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Review Article

Faulty ribosomes and human diseases: mistakes in "assembly line" going unnoticed ?

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Abstract

Ribosomes are molecular machineries that decode the information within mRNAs and generate all the proteins required for cellular activities. Ribosomes are essential to every living organism. The synthesis of ribosome is an intricate process, which is carried out in multiple steps throughout the cell in a highly coordinated fashion. For many years, the general perception was that any defects in the "ribosome assembly line" would have fatal consequences on cell. However, it has now become clear that production of defective ribosomes does not lead to lethality in human embryos. Rather, it manifests as specific disease conditions called ribosomopathies, which are rare genetic disorders affecting the bone marrow. This group of diseases has received considerable attention in recent years because of the mystery associated with them i.e. the tissue-specific nature of the clinical phenotypes despite the fact that the genes mutated in patients code for proteins that are absolutely essential and are housekeeping in nature. Despite considerable progress in understanding these diseases, it still remains unclear why defects in the production of a macromolecule as indispensable and as ubiquitous as the ribosome go unnoticed and why the effects are not universal but rather are restricted to specific cell types. This review is aimed at introducing the readers to important ribosomopathies with a brief description about the clinical symptoms, molecular genetics, and the treatments strategies.

Key words: Ribosome, Ribosomopathies, Ribosomal Proteins, Inherited Bone Marrow Failure Syndromes, Anemia,

Introduction

The last step in the central dogma of molecular biology, i.e. the conversion of genetic information from messenger RNA (mRNA) into protein is carried out by ribosomes, the molecular machineries found in all cells. Ribosome is basically a protein/RNA complex,organized into two subunits, large and small, designated by their sedimentation coefficients. In eukaryotes, the larger subunit (60S) is composed of three species of ribosomal rRNA (rRNA; 28S, 5.8S, and 5S) and 47 different ribosomal proteins (RPs) whereas the smaller subunit (40S)is composed of a single species of rRNA (18S) and 32 different RPs [1,2] (Figure 1).Although the numbers of rRNA species and RPs vary between eukaryotes and prokaryotes, the ribosomal components have been significantly conserved throughout the evolution[3,4]. Ribosome biogenesis is a major metabolic activity in cells and it requires a substantial amount of cellular energy[5]. The rate of ribosome production is directly linked to growth and proliferation, two closely connected events in a cell. During favorable stimuli, cells induce ribosome production because growing cells require more proteins whereas in stress situations, cells downregulate ribosome production to reduce protein synthesis. Thus, the ribosome activity is well balanced in normal cells and loss of this balance may lead to deregulated cell growth as seen in cancer. Indeed, star oncoprotein and tumor suppressor genes namely *c-Myc* and *p53*, which are frequently mutated in cancers, are known regulators of ribosome biogenesis[6].

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The process of ribosome synthesis

The synthesis of the ribosome is a tightly regulated sequential chain of events that begins in the nucleolus and

ends in the cytoplasm[7]. During this process, many co-factors or accessory proteins(remodeling factors, transcription factors, processing factors, export factors and assembly factors) and small noncoding RNAs (snoRNAs)attach with and dissociate from the preassembled particles at various steps, to finally form the mature rRNA-RP complex. The process is very similar to an "assembly line" of a car where different parts are brought together in a sequential manner to make the final product[8]. Although ribosome biogenesis continues throughout the cell, the majority occurs within the nucleolus, the most conspicuous organelle inside the nucleus. The nucleolus is a transient structurethat assembles around the ribosomal DNA (rDNA) repeats during telophase and disassembles during mitosis phase of cell cycle[9]. A mammalian nucleolus has three morphologically distinct sub-compartments: the fibrillar centre (FC), the dense fibrillar centre (DFC), and the granular component (GC).[9] The first step in ribosome biogenesis is the transcription of rDNA repeats into a single pre-rRNA precursor (47S) by RNA polymerase (Pol) I in the FCs.This pre-RNA precursor is then cleaved and modified by several accessory proteins and snoRNAs within the DFCs to form three species of rRNA (18S, 5.8S, and 28S). Pol III transcribes the fourth species, the 5S rRNA and Pol II transcribes the protein components of the ribosome, the RPs, separately in the nucleoplasm. The 5S rRNA and the RPs are imported within the nucleolus, and assembled with other rRNAspecies in the GCs to form the small (40S) and the large (60S) subunits. These pre-assembled particles are then exported to the cytoplasm, where additional maturation occurs to finally yield the mature (80S) ribosome [9,10] (Figure 2).

Human pathologies associated with defects in ribosome synthesis

In the last two decades, there has been a paradigm shift in our understanding of the ribosomes. In the past, the accepted notion was that the ribosomes are absolutely essential for cells and hence any mistakes in ribosome biogenesis would directly affectembryonic viability. However, several path-breaking findings have changed this perception and it has now become clear that production of faulty ribosomes does not necessarily lead to lethal effects in humans. Instead, it manifests as rare genetic diseases, mostly inherited.These diseases collectively referred to as "Ribosomopathies", result from mutations in genes encoding either ribosomal proteins or ribosome biogenesis associated factors[11]. The majority of these diseases exhibit tissue-specific phenotypes, most often involving the hematopoietic components of the bone marrow. Interestingly, they are also associated with an increased risk of developing cancer. Other associated pleiotropic anomalies include growth retardation, craniofacial abnormalities, and physical deformities. The literature cites a large number of diseases under this category and describing all of them is not within the purview of this article. Moreover, the role of ribosome or ribosomal components in the clinical manifestation is not clear for many of these diseases. The review by Freed et al (2010)[12] describes the ribosomal diseases in a comprehensive manner. Here we have focused on the most important ones, particularly those in which the ribosomal components have been clearly demonstrated as the causative agents (Table 1) and where the molecular mechanisms underlying the disease pathogenesis have been explored through functional studies in yeast, mice and zebrafish models.

Diamond Blackfan Anemia (DBA, OMIM # 105650)

DBA is a rare congenital disease characterized by red cell aplasia that presents with severe anaemia in early infancy, usually within the first six months of age. Approximately 50% of the patients exhibit physical anomalies such as craniofacial deformities and thumb abnormalities, including the classical triphalangeal thumb and cleft lip and/or palate. The disease is also associated with an increased risk of cancer, such as acute myeloid leukemia, osteogenic sarcoma, and other solid organ cancers. The classical presentation of DBA includes a usually macrocytic, or occasionally normocytic, anemia with reticulocytopenia, near normal or variable neutrophil and platelet counts and a normocellular bone marrow (BM) with a paucity of erythroid precursors, in a child less than one year[13]. These clinical diagnostic criteria are usually supported by

mutation analysis of "known DBA genes". DBA is caused by mutations in either small or large subunit-associated RP genes, which are the structural components of ribosome. Mutationsin a single allele are sufficient for the disease to precipitate, indicating haploinsufficiency of the encoded ribosomal proteins. At present, mutations have been identified in 16 RP genes with *RPS19* being the most frequently mutated gene in DBA patients (in 25% of the patients) [7]. However, while known RP mutations now account for approximately half of DBA cases, the genes mutated in the other half of DBA patients remain unknown. The pathophysiology of DBA has been studied quite extensively in a variety of animal models and several interesting hypotheses have been proposed[6]. A p53-dependent apoptotic pathway, presumably resulting in erythroid cell death, appears to be the most commonly accepted pathophysiology mechanism[6]. However, it is still uncertain why p53 would target only the erythroid cells, while allowing other cells to grow. The current mainstays of treatment include red cell transfusions and iron chelation, corticosteroids, and hematopoietic stem cell transplantation (HSCT)[14].

Shwachman Diamond Syndrome (SDS, OMIM # 260400)

SDS is a rare autosomal recessive disease characterized by bone marrow dysfunction (variable cellularity), exocrine pancreatic insufficiency and an increased risk for myelodysplasia and acute myelogenous leukemia (AML). Neutropenia is a hallmark of the bone marrow failure in SDS. However, reticulocytopenia and thrombocytopenia are also frequently observed in the patients. Other clinical features include skeletal abnormalties, cardiac malfunction, immunological deficiencies, and hepatomegaly with elevated levels of liver enzymes[15]. Approximately 90% of the patients have biallellic mutations in the Shwachman-Bodian-Diamond Sydrome (*SBDS*) gene[16]. Homozygous deletion of *SBDS* in mice results in embryonic lethality, indicating that it is an essential gene[17]. Although studies in yeast and mammalian models have shown that *SBDS* is essential for ribosome biogenesis[18,19], the exact role of this gene was understood only recently from the work of Finch et al[20] who have shown that *SBDS* is required for promoting the release of eukaryotic initiation factor 6 (eIF6) from the 60S subunit. eIF6 keeps the 60S subunit in a functionally inactive state and must be removed before the large subunit (60S) can join the small subunit to initiate translation. However, despite these elegant findings, it still remains unclear how ribosomal malfunction specifically affects the pancreas and the bone marrow in patients with SDS. Therapeutic strategies include transfusions, oral pancreatic enzyme supplementation, antibiotics and granulocyte colony stimulating factor. However, the only definitive therapy is HSCT[15].

X-linked Dyskeratosis Congenita (X-DC, OMIM # 305000)

X-DC is a recessive condition associated with the simultaneous presence of abnormal skin pigmentation, nail dystrophy, and mucosal leukoplakia (main mucocutaneous triad). More than 80% of the patients have pancytopenia due to BM failure. Additional clinical features includepulmonary fibrosis, and very high risk of cancer, particularly AML[21]. The X-DC patients harbor mutations in the *DKC1* gene, which encodes Dyskerin, a nucleolar protein[22]. Dyskerin associates with box H/ACA snoRNPs to catalyze post-transcriptional modification (pseudouridylation) of rRNAs[23]. Dyskerin is also a member of the telomerase complex that is responsible for maintaining telomere length[24].X-DC patients usually have shortened telomeres and assessment of telomere length is often necessary to confirm the clinical diagnosis of X-DC[22]. However, X-DC patients with normal telomere length have also been identified[25]. Thus, at present X-DC is considered a disease of defective rRNA processing and defective telomere disorder. X-DC patients display impaired translation of *p53* mRNA resulting in reduced p53 expression, thus providing a basis for their increased susceptibility to cancer[26]. Since majority of the patients exhibit severe BM failure, BM transplant is the most definitive treatment strategy available. Recently, the use of induced pluoripotent stem (iPS) cellhas shown promise as an alternative therapeutic strategy[27].

5qDeletion Syndrome (5q$^-$, OMIM # 153550)

5q$^-$ syndrome is an acquired myelodysplastic (MDS) disorder characterized by macrocytic anemia, normal or elevated platelet count, and erythroid hypoplasia and hypolobulated megakaryocytes in the bone marrow[28]. The

patients usually have a deletion in the long arm of the chromosome 5, which results in the loss of 40 genes[29]. The erythroid phenotype in the patients, which closely resembles DBA, is caused by mutation in *RPS14* gene that is located in the common deleted region and a member of the small subunit of the ribosome[30]. Interestingly, the other hematological phenotypes such as elevated platelet counts and defective megakaryocytes are caused by the loss of two microRNAs, namely miR-145 and miR-146a[31], which are also transcribed from the same deleted region of chromosome 5. The standard treatment strategies include use of immunomodulatory drugs such as lenalidomide. As for any MDS disorders, 5 q^- patients also have a risk of AML. However, those who respond well to lenalidomide have a low risk of AML whereas in the non-responders, the risk is substantially higher.

Treacher Collins Syndrome 1 (TCS, OMIM # 154500)

TCS is an autosomal dominant condition characterized by craniofacial disorders affecting face, ears, eyes and mouth. The clinical features include antimongoloid slant of the eyes, coloboma of the lid, micrognathia, microtia, hypoplastic zygomatic arches, and macrostomia[32]. TCS is caused by heterozygous mutations in *TCOF1,* which encodes Treacle, a nucleolar protein involved in transcription of rDNA and methylation of 18SrRNA[33,34]. TCS patients are not predisposed to any form of tumors. Treatment planning generally involves a comprehensive staged reconstructive approach[35].

Isolated Congenital Asplenia (ICA, OMIM # 271400)

ICA is an autosomal dominant condition characterized by the absence of spleen at birth without any other developmental defects[36]. It is a life-threatening condition due to recurrent severe and invasive microbial infections, particularly by *Streptococcus pneumoniae.* The disease is caused by mutations in the *RPSA* gene, which encodes ribosomal protein SA, a component of the small subunit of ribosome[37]. The treatment strategies include antibiotic prophylaxis (transient or lifelong), immunization at the recommended age, especially against encapsulated bacteria, efficient management of suspected infection, and most importantly, parent education explaining the risks involved.

North American Indian Childhood Cirrhosis (NAIC, OMIM # 604901)

NAIC is an autosomal recessive intrahepatic cholestasis first described in Ojibway-Cree children from northwestern Quebec. It typically presents with neonatal jaundice in an otherwise healthy child and progresses to biliary cirrhosis. The disease is caused by a homozygous mutation (a missense mutation; R565W) in the hUT4/Cirhin, which is encoded by *CIRH1A*[38]. hUTP4/Cirhin along with UTP15 and WDR43are the core components of t-UTP subcomplex. t-UTPis a member of the small subunit (SSU) processome, which is involved in the processing of 18SrRNA in human[39]. Liver transplantation is the only definitive therapy for this disease[40].

Conclusion and Future Perspectives

The discovery of ribosomopathies and the tissue-specific manifestation of these diseases has made it very clear that the outcome of ribosomal defects is not uniform, but variable in different tissues. Several hypotheses have been proposed to explain this tissue specificity, however, the exact mechanisms are yet to be defined[41]. Although highly speculative, recent evidence seem to suggest that cells might possess "specialized ribosomes", ribosomes that are heterogeneous in their composition and vary in different cell types[42]. For example, loss of *Rpl38* in mice does not affect global translation, but specifically alters translation of a subset of mRNAs that encode homeobox genes[43]. Thus, it is conceivable that cells have "ribosome code" where the individual components of the ribosomes influence translation of specific mRNAs in a tissue-specific manner. A challenge for future will be to prove this hypothesis and to identify these mRNAs. In addition, functional studies in integrated model systems will be crucial in designing effective diagnostic and treatment strategies for human ribosomopathies.

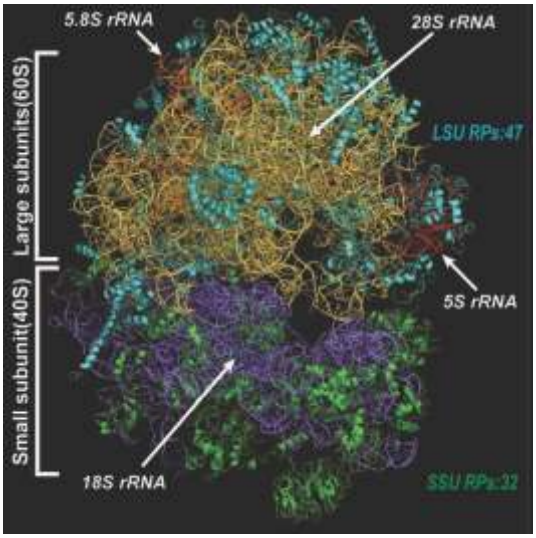

Fig. 1 : Crystal structure of the eukaryotic ribosome (80S) [PDBID: 4V7R (Ben-Shem et al, 2010, *Science* 330: 1203-1209]. The figure was generated using PyMOL software (The PyMOL Molecular Graphics System, Version 1.1r2pre, DeLano Scientific LLC.).

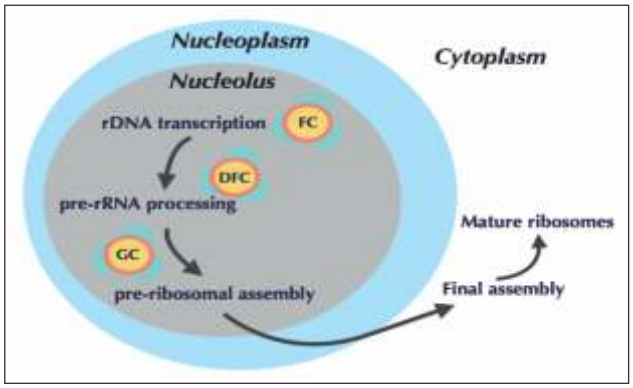

Fig. 2 : A simplifiedschematic representation of the process of ribosome biogenesis. See text for details. FC: Fibrillar Centre, DFC: Dense Fibrillar Centre, GC: Granular Component.

Table 1 : Major Ribosomopathies in Human

Disease	Mutated Gene	Tissue-specific phenotype	Ribosomal effects
Diamond-Blackfan anemia (DBA)	*RPS19* and fifteen other RP genes	Red cell aplasia	Impaired 40S and 60S biogenesis
Shwachman Diamond Syndrome (SDS)	*SBDS*	Neutropenia, Exocrine pancreatic insufficiency	Impaired maturation of 60S subunit
X linked dyskeratosis congenita (X-DC)	*DKC1*	Mucocutaneous triad (abnormal skin pigmentation, nail dystrophy, and mucosal leukoplakia)	Impaired posttranscriptional modification of rRNA
5qdeletion syndrome (5q$^-$)	*RPS14,* miR-145, miR-146a	Macrocytic anemia, Normal or high platelet count, Hypolobulated megakaryocytes	Defective 18SrRNA processing, 40S subunit deficiency
Treacher Collins syndrome 1 (TCS)	*TCOF1*	Craniofacial anomalies	Impaired rRNA transcription
Isolated Congenital Asplenia (ICA)	*RPSA*	Absence of spleen	Impaired 40S biogenesis
North American Indian Childhood Cirrhosis (NAIC)	*CIRH1A*	Biliary cirrhosis	Defective 18SrRNA processing

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