FEBS Letters xxx (2014) xxx–xxx

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 xxxx

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]