Ribosomopathies: Global process, tissue specific defects

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Introduction

Ribosome biogenesis describes the process of making ribosomes, which are large ribonucleoprotein complexes that translate mRNA into protein, thus synthesising all the protein within the cell. Ribosomes are comprised of 4 distinct rRNAs transcribed by RNA polymerases I and III, which are complexed together with numerous ribosomal proteins, accessory proteins, and small nucleolar RNAs (snoRNAs) all of which are transcribed by RNA polymerase II.1,2 Ribosome biogenesis begins with transcription of both the 47S precursor rRNA (rRNA) by RNA polymerase I (RNA Pol I), and the 5S rRNA by RNA polymerase III, in the nucleolus, and nucleus, respectively. The 47S rRNA precursor is then modified, processed and cleaved into 5.8S, 18S, and 28S rRNAs. The 18S rRNA together with 32 small subunit ribosomal proteins (RPSs) forms the 40S subunit, which decodes the mRNA sequences. In contrast, the 5S, 5.8S, and 28S along with 47 large subunit ribosomal proteins (RPLs) comprise the 60S ribosomal subunit, which links amino acids through peptide bonds.3,1 These ribosomal subunits unite to form the translationally active mature 80S ribosome as they are exported to the cytoplasm.

Transcription of the tandem repeat rDNA genes in mammalian cells is catalyzed by the RNA Pol I machinery, whose activities are regulated by reversible acetylation and phosphorylation.4–9 The transcription of rRNA is one of the rate-limiting steps during ribosome biogenesis, and accounts for about 60% of overall transcription activity in eukaryotic cells.10 However, a significant proportion of mRNA transcription by RNA polymerase II in the nucleus is also required for the production of the ribosomal proteins.11 Hence ribosome biogenesis is a complex and metabolically expensive endeavor. Through its roles in regulating the quality and quantity of proteins in a cell, ribosome biogenesis is integral to all cell growth, proliferation and differentiation.12 Consequently, perturbation of any one of the steps during the process of ribosome biogenesis can result in disorders in embryonic development or adult homeostasis.

Here we discuss ribosome biogenesis and the conundrum that disruption of a purportedly global process can result in in the pathogenesis of tissue specific diseases and disorders, which are commonly referred to as ribosomopathies. We will highlight a few of the many recent publications, including characterizations of novel ribosome biogenesis mutant animal models, which have significantly improved our understanding of roles for ribosome biogenesis and function in tissue differentiation and disease.

Ribosomopathy Phenotypes

Although ribosome biogenesis is a global process that occurs in all cells, a growing body of literature has revealed that certain mutations in ribosomal proteins (RPs) can result in tissue specific defects. A summary of identified human ribosomal gene mutations, and existing animal models, presented in Table 1, shows that specific ribosomal gene mutations can result in tissue specific defects in post-embryonic development. The following brief
| Human Ribosomopathy Disease | Human Ribosomal Gene mutations | Human Phenotype | Mouse Phenotype | Zebrafish Phenotype | Yeast Phenotype |
|-----------------------------|--------------------------------|----------------|----------------|---------------------|----------------|
| Treacher Collins Syndrome (TCS) 1:50,000 | Treacle/Tcof1 RNA Pol I RNA Pol III POLR1C, POLR1D | Severe craniofacial defects including dysmorphic: • Face • Eyes • Mandible • Ears\(^{110}\) | Craniofacial anomalies including: • agenesis of nasal passage • abnormal maxilla development • exencephaly • anophthalmia • increased apoptosis in pre-fusion neural folds\(^{111}\) | • Craniofacial defects • reduced cell proliferation\(^{87}\) | Inhibition of: • rDNA transcription • cell growth\(^{17}\) |
| Postaxial acrofacial dysostosis (POADS) Less than 1:1,000,000 | DHODH | • Hypoplasia of the femora • Ossification defects in ischium and pubis • Bilobed tongue • Lung hypoplasia\(^{112,113}\) • Absent lower eyelashes • down slanting palpebral fissures • deformed external ears • malar hypoplasia • micrognathia • Pro-apoptotic hematopoiesis leading to bone marrow failure • congenital anomalies • predisposition to cancer • Acetylation defects • Mental retardation • Limb deformities • Craniofacial defects • Heterochromatic repulsion\(^{12}\) | • inhibitors of DHODH led to an almost complete abrogation of neural crest development\(^{22}\) | • Reduced pyrimidine synthesis • Reduced DHODenase activity\(^{14}\) | |
| Diamond-Blackfan anemia (DBA) (5–7 cases per Million live births 1:200,000 ete abrogati) | At least 11 Ribosomal proteins including: RPS19, RPS26, RPS27, RPL27, T5R2, RPS28, L5, L1, GATA1\(^{115–118}\) | Absent lower eyelashes down slanting palpebral fissures deformed external ears malar hypoplasia micrognathia • Pro-apoptotic hematopoiesis leading to bone marrow failure congenital anomalies predisposition to cancer Acetylation defects Mental retardation Limb deformities Craniofacial defects Heterochromatic repulsion\(^{12}\) | • Constitutive expression of RSP19 mutation results in lethality • Conditional expression resulted in growth retardation, mild anemia, inhibited terminal erythroid maturation\(^{119}\) | • Disruption of cell cycle • high levels of apoptosis\(^{33}\) | |
| Roberts syndrome (RBS) | ESCO2 | | | | Reduced rDNA transcription • transcriptional signature of starvation • deletion of FOB corrects genome-wide replication defects, nucleolar structure and rDNA segregation defects\(^{32}\) | |
| Shwachman-Diamond syndrome (SDS) | SBDS, essential cofactor for elongation factor 1 | Exocrine pancreatic dysfunction mild neutropenia metaphyseal dysostosis mild mental retardation organ dysfunctions\(^{22}\) | Early embryonic lethality in null animals\(^{123}\) | Disruption of 60S subunit maturation at later stage relatively stable pre-60S particles\(^{34}\) | |
| Condition                                      | Genes/Features                                                                 | Phenotypic Manifestations                                                                 |
|------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Cartilage hair hypoplasia (CHH)               | RMRP, an RNA component of the mitochondrial RNA processing ribonuclease       | • Disproportionate short stature<br>• Sparse hair<br>• Metaphyseal dysplasia<br>• Anemia<br>• Immune deficiency<br>• Increased incidence of cancer<br>• Altered cytokine signaling<br>• Defects in cell cycle progression<br>• Differentiated lymphocytic and chondrocytic cell lineages<br>• Normal mitochondrial function<br>• Normal chromosomal segregation<br>• Normal cell cycle progression<br>• Normal ribosomal processing and ratio of short versus long forms of the 5.8S rRNA<br>• Increased incidence of cancer<br>• Embryonic lethality in either conditional or homozygous RMRP null mice<sup>121,122</sup> |
| Bowen-Conradi syndrome (BCS)                  | EMG1 Trisomy 18 Nep1 (Emg1) SPOUT-class methyltransferase<sup>59</sup>          | • Early lethality prior to blastocyst stage development<br>• Psychomotor retardation<br>• Death in early childhood<sup>129</sup><br>• Methylation defects<br>• Defined dual Nep1 function as a methyltransferase and ribosome assembly factor<br>• BCS mutation prevents nucleolar accumulation of Nep1<sup>59</sup> |
| North American Indian Childhood Cirrhosis (NAIC) | CIRH1a/Utp4 NOL1<sup>156,79,126,127</sup>                                      | • Cirrhosis of the liver, liver disease<br>• Neonatal cholestatic jaundice<br>• Hepatosplenomegaly<sup>63</sup><br>• Expressed in embryonic mouse liver<sup>61</sup><br>• Upregulated transcriptional targets of p53<br>• Defects in canalicular and biliary morphology<sup>94</sup><br>• Stabilization and nuclear accumulation of p53<sup>9</sup><br>• p53-mediated cell cycle arrest<br>• Apoptosis<sup>152</sup> |
| CIRH1a/Utp4                                    |                                                                               |                                                                                          |
| CIRH1a/Utp4                                    |                                                                               |                                                                                          |
| CIRH1a/Utp4                                    |                                                                               |                                                                                          |
descriptions of ribosomopathy phenotypes, summarized in Table 1, are provided in order to emphasize the similarities and distinct differences between RP gene mutations.

**Treacher Collins syndrome (TCS)**

TCS occurs with a frequency of 1 in 10,000–50,000 births, and arises primarily due to autosomal dominant mutations in the TCOF1 gene. TCS is a congenital birth defect characterized by midface hypoplasia and underdeveloped external ears and inner ear anomalies, and may include developmental brain abnormalities. TCOF1 gene mutations have been mapped in more than 200 families to date, and include splice site, missense and nonsense mutations, insertions and deletions commonly ranging in size from 1 to 40 nucleotides, including a 5 bp deletion in exon 24 which accounts for nearly 20% of all TCS cases. The considerable inter- and intra-familial variability in the severity of TCS suggests that environmental factors and/or genetic background may contribute to the observed clinical variability in TCS patients. The nuclear phosphoprotein Treacle, which is encoded by the TCOF1 gene, and co-localizes with UBF1 and RNA Pol I, and plays an essential role both in rDNA transcription and rRNA processing. The multiple functional requirements for Treacle in ribosome biogenesis suggest that defective ribosome biogenesis may underlie the etiology of TCS. Mouse models for human TCS revealed that upregulated p53 signaling and subsequent apoptosis resulted in a 25% reduction in neural crest cells (NCC), demonstrating how Tcof1 can influence NCC formation and survival through the regulation of ribosome biogenesis. The recent identification of POLR1C and POLR1D gene mutations in human TCS patients, both of whose gene products participate in rDNA transcription, provides further evidence that TCS is a ribosomopathy disorder.

**Postaxial acrofacial dysostosis (POADS)**

POADS, caused by compound heterozygous mutations in the gene coding for dihydroorotate dehydrogenase (DHODH), is an acrofacial dysostosis syndrome resulting in craniofacial defects similar to those of TCS, with the addition to defects in the postaxial limb skeleton, including the absence of either the fifth or both the fourth and fifth rays of the hands and feet, and ulnar and fibular hypoplasia. DHODH is an enzyme that is required for de novo pyrimidine synthesis, including uracil monophosphate, a constituent base of RNA, and is therefore critical to ribosome biogenesis. Therefore, POADS may also be the result of deficient ribosome biogenesis. Interestingly, analyses of Dhodh activity have revealed spatiotemporally specific expression in the pharyngeal arches, forelimbs, hindlimbs and somites, consistent the domains of observed defects in humans. Furthermore, zebrafish treated with a DHODH inhibitor (leflunomide) display severe defects in NCC development due to blocked transcriptional elongation of genes critical to NCC function. These results suggest similarities between the deficient NCC numbers observed in POADS and TCS. Curiously, mutations in genes that function immediately downstream of DHODH do not exhibit obvious skeletal and/or craniofacial defects, but rather exhibit orotic aciduria and megaloblastic anemia, which, in contrast to TCS can be rescued by dietary uridine supplementation. It is important to note that although orotate dehydrogenase is needed to make pyrimidines and that this deficiency could affect ribosome biogenesis and thus account for the skeletal abnormalities observed in this disease, it remains to be formally proven that POADS is indeed a ribosomopathy. As mentioned, a deficiency of the next enzyme in the pyrimidine synthesis pathway causes orotic aciduria, which has the classic features one might expect from a reduced amount of pyrimidines, megaloblastic anemia. Orotic aciduria can be effectively treated with uridine, clearly demonstrating that the lack of pyrimidines are driving the disease state. But if POADS is a consequence of reduced amounts of pyrimidines, which in turn affects ribosome synthesis, it doesn’t explain why individuals with POADS don’t have megaloblastic anemia, or alternatively why individuals with orotic aciduria don’t have skeletal deformations. Together, these data suggest that the underlying basis for POADS may not be restricted to pyrimidine synthesis, and that further biochemical and cellular analyses in suitable animal studies are needed to fully elucidate the molecular mechanisms underlying the POADS phenotype.

**Diamond-blackfan anemia (DBA)**

DBA is a congenital erythroid dysplasia typified by anemia caused by selective decrease or absence of erythroid precursors, and reticulocytopenia and macrocytosis. Individuals with DBA present with craniofacial defects resembling those of TCS, together with cardiac defects, and thumb abnormalities. DBA is caused by mutations in a variety of ribosomal protein genes including most commonly RPS19, and also RPL5 and RPL11, although these mutations only account for 50% of DBA patients. As for TCS, analyses of animal models of DBA have shown that inhibition of upregulated p53 signaling and resulting apoptosis can rescue the developmental craniofacial and other defects observed in these animals, suggesting commonality to the pathogenesis of both diseases. Interestingly, dietary supplementation with L-leucine has been found to rescue the craniofacial defects in DBA animal models, and anemia in certain DBA patients. Although DBA is not thought to arise through deficient rRNA transcription, the use of amino acid supplements to induce the TORC1 pathway, and in turn activate ribosome biogenesis, may be a fruitful treatment plan for a variety of neurocristopathies.

**Robert syndrome (RBS)**

RBS, an inherited disorder characterized by growth retardation, bilateral symmetric limb reduction and craniofacial defects, is caused by homoyzogous or compound heterozygous mutations in the ESC02 gene, which functions in rRNA production. Zebrafish models for RBS have been used to reveal increased NCC death that is independent of p53 signaling, making it distinct from TCS and POADS. Yeast models for RBS showed that esd1 mutants exhibited ribosome biogenesis defects and reduced protein translation, which was also observed in
fibroblasts cultured from human RBS patients. Recently, connections between cohesinopathy mutations and RBS have been made, implicating roles for cohesin proteins in NCC formation, migration and differentiation.

**Shwachman-diamond syndrome (SDS)**

SDS occurs in 1 in 50,000 live births and is associated with compound heterozygous, or homozygous mutations in the gene SBDS which is located on chromosome 7. SDS is characterized by abnormal dermal and endochondral bone formation resulting in short stature and progressive pathological bone conditions including osteopenia, osteoporotic vertebral anomalies, and fractures. SDS patients exhibit considerable variability in inherited phenotypes, likely reflecting variable residual SBDS activity and threshold requirements for the development of diverse tissues. Cells derived from SDS patients exhibit perturbed activity of ribosome biogenesis associated genes that govern both rRNA and mRNA processing, and cell survival and growth. Mutations in SBDS can have wide ranging effects, as SBDS functions both early in ribosome biogenesis, and also later in ribosomal subunit maturation and function. Consistent with the observed bone defects observed in SDS patients, differentiating chondrocytes and osteoblasts normally require high protein secretion capacity, which can be compromised by SBDS mutations. Mutations in SBDS may affect either general protein translation, or more specifically proteins expressed in differentiating cartilage and bone cells. SDS has been classified as a ribosomopathy phenotype due to the fact that it is primarily caused by impaired release of eIF6, resulting in deficient 80S translational activity.

**Cartilage hair hypoplasia (CHH)**

CHH is an autosomal recessive disorder arising from mutations in the RMRP gene, which encodes the untranslated snorRNA subunit of the ribonucleoprotein endoribonuclease processing complex, RNase MRP. CHH is characterized by short-limb dwarfism resulting from metaphyseal or spondyloepiphyseal dysplasia, affecting both limbs and ribs. CHH is also distinguished by a hair phenotype, consisting of sparse, fine and thin hair. Other abnormalities may include ligeamentous laxity, defective T- and/or B-cell mediated immunity, hypoplastic anemia, and intestinal abnormalities consistent with Hirschsprung disease in some individuals. Strong evidence that CHH is a ribosomopathy is provided by studies in yeast, which demonstrate that RMRP (nme1 in Yeast) gene mutations affect yeast cell growth and are directly proportional to the observed defects in 5.8S rRNA processing. Furthermore, defects in a single subunit of the 60S ribosome can result in disintegration of the entire 60S ribosome and interfere with crosstalk between the secretory machinery and ribosome biogenesis. Recent publications also indicate roles for RMRP functions in gene-silencing.

Study of skeletal variants of this disease, caused by different point mutations in RMRP, will contribute to a better understanding of roles for RMRP, and ribosome biogenesis, in skeletal development. It is important here to address the controversy of whether RNase MRP is required for pre-rRNA processing in humans, which could argue against CHH being a ribosomopathy. RNase MRP was first shown to be required for processing of rRNA in yeast and this is supported by more recent data in yeast. Currently however there is no direct evidence for overproduction of the long non-natural form of 5.8S rRNA in CHH patients as observed in yeast. Furthermore it has been suggested that RNase MRp has three RNA-processing activities, and that mutations of RMRP gene would negatively affect all 3 physiological functions, thus rendering the pathogenesis of CHH a consequence of disruption of all three known functions of RNase MRp, not just one or two. Although successful gene knock-in models of CHH have yet to be reported, such models would help clarify these and other questions regarding CHH.

**Bowen-conradi syndrome (BWCNS)**

BWCNS, an autosomal recessive disorder caused by mutations in EMG1 that result in death within the first year of life, occurs in some populations at an incidence of 1 in 355. EMG1 participates in ribosome biogenesis, maturation and processing of the 18S rRNA, and 40S ribosome biogenesis, through methylation. EMG1 is broadly expressed in most embryonic and adult tissues, and mutations in EMG1 have been found to cause impaired ribosome biogenesis resulting in impaired cell division and proliferation.

**North American Indian childhood cirrhosis (NAIC)**

NAIC is a rare autosomal recessive mutation in human UTP4/Cirhin that results in cholestasis, the inability for bile to flow from the liver to the duodenum due to metabolic defects induced by genetic mutations. The only known cure for NAIC to date is orthotopic liver transplantation. In humans, UTP4 is required for pre-18S rRNA processing, but not for pre-rRNA transcription (in contrast to Yeast where it is required for both), and is highly expressed in E11.5 mouse fetal liver as well as other developing tissues. Evidence that nucleolar dysfunction is the cause of NAIC is provided by the fact that yeast UTP4 binds to multiple UTPs in the t-UTP/UTPA subcomplex, and that rRNA biogenesis and processing defects are observed in yeast defective in many of these genes. Further analyses of human UTP4/Cirhin gene mutations in mouse and zebrafish models are needed to fully elucidate the etiology of NAIC in humans.

**Schleroderma**

Lastly, mutations in a variety of ribosomal protein genes including POLR3A and hUTP14a have been found to be linked to Schleroderma, a disorder resulting in small blood vessel disease, autoimmune problems, and fibrosis of connective tissue. Infertility and ovarian cancer also are linked to hUTP14a gene mutations, as well as epigenetic repression of bone morphogenetic protein receptor II. Clearly, additional studies of the role of ribosomal protein mutations in Schleroderma are needed in order to better understand the molecular connections between ribosome biogenesis and autoimmune diseases.
Many questions and a few answers

Interestingly, it has been established that p53 is a negative regulator of ribosome biogenesis when induced by the stress response caused by deficient mature ribosome biogenesis. Furthermore, it has been shown that p53 can repress RNA Polymerase I activity by preventing the interactions of UBF and SLI, and in doing so directly interfere with transcriptional initiation at the rRNA promoter. Thus, p53 can inhibit cell proliferation via its role as a negative regulator of ribosome biogenesis. This directly contrasts with Treacle/Tcof1, which is a positive regulator of ribosome biogenesis, and in turn cell proliferation, through its ability to bind UBF and promote RNA polymerase 1 transcriptional activity. The p53 checkpoint control mechanism may have evolved to monitor ribosome production in the nucleolus, and activate a cell-cycle inhibitory response when confronted by nucleolar stress or other defects in ribosome biogenesis.

Many ribosomopathy phenotypes exhibit upregulated p53 signaling, resulting in cell cycle arrest or apoptosis mediated through the nucleolar stress response. As such, the connection between Tcof1 and p53 in ribosome biogenesis has important implications in our understanding of cancer and tumorigenesis. The extent to which ribosome function is directly modulated by tumor suppressors and oncogenes, and whether this represents a cause or consequence of cancer progression, is the subject of increasing scrutiny.

For example, in dyskeratosis congenita (DC), a disease characterized by premature aging and increased tumor susceptibility, work from Pandolfi and Ruggero’s research groups identified that mutations in the DKC1 gene affect rRNA pseudouridylation that leads to the production of under-modified ribosomes. Such ribosomes may be involved in DC development. The ability of p53 inhibition to rescue haploinsufficiency of Tcof1 raises the question as to whether the reverse is also true – whether ribosomal proteins can modulate tumor suppressors and oncogenes. Interestingly, despite extensive searching, we have yet to discover individuals with mutations in TCOF1, POLR1C or POLR1D resulting in Treacher Collins Syndrome (TCS) that also develop cancer or related tumors. This does not mean that such individuals do not exist, as they would be extremely rare—the incidence of TCS alone is 1 in 50,000. However it does suggest that in cases where tumors are associated with enhanced ribosome biogenesis, that Tcof1 could be a potential modifier of tumor progression. It will be interesting in future analyses to examine the effects of Tcof1 over-expression on ribosome biogenesis, and to determine whether there is any prevention or delay in the onset of tumorigenesis in cancer animal models that are also deficient for Tcof1.

Under normal cellular growth conditions, Mdm2 targets p53 for degradation through polyubiquitination. In contrast, under conditions of perturbed ribosome biogenesis and nucleolar stress, unincorporated ribosomal proteins bind to Mdm2 inhibiting its polyubiquitination capacity (reviewed in 26). This leads to activation and stabilization of p53 and ultimately cell death. As a case in point, direct inhibition of p53 dependent apoptosis can successfully prevent the manifestation of ribosomopathy disorders such as TCS (Tcof1) and DBA (Rps19) in animal models. However, p53 functions as a tumor suppressor and any inhibition of p53 would therefore carry a substantial risk of cancer or tumorigenesis side-effects. This highlights the need to explore other avenues for ribosomopathy prevention. Interestingly, L-leucine supplementation has recently been used to successfully treat DBA in humans, and in animal models.

Zebralsh and mouse embryos that model DBA showed considerably improved craniofacial and haematopoietic development when their diets were supplemented with L-leucine. The mechanistic basis for this is in the craniofacial region, is that L-leucine stimulates ribosome biogenesis through the mTOR pathway, and thus counters the p53 dependent apoptotic loss of neural crest cells. Thus L-Leucine supplementation may be a possible treatment option for other disorders of ribosome biogenesis. Consistent with this idea, L-leucine has been shown to ameliorate the development of Roberts syndrome-like abnormalities in zebrafish, and in patient specific cell based models of the disorder, as well as more recently with respect to Cornelia de Lange syndrome.

In contrast, p53 independent roles in ribosomopathy phenotypes have also been found in a variety of ribosomopathies. Further analyses of both p53 dependent and independent functions in ribosomopathy phenotypes are clearly needed to obtain a full appreciation of possible approaches to circumvent these deficiencies to improve phenotypic outcomes.

Future approaches and anticipated outcomes

Ribosomes are universally responsible for the quality and quantity of proteins in all cells. Ribosome production therefore, is highly regulated by and must be integrated with many cellular processes including growth, proliferation and differentiation. Considering the global importance of ribosome biogenesis in all cell types, and that ribosomal proteins are widely if not ubiquitously expressed, it is therefore surprising that disruptions in ribosome biogenesis are associated with specific cell and tissue defects in the pathogenesis of neurocristopathies. Furthermore, there is considerable variability in the phenotypic spectrum of individual ribosomopathy disorders. The variability in the severity of ribosomopathy phenotypes, combined with the observed distinct modes of inheritance, presents a complex challenge to understanding these diseases at a mechanistic level.

As a case in point, some ribosomopathies specifically affect the craniofacial skeleton (i.e. Treacher Collins Syndrome), while other ribosomopathies encompass combinatorial malformations of the craniofacial, axial and/or limb skeletal systems (Diamond-Blackfan Anemia, Postaxial acrofacial dysostosis, Roberts syndrome, Schwachman-Diamond syndrome, Cartilage Hair hypoplasia and Bowen-Conradi syndrome). Similarly, bone marrow failure may or may not be present as part of the clinical spectrum of skeletal anomalies. Bone marrow failure is a defining feature of Diamond-Blackfan Anemia, Schwachman-Diamond Syndrome and Cartilage Hair Hypoplasia but is not a recognized component of Treacher Collins syndrome or Postacrofacial dysostosis.
This raises fundamental questions about how mutations in genes critical for ribosome biogenesis, which might normally have global or widespread roles during organism development, can lead to such selective traits.

The phenomenon of ubiquitously expressed genes or very broadly active proteins exhibiting cell or tissue specific functions is not unique or exclusive to ribosomal genes. However, with respect to ribosomal genes and proteins, there is currently no single unifying factor that collectively links ribosomal genes and proteins except for their roles in various aspects of ribosome biogenesis and the clinical pathogenesis of ribosomopathies.

One of the rate-limiting steps of ribosome biogenesis lies in transcription of the 47S rRNA. Therefore it is interesting to note the recent discovery of ribosomal protein variants that may influence the absolute transcriptional levels and or possible isoforms of rDNA transcription. Another possible mechanism that may account for some of the clinical differences and their variability is how each specific mutation affects the function of the gene product. For example, Cartilage Hair Hypoplasia and Anauxetic Dysplasia are associated with distinct mutations in the same RMRP gene. Mutations in RMRP that reduce rRNA (rRNA) cleavage are associated with the bone dysplasia characteristic of Cartilage Hair Hypoplasia, while in contrast, mutations in RMRP that affect mRNA (mRNA) cleavage are associated with hair hypoplasia, immunodeficiency, and dermatologic abnormalities typical of Anauxetic Dysplasia. Therefore, the observed clinical differences and variabilities may be explained by the types of alterations in gene function, together with the magnitude of their effect on ribosome biogenesis in specific tissues at specific developmental times.

It is also possible, and perhaps even more likely, that ribosome biogenesis is spatiotemporally dynamic, and furthermore that different threshold levels of activity may be required in one tissue versus another at different times, in order to effect normal development. Consistent with this idea, such a cell type specific requirement has been postulated in the pathogenesis of TCS, with respect to the demands of high rates of proliferation of neop epithelial cells and neural crest cells. Hence it is possible that tissue-specific ribosomes themselves may be specialized, and composed of diverse rRNA and ribosomal protein combinations, along with different associated factors such as variable post-translational modifications. This type of diversity could conceivably have a considerable impact on how mRNA templates are translated into functional proteins. Currently, we also have a poor understanding of the stability of the subunit composition of RNA Pol I and III, or how subunit specificity might influence development and disease. For example, it is important to consider the possibility that the subunit composition of RNA Pol I and III is also spatiotemporally dynamic. Subunits such as Polr1c and Polr1d, defects in which are associated with TCS, exist on the periphery of the structure of RNA Pol I and III, while other subunits are thought to specifically occupy the core. It is tempting to speculate that subunits in the core of RNA Pol I and III may function as part of the basal machinery, whereas those subunits occupying the periphery may provide tissue or activity specificity. It will be interesting in the future to isolate the RNA Pol I and III complexes from different cells and tissues, and to determine whether their composition is constant or if there is any evidence for dynamic cellular or tissue specific subunit composition.

In contrast to our understanding of the many levels of regulation controlling gene expression, our knowledge of the regulatory control of protein production remains relatively poor. The historic idea that ribosomes function constitutively to translate the genetic code continues to be challenged. Even core ribosome components may exert selective activity through their interactions with specific cis-acting regulatory elements present within subsets of mRNAs. Thus ribosome activity appears to be highly regulated, and may provide an important new level of control governing spatiotemporal gene expression during normal embryonic development, adult homeostasis, and in the pathogenesis of diseases and disorders that comprise ribosomopathies. Understanding how the mechanisms of ribosomopathies overlap and diverge will be instrumental in designing realistic avenues for their therapeutic prevention. As a first step, it will be critical to determine if there is any evidence for spatiotemporal activity for the genes, RNAs and proteins that constitute the ribosomes.

**Closing thoughts**

Here we consider a few additional levels of control regulating ribosome biogenesis, to further highlight the complexities of human ribosomopathy disorders and possible connections with the etiology of cancer.

RNA Pol I complex interactions with other nucleolar proteins effect the regulation of transcription, elongation, and termination of pre-rRNA production. RNA Pol I transcription is initiated by an interaction between the upstream binding factor (UBF), and the species-specific promoter selectivity factor, SL1. Specifically, UBF interacts with TATA binding protein and TAF1, which are components of the SL1 complex, and PAF53. UBF also interacts with pRb, which inhibits RNA Pol I activity. As ribosomes determine the capacity for protein production and their synthesis commandeer much of the cell’s metabolic efforts, ribosome biogenesis determines growth, cell division rates, and survival. Therefore, the etiology and pathogenesis of ribosomopathies can reveal new information about the role of ribosome biogenesis in proliferation, growth, differentiation and also importantly in cancer. The ribosome plays a unique role in the maintenance of the species, translating mRNAs into functional proteins. Moreover, it has been known for many decades now that the affinity of the translational apparatus for any single mRNA species is unique. Therefore, given that there is an excess in the number of mRNA transcripts to ribosomes, a decrease in ribosome number would impinge not only on the rates of translation, but also on the patterns of translation. This is because as the number of ribosomes to mRNA transcripts decreases, those mRNAs for which the translational apparatus has high affinity will continue to be translated, whereas the translation of those mRNAs for which the protein synthetic apparatus has low affinity will decrease. Importantly, changes in gene expression, caused by alterations in ribosome...
number, have been implicated in aberrant growth and human pathologies. Evidence in support of this concept initially came from findings in model systems showing that ribosomal proteins (RPs) act as haploinsufficient tumor suppressors. More recently, it has become evident that patients affected by Diamond-Blackfan anemia (DBA) or 5q syndrome, pathological conditions characterized by heterozygous loss-of-function mutations in RP genes, have a propensity to develop tumors later in life. There are, however, well recognized differences between DBA and 5q deletion syndrome. Certain characteristic features of the 5q- syndrome, namely thrombocytosis, megalakaryocytic hyperplasia and clonal dominance, have not been explained by RPS14 haploinsufficiency. This indicates that the full phenotype may be a consequence of allelic insufficiency of multiple genes and/or noncoding regions within the critical deletion region. In agreement with this idea, a number of non-coding miRNAs are deleted in patients with 5q- syndrome. Some of the miRNAs target TRAF6, and overexpression of TRAF6 is consistent with thrombocytosis, mild neutropenia, dysplastic megalakaryopoiesis, and a propensity to AML, all of which are features of 5q- syndrome. Thus, although there are clear genetic differences between DBA and the 5q- syndrome, with germline mutations in the ribosomal proteins in the former and somatic deletions between DBA and the 5q- syndrome, with germline mutations in RP genes, there are clear genetic differences between the two syndromes. Therefore, the full phenotype in 5q- may be due to both cell non-autonomous and cell autonomous factors.

In summary, the disorders described in this review arise due to deficient ribosome biogenesis. However, the converse is also true, that excessive ribosome biogenesis can also lead to developmental anomalies. This is particularly evident in bent bone dysplasia, a congenital disorder of skeletal development, which was recently shown to be caused by excessive ribosome biogenesis in association with mutations in FGFR2. It is reasonable to expect that perturbations in regulatory signals lying upstream of ribosome biogenesis in bone may be able to elicit such effects and consistent with this idea, it has long been known that signaling molecules such as FGF, BMP, Wnt, and Hedgehog spatiotemporally regulate growth, proliferation and differentiation. Yet, how these signals are integrated with ribosome biogenesis as a means to adapt to changing requirements for protein synthesis during bone and general tissue formation and homeostasis remains an open question. The answers however will provide a better understanding of why bone is particularly sensitive to specific levels of ribosome biogenesis. What is clear, is that the convergence of developmental signaling pathways with ribosome biogenesis provides additional levels of translational specificity that influence fundamental aspects of cell growth and proliferation in the context of embryonic development, evolution and congenital disease.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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