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Growth control and ribosomopathies

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Ribosome biogenesis and protein synthesis are two of the most energy consuming processes in a growing cell. Moreover, defects in their molecular components can alter the pattern of gene expression [1,2]. Thus it is understandable that cells have developed a surveillance system to monitor the status of the translational machinery. Recent discoveries of causative mutations and deletions in genes linked to ribosome biogenesis have defined a group of similar pathologies termed ribosomopathies. Over the past decade, much has been learned regarding the relationship between growth control and ribosome biogenesis. The discovery of extra-ribosomal functions of several ribosome proteins and their regulation of p53 levels has provided a link from ribosome impairment to cell cycle regulation. Yet, evidence suggesting p53 and/or Hdm2 independent pathways also exists. In this review, we summarize recent advances in understanding the mechanisms underlying the pathologies of ribosomopathies and discuss the relationship between ribosome production and tumorigenesis.

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Introduction

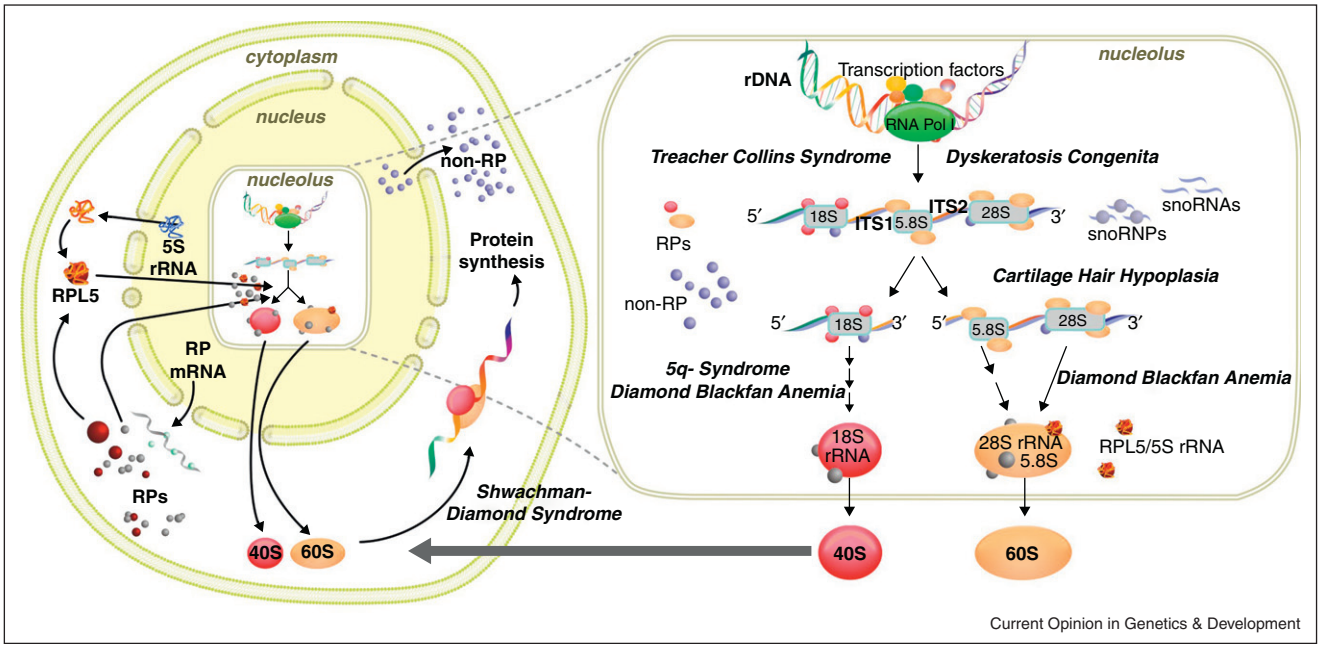
Increased synthesis of new proteins is required for a cell to proliferate and generate two daughter cells. A large share of newly translated proteins includes ribosomes and other factors of the translational machinery. The biogenesis of ribosomes is an energy-consuming, complex process that requires the synthesis, modification, assembly and transport of large and small ribosomal subunits, composed of ~80 ribosomal proteins (RPs) and 4 ribosomal RNAs (rRNAs) [3–5]. All three RNA polymerases are required for ribosome biogenesis [6]. 18S, 28S and 5.8S rRNA are transcribed in the nucleolus as a polycistronic precursor rRNA by RNA polymerase I, before being modified and processed by small nucleolar RNAs (snoRNAs) and protein cofactors into their mature forms [7,8]. Transcription of 5S rRNA by RNA polymerase III occurs in the nucleoplasm, as does transcription of the RP mRNAs by RNA polymerase II. The RP mRNAs are translocated to the cytoplasm where they are translated into RPs, which travel back to the nucleolus carrying mature 5S rRNA bound to RPL5, for processing of the rRNAs and assembly into 40S and 60S ribosomal subunits [9,10,11•] (Figure 1).

What are ribosomopathies?

The pathologies collectively known as ribosomopathies are defined by defects in ribosome biogenesis (Table 1). Two of these with mutations or deletions affecting RPs are the bone marrow failure syndromes, Diamond Blackfan Anemia (DBA) and *5q-* syndrome. DBA is a congenital disease characterized by macrocytic anemia and insufficiency of erythroid precursors, with symptoms of growth retardation and congenital malformations apparent in approximately 40% of patients [12]. Following the first evidence in 1999 that RPS19 was mutated in DBA patients [13], heterozygous mutations or deletions of other RPs, including RPS24, RPL35a, RPS17, RPL5, RPL11, RPS7, RPS10 and RPS26, have been identified in approximately 60–70% of DBA patients [14–22]. *5q-* syndrome is an acquired myelodysplastic syndrome (MDS) characterized by refractory macrocytic anemia and thrombocytosis [23]. Cytogenetically, *5q-* syndrome is caused by specific deletions of the long arm of chromosome 5 which share a common deleted region (CDR). Of the approximately 40 genes deleted in the CDR, deletion of RPS14 was shown to be specifically responsible for the macrocytic anemia, strengthening the link between defects in ribosome biogenesis and failed erythropoiesis [24].

Other non-RP ribosomopathies include Shwachman–Diamond syndrome (SDS), Dyskeratosis congenita (DKC), Cartilage hair hypoplasia (CHH), and Treacher Collins syndrome (TCS) (Table 1). SDS is an autosomal recessive disorder characterized by non-hematological defects, such as pancreatic insufficiency and short stature, and hematological defects, particularly neutropenia, but also anemia and thrombocytopenia. The risk of MDS and AML in SDS patients is high [25]. Approximately 90% of SDS patients have bi-allelic mutations in the *SBDS* gene, whose product, in cooperation with the GTPase EFL1, is thought to release eIF6 from the pre60S subunit, allowing the 60S large and 40S small subunits to bind and form a

Figure 1



Ribosome biogenesis starts with transcription of the polycistronic 47S rRNA precursor by RNA polymerase I in the eukaryotic nucleolus. The pre-rRNA is subsequently modified and processed by numerous small nucleolus RNAs (snoRNAs) and protein co-factors into 18S, 28S and 5.8S rRNAs, which serve as the catalytic core of the ribosome. A simplified schematic of rRNA processing in the nucleolus is shown in the 'flyout' on the right. 5S rRNA is transcribed by RNA polymerase III in the nucleoplasm, undergoes maturation in the cytoplasm, and is transported to the nucleolus with RPL5. Similarly, ~80 RP mRNAs are transcribed by RNA polymerase II in the nucleoplasm, translated into mature RP proteins in the cytoplasm, and travel to the nucleolus where they participate in pre-rRNA processing, 90S pre-ribosome assembly, and transport of pre-40S and pre-60S subunits to the cytoplasm for final maturation. The step in ribosome biogenesis that is thought to be affected by each ribosomopathy is depicted.

functional 80S ribosome [26–28]. Importantly, evidence of a defect in ribosomal subunit joining has recently been shown in lymphoblasts isolated from SDS patients [27]. DKC, which was classically characterized by reticular skin pigmentation, nail dystrophy and mucosal leukoplakia, is now known as an inherited bone marrow failure syndrome. DKC is a heterogeneous disease with causal mutations in multiple genes which are generally associated with telomere maintenance. The mutation in X-linked DKC or Hoyeraal Hreidarrson syndrome (HH), the more severe forms of DKC, is found in dyskerin (DKC1), a nucleolar protein associated with snoRNAs in H/ACA small nucleolar ribonucleoprotein (snoRNP) complexes [29,30]. DKC1 is a highly conserved pseudouridine synthase that catalyzes pseudouridylation in rRNA, and also binds telomerase RNA (TERC). It has been shown that mice with DKC1 mutations are phenotypically similar to the human disease, with impairment in ribosome RNA processing and ribosome function that manifests itself before signs of a defect in telomerase activity [30,31]. Further, it was shown in yeast and human cells that rRNA pseudouridylation affects the affinity of the ribosome for tRNA and internal ribosome entry sites (IRES), underlying the importance of pseudouridylation for translational fidelity [32]. CHH is an autosomal recessive syndrome characterized by bone dysplasia and short-limbed dwarfism, defects in cellular immunity, anemia, gastrointestinal malabsorption and a predisposition to develop lymphoma and other cancers. The mutation in CHH is found in the *RMRP* gene, which encodes the untranslated RNA component of the mitochondrial RNA processing ribonuclease (RNase MRP), which is localized to the nucleolus and mitochondria [33,34]. RNase MRP activity in humans is required for cleavage of 5.8S rRNA and Cyclin B mRNA, affecting both ribosome biogenesis and cell cycle regulation [35]. Interestingly, recent data suggests that RMRP interacts with the telomerase catalytic subunit (hTERT) [36], making CHH the second ribosomopathy with shared defects in rRNA and telomere maintenance. Finally, TCS is linked to mutations in the *TCOF1* gene which encodes treacle, a nucleolar phosphoprotein linked to multiple steps of rRNA and RP transcription and modification, affecting growth and differentiation, particularly in cranial neural crest cells [37–39]. Recently, mutations in key components of the subunits of RNA polymerase I and III were found in a subgroup of TCS patients, further supporting the link between TCS and impaired ribosome production [40•]. Of all the ribosomopathies, TCS is the only syndrome not linked to bone marrow dysfunction or increased risk of cancer. The mutations in the non-RP group are more heterogeneous, affecting various aspects