FEBS Letters 588 (2014) 1491–1500

journal homepage: www.FEBSLetters.org

Review

Diverse diseases from a ubiquitous process: The ribosomopathy paradox

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ARTICLE INFO

Article history:
Received 9 January 2014
Revised 8 March 2014
Accepted 12 March 2014
Available online 19 March 2014

Edited by Ulrike Kutay

Keywords:
Ribosomopathy
Ribosome biogenesis
Tissue specificity
IRES elements

ABSTRACT

Collectively, the ribosomopathies are caused by defects in ribosome biogenesis. Although these disorders encompass deficiencies in a ubiquitous and fundamental process, the clinical manifestations are extremely variable and typically display tissue specificity. Research into this paradox has offered fascinating new insights into the role of the ribosome in the regulation of mRNA translation, cell cycle control, and signaling pathways involving TP53, MYC and mTOR. Several common features of ribosomopathies such as small stature, cancer predisposition, and hematological defects, point to how these diverse diseases may be related at a molecular level.

1. Introduction

The ribosomopathies are a diverse group of disorders which, despite their heterogeneity at a clinical level, affect the same biochemical process. They are each caused by mutations in a gene encoding either a ribosomal protein, or a component of the apparatus required for ribosome biosynthesis. Ribosomes are large and complex molecules comprised of both RNA and protein, assembled into a functional, multi-subunit enzyme. The large or 60S ribosomal subunit is composed of the 28S, 5S and 5.8S rRNAs, and 47 proteins; the small or 40S ribosomal subunit is composed of the 18S rRNA and 33 proteins. Assembly of a functional 80S ribosome, containing both the small and large subunits, is a complex, multi-step process. It requires the coordinated activities of all three RNA polymerases, 75 small nucleolar RNAs (snoRNAs), and roughly 200 other non-ribosomal factors that are involved in the transcription, export, translation, re-importation, modification, assembly, and maturation of the ribosomal subunit components. These non-ribosomal factors include helicases, exo- and endonucleases, methyltransferases, and isomerases which modify the nascent rRNA [1–3]. To generate the mature 18S, 28S, and 5.8S rRNAs, a precursor 45S rRNA is transcribed by RNA polymerase I as a long polycistronic transcript which is then extensively processed through cleavage and modification events, ensuring equimolar amounts of these rRNA species. The 5S rRNA is transcribed independently by RNA polymerase III in the nucleoplasm, undergoing its own maturation pathway before re-importation into the nucleolus [4]. The ribosomal protein genes are transcribed by RNA polymerase II, and assembled with nascent rRNA in the nucleolus. The pre-60S and pre-40S ribosomal subunits are exported into the cytoplasm where they undergo final maturation steps to become the mature 60S and 40S subunits, which can then join to form the 80S ribosome.

Individually, the ribosomopathies are rare and phenotypically unique. Intuitively, mutations affecting the ribosome, a molecule essential for protein synthesis in every cell, should affect all tissues and cell types. On the contrary, ribosome biogenesis disorders are highly heterogeneous in both their physical manifestations and modes of inheritance, and there is a surprising tendency toward tissue specificity in these diseases (Table 1). Among the autosomal dominant ribosomopathies are Diamond–Blackfan anemia (OMIM #105650), primarily characterized by macrocytic anemia [5–9]; Treacher Collins syndrome (OMIM #154500 and #613717), which also has an autosomal recessive form (OMIM #248390) and is primarily a disorder of craniofacial abnormalities [10–14]; isolated congenital asplenia (OMIM #271400), a disorder of spleen development leading to severe bacterial infections [15]; and the autosomal dominant form of aplasia cutis congenita (OMIM %107600), a non-syndromic disorder of skin development usually localized to the scalp [16]. The ribosomopathies inherited in an autosomal recessive fashion include Shwachman–Diamond syndrome (OMIM

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http://dx.doi.org/10.1016/j.febslet.2014.03.024
0014-5793/

Table 1
The ribosomopathies, including putative mechanisms causing tissue specificity.

Disease	Clinical manifestations	Gene	Function in ribosome biogenesis	Occurrence	Putative mechanism of specificity	References
Autosomal dominant						
Diamond–Blackfan anemia	Anemia, bone marrow failure, craniofacial abnormalities, cardiac defects, cancer predisposition, pre- and postnatal growth retardation, thumb abnormalities, heart defects	*RPS7, RPS10, RPS17, RPS19 RPS24, RPS26, RPL5, RPL11, RPL26, RPL35A*	Ribosomal proteins	1 in 100 000-1 in 200 000 live births	Translation of IRES-containing *BAG1* and *CSDE1* mRNAs in erythroid progenitors	[5–9,38]
Treacher Collins syndrome	Craniofacial abnormalities, occasional microcephaly, mental retardation and psychomotor delay	*TCOF1, POLR1D, POLR1C*	Transcription of rRNA genes	1 in 40 000-1 in 70 000	Treacle strongly expressed in neural crest cells; Treacle interaction with UBF, fibrillarin, NOP56, Plk1	[10,12–14,39,40]
Isolated congential asplenia	Agenesis or hypoplasia of spleen leading to immunodeficiency	*RPSA*	Small subunit ribosomal protein	73 cases reported	Unknown	[15,41,42]
Aplasia cutis congenita	Agenesis of skin, usually on scalp vertex	*BMS1*	Ribosomal GTPase	>500 cases	Unknown	[16,43,44]
Autosomal recessive						
Shwachman–Diamond syndrome	Exocrine pancreas insufficiency, growth retardation, hematologic defects, skeletal abnormalities, cancer predisposition	*SBDS*	Removal of eIF6 from 60S in final maturation step, allowing binding of 40S and 60S subunits	1 in 76 000 live births	SBDS strongly expressed in developing pancreas	[17,18,45–48]
Bowen–Conradi syndrome	Severe pre- and postnatal growth retardation, psychomotor retardation, microcephaly, micrognathia, joint contractures, rockerbottom feet	*EMG1*	Pseudouridine-N1-specific methyltransferase	1 in 355 live births in Hutterite population	Unknown	[19,49–52]
Cartilage hair hypoplasia	Short stature, sparse hair, immunologic defects, hematological defects, malabsorption, cancer predisposition	*RMRP*	Pre-rRNA cleavage	Amish: 1 in 500-1 in 1000; Finnish: 1 in 23 000	Short stature related to rRNA cleavage defect; cancer predisposition putatively caused by defective cyclin B cleavage	[20,21,53,54]
Anauxetic dysplasia	Severe short stature, hypodontia, mental retardation	*RMRP*	Pre-rRNA cleavage	7 cases reported	Short stature related to rRNA cleavage defect; cyclin B cleavage unaffected thus no cancer predisposition	[20,21,53,54]
Alopecia, neurological defects and endocrinopathy syndrome	Hypoplastic hair, microcephaly, mental retardation, progressive motor retardation, adrenal insufficiency	*RBM28*	Nucleolar component of the spliceosomal small nucleolar ribonucleoprotein, necessary for 60S biogenesis	5 cases reported	Unknown	[23,55,56]
North American Indian childhood cirrhosis	Transient neonatal jaundice progressing to biliary cirrhosis	*CIRH1A*	Pre-rRNA processing	Carrier status: 1 in 10 in Quebec Ojibway-Cree population	Cirhin strongly expressed in developing liver	[24,25,57–59]
X-linked recessive						
X-linked dyskeratosis congenita and Hoyeraal–Hreidarsson syndrome	Abnormal skin pigmentation, nail dystrophy, leukoplakia, bone marrow failure, cancer predisposition, short stature, microcephaly, immunodeficiency	*DKC1*	Pseudouridine synthase	1 in 1000 000	Translation of IRES-containing mRNAs including *p27*, *XIAP*, *Bcl-xL*	[26,28,60–62]
Sporadic						
5q$^-$ syndrome	Macrocytic anemia, predisposition to acute myeloid leukemia	*RPS14*	Small subunit ribosomal protein	Unknown	Unknown	[31]
T cell acute lymphoblastic leukemia	Leukemia affecting the T-cell lineage	*RPL5, RPL10, RPL22*	Large subunit ribosomal proteins	In T-ALL: *RPL5* mutations 5.2%, *RPL10* mutations 1.9%, *RPL22* deletions 10%	RPL22 deficiency blocks αβ T cell development, unknown	[32,33,63]

#260400), primarily characterized by exocrine pancreas insufficiency [17,18]; Bowen–Conradi syndrome (#211180), characterized by severe growth and psychomotor delay, and death in early childhood [19]; cartilage hair hypoplasia (OMIM #250250), a disorder of short stature and hypoplastic hair [20,21], and its variants anauxetic dysplasia (OMIM #607095) [21] and metaphyseal dysplasia without hypotrichosis (OMIM #250460) [22]; alopecia, neurological defects, and endocrinopathy syndrome (OMIM #612079), causing hair loss, microcephaly, mental retardation, and adrenal insufficiency [23]; and North American Indian childhood cirrhosis (OMIM #604901), which results in biliary cirrhosis [24,25]. Dyskeratosis congenita, characterized by abnormal skin pigmentation, nail dystrophy, and leukoplakia, has an X-linked form (OMIM #305000, including the severe form known as Hoyeraal–Hreidarsson syndrome), autosomal dominant (OMIM #127550, #613989, #613990) and autosomal recessive forms (OMIM #224230, #613988), although the best evidence for a ribosome biogenesis defect is found in the X-linked form [26–30]. Many ribosomopathies are accompanied by a predisposition to cancer, and evidence that ribosomal defects can drive malignant transformation is mounting; $5q^-$ syndrome, a form of macrocytic anemia with predisposition to cancer, is caused by haploinsufficiency of RPS14 due to the sporadic deletion of part of the long arm of chromosome 5 [31]. Somatic mutations in *RPL5*, *RPL10*, and *RPL22* have been associated with T-cell acute lymphoblastic leukemia [32,33]. Despite the phenotypic heterogeneity, several characteristics, including small stature, microcephaly, hematological defects, and predisposition to cancer [34–36] are shared among many of the disorders. Immune defects have also been proposed to be a hallmark of ribosomopathies [37].

Although the specific mechanism underlying the ribosomopathies is frequently unclear, the generally accepted etiology is that processing delays or defects in rRNA maturation, resulting in an imbalance of mature ribosomes, lead to reduced rates of protein synthesis and cell proliferation. However, it has become clear that the specificity and activity of the ribosome is regulated, and changes to its composition may begin to explain the heterogeneity among ribosomopathies. Examples of ribosome diversity in numerous organisms are increasingly common, and will not be covered in full here as the topic has been extensively reviewed elsewhere (see [64–66]). Instead, we will focus on vertebrate ribosome heterogeneity and its relevance to human disease. Herein, we review several different mechanisms which have been proposed to underlie the tissue specificity of ribosome biogenesis disorders, including the selective translation of specific mRNAs directed by the ribosome, extra-ribosomal functions of ribosomal proteins and ribosomal biogenesis factors, and differential requirements for ribosomes in different tissues. In addition, the diverse roles played by regulatory pathways in modulating ribosome biogenesis disorders will be discussed.

2. Mechanisms underlying tissue specificity in ribosomopathies

2.1. Selective translation of internal ribosome entry site mRNAs: X-linked dyskeratosis congenita and Diamond–Blackfan anemia

Several studies have shown that the cellular environment can cause the ribosome to display a preference for translating specific types of mRNAs. The discovery that ribosomes can preferentially translate certain mRNAs was first described in the context of viral infection, when cap-dependent translation is repressed in favor of the translation of viral mRNAs [67,68]. These viral mRNAs contain internal ribosomal entry sites (IRESs) in their 5′-untranslated region (UTR) which allow ribosome binding even in the absence of a cap. IRES-directed translation has since been found in numerous cellular mRNAs, often in response to stress [69,70]. For example, cap-dependent translation is repressed during apoptosis, hypoxia, and mitosis, allowing translation of IRES-containing mRNAs which include TP53, X-linked inhibitor of apoptosis (XIAP), MYC, and certain cyclin-dependent kinases [70,71]. When cap-dependent translation is down-regulated during mitosis, roughly 3% of mRNAs, many of which contain IRESs, remain associated with polysomes [72]. However, there are likely other levels of control over IRES-containing mRNAs, as translation from only a subset of IRES elements occurs under a given condition. For example, of the IRES-containing mRNAs, one isoform of cyclin-dependent kinase 11, CDK^{p58}, is translated during mitosis, however c-MYC is not. On the other hand, c-MYC mRNA is translated during apoptosis, while the IRES-containing nucleophosmin mRNA is not [70,73]. This second layer of specificity may be mediated by binding of cell-cycle or tissue-related factors to specific mRNAs, or it could be due to alterations in the ribosome itself, which change its ability to recognize and bind different IRES elements under different conditions.

X-linked dyskeratosis congenita is caused by mutations in *DKC1*, encoding dyskerin, a component of an H/ACA box small nucleolar ribonuclear particle (snoRNP) responsible for isomerisation of uridine to pseudouridine [26,60,74]. Dyskerin is also a part of the telomerase complex, and defects in both ribosome biogenesis and telomere maintenance have been shown in patient cells and in mouse models of the disease [26–28,75,76]. Alterations in rRNA pseudouridylation have been shown to be deleterious for ribosome biogenesis and function in numerous organisms, most likely by altering the affinity of the ribosome for mRNAs [77,78]. Mutations causing X-linked dyskeratosis congenita result in a specific reduction of IRES-mediated mRNA translation in patient lymphoblasts and fibroblasts, without affecting global levels of protein synthesis [61]. In particular, translation of the tumor suppressor p27, and the anti-apoptotic proteins XIAP and Bcl-xL, is significantly reduced. The cells are also deficient in translation of exogenous viral IRES-containing mRNAs, suggesting a global reduction of IRES element translation due to the loss of rRNA pseudouridylation.

IRES-directed translation can affect the organism at multiple levels; in dyskeratosis congenita, apoptosis, tumor suppression, and cell cycle progression are all misregulated. The misregulation of apoptosis, reflected by increased apoptosis in hematopoietic progenitors and stem cells, results in a bone marrow defect. The increased cancer susceptibility seen in X-linked dyskeratosis congenita patients [61] is likely secondary to the IRES-mediated reduction in p27 levels. Additionally, disruption of dyskerin leads to accumulation of cells in the G2/M phase of the cell cycle, resulting in reduced proliferation rates [79,80], which may be attributed to failure to complete IRES-directed translation following down-regulation of cap-dependent translation at the beginning of mitosis. The translation of CDK^{p58} is directed by an IRES element, and the resulting protein is necessary for progression through M phase [81]. These findings demonstrate not only that rRNA modification is crucial for ribosome specificity, but also that defective rRNA modification can lead to disruption of IRES-based translation. Given that IRES-containing mRNAs are expressed under particular conditions, it seems likely that these defects would only be present at specific times or in specific tissues.

Diamond–Blackfan anemia (DBA) is characterized by macrocytic anemia with reduced numbers of erythroid progenitors in the bone marrow. It is caused by mutations in genes encoding components of either the small or large ribosomal subunits, including *RPS19, RPS7, RPS10, RPS17, RPS24, RPS26, RPL5, RPL11, RPL35A,* and *RPL26*. As *RPS19* mutations account for 25% of DBA cases [5,9,82], this gene has been the most extensively studied.

Knockdown of *RPS19* in healthy CD34+ cells reduces their proliferative capacity by stalling the cell cycle at G0, in addition to impairing erythroid differentiation, but without significantly affecting myeloid differentiation [83,84]. In mice, mutations in *Rps19* and *Rpl11* result in deficient IRES-mediated translation of BCL2-associated anathogene 1 (*Bag1*) and cold shock containing domain E1 (*Csde1*) in erythroblasts. Reduced translation of BAG1 and CSDE1, due to an alteration in ribosome specificity for IRES-containing mRNAs, is also detected in DBA patient cells [38]. Because these proteins are necessary for erythroid generation, their deficiency results in an erythroid progenitor defect in DBA patient cells. Further evidence comes from studies in mice where the normal expression levels of *Bag1* and *Csde1* are low in myeloid progenitor cells but high in erythroid progenitors. A *Bag1* knockout shows a reduction in erythroid progenitors, and shRNA knockdown of *Csde1* in erythroblasts inhibits their proliferation and maturation [38]. This suggests that ribosomal proteins play a role in the recognition of specific mRNAs for translation, although it is not clear if this is the case for mutations in ribosomal protein-encoding genes other than *RPS19* and *RPL11*. Notably, knockdown of RPS19 and RPL11 both negatively affect translation of a control IRES mRNA as well, indicating that cap-independent translation as a whole may be deficient [38]. Further investigation is necessary to determine whether IRES-dependent mRNAs aside from BAG1 and CSDE1 are relevant to the DBA phenotype.

Although macrocytic anemia is consistently detected in DBA patients, other phenotypes are variable and establishing genotype-phenotype correlations has been difficult [85,86]. Despite this, a few correlations have been made. For example, *RPL5* mutations are correlated with craniofacial malformations including cleft palate, and *RPL11* mutations are associated with thumb abnormalities [86]. This suggests that the mechanism leading to macrocytic anemia is common to these deficiencies, but that each ribosomal protein may also have unique roles in mediating the other phenotypes of DBA, whether through their function within the ribosome, or via extra-ribosomal functions.

2.2. Extra-ribosomal functions and binding partners: Treacher Collins syndrome and cartilage hair hypoplasia/anauxetic dysplasia

Numerous ribosomal proteins seem to have functions outside their role in the ribosome, the best-studied of which is mediation of the cell cycle (see TP53 section below). Extra-ribosomal functions of ribosome biogenesis factors are also common. Perturbation of these functions may contribute to the phenotype in ribosome biogenesis disorders, mediated at least in part by their interacting partners. Treacher Collins syndrome (TCS) is a disorder of craniofacial development caused by mutations in *TCOF1* (encoding the protein Treacle), *POLR1C*, or *POLR1D* (encoding subunits of RNA polymerase I and RNA polymerase III respectively) [14]. Autosomal dominant TCS caused by mutations in *TCOF1* accounts for the majority of cases [87,88]. There is a clear temporal aspect to the disease, as *Tcof1* expression in the mouse embryo is strong in embryonic development, particularly in the developing branchial arches, and diminishes to near background levels by embryonic day 10.0 [10]. Mouse and zebrafish models of the disease have revealed a deficiency specifically in migrating neural crest cells due to reduced proliferation rates and increased apoptosis [13,89]. This defect in neural crest cells is proposed to underlie the hearing loss in Treacher Collins syndrome, as the affected middle ear is neural-crest derived, while the unaffected inner ear does not originate from neural crest cells [90]. Although the exact function of Treacle is unknown, the phenotype of Treacher Collins syndrome appears to be directly mediated by binding of Treacle to other factors. For instance, Treacle interacts with upstream binding factor (UBF), which modulates RNA polymerase I activity, and a reduction in Treacle levels inhibits transcription of the rRNA genes [12]. In *Xenopus* oocytes, Treacle was shown to interact with fibrillarin, an RNA and DNA methyltransferase [91,92], and NOP56, a component of an RNP methyltransferase complex [93]. *TCOF1* knockdown therefore causes a reduction in 2′-OH methylation in nascent rRNA [39]. Reduction of rRNA transcription and modification due to Treacle haploinsufficiency is thus proposed to underlie the proliferation defect in neural crest cells, which in turn leads to hypoplasia of the facial bones [12,39].

In addition to craniofacial abnormalities, Treacher Collins syndrome patients may present with microcephaly and psychomotor retardation, indicating a neurological defect. A mouse model of Treacher Collins syndrome displaying reduced brain size has revealed that Treacle also has an important role outside of ribosome biogenesis. This appears to be mediated by an interaction with Polo-like kinase 1 (Plk1), which is necessary for mitotic progression via its role in spindle orientation [40]. A reduction in the Treacle-Plk1 interaction is thought to underlie a reduction in neural progenitors during cortical neurogenesis, due to improper mitotic spindle formation. This suggests that the neurological phenotype in Treacher Collins syndrome is mediated by extra-ribosomal functions of Treacle, in addition to its role in ribosome biogenesis, which is linked to the craniofacial phenotype. Interestingly, mitotic spindle localization has been shown for other ribosomopathy-associated proteins. SBDS, the Shwachman–Diamond syndrome protein, binds to the mitotic spindle in bone marrow cells, lymphoblasts, and skin fibroblasts, and knockdown by siRNA increases the number of atypical mitoses in human fibroblasts [94]. Knocking down dyskerin also leads to multi-polar mitotic spindle defects in HeLa cells, possibly through the association of dyskerin with CDK^{p58} [79,81,95]. Additionally, dyskerin-depleted U2OS cells (a telomerase-negative osteosarcoma cell line) [79], and mouse embryonic fibroblasts [80] arrest in G2/M phase, although this is not the case in the telomerase-positive UM-SCC1 oral squamous cell carcinoma or HeLa cell lines [79]. The yeast homolog of EMG1, the protein associated with Bowen–Conradi syndrome, shows spindle localization [96], and lymphoblasts from Bowen–Conradi syndrome patients accumulate in G2/M phase, indicating a possible defect in mitotic progression (Armistead et al., unpublished data). In HeLa cells stably expressing either His-tagged or EGFP-tagged Cirhin, the protein associated with North American Indian childhood cirrhosis, Cirhin is localized to the chromosome periphery throughout mitosis. Similar localization was shown for HepG2 cells, a hepatocyte-like cell line [97]. Mitotic spindle association may be a common extra-ribosomal function of many proteins associated with ribosome biogenesis disorders, and future work will show if this is a contributing factor in cell proliferation defects and cancer progression.

Cartilage hair hypoplasia (CHH) is a form of short-limbed dwarfism, accompanied by sparse hair, immunologic and hematological defects, and increased instances of malignancy [20,22]. The related disease, anauxetic dysplasia (AD), is characterized by a more severe skeletal phenotype of extreme short stature, but AD patients do not display increased cancer susceptibility [21]. Both diseases are caused by mutations in *RMRP*, the RNA component of the mitochondrial RNA-processing endoribonuclease RNase MRP, an enzyme with numerous substrates in the nucleolus and in mitochondria, including rRNA and mRNA [54]. The short stature in CHH and AD has been attributed to failure of 5.8S rRNA cleavage during maturation, leading to reduced proliferation specifically in chondrocytes [21,53]. On the other hand, susceptibility to cancer in CHH has been attributed to the impairment of cyclin B mRNA degradation by RNase MRP, which alters the spindle assembly checkpoint during mitosis [21]. Patients with AD do not accumulate cyclin B mRNA and are not predisposed to malignancy [21]. Thus, in a rare clear-cut example, the phenotypic differences

between CHH and AD can be traced back to the discrete functions of RNase MRP, as CHH patients display defects in both rRNA and mRNA cleavage, while AD patients are only deficient in rRNA cleavage.

A less understood, though well-studied, example is dyskeratosis congenita; the contribution of defects in ribosome biogenesis versus defects in telomerase function to the phenotype are difficult to unravel [26–28,75,76]. Ribosome biogenesis defects in mouse models of the disease, causing a proliferative defect not associated with short telomeres, would seem to point to a purely ribosome-related disease [29]. Other studies in cell lines from dyskeratosis congenita patients indicate that the reduced proliferation rates are unrelated to ribosome biogenesis defects [27]. It may not be possible to resolve this apparent paradox using mouse models of the disease, since the much longer telomeres in mice mean that they do not completely recapitulate the human condition [98].

2.3. Differential requirement for ribosome biogenesis factors: North American Indian childhood cirrhosis, Shwachman–Diamond syndrome, and Tail short mouse

Although the ribosomal genes are generally considered to be "housekeeping" genes due to their ubiquity, it is becoming understood that at least some of the ribosomal protein genes display temporal and spatial variation, despite a general tendency toward coordinate regulation [99–102]. A screen of 72 ribosomal proteins in 14 tissue and cell types of the mouse embryo showed heterogeneous and non-overlapping patterns of expression [103]. A recent study in mouse suggests that the most recently evolved ribosomal protein paralogs are more likely to display tissue-specific variation, indicating an evolutionary need for ribosome variation [104]. If the ribosomal proteins have variable expression, it seems likely that variation in ribosome biogenesis factor distribution among tissues and throughout development also contribute to ribosomopathy phenotypes.

North American Indian childhood cirrhosis (NAIC) is caused by a mutation in *CIRH1A*, encoding the protein Cirhin [58]. NAIC presents in childhood as transient jaundice, progresses to biliary cirrhosis and portal hypertension, and liver transplantation is currently the only treatment. Among the ribosomopathies, NAIC has the distinction of affecting a single organ, making analysis of the defect more straightforward. The yeast homolog of Cirhin, Utp4, is a member of the small ribosomal subunit processome and is essential for ribosomal RNA maturation [24,25]. During mouse embryonic development, *Cirhin* is highly expressed in the liver at embryonic day 11.5, with much lower levels of expression in the somites, brain, and craniofacial structures [58]. Zebrafish show similar results, with widespread expression of *cirh1a* at 20 h post fertilization, peak expression at 3 days post fertilization restricted to the liver, gallbladder, pancreas, and anterior intestine, and much lower levels in the brain and eye [59]. When *cirh1a* was knocked down by morpholino injection, morphants showed tp53-dependent defects in development of the biliary system, with no defects observed in other tissues [59]. In this case, it seems that the high requirement for Cirhin in the liver makes it most sensitive to a loss of Cirhin function.

Shwachman–Diamond syndrome (SDS) is a disorder of exocrine pancreas insufficiency, bone marrow dysfunction and increased cancer risk. In SDS, mutations in the *SBDS* gene result in deficiencies in the 60S ribosomal subunit because of a failure in the removal of eukaryotic translation initiation factor 6 (eIF6) from the ribosome in a final maturation step [47,105]. SDS patients suffer from exocrine pancreatic insufficiency, and it has never been clear whether the symptoms result from reduced protein synthesis rates in the pancreas that lead to insufficient levels of pancreatic enzymes, or whether the pancreas simply does not develop properly. An examination of *sbds* expression in zebrafish throughout development showed that *sbds* in the developing pancreas persists over time, while it diminishes in other tissues including the adjacent gut and liver [45]. Knockdown of *sbds* in zebrafish results in reduced expansion specifically in exocrine pancreatic cells without affecting cell proliferation in other tissues [45,48]. Notably, the pancreas defect precedes the production of pancreatic enzymes, indicating a developmental problem rather than a simple protein synthesis deficiency resulting in insufficient enzymes [48]. Together, these zebrafish models of SDS suggest that the strong pancreatic phenotype correlates with the high and continuing levels of *sbds* expression, and that visceral organs with lower expression such as gut and liver are affected to a lesser extent. It becomes more difficult to unravel the phenotype when it is considered that SDS patients also display hematological defects, even though bone marrow has relatively low levels of *SBDS* expression in humans [17].

Differential expression of the ribosomal protein Rpl38 has also been shown to play a role in mediating the phenotype in mice deficient in ribosome biogenesis. This is demonstrated in the spontaneous dominant mouse mutant, Tail short, which is characterized by a short and kinky tail, homeotic transformations of the skeleton, facial malformations, and eye abnormalities. Mutations in the large ribosomal subunit protein gene *Rpl38* result in the reduction of translation of a subset of Homeobox (Hox) mRNAs. Global protein synthesis is unchanged, and the specific translation of the *Hox* mRNAs is unrelated to IRES elements [103]. Similar to the zebrafish models of NAIC and SDS, *Rpl38* expression varies among tissues, and in general, the highest expression is found in the most severely affected tissues. In particular, *Rpl38* expression is enriched in the somites along the entire anterior-posterior axis during somitogenesis, pointing to a role in axial vertebral patterning. The Hox translation defect was detected in the embryo at approximately embryonic day 11, long before the morphological defects become evident. This suggests that the specific translational control of a subset of mRNAs, mediated by *Rpl38* itself, underlies the development of the patterning defects. The tissue-specific effect reflects the fact that the tissues most sensitive to *Rpl38* perturbation are those expressing the highest levels of the protein [103].

Thus, differential expression of ribosome biogenesis factors and ribosomal proteins can affect the phenotype of a disease. It should be noted however, that this hypothesis cannot completely explain the tissue specificity. For example, high *Rpl38* expression was also found in the mouse kidney, an organ which is unaffected in the *Rpl38* mutant. This, combined with the bone marrow dysfunction seen in Shwachman–Diamond syndrome despite low levels of *SBDS* expression in that tissue, suggests that expression levels do not always predict demand.

3. The diverse roles of regulatory pathways in ribosome biogenesis

3.1. Tp53

The TP53 tumor suppressor pathway stands as a strong checkpoint to verify that ribosome biogenesis is intact before allowing cell division. In a healthy cell, the E3 ubiquitin ligase MDM2 binds and ubiquitinates TP53, thereby targeting it for degradation by the proteasome and maintaining it at low levels. In a cell where ribosome biogenesis has been perturbed, the balance between rRNA and ribosomal protein synthesis becomes uncoupled, leading to free ribosomal proteins that cannot be incorporated into a functional ribosome [106–110]. In another example of an extra-ribosomal function for ribosomal factors, certain free ribosomal proteins including RPL5 [111], RPL11 [112], RPL23 [113,114], RPL26 [115], RPS3 [116] and RPS7 [117] bind and segregate

MDM2, which leads to the stabilization of TP53. Cell cycle arrest and/or apoptosis ensue, ensuring that cells with deficiencies in ribosome biogenesis do not survive [107,109,118–121]. Perturbation of ribosomal proteins can thus lead to the activation of a TP53-mediated nucleolar stress response [119,121], although the TP53 response can vary depending on the ribosomal protein involved [122], and TP53 stabilization has been observed even in the absence of nucleolar disruption [120].

The link between the TP53 pathway and ribosome biogenesis has been exploited in animal models of ribosome biogenesis as a treatment for the disorder. Remarkably, in a mouse model of Treacher Collins syndrome, loss of one *Trp53* allele completely rescues the phenotype by decreasing apoptosis in neuroepithelial and neural crest cells [123]. Other examples of ribosome insufficiency, including mutations in *Rps20* [124], *Rpl24* [125], *Rps7* [126], and the 5q$^-$ syndrome-associated protein *Rps14* [127], can all be rescued in mice by the ablation of the Trp53 pathway. However, the contribution of TP53 to the regulation of ribosome biogenesis is far from clear, as recent studies have shown variable responses to Trp53 inhibition or knockout. In *Rpl38*, *Rps19*, and *Rpl11* mutant mice, as well as an *Emg1* knockout mouse, the phenotype is refractory to Trp53 inhibition [38,103,128]. Interestingly, ablation of the TP53 checkpoint in *sbds* knockdown zebrafish ameliorates the skeletal phenotype and improves the overall health of the embryos [48]. However, the pancreatic organogenesis defect is not rescued, suggesting that the phenotype is only partially mediated by the TP53 pathway. Similarly, TP53 knock down in a zebrafish model of Diamond–Blackfan anemia rescued the morphological abnormalities, but did not alter the erythropoietic defect [129,130]. The selective contribution of the TP53 checkpoint to individual ribosomopathies likely plays a role in the variable phenotypes in ribosome biogenesis disorders, including cancer progression, and is just beginning to be appreciated. Other pathways may mediate the phenotype in the absence of TP53 involvement; for example, p21 is sometimes up-regulated in ribosome biogenesis disorders even in the absence of TP53 stabilization [16,131]. Another TP53-independent mechanism involves dysregulation of retinoblastoma phosphorylation. When ribosome biogenesis is impaired, for example by depletion of ribosome biogenesis factor pescadillo [132], the cyclin-dependent kinase inhibitor p27 is up-regulated, leading to reduced phosphorylation of the retinoblastoma protein. In the absence of phosphorylation, the retinoblastoma protein remains bound to transcription factor E2F1, preventing translation of genes necessary for S-phase progression [133].

3.2. mTOR

Ribosome biogenesis and cellular environment are linked by the mammalian target of rapamycin (mTOR) pathway, which senses nutrient availability, hormones, energy levels and cellular stress. In situations where increased ribosome biogenesis is required, mTOR complex 1 promotes rDNA transcription by positively regulating RNA polymerase I, and plays a role in the processing of pre-rRNA to its mature forms [134]. In addition, it phosphorylates S6K1, which in turn phosphorylates small ribosomal subunit protein RPS6. The phosphorylated RPS6 appears to alter the specificity of the ribosome, conferring it with a preference for translating 5′ terminal oligopyrimidine (5′-TOP) mRNAs, a group of mRNAs which includes ribosomal protein genes [135–137]. Thus, the activity of mTOR, modulated by the local environment in a given tissue, can directly regulate ribosome biogenesis. In an example relevant to Diamond–Blackfan anemia, mTOR is activated in response to erythropoietin, resulting in increased formation of the ribosome scanning complex specifically in erythroblasts [38,138]. Differential effects of ribosome biogenesis deficiency on mTOR signaling have also been shown in the brain. When rRNA transcription is inhibited, mTOR signaling, as measured by RPS6 phosphorylation, in increased in hippocampal neurons [139], but inhibited in dopaminergic neurons [140]. However, unlike TP53 stabilization, mTOR pathway activity is rarely investigated in ribosome biogenesis disorders, making it difficult to assess its role in ribosomopathy phenotypes.

3.3. Myc

Another master coordinator of cell growth and division, the oncogenic transcription factor MYC, has been shown to directly bind and stimulate the transcription of the rRNA genes [141]. MYC recruits the selectivity factor 1 (SL1) complex and influences transcription by RNA polymerase I via stabilization of the SL1-UBF complex. Thus deregulation of MYC activity can increase ribosome production, and drive uncontrolled cell proliferation. One example is the myelodysplastic 5q$^-$ syndrome. In a healthy cell, the small ribosomal subunit protein RPS14 binds c-MYC and inhibits its activity, reducing cell proliferation [142]. In 5q$^-$ syndrome, RPS14 is haploinsufficient [31], removing one layer of MYC regulation and promoting uncontrolled cell growth. It appears that in some cases ribosome biogenesis and MYC are interdependent, as haploinsufficiency for ribosomal protein genes, which reduces ribosome levels to normal in cancerous cells, is able to suppress the oncogenic activity of MYC [143]. While this is difficult to reconcile with the *increased* incidence of cancer in ribosomopathy patients, who are haploinsufficient for ribosomal proteins, the disruption of ribosome biogenesis may dysregulate MYC function, and eventually lead to cancer. Which cell types and tissues are affected is likely dictated by many of the factors described above. Notably, MYC translation is mediated by an IRES, and mutations in ribosomal proteins or ribosome biogenesis factors which alter the specificity of the ribosome could disrupt the balance of MYC synthesis.

The TP53, mTOR, and MYC pathways are evidently each important for ribosome biogenesis, although their individual contributions to tissue-specific effects in ribosomopathies are currently unclear. It has become apparent, however, that these pathways interact and influence each other. It has been shown that in MYC-dependent cancers, tumor initiation and maintenance requires the phosphorylation of eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1) by mTOR [144]. Phosphorylation of 4EBP1 prevents it from negatively regulating the translation initiation factor eIF4E, which binds the 5′ cap on mRNA and recruits the 40S ribosomal subunit, driving the increased protein synthesis necessary in cancer cells. Thus, blocking mTOR-dependent 4EBP1 phosphorylation may be a therapeutic target in cancers driven by MYC. The TP53 pathway and MYC are both directly influenced by the Diamond–Blackfan anemia-associated ribosomal protein RPL11. Free RPL11 stabilizes TP53 by binding and sequestering MDM2 (see above), and can also bind the N-terminus of MYC [145]. MYC induces *RPL11* transcription, and RPL11 overexpression represses MYC transactivation in a negative feedback loop [145,146]. Thus, RPL11 can act through both TP53 and MYC to arrest the cell cycle during situations of aberrant ribosome biogenesis. Given the layers of interaction in ribosomal biogenesis regulatory pathways, it remains a major challenge to define their discrete roles in mediating particular ribosomopathy phenotypes.

4. Conclusions

The tissue-specific effects commonly displayed in the ribosomopathies can clearly be caused by multiple factors. These include alteration of ribosome specificity due to changes in rRNA modification or changes in ribosomal protein content, differential

expression of the affected gene required for ribosome biogenesis, alterations in binding with partners of the affected protein, and differential response to regulatory signaling pathways such as TP53. The contributions of these factors to ribosome biogenesis disorders are not mutually exclusive, and the etiologies of ribosomopathies are likely highly complex. The role of these factors in the phenotype of a ribosomopathy must be evaluated before an effective treatment can be developed, and careful analysis is needed in studies of each ribosomopathy to tease out which factors hold the most promise as targets for treatment.

Innovative use of existing techniques has already proven successful in investigating spatial and temporal differences in ribosome function. Dicistronic reporter transcripts have been used previously to measure levels of cap-dependent versus IRES-dependent translation [61,147]. Bellodi *et al.* generated a translation reporter mouse using a similar system, which systemically expresses a *Renilla* luciferase reporter driven by cap-dependent translation, and a firefly luciferase reporter driven by the hepatitis C virus (HCV) IRES element. This mouse was employed to determine if IRES-dependent translation was altered in a model of X-linked dyskeratosis congenita [148] and in an *Rpl38* mutant mouse [103]. This tool could be used to further characterize changes in cap-dependent versus IRES-dependent translation in multiple different tissues, and at different stages of development, in health and disease. Other *cis*-regulatory elements contained within the mRNA 5′ untranslated region, such as upstream open reading frames and 5′-TOPs, can also mediate translation, and may also play a role in the phenotype of ribosome biogenesis disorders [65,70,136,137]. It is easy to envision how modified versions of the HCV IRES reporter mouse could explore how other *cis*-regulatory elements drive translation *in vivo*, by replacing the IRES reporter with the *cis*-element of interest. Equally, they could be used to test ribosome fidelity in mouse models of ribosomopathies by measuring frameshifting and stop codon readthrough [147,149]. Kondrashov *et al.* have also optimized microscale polysome analysis, isolating translationally active ribosomes from minute tissue samples during mouse development, followed by quantitative PCR in order to identify preferentially-translated mRNAs [103]. Ribosome profiling techniques involving deep sequencing of ribosome-protected mRNAs, offer an unbiased approach to identifying the population of mRNAs translated in a given tissue at a given time [150].

As new ribosome biogenesis disorders are identified and new tools become available to unravel their molecular causes, it may become easier to resolve the ribosomopathy paradox. Overall, it is increasingly clear that the ribosomopathies are not simply due to reduced protein synthesis, and are revealing the complex interrelationships between ribosome biogenesis and its regulatory pathways, the cell cycle, and development of multiple tissues.

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