment are likely to emerge.

The Bowen – Conradi syndrome protein EMG1

Bowen – Conradi syndrome (BCS) is a rare genetic disorder characterized by severe developmental abnormalities, including failure to thrive, developmental delay, and distinctive craniofacial features such as micrognathia (small jaw), a prominent nasal bridge, a narrow face, and microcephaly (small head) [48].

Essential for mitotic growth 1 (**EMG1**) is another SAM-dependent pseudouridine N^1-methyltransferase responsible for the methylation of a pseudouridine at position 1248 in 18S rRNA, forming $m^1\Psi_{1248}$ [49,50]. The Asp86 to Gly (D86G) variant in EMG1 is a founder mutation in Bowen – Conradi syndrome and is present in most patients [48]. The 18S rRNA residue 1248 forms part of the P-site of the small ribosomal subunit (40S) and it is further hypermodified into N^1-methyl-N^3-aminocarboxypropyl-pseudouridine ($m^1acp^3\Psi_{1248}$) through three consecutive steps [50,51].

First, the uridine at position 1248 is converted to pseudouridine by dyskerin (DKC1), guided by the H/ACA snoRNA SNORA13. Interestingly, SNORA13 has additional functions in senescence, where it interacts with ribosomal protein RPL23, thereby decreasing its incorporation into maturing 60S subunits, thus leading to p53 stabilization [52]. Second, EMG1 catalyzes the methylation of pseudouridine 1248, forming $m^1\Psi$1248. Third, TSR3 introduces an aminocarboxypropyl (acp) group at position N^3, yielding the final hypermodified $m^1acp^3\Psi_{1248}$ [51]. Notably, step 2 strictly depends on step 1, which generates the pseudouridine substrate, whereas step 3 is independent.

EMG1 is a SPOUT methyltransferase comprising a Rossmann-like fold with a central β-sheet flanked by α-helices on either side [53–55]. Interestingly, the BCS mutation D86G does not significantly alter EMG1's methyltransferase activity but instead reduces its ability to localize to the nucleolus [50,53,56]. In addition, this mutation decreases EMG1's stability, leading to the formation of protein aggregates in nuclear foci within the nucleoplasm [56]. This impaired nucleolar localization is likely a key feature of Bowen – Conradi syndrome in patients homozygous for this mutation [48].

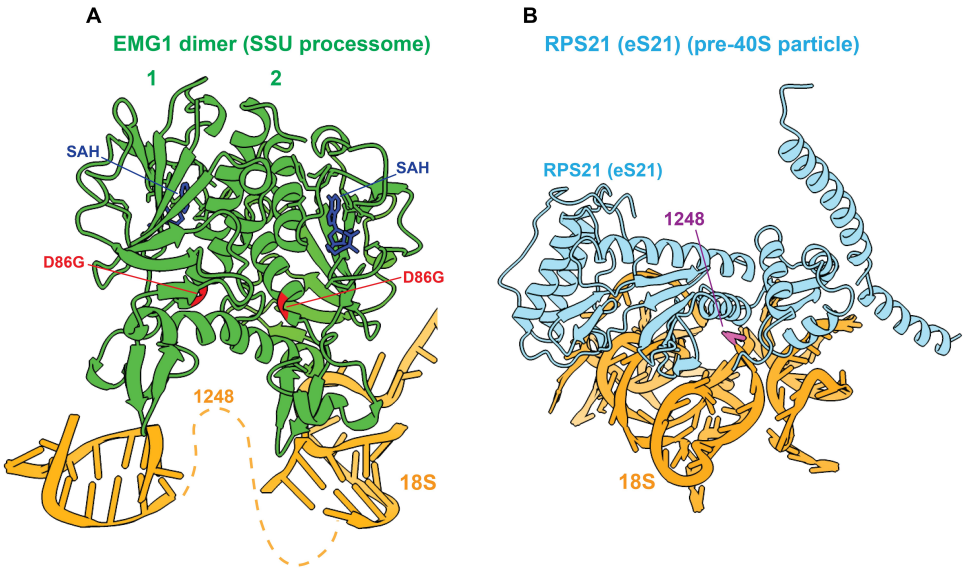

Figure 5. Bowen Conradi syndrome and EMG1. a) EMG1 dimer (green, 1 and 2) binding in the vicinity of 18S residue 1248 in the structure of the SSU processome (PDB: 7MQ8). The D86G point mutation observed in Bowen Conradi Syndrome patients has been highlighted (red) along with two S-Adenosyl-L-homocysteine (SAH) molecules (blue). A dashed line is used to denote the potential position of 1248, in close proximity to the EMG1 dimer. b) RPS21 (eS21) bound in vicinity of residue 1248 in the structure of a human pre-40S particle (PDB:6G51). Residue 1248 is labeled and highlighted in purple.

EMG1 forms a dimer within the SSU processome (Figure 5a [12]), where it binds an 18S rRNA precursor in the vicinity of residue 1248, indicating that methylation of Ψ1248 occurs at an early stage of pre-ribosome assembly within the nucleolus. The presence of EMG1-bound S-adenosyl-L-homocysteine (SAH), a by-product of SAM-dependent methylation, further supports the notion that the EMG1 dimer is catalytically active within the SSU processome (Figure 5a). A lack of mutant EMG1 (D86G) in nucleoli of BCS patient cells would lead to its exclusion from the SSU processome, resulting in hypomethylation of residue 1248. This loss is likely to alter the structure of the P-site and, consequently, ribosome function.

It is therefore interesting to consider whether loss of this modification is a driver of BCS. Since mutant EMG1 accumulates in the nucleoplasm, it is conceivable that it could access residue 1248 at later stages of ribosome biogenesis. However, structural rearrangements of 18S rRNA observed in late pre-40S intermediates in the nucleoplasm and cytoplasm reveal that this residue may no longer be accessible at these stages, effectively preventing mutant EMG1 from modifying it (see Figure 5b, where RPS21 assembly would sterically clash with EMG1 binding). The importance of this residue is underscored by studies reporting near complete modification (~100%) in human rRNAs [57]. Whether BCS patients lack this methylation remains to be determined.

It is interesting to note that TSR3 is an unusual member of the SPOUT class of enzymes in which the universal methyl donor, SAM, adopts an inverted orientation in the catalytic pocket, resulting in the transfer of an acp group instead of a methyl group [51]. By comparison, in EMG1, SAM is positioned in a manner that promotes transfer of a methyl group. Moreover, loss of the N^3-aminocarboxypropyl modification at this site has been associated with colon cancer [58].

Our hypothesis is that the severity of Bowen – Conradi syndrome may stem from the production of defective ribosomes lacking methylation at position 1248. Future studies, particularly those combining organoid-based models of development with precise tracking of rRNA modifications at this site will be essential to elucidate the aetiology and progression of BCS. More broadly, such work will help define the functional roles of rRNA modifications in cellular physiology.

Conclusions

Ribosome biogenesis is increasingly recognized as a major contributor to human disease, reflecting the fundamental role of ribosomes in gene expression. However, the striking tissue specificity of

disorders caused by defects in this process remains poorly understood [4]. Another unresolved question is how distinct mutations in the same ribosomal protein or assembly factor can produce widely divergent clinical outcomes, varying in both disease severity and the spectrum of affected tissues. Addressing these challenges will be central to understanding the molecular basis of ribosome-related pathologies.

One approach to tackling these questions is to analyse high-resolution precursor ribosome structures, map pathogenic variants, and infer which molecular interactions or structural environments may be disrupted. Here, using selected examples, we have provided structural insights into ribosome biogenesis disorders. Specifically, we discussed (i) AROS as a candidate DBA gene encoding a putative facilitator of RPS19 assembly; (ii) the DBA-associated protein HEATR3, which, similar to its yeast counterpart, may promote RPL11 (uL5) assembly in addition to its established role in RPL5 (uL18) assembly; (iii) how mutations in the primary microcephaly gene *RRP7A* may disrupt its interaction with NOL6; and (iv) how the Bowen – Conradi syndrome founder mutation in EMG1 may impair hypermodification of residue Ψ1248.

Although the identification, functional characterization and structural mapping of pathogenic variants in ribosomal proteins and assembly factors have progressed rapidly in recent years, the contribution of non-coding RNAs involved in ribosome biogenesis remains largely unexplored. With the exception of a few examples – including the box C/D snoRNA U8, which is required for 3′ ETS processing and is associated with leukoencephalopathy with calcifications and cysts (Labrune syndrome) [59], and the RNA component of RNase MRP linked to cartilage – hair hypoplasia [60] — our understanding is still limited. Yet numerous non-coding RNAs, including snoRNAs that guide rRNA modification and processing, as well as lncRNAs involved in nucleolar organization, play critical roles in ribosome biogenesis, and are likely to contribute to disease.

Ribosome biogenesis governs the assembly of one of the most evolutionarily conserved and essential molecular machines in the cell and is therefore central to fundamental biology. Progress in the field will require multidisciplinary approaches integrating structural biology, cell and molecular biology, medicinal chemistry and biophysics, particularly in the light of recent advances linking nucleolar function to biomolecular condensates. Emerging fields such as AI-driven modelling and *in situ* structural biology [61,62], together with high-resolution technologies – including single-nucleotide mapping of pre-rRNA processing and modification, and long-read nanopore sequencing approaches such as NanoRibolyzer [63]— are poised to accelerate discovery.

Importantly, we are entering an era in which therapeutic strategies targeting ribosomopathies are becoming increasingly tangible [64], with promising avenues including gene editing technologies (CRISPR and base editors) and mRNA-based therapies. More broadly, the study of rare genetic disorders affecting ribosome biogenesis is likely to provide fundamental insights into mechanisms underlying more common diseases, thereby extending the impact of this field well beyond its immediate scope.

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S.S. prepared the figures and tables. S.S. and DLJL drafted the manuscript together. DLJL finalized the manuscript. Both authors have reviewed and approved the final version of the manuscript.

Author contributions

CRediT: **Sameer Singh:** Conceptualization, Funding acquisition, Resources, Writing – original draft, Writing – review & editing; **Denis L.J. Lafontaine:** Conceptualization, Funding acquisition, Resources, Writing – original draft, Writing – review & editing.

Disclosure statement

S.S. is a founder of Transcript Life Sciences. DLJL declares no conflicts of interest—financial, professional, political, societal, or personal—with any institution, organization, commercial entity, or individual in relation to this work.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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