HHS Public Access

Author manuscript

Med Res Rev. Author manuscript; available in PMC 2016 March 01.

Published in final edited form as:

Med Res Rev. 2015 March ; 35(2): 225–285. doi:10.1002/med.21327.

Ribosomal Proteins and Human Diseases: Pathogenesis, Molecular Mechanisms, and Therapeutic Implications

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Abstract

Ribosomes are essential components of the protein synthesis machinery. The process of ribosome biogenesis is well organized and tightly regulated. Recent studies have shown that ribosomal proteins (RPs) have extraribosomal functions that are involved in cell proliferation, differentiation, apoptosis, DNA repair, and other cellular processes. The dysfunction of RPs has been linked to the development and progression of hematological, metabolic, and cardiovascular diseases and cancer. Perturbation of ribosome biogenesis results in ribosomal stress, which triggers activation of the p53 signaling pathway through RPs-MDM2 interactions, resulting in p53-dependent cell cycle arrest and apoptosis. RPs also regulate cellular functions through p53-independent mechanisms. We herein review the recent advances in several forefronts of RP research, including the understanding of their biological features and roles in regulating cellular functions, maintaining cell homeostasis, and their involvement in the pathogenesis of human diseases. We also highlight the translational potential of this research for the identification of molecular biomarkers, and in the discovery and development of novel treatments for human diseases.

Keywords

ribosomal protein; RP-MDM2-p53 pathway; ribosomopathy; cancer; drug discovery

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1. INTRODUCTION

There is increasing evidence indicating that the ribosome (comprising RNA and proteins) plays a critical role in normal cellular physiology, the cellular responses to internal and external environmental stimuli, and the pathogenesis of human diseases. The synthesis of the ribosome, called ribosome biogenesis, is a highly ordered cellular process that requires a substantial expenditure of energy, therefore, it occurs primarily under nutrient-rich and growth-friendly circumstances.[1] Under stress situations, the reverse phenomenon is seen, with decreased ribosome activity, reduced protein synthesis and subsequent growth arrest. Thus, ribosome biogenesis is a critical element involved in controlling cell growth and proliferation; any dysregulation of this process may result in aberrant cell proliferation and clinical manifestations of pathological states, such as cancer and metabolic disorders.[2]

Unraveling the mechanisms responsible for maintaining the integrity of ribosome biogenesis is critical for understanding these cellular functions, and the link between dysfunctions and the pathogenesis of diseases. In addition to being the “workshop” for ribosome biogenesis, the nucleolus is also a central hub for stress sensors.[3] Disruption of ribosome biogenesis leads to nucleolar stress (also termed ribosomal stress),[2] which activates the p53 signaling pathway, leading to cell cycle arrest and apoptosis.[4] Additionally, ribosomal proteins (RPs) have critical roles in diverse cellular functions that are distinct from their primary role in ribosome biogenesis.[5,6] These extraribosomal functions of RPs include cell growth and proliferation,[7–9] apoptosis,[10,11] DNA repair,[12,13] cellular development[14,15] and differentiation.[16,17] Interestingly, a subset of RPs also acts as “watchguards” to detect the defects in ribosome biogenesis.[18–22]

Several human diseases have been demonstrated to be associated with defects in ribosome biogenesis, including increased cancer susceptibility.[2,23] Perturbation in the extraribosomal functions of RPs is known to be involved in carcinogenesis, and aberrant ribosomal function is either a consequence or an associated feature of cancer. Diamond-Blackfan anemia (DBA)[24] and 5q- syndrome[25] are two clinical syndromes associated with impairments in erythropoiesis that are attributed to ribosomal gene mutations. Although previous studies demonstrated that the induction of p53 following ribosomal stress promotes extensive apoptosis in certain progenitor cell types, leading to ribosomopathies, the reason why the patients with these diseases exhibit a high incidence of malignancies remains elusive. Recent evidence suggests that the links connecting defects in ribosome biogenesis and p53 signaling pathway are very complex, and multiple factors and regulatory mechanisms are involved in this network.[26,27] Additionally, it is still not well understood why the effects of ribosome dysfunction are not observed universally, but are confined to specific organ systems and cell types, such as the hematological system (erythrocytes), neurons, or skin cells.[28]

There is an increasing interest in further elucidating the roles of RPs in both normal physiological processes and in the pathogenesis of human diseases. Recently, several excellent reviews have been published, and interested readers are referred to those publications.[3,6,18,19,28–35] In this review, we focus on the recent progress toward understanding the newly appreciated, yet still under-explored ribosomal stress pathways, with an emphasis on the extraribosomal functions of RPs and their underlying mechanisms

of action. We will also highlight the roles of RPs in ribosomal anomalies and the potential of using RPs as biomarkers and molecular targets in the diagnosis and treatment of human diseases. We believe that a better understanding of the relationships between RP dysfunction and human diseases would provide new avenues for the early diagnosis of chronic diseases, such as cancer and cardiovascular diseases, and would provide novel drug targets and biomarkers for these diseases.

2. RIBOSOMAL PROTEINS AND RIBOSOME BIOGENESIS

A. Ribosome Biogenesis

The ribosome structure is complex, and considering the universal role it plays in catalyzing protein synthesis, it can be compared to a “molecular machine” composed of several distinct elements functioning as a single entity.[35] Protein synthesis is a highly accurate but rapid process, and hence, ribosome biogenesis needs to be highly coordinated.

In recent years, advances in imaging technologies have unraveled the structural details of the eukaryotic ribosome and revealed more details of its interactions with messenger RNA (mRNA) and transfer RNA (tRNA).[35] The full assignment of RPs in yeast and fungal 80S ribosomes have also become possible with the improved resolution.[36,37] These observations led to the conclusion that the ribosome is a collection of enzymes (the ribozyme), in which ribosomal RNAs (rRNAs) function as the catalytic elements, with the RPs serving as structural ‘scaffolding’ units that organize the RNAs into appropriate configurations.[35] Although the elements of the ribosome that are essential for protein synthesis have been universally conserved throughout evolution, the eukaryotic ribosomes differ from their prokaryotic counterparts in many respects, particularly regarding the presence of rRNA expansion segments and eukaryote-specific RPs, which are located on the surface of the ribosome, enveloping the evolutionarily-conserved core.[34]

Across all evolutionary levels, ribosomes form the crux of the translational apparatus, regulating the main step in the expression of genes. Ribosomes decode genetic information, as well as form the peptide bonds during translation. The small subunit performs the former function and the large subunit catalyzes the formation of the peptide bonds.[1,35] Ribosome biogenesis is a dynamic, energy-demanding, and strictly coordinated multistep process that involves the synthesis, processing, and modification of pre-rRNAs, assembly with RPs and interaction with several non-ribosomal factors, which associate with the evolving pre-ribosomal particles. In eukaryotes, ribosomes are preassembled in the nucleolus before being transferred to the cytoplasm. The process of ribosome synthesis includes the formation of pre-ribosomal particles in the nucleolus and assembly of two subunits in the cytoplasm. The full ribosome includes one large (60 S) and one small (40 S) subunit (Fig. 1).

Ribosome biogenesis begins in the nucleolus, where RNA polymerase I (Pol I) first transcribes the rRNA genes into a single polycistronic transcript, which is cleaved to form 18S, 5.8S, and 28S rRNA. In yeast, Pol I transcription commences by recruiting a Pol I initiation complex at the rDNA promoter using two basal transcription factor complexes, UAF (upstream activating factor) and CF (core factor). As the transcript develops, many small nucleolar ribonucleoparticles (snoRNPs) facilitate the co-transcriptional covalent

modification of numerous rRNA residues.[35,38] These site-specific modifications include pseudouridylation (ψ) and methylation (M), and play an important role in ribosome function. For example, the loss of rRNA pseudouridylation decreases the translational fidelity. These RNA transcripts form ball-like structures on the 5' end of the nascent transcripts and comprise the pre-ribosomes, corresponding to the 90S or small subunit (SSU) 'processome' complexes. Subsequently, the 90S–SSU processome is cleaved to form pre-40S and pre-60S particles. Meanwhile, in the nucleoplasm, RNA polymerase II (Pol II) and RNA polymerase III (Pol III) transcribe the RPs and 5S rRNA genes, respectively.[39] These transcripts are then transported to the cytoplasm for translation. Upon translation, the RPs and 5S RNA are imported back into the nucleolus, where they form the pre-40S and pre-60S ribosomal subunits, along with the rRNA.[40] These two subunits are then exported into the cytoplasm, where substantial structural rearrangements occur to convert the inactive pre-40S and pre-60S into functional 40S and 60S subunits (Fig. 1). Once the pre-60S has been exported into the cytoplasm, the residual large subunit ribosomal proteins associate with the non-ribosomal transacting factors, which are then recycled back to the nucleus. The process of cytoplasmic 60S ribosome maturation is essentially mediated by GTPases, such as Lsg1, and ATPases, such as Drg1.[41]

Functional studies of some mammalian ribosomal proteins, mostly those associated with disease states, have revealed that they are involved at various stages of pre-rRNA processing.[42–45] Ribosomal proteins have been shown to be involved in the stabilization of both small and large subunit structures, rRNA processing and pre-ribosome transport, RNA folding, and/or interactions with other factors required for either ribosome synthesis or translation.[46] In an elegant study by Donohue et al., the authors demonstrated that the ribosomal protein small subunit (RPS) proteins are essential for the production of the 40S ribosomal subunit, with some strictly required for initiation steps in pre-ribosome synthesis. Other RPS proteins are essentially involved in the progression of the nuclear and cytoplasmic maturation of the pre-ribosome and for nuclear export.[46]

Ribosomal proteins have also been speculated to stabilize secondary structures in the rRNA, to promote the formation of tertiary structures, and prevent misfolding. Ribosomal proteins also play an important role in the final large subunit structure and function. For example, L24 is essential for the proper functioning of the ribosome exit tunnel, the point of polypeptide emergence during translation, while the formation of the 60S stalk requires the incorporation of the ribosomal protein, P0.[34] On the other hand, 40S cytoplasmic maturation also involves the stabilization of S3 and the endonuclease, Nob1, which mediates one of the final steps in the maturation of the small subunit i.e. the final cleavage of 20S pre-rRNA to 18S rRNA.[47] In total, the two mature subunits contain four different types of rRNA, 80 different RPs and three different RNA polymerases (Pol I, Pol II, and Pol III) along with several accessory factors, all of which are apparently required for the synthesis, modification, and final assembly into the mature 80S ribosome.[39]

B. Ribosomal Protein Expression and Regulation

As discussed, ribosomal proteins form the basic building blocks in the ribosome assembly, playing seminal roles in the assembly and structure of ribosomes or in the initiation,

elongation, or termination phases of protein translation. RPs are typically small (50–150 amino acid residues) and basic proteins with high isoelectric points (pI); their positive residues facilitate the interaction with the negatively charged phosphate groups of rRNAs or with mRNAs and tRNAs during translation.[35,48] Human RPs have an average molecular weight of 18,877 Da, contain 167 amino acids and have a pI of 10.63.

Although these proteins function together, their amino acid sequences are dissimilar. Even the basic residues within the RPs are not equally distributed; instead, they occur in scattered clusters of three to four basic residues. In some RPs (e.g., S8, S9, L5, L22, L31, and the P proteins), the C-terminus contains a cluster of acidic amino acids. Although most of the RPs are basic, four RPs (the three P proteins and Sa) have acidic pI values.[49] Of note, the RPs are remarkably well conserved in both structure and function, and have been throughout evolution.[35]

An analysis of the spatial structures of ribosomes indicates that ribosomal proteins usually contain one or several globular domains. Based on the structural packing, these proteins can be classified as α-proteins, β-barrel-containing proteins, α/β-proteins, and α+β-proteins. Most ribosomal proteins contain α-helices, β-strands that are packed into β-barrels (e.g.S12, S17, L2, L3, L14, and L24,), or α/β sandwiches (e.g. S3, S5, S6, L5, L6, L23, and L30). In addition to this compact domain, several ribosomal proteins possess elongated loops or N and C-terminal “tails” (e.g. S5, S7, S9-S14, S17, L2-L5, L15, L22, and L24), which impart substantial intramolecular mobility.[49]

Ribosomal proteins interact with several domains of rRNAs, acting as inter-domain clips, and help to maintain the structural integrity of the ribosomal assembly. The aforementioned elongated loops or N and C-terminal tails facilitate interactions with one or more domains of ribosomal RNA, forming inter-domain connections, as well as subunit bridges. For example, the intersubunit bridges produced by proteins S13 and L5 located on the ribosome periphery are postulated to play an important role in large-scale conformational rearrangements, e.g. in the translocation of tRNA. RPs like L24 are involved in the formation of the exit tunnel of the 60S subparticle, in addition to movement within the ribosome, thus providing translation accuracy.[50] Ribosomal proteins also affect the elongation of the nascent peptide by binding to the EF-GTPase factors.

Many RPs undergo post-translational modifications. A common feature of all RP mRNAs is the 5’ terminal oligopyrimidine tract (TOP), which is made up of a cytidine (C) residue at the beginning, followed by an uninterrupted stretch of up to 5–15 pyrimidines.[51] The external signals and stresses rapidly and reversibly modulate the translation of TOP mRNAs. The putative transacting factors for RP translational regulation remain elusive. For instance, it has been well documented that the La protein physically binds to TOP mRNAs, but the effects of La on their translation remain to be elucidated.[52–54] It is known that the La protein is ubiquitously expressed in eukaryotic cells and associates with the 3' termini of several newly synthesized small RNAs, ultimately protecting these ends from exonucleases.[55] In addition, epigenetic factors such as microRNA miR-10a has been shown to promote RP mRNAs translation by binding to the 5’ untranslated regions (UTRs).[56]

Post-translational modifications, such as phosphorylation, which is mediated by kinases such as phosphoinositide-3-kinase (PI3K), are involved in the regulation of TOP mRNA translation, particularly after mitogenic stimulation.[57] The ribosomal protein S6, a well-established downstream target of the PI3K pathway, is phosphorylated at its C-terminus by two kinases (S6K1 and S6K2) subsequent to mitogenic stimulation. A clear correlation has been noted between the translational activation of TOP mRNAs and the hyperphosphorylation of S6, leading to the hypothesis that S6 phosphorylation is essential for recruiting TOP mRNAs to the polysomes. However, a lack of phosphorylation sites in S6 does not affect the translational control of the TOP mRNA,[58] indicating that alternative signaling pathways are involved in the translational regulation of TOP mRNAs. The acidic RPs; P0, P1, and P2, which are involved in the formation of the ribosome stalk, also undergo phosphorylation.[59] These post-translational modifications may be influenced by environmental factors or may be basal in nature; they may confer extraribosomal functions to these proteins.

Apart from phosphorylation, the RP production in the cell (ultimately controlling the cellular ribosome synthesis) is regulated *via* the proteasomal degradation of nucleolar RPs. Although the proteasome plays a prominent role in maintaining the turnover of RPs,[60] in some cases, the ubiquitination of the amino acid residues of RPs can actually enhance the translational proficiency of the ribosomes.[61] For example, S27a, S30, and L40 are generated as ubiquitin fusion proteins,[32] but the actual function of the ubiquitin moiety remains unknown.[32] An interesting phenomenon occurs in *S. cerevisae*, where a selective type of autophagy, known as ribophagy, which regulates the amount of ribosomes and acts as a quality control mechanism to induce the elimination of defective or wrongly assembled ribosomes, occurs under conditions of nutrient deprivation.[62]

C. Differences of Free and Structural Ribosomal Proteins

In eukaryotic cells, ribosomes are found either freely scattered in the cell cytoplasm or closely attached to endoplasmic reticulum (ER) membrane.[63] Free and membrane-bound ribosomes are structurally and functionally identical. They differ only in their spatial distribution. Protein synthesis is usually compartmentalized with soluble proteins synthesized on free ribosomes and membrane (or secretory) proteins being synthesized on bound ribosomes.[64,65] Interestingly, the proportion of the two forms of the ribosome is dependent on the physiological state and role played by the different types of tissues. Individual ribosomal subunits transform randomly between the two states (free and membrane-bound) depending upon the abundance of the particular type of mRNA molecules (those possessing ER signal sequences and those without them).[66] If the protein being synthesized contains an ER signal sequence, the ribosome is directed to the ER membrane. Since several ribosomes are capable of binding to a solitary mRNA molecule, a polyribosome (also known as polysomes) is formed. The polyribosome attaches to the ER membrane following recognition of the nascent peptide chain by the signal recognition particle (SRP). As translation near the 3′ end of the mRNA molecule is completed, individual ribosomes are redirected to the cytosol.[66,67] On the other hand, if the protein being encoded by the mRNA sequence lacks an ER signal sequence, the polyribosome is suspended freely in the cytosol and the protein product is formed in the cytosol itself.[66,67]

Both free and membrane-bound ribosomes comprise an interchangeable population and the cell can adjust their numbers on the basis of metabolic needs.

3. EXTRARIBOSOMAL FUNCTIONS OF RIBOSOMAL PROTEINS

In addition to participating in the assembly of the basal translational machinery, RPs perform additional functions in the cell, called extraribosomal functions, including regulation of the cell growth and proliferation, differentiation, apoptosis, and DNA repair.[7–17] As suggested by Warner and McIntosh,[6] the extraribosomal capacity of a RP can be determined based on the following criteria: 1) specific interaction(s) with some non-ribosomal component of the cell, presumably RNA or protein; 2) the interaction having an effect on cellular function; and 3) the process occurring away from the ribosome. There have been numerous reports on the extraribosomal functions of individual RPs (Table I).

A. Regulation of Gene Expression

It has been reported that RPs directly control gene transcription and functionally modulate transcriptional regulators, independent of their ribosomal function.[5,6] For example, the translationally important K homology (KH)-domain containing S3, which is a component of the 40S ribosome subunit, also functions as a non-Rel subunit of the nuclear factor kappa B (NFκB) p65 homodimer to enhance DNA binding.[73] Indeed, S3 knockdown reduces the ability of NFκB to induce selected target gene transcription.[73] In addition, L7 has been identified as a co-regulator (repressor) of vitamin D receptor (VDR)-retinoid X receptor (RXR)-mediated transactivation *via* its interaction with the VDR.[153] Similarly, L11 interacts with PPARα (peroxisome proliferator-activated receptor-α), inhibiting its ligand-dependent transcriptional activity through decreased binding to the PPAR-response element (PPRE).[154]

In addition to the control of specific gene transcription, RPs regulate the translation of individual proteins by a feedback mechanism. For example, S3 translation is repressed by the interaction of its C-terminal domain with its own mRNA, independent of the KH domain.[155] Similarly, in response to interferon-γ, L13a is phosphorylated, released from the 60S subunit, and then specifically binds to the 3'-UTR GAIT (interferon-gamma-activated inhibitor of translation) element of ceruloplasmin (Cp) mRNA, and subsequently silences translation.[131] L13a regulates the translation of specific mRNAs as part of a non-ribosomal complex, suggesting that, in addition to serving as an important part of the protein synthesis machinery, the ribosome is also a depot for proteins that modulate translation. In addition, L26 binds to the p53 mRNA 5'UTR and upregulates p53 translation after DNA damage.[140]

B. Cell Cycle Control

In addition to regulating gene expression,[156] RPs affect cell cycle progression *via* various mechanisms.[157–159] When expressed constitutively in Jurkat T-lymphoma cells, L7 leads to G1 arrest *via* the modulation of cell cycle progression-related proteins.[157] In contrast, the overexpression of L15 promotes cell proliferation, while the downregulation of L15 inhibits the tumorigenicity of gastric cancer cells in nude mice.[158] RPs are also required for normal cell proliferation. For example, concomitant overexpression of the nucleolar protein, nucleophosmin (NPM), facilitates the nucleolar storage of S9, facilitating ribosome

biogenesis and cell proliferation.[7] However, the depletion of S9 results in reduced protein synthesis and induces G1 cell cycle arrest, along with activation of p53 target genes.[7] S3 is localized to the mitotic spindle and regulates the spindle dynamics by acting as a microtubule-associated protein (MAP) during mitosis.[159] The depletion of S3 results in metaphase arrest, spindle abnormalities and defective chromosome movement.[159]

C. Regulation of Programed Cell Death

RPs have also been shown to be important in regulating apoptosis.[6] S29 augments the apoptotic effects of anticancer drugs by reducing the expression of anti-apoptotic proteins and increasing the levels of pro-apoptotic proteins.[113] In contrast, cancer cells overexpressing L35a exhibit reduced cell apoptosis and are more resistant to apoptosis-inducing agents than control cells, suggesting that it has a role in the response to cytotoxic damage.[147] S3 induces apoptosis in response to extracellular stresses by activating JNK (c-Jun N-terminal kinases) in a caspase-dependent manner.[77] This physical interaction between S3 and TRADD (tumor necrosis factor receptor (TNFR)-associated death domain) is responsible for inducing apoptosis.[77] Additionally, the Akt-dependent phosphorylation of S3 inhibits its pro-apoptotic function.[70] Knockdown of S3 increases the viability of HEK293 cells exposed to DNA-damaging agents, indicating that S3 is involved in DNA damage-induced cell death.[71]

D. Modulation of DNA Repair

There is also evidence that RPs are also involved in DNA repair.[5,6] For example, S3 exhibits high binding affinity for the oxidative damage-induced 7, 8-dihydro-8-oxoguanine (8-oxoG) residues in DNA;[72] it interacts with OGG1, the human base excision repair (BER) enzyme, and increases its catalytic activity towards DNA oligonucleotides containing embedded 8-oxoG residues.[12] Exposure to DNA damaging agents leads to an extracellular-signal-regulated kinases (ERK)-dependent translocation of S3 to the nucleus, where it co-localizes with 8-oxoG DNA lesions.[160] In addition, S3 binds to p53 and protects it from MDM2 (murine double minute 2)-mediated degradation,[74] suggesting that S3 may be involved in maintaining the genomic integrity through both direct and indirect mechanisms.

E. Regulation of Development and Differentiation

RPs play a seminal role in embryonic development.[5,6] S7-deficient zebrafish embryos show development defects, including impaired hematopoiesis and abnormalities in the brain.[161,162] Homozygous disruption of S19 causes embryonic lethality in mice, while mice deficient in one S19 allele show a normal growth rate and weight.[105] L22 deficiency selectively stops the development of αβ-lineage T cells at the β-selection checkpoint by inducing their death, which is led by p53 induction and activation.[163,164] Downregulation of the RP levels during retinoic acid-induced neuronal differentiation has also been shown.[165] L29 deficiency delays osteogenesis and leads to adult bone fragility in mice.[143] In addition, knockdown of L29 induces cellular differentiation.[166] The depletion of S9 in glioma cells impairs 18S ribosomal RNA production, activates p53, and induces morphological differentiation in a p53-dependent manner.[90] The transcriptional inactivation of S5 leads to the erythroid differentiation of murine erythroleukemia (MEL) cells, and S5 overexpression in MEL cells delays the onset of differentiation.[82]

F. Modulation of Cell Migration and Invasion

The differential expression of RPs in several types of metastatic cancer cells has been identified by proteomic studies using two-dimensional liquid chromatography and mass spectrometry (2D-LC/MS-MS).[167] For example, overexpression of S27 (also known as metallopanstimulin-1, MPS-1) in gastric cancer tissues is correlated with metastasis. Altered S27 expression was also demonstrated to regulate gastric cancer cell migration and invasion both *in vitro* and *in vivo*.[111] Integrin β4 (ITGB4) has been identified as a downstream target of S27 that mediates its effects on cell metastasis.[111] L23 also plays a role in cell motility and metastasis, as demonstrated by the fact that the overexpression of L23 alters lung cancer cell morphology and enhances its invasiveness.[168] The level of phosphorylated S6 is elevated in metastatic lung adenocarcinoma, which is associated with a shorter metastasis-free survival,[169] indicating a role for S6 phosphorylation in cancer metastasis.

G. Regulation of Cell Transformation

Several RPs have been shown to be involved in the malignant transformation of cells.[5,6] The monoallelic loss of L22 predisposes T lineage progenitors to transformation and accelerated the development of thymic lymphoma in a mouse model of T cell malignancy.[136] Indeed, L22 is found to be inactivated in ~10% of human acute T cell lymphoblastic leukemia.[152] In addition, S3a overexpression induces cell transformation, as assessed by the formation of cancer foci and anchorage-independent growth *in vitro*, and the formation of tumors in nude mice.[78] P1 induces an increase in the expression of E2F1 and upregulation of cyclin E. Co-transfection of P1 with mutant rasVal12 contributed to *in vitro* cell transformation in NIH3T3 cells.[152]

H. Regulation of Angiogenesis

Angiogenesis is crucial for cancer development and progression. The loss of L29 expression markedly reduced the vascular endothelial growth factor (VEGF)-stimulated microvessel formation.[124] The tumor blood vessel density in subcutaneously grown Lewis lung carcinomas was significantly reduced in L29-mutant mice, suggesting that L29 can regulate angiogenesis.[142]

4. RIBOSOMAL PROTEINS AND NUCLEOLAR STRESS

The nucleolus is one of the functional nuclear compartments, and is where ribosome biogenesis occurs. As discussed earlier, in response to cellular stress, the synthesis of ribosomal RNA is rapidly downregulated, probably due to the disruption of the nucleolar integrity, stabilization of p53 and induction of cell cycle arrest.[3] It is interesting to note how the nucleolus transmits cellular stress signals to the p53 pathway, thus triggering cell cycle arrest and/or apoptosis based on the extent of damage and the capacity of the cell to recover.[3] Disruption of the nucleolus is believed to stabilize p53 and activate the pro-apoptotic p53 signaling pathway.[170] However, it has been shown that p53 stability is also regulated by an intact structure and function of the nucleolus.[171]

Nucleolar integrity is required to maintain ribosome biogenesis and controlling cell proliferation. As noted above, nucleolar stress, characterized by a loss of nucleolar integrity,

disturbs ribosome biogenesis and halts cell proliferation.[3] Nucleolar stress results in the redistribution of nucleolar proteins to the nucleoplasm, altering their interactions with MDM2 and resulting in p53 activation.[18,172] These redistributed proteins include RPs, ARF (ADP-ribosylation factor), nucleophosmin (NPM/B23), nucleostemin (NS) and nucleolin, among many others. Perturbations of ribosome biogenesis, either due to impaired rRNA synthesis or RP deficiency, have been defined to cause nucleolar stress that activates p53 signaling. As would be expected given these effects, the p53 pathway is associated with many ribosomal diseases, such as DBA and the 5q- syndrome.[24,25] Distinct intrinsic and extrinsic factors that disturb ribosome biogenesis and trigger nucleolar stress have been reported.[1,3] This section is focused on these stresses and their consequent biological effects.

A. Impairment in rRNA Synthesis and Processing

One of the major causes of ribosomal stress is incorrect rRNA synthesis. Several proteins, such as the nucleolar protein block of proliferation 1 (Bop1), are involved in rRNA processing and ribosome assembly.[173] A dominant negative Bop1 mutant inhibits ribosome biogenesis, leading to p53 activation and subsequent cell cycle arrest.[20] Inactivation of p53 abrogates the mutant Bop1-induced cell cycle arrest.[20] Selective inhibition of other rRNA processing factors, such as WDR3 (WD repeat 3)[174] and hUTP18[175], can also activate p53, reduce proliferation, and cause cell cycle arrest. The unfolded protein response (UPR) is activated in the presence of unfolded or misfolded proteins that accumulate in the endoplasmic reticulum lumen, and this also triggers p53 accumulation and activation in a PERK (PKR-like ER kinase)-dependent manner.[176]

The suppression of POLR1A (RNA polymerase I polypeptide A), the RNA polymerase I catalytic subunit, stabilizes p53, but upregulation of rRNA synthesis abrogates this effect,[177] suggesting that the imbalance between rRNA and RPs is an inducer of ribosomal stress. On the other hand, transcription initiation factor IA (TIF-IA), a nucleolar target for the downregulation of rRNA transcription, which modulates the transcriptional activity of Pol I, mediates growth-dependent regulation of rRNA synthesis.[178] The depletion of TIF-IA in mouse embryonic fibroblasts (MEFs) led to nucleolar disruption, activation of p53, cell cycle arrest and the induction of apoptosis.[179] Knockdown of p53 by RNAi can overcome the cell cycle arrest and apoptosis in response to TIF-IA ablation, indicating that the nucleolus acts as a cellular stress sensor that regulates p53 stability and activity.[179]

Ribosome biogenesis is also a target for numerous chemotherapeutic drugs.[180] Low concentrations of actinomycin D (Act D) (< 10 nM) inhibit RNA polymerase I, and consequently prevent the transcription of rRNA, which leads to nucleolar stress.[117] Similar results have been seen following exposure to 5-fluorouracil (5-FU)[181] or mycophenolic acid (MPA).[182] In addition, p53-dependent G1 cell cycle arrest is caused by growth adverse conditions, such as serum deprivation or cell contact inhibition. This growth inhibition, possibly due to the decreased nucleolar rRNA production, facilitates L11 translocation into the nucleoplasm, inhibiting MDM2 and activating the p53 signaling pathway.[128]

B. Nucleolar Protein Deficiency or Malfunction

The malfunction of nucleolar proteins induces nucleolar stress, which leads to p53 activation and subsequent cell cycle arrest and apoptosis.[33] The nucleolar protein nucleostemin (NS) is crucial for cell proliferation and early embryogenesis.[183] NS overexpression stabilizes p53 by directly binding to MDM2. Surprisingly, knockdown of NS also leads to p53 induction and activation.[183] Nucleostemin is a nucleolar GTP-binding protein and that is extensively degraded in response to GTP depletion by mycophenolic acid.[184] The degradation of NS induces ribosomal stress, and activates p53 through an L11-dependent mechanism.[183] On the other hand, the nucleolar protein PAK1IP1 (p21-activated protein kinase-interacting protein 1) is induced upon nucleolar disruption with 5-FU and Act D. PAK1IP1 binds to MDM2, inhibiting its ability to cause p53 ubiquitination and degradation.[166] Interestingly, both PAK1IP1 overexpression and knockdown inhibit cell proliferation and induce p53-dependent G1 cell cycle arrest.[185] The mechanisms underlying these effects are not fully understood.

The tumor suppressor ARF, an important player in the p53-MDM2 interaction, is known to induce both p53-dependent and -independent cell cycle arrest.[186] ARF interacts with nucleophosmin B23, a multifunctional nucleolar protein implicated in ribosome synthesis, and promotes B23 polyubiquitination and degradation.[186] B23 knockdown inhibits the pre-ribosomal RNA processing and induces cell death.[186] Thus, ARF regulates ribosome synthesis and cell proliferation by inhibiting B23, suggesting a role for ARF in tumor surveillance. Additionally, ARF also causes the nucleoplasmic accumulation of the RNA Pol I transcription termination factor I (TTF-I) *via* the inhibition of B23.[187] In the absence of ARF, TTF-I is targeted for ubiquitination and proteasomal degradation by MDM2.[188] Moreover, ARF interacts with the upstream binding factor (UBF) and inhibits its phosphorylation, disturbing the assembly of the transcription machinery complex.[189] These findings define a new pathway that regulates the cell cycle- the negative control of rRNA transcription by ARF.

The deficiency of individual RPs also causes defective ribosome biogenesis and triggers ribosomal stress, leading to p53-dependent cell cycle arrest and apoptosis.[33] For example, L29 or L30 depletion disturbs 60S ribosome biogenesis and results in p53 activation.[190] The effects of the hematopoietic defects in L29 mutant zebrafish depend upon p53 activation.[191] L37 degradation and p53 activation are both observed in response to DNA damage.[149] A deficiency of L11 in the zebrafish model also activates the p53 pathway, resulting in abnormal brain development and embryonic lethality.[192] Simultaneous depletion of p53 rescues the fish from both developmental defects and apoptosis. L11 mutation in zebrafish also leads to metabolic defects, the upregulation of p53 target genes and the induction of global changes in metabolism.[193]

Haploinsufficiency or deficiency in small subunit ribosomal proteins can also activate proapoptotic p53 signaling pathways. For example, deletion of one allele of S6 in mouse embryos inhibits their entry into the M-phase of the cell cycle, ultimately leading to perigastrulation lethality.[83] Conditional knockout of S6 in T lymphocytes suppresses their division and splenic and lymph node accumulation due to p53 activation.[194] Additionally,

similar erythroid phenotypes are observed in S6 knockout mice and patients with DBA and the 5q- syndrome.[195] S19 deficient mice develop macrocytic anemia and bone marrow failure; p53 knockout can rescue the DBA phenotype.[101] S7 knockout in zebrafish induces p53 activation and cell cycle arrest.[161] In addition, aberrant movement of RPs between the nucleus and the cytoplasm also triggers nucleolar stress. Members of the β-karyopherin family, such as importin 7 (IPO7) and exportin 1 (XPO1), mediate the nuclear import of RPs and export of ribosomal subunits. Partial depletion of IPO7 induces p53 activation and p53-dependent cell growth arrest.[196] Thus, defects in both the initial and later stages of ribosome synthesis cause ribosomal stress, leading to the activation of p53.

C. The RPs-MDM2-p53 Pathway

The p53 tumor suppressor regulates the expression of downstream target genes whose protein products induce cell cycle arrest, apoptosis, DNA repair, and senescence in response to various stresses,[172,197–200] protecting cells from transformation and tumorigenesis. p53 is essential for maintaining the genomic stability during cell growth and division.[172] Cancer cells can escape from p53 surveillance either by mutating its encoding gene, *TP53*, or by activating a number of proteins that suppress p53 activity.[172,201–206] The predominant negative regulator of p53 is MDM2.[172,201–203] MDM2 and p53 form a negative feedback loop, in which p53 activates MDM2 transcription and MDM2, in turn, inactivates p53 by targeting it for ubiquitination and proteasomal degradation.[201–206] In normal cells, the p53 protein is maintained at low levels through this MDM2-p53 negative feedback loop. In response to various stress signals, the inhibitory effect of MDM2 on p53 can be circumvented by multiple cellular mechanisms.[172,207–211] DNA damage can lead to the inhibition of MDM2-mediated p53 degradation by the phosphorylation of MDM2 at multiple sites[207] or by the induction of SCF destruction complex-mediated MDM2 turnover.[208] DNA damage signals also cause the acetylation of p53 at specific lysine residues, which activates p53 by preventing MDM2-facilitated p53 degradation.[209] Oncogenic stress is another type of stress that can prevent the inhibition of p53 by MDM2. It is often associated with the overexpression of oncoproteins such as Ras (resistance to audiogenic seizures) and c-Myc (cellular myelocytomatosis oncogene). These oncogenic insults stimulate the expression of the ARF tumor suppressor, which in turn interacts with MDM2 and inhibits its ubiquitination of p53.[210,211] More recently, there have been several reports supporting that the MDM2-p53 interaction is modulated by many other internal and external factors.[172,212,213]

Over the past decade or so, increasing evidence has revealed the previously less-appreciated ribosomal stress-induced interactions among RPs, MDM2, p53 and related molecules, termed the RPs-MDM2-p53 pathway (Fig. 2).[18] In response to nucleolar stress, several RPs translocate to the nucleoplasm, where they bind to MDM2 and inhibit the MDM2-mediated ubiquitination and degradation of p53, resulting in p53-dependent cell cycle arrest and apoptosis.[18,31] The RPs-MDM2-p53 signaling pathway constitutes a “surveillance network” that monitors the integrity of ribosome biogenesis.[18] In the following section, we summarize the recent findings on several RPs as regulators of the MDM2-p53 pathway.

During ribosome biogenesis, the 5S rRNA assembles with RPs L5 and L11 as a complex, before being recruited to the 60S ribosomal subunit. It was shown more than two decades ago that L5 and 5S rRNA assemble along with the MDM2 protein and the MDM2-p53 complex in murine cells,[214] although the functional significance of this association was not recognized until about ten years later. L5 binds to MDM2 and inhibits p53 ubiquitination and degradation, leading to enhanced p53 transcriptional activity and p53-dependent G1 cell cycle arrest.[117] The interaction of L5 with MDM2 is enhanced by treatment with a low dose of Act D; the Act D-induced p53 activation is inhibited by treatment with an siRNA (small interfering RNA) against L5. Another RP, L11, also interacts with MDM2 and inhibits MDM2 function, thus leading to p53 stabilization and activation.[4,127] Further investigations showed that L11, unlike L5, inhibits the degradation of ubiquitinated MDM2, independent of its effects on p53.[111] Recently, the existence of a L5-L11-5S rRNA pre-ribosomal complex has been demonstrated, and it is a part of an MDM2 inhibitory complex that stabilizes p53 in a mutually dependent manner. The complex is redirected from assembly into nascent 60S ribosomes to MDM2 inhibition as a result of defective ribosome biogenesis.[215]

Another ribosomal protein, L23, has also been found to activate p53 by inhibiting MDM2 function in response to ribosomal stress.[137,138] However, knockdown of L23 also induces ribosomal stress and causes B23 translocation from the nucleolus to the nucleoplasm, leading to stabilization and activation of p53, suggesting that L23 functions as both an effector and a sensor in this pathway. Additionally, a synergistic effect between L5 and L11 with regard to p53 activation has been found.[118] L11 cooperates with L5, resulting in a strong inhibition of MDM2's E3 ligase activity, resulting in p53 stabilization and activation to an extent similar to that achieved by ARF.[118] The capacity of L11 to bind the 5S rRNA is important for the cooperation with L5, because the mutant L11 that does not have the 5S rRNA-binding activity cannot increase the effects of L5 on MDM2.[118] Preventing the degradation of both L5 and L11 is critical for p53 activation following ribosomal stress. The ribosomal stress induced by Act D results in proteasomal degradation of the newly synthesized RPs, but does not affect the ribosome-free L5 and L11, which bind to MDM2 and ubiquitinate it. Subsequent to the disruption of the nucleolus, the newly synthesized L5 and L11 continue to be imported into the nucleoli, accumulate therein, and co-localize with p53 and MDM2.[216] Thus, the disrupted nucleolus, in essence, provides a "platform" for the interaction of L5 and L11 with p53/MDM2, explaining their role in p53 activation.

More recently, several investigations, including our own studies, have led to the discovery of additional RPs that modulate the MDM2-p53 pathway, including L6,[122] L26,[217] S3,[74] S7,[85,86] S14,[93] S25,[106] S26,[108] S27,[109] and S27a[112] (Fig. 3). These RPs show similar, but not identical, mechanisms with regard to regulating p53 in response to ribosomal stress. For example, L6 binds to and inhibits MDM2's E3 ubiquitin ligase activity, inhibiting MDM2-mediated p53 polyubiquitination and degradation. L6 shuttles from the nucleolus to the nucleoplasm under ribosomal stress, facilitating its binding with MDM2.[122] Since all of these RPs can inhibit MDM2-mediated p53 ubiquitination, it is likely that they execute such inhibitory effects by physically interacting with MDM2 and preventing the transfer of the ubiquitin to p53. These RPs tend to bind to the central portion of MDM2, which contains the acidic domain and zinc finger domain.[18,172] The acidic domain is also critical for MDM2-

mediated p53 degradation,[218] although how exactly the acidic domain of MDM2 contributes to the regulation of p53 stability is unclear. The binding of RPs to MDM2 may cause a conformational change in MDM2 that alters its tertiary structure within its central region, and this change might reduce its binding affinity for p53, thus weakening its ability to ubiquitinate p53. It has recently been demonstrated that the acidic and polar residues within the zinc finger domain of MDM2 are essential for its interaction with the basic residues in L11.[219] However, more studies, including crystallographic studies, are needed to provide more information about the structure of the RPs-MDM2-p53 complex(es).

Several modulators of the RPs-MDM2-p53 pathway have recently been identified, including MDMX (murine double minute 4), PICT1 (protein interacting with the C terminus 1), MYBBP1A (Myb-binding protein 1A), and hCINAP, among others.[26,30,31,94] MDMX is an important negative regulator of the p53 response to ribosomal stress.[26] L11 prompts MDM2-mediated ubiquitination and degradation of MDMX. Abundant MDMX in cancer cells results in decreased sensitivity to Act D due to the formation of inactive p53-MDMX complexes.[26] In addition, 5S RNA binds and stabilizes the MDMX protein, and the binding between the 5S RNA and MDMX is disrupted, and MDMX is quickly degraded by MDM2, in response to ribosomal stress.[220] However, the detailed role of MDMX in modulating the RPs-MDM2-p53 pathway remains unclear. For example, MDMX has been shown to facilitate the inhibition of MDM2's E3 ligase activity by S7.[86] MDMX also facilitates the S25–MDM2 interaction to modulate the E3 ubiquitin ligase activity of MDM2, but the interaction does not depend on MDMX.[106]

The initial description of PICT1 (also known as GLTSCR2, glioma tumor suppressor candidate region gene 2) is a tumor suppressor that interacts with and stabilizes PTEN (phosphatase and tensin homolog).[221] The low levels of PICT1 in glioma tissues are associated with tumor malignancy and progression, and PICT1 overexpression enhances apoptosis in glioma cells.[222] Contrarily, studies with genetic mouse models suggest PICT1 acts as an oncogene.[223] *Pict1*$^{-/-}$ mice are embryonic lethal, while *Pict1*$^{+/-}$ mice develop normally. Co-depletion of p53 rescues *Pict1*$^{-/-}$ embryonic stem (ES) cells from cell cycle arrest and apoptosis.[223] In a chemically-induced skin cancer model, *Pict1*$^{+/-}$ mice developed papillomas more slowly compared to their wild-type counterparts.[223] Moreover, PICT1 shRNA (short hairpin RNA) induced p53-dependent growth inhibition in brain, colorectal and ovarian tumor cell lines.[223] PICT1 interacts with L11 and sequesters it in the nucleolus, which inhibits the interaction between L11 and MDM2.[223] Forced expression of PICT1 may protect tumor cells from nucleolar stress. Intriguingly, it has been reported that PICT1 directly binds to and stabilizes p53.[224] Upon translocation to the nucleoplasm from the nucleolus following nucleolar stress, PICT1 prevents MDM2-mediated p53 degradation and induces p53 oligomerization. Thus, both deficiency and overexpression of PICT1 can result in p53 activation, which is similar to the findings observed with nucleostemin.[225] PICT1 depletion during mammalian ribosome synthesis results in nucleolar stress and cell cycle arrest.[225] Marginal elevations of PICT1 may cause L11 nucleolar localization, while high levels of PICT1 can allow the protein to "spill over" to the nucleoplasm and bind to p53, which may explain the different effects of PICT1 observed under different conditions.[225]

MYBBP1A is involved in p53 acetylation upon ribosomal stress. Acetylation is essential for p53 activation.[226] As a co-factor for transcriptional regulation,[227] MYBBP1A is tethered to the nucleolus through its binding to nucleolar RNA. During situations of nucleolar stress, MYBBP1A translocates from the nucleolus to the nucleoplasm, facilitates the interaction between p53 and p300, and promotes p53 acetylation.[228] The depletion of L5 and L11 inhibits the translocation of MYBBP1A and the activation p53,[228] indicating that there is a dynamic balance between RNA generation and export, and any disturbances (due to nucleolar stress) may alter the nucleolar RNA content and affect p53 activity through MYBBP1A.

hCINAP (human coilin-interacting nuclear ATPase protein) is an ubiquitously expressed eukaryotic nucleoplasmic enzyme that associates with Cajal bodies in the nucleoplasm, playing diverse roles in transcription and nucleotide homeostasis.[229,230] It is a novel partner of S14.[94] S14 stabilizes p53 by inhibiting MDM2-mediated p53 degradation,[93] and this process is facilitated by S14 neddylation. hCINAP inhibits S14 neddylation, leading to reduced S14 stability and increased p53 degradation.[94] Thus, hCINAP may be considered to be an important regulator of the RP-MDM2-p53 pathway.

Recent studies suggest that there is a direct link between RPs and p53 that is independent of MDM2 binding.[30,31] Based on a loss-of-function genetic screening, a group of RPs was shown to directly regulate p53 function.[231] The reduction of RP levels decreased the p53 levels by inhibiting p53-specific translation.[30,31] RP gene mutations can cause a loss of p53 synthesis, and predispose zebrafish to the development of malignant peripheral nerve sheath tumors (MPNSTs).[232] Cells extracted from MPNSTs are unable to produce p53 protein even with treated with proteasome inhibitors and γ-irradiation, which typically are strong inducers of p53.[232] Interestingly, the wild-type *TP53* gene is unaffected, the rates of overall protein production are normal, but the synthesis of p53 protein is not induced by the usual stimuli, indicating a potential role for RPs in the control of p53 translation.[232] Supporting this idea, the specific regulation of p53 translation by individual RPs has been revealed.[33] For example, in response to DNA damage, L26 binds to the p53 mRNA 5'-UTR and increases the rate of p53 protein translation,[140] indicating that the direct control of p53 mRNA translation after DNA damage may represent another layer of p53 regulation by RPs. In contrast, L22 deficiency results in the selective upregulation of p53 in αβ-lineage T cells, partially through the induction of p53 synthesis,[15] suggesting that L22 may have cell type-specific and stage-specific functions in T cell development.

Actively growing cells require the continuous synthesis of ribosomal RNA, RPs, and other factors to sustain cellular biosynthesis; p53 represses ribosomal gene transcription and restricts cell proliferation.[233,234] In addition to rRNA, p53 also regulates the transcription of RP genes.[233] For instance, p53 directly induces the expression of a RP, S27L,[10,235] which is critical for DNA damage-induced cell apoptosis. We have recently demonstrated that S25 is a novel p53 downstream target.[106] S25 activates p53 through its interaction with MDM2, and in turn, the activated p53 represses S25 gene transcription, forming a negative feedback loop.[106] The regulation of RP gene expression is not only restricted to wild type p53; the mutant p53 (R248W) upregulates the expression of L37, P1, and S2, suggesting a mechanism for the overexpression of these RPs in human tumors.[236]

D. p53-Independent Pathways in Response to Ribosomal Stress

There is emerging evidence supporting that RPs are involved in the cellular response to ribosomal stress through p53-independent pathways.[237] As depicted in Fig. 4, both p53-dependent and –independent mechanisms are responsible for the coordination of cell growth, proliferation, and apoptosis. These pathways can provide a basis for the development and application of biomarkers and therapeutic drugs that specifically impact ribosome biogenesis, irrespective of the p53 status.

In addition to modulating the MDM2-p53 pathway, L11 regulates c-Myc mRNA decay and protein turnover (Fig. 4A).[238,239] L11 blocks the recruitment of TRRAP (transformation/transcription domain-associated protein), the co-activator of c-Myc, to the promoter regions of c-Myc target genes.[130,240] Nucleolar stress can increase the binding of L11 to its targets, and decreases the TRRAP binding to c-Myc, inhibiting the expression of c-Myc downstream genes (such as E2F2 and 5S rRNA) and thus decreasing cell proliferation. Furthermore, L11 binds to the c-Myc 3'-UTR, leading to c-Myc mRNA degradation.[240] Ribosomal stress inhibits c-Myc expression and activity in an L11-dependent manner.[241] All of these observations suggest that L11 is a principal player in ribosome biogenesis and the cell growth process, due to its ability to modulate the functions and activities of c-Myc, a master regulator of ribosome and protein synthesis.[242] Similarly, S14 has recently been suggested to be a negative regulator of c-Myc, also through the inhibition of TRRAP co-activator recruitment and c-Myc mRNA stability (Fig. 4A).[92]

Another protein, PIM1 (proviral integration site for Moloney murine leukemia virus 1) kinase which drives cell cycle progression, has been associated with RPs, such as S19.[243] S19 deficiency dramatically destabilizes PIM1, which increases p27, inhibits cell cycle progression and reduces cell proliferation, even in the absence of p53 (Fig. 4B).[243] Exogenous restoration of the PIM1 levels leads to a recovery of all of these effects, indicating that PIM1 may act as a sensor for ribosomal stress though either p53-independent or p53-dependent mechanisms.

On the other hand, siRNA knockdown of the *POLR1A* gene inhibits rRNA synthesis and cell cycle progression, and downregulates E2F1 in inactive p53 cells.[244] The downregulation of E2F1 is due to the release of L11, which inhibits MDM2-mediated stabilization of E2F1. Thus, targeting the RNA polymerase I transcription apparatus may selectively inhibit cellular proliferation in p53-deficient environments (Fig. 4C).

The activating transcription factor 4 (ATF4) is a major coordinator of cell survival during nucleolar stress, and is commonly overexpressed in cancer. L41 induces ATF4 phosphorylation at serine 219, leading to its translocation from the nucleus to the cytoplasm for proteosomal degradation.[151] L41 overexpression induces cell death and increases chemosensitivity in cancer cells (Fig. 4D).[151]

A negative feedback circuit between Miz-1 (Myc-associated zinc-finger protein 1) and L23 has been reported. Miz-1 inhibits cell proliferation and induces p15 and p21 expression. In the nucleolus, L23 (a direct target gene of Myc) negatively regulates Miz1-dependent transactivation by retaining B23, which is necessary for Miz1 transactivation.[245] This

regulatory feedback mechanism may be the link between Myc-dependent translation and Miz-1-dependent cell cycle arrest (Fig. 4E).

L3 has been suggested to be a new regulator of the cell cycle and apoptosis that positively regulates p21 expression, independent p53.[246] The specific interaction between L3 and Sp1 is required for L3-mediated p21 upregulation (Fig. 4F). Furthermore, p21 overexpression leads to activation of G1/S cell cycle arrest or the induction of mitochondrial apoptotic pathways, depending on its intracellular levels.

The S27 gene is a growth factor-inducible gene. Knockdown of S27 leads to spontaneous apoptosis and growth retardation in gastric cancer cells.[247] Silencing of S27 inhibits NFκB activity by reducing the phosphorylation of p65 at Ser536 and IκBα at Ser32, blocking NFκB nuclear translocation, and reducing its DNA binding activity.[110] S27 knockdown-induced apoptosis is mediated by Gadd45β (growth arrest DNA damage inducible gene 45β), a direct NFκB target gene.[110] Furthermore, knockdown of S27 expression inhibits invasion and migration, and reduces ITGB4 mRNA and protein expression in gastric cancer models (Fig. 4G).[111] The overexpression of ITGB4 in S27 knockdown cells enhances cell invasion and migration, while knockdown of ITGB4 partially reduces these effects induced by S27 overexpression.[111]

S7 forms a complex with GADD45α (growth arrest and DNA damage inducible gene 45α), which regulates DNA repair, cell cycle checkpoints and apoptosis. S7 interacts with both MDM2 and GADD45α, protecting GADD45α from MDM2-mediated ubiquitination and degradation.[87] However, S7 mutants lacking the ability to bind MDM2 do not stabilize GADD45α, indicating the importance of the RP-MDM2 interplay (Fig. 4H).[87]

E. Post-translational Modifications of Ribosomal Proteins

Post-translational modifications of RPs maintain the integrity and accuracy of the decoding machinery employed in protein translation. In the following sections, we will discuss the different post-translational modifications with respect to their stability, metabolism and biological effects.

1). RP Ubiquitination—The interaction between MDM2 and RPs modulates the protein levels and activity of RPs by post-translational modifications, including ubiquitination.[19] The binding of MDM2 to L26 promotes the ubiquitination and proteasomal degradation of L26, disrupts the association of L26 with p53 mRNA, and inhibits the p53 protein synthesis mediated by L26.[141] S7 is also a substrate for MDM2-mediated ubiquitination.[86] The S7-ubiquitin fusion protein (S7-Ub) selectively inhibits MDM2-mediated p53 degradation and induces apoptosis better than unmodified S7.[86] Of note, MDM2-mediated ubiquitination has no effect on the S7 protein level indicating that the ubiquitination of S7 by MDM2 does not target it for proteasomal degradation.[86] S27a[112] and S27/S27L[109] are also targets of MDM2-mediated ubiquitination, but the ubiquitination of these proteins leads to their proteasomal degradation. These findings suggest that there is a feedback loop for the RPs-MDM2 interactions that regulates the magnitude and outcome of ribosomal stress.

2). RP Neddylation—The ubiquitin-like molecule, NEDD8 (Neural Precursor Cell Expressed, Developmentally Down-Regulated 8)-induced protein modification also plays an important role in regulating protein stability and activity.[248] For instance, MDM2-mediated p53 neddylation inhibits its transcriptional activity.[249] Intriguingly, the neddylation of RPs is required for p53 signaling in response to nucleolar stress.[250] The MDM2-interacting RPs, such as S3, S7, and L11, are targets of the neddylation pathway.[250] MDM2 neddylates L11 in the cytoplasm and stabilizes it, leading to its enhanced nucleolar localization. In the early stage of nucleolar stress, L11 is deneddylated by NEDD8-specific protease 1(NEDP1) and translocates from the nucleolus to the nucleoplasm, where it interacts with MDM2 and activates p53. Thus, nucleolar stress can trigger L11-mediated p53 activation that is dependent on NEDD8.[27] In addition, L11 deneddylation allows it to be transiently recruited to promoter sites of p53-regulated genes, and promotes the access and binding of p53 transcriptional co-activators p300/CBP.[251] However, prolonged deneddylation may induce the proteosomal degradation of L11.[251] S14 is also specifically modified by NEDD8.[93] hCINAP negatively regulates S14 neddylation by recruiting NEDP1.[94] The decrease in S14 neddylation leads to reduced stability, incorrect localization, and an attenuated S14-MDM2 interaction, suggesting that hCINAP acts as an important regulator of the S14-MDM2-p53 pathway through the control of S14 neddylation.

3). RP Phosphorylation—Phosphorylation is one of the most common post-translational protein modifications, and is often required for functional activity of proteins. The small subunit, RPS3, is crucial for both translation initiation and the processing of DNA damage (functioning as a DNA endonuclease).[13,252] Recent studies indicate that the functional switch for S3 between translation and DNA repair is regulated by its phosphorylation at different residues.[253] Oxidative stress activates PKCδ (protein kinase C delta type), which phosphorylates S3 at Ser6 and Thr221, leading to its nuclear mobilization and DNA repair actvity.[253,254] Upon NGF (nerve growth factor) stimulation, Akt interact with and phosphorylates S3 (Thr70), which disturbs its association with E2F1 and enhances S3 nuclear translocation, resulting in increased DNA repair activity and sustained neuronal survival.[70] On the other hand, genotoxic stress induces the translocation of S3 to damage sites through ERK-mediated phosphorylation of S3 at Thr42.[77,255] In addition, the phosphorylation of S3 mediates radioresistance in non-small cell lung cancer (NSCLC) cells.[254] In those cells, ionizing radiation (IR) induces CK2α-mediated S3 phosphorylation (Thr221) and dissociation from TRAF2 (TNF receptor-associated factor 2), resulting in NFκB activation and upregulation of prosurvival genes. This is because S3 is a NFκB subunit and contributes to p65 DNA binding and specificity. The IKKβ (IκB kinase β) kinase-mediated phosphorylation of S3 (Ser209) is crucial for NFκB activation and anti-infective immunity.[75]

S6 is another example of a phospho-regulated RP.[256] Mitogenic stimulation causes S6 C-terminal phosphorylation by p70 S6 kinases (S6Ks) and p90 ribosomal S6 kinases (RSKs) on Ser-235, Ser-236, Ser-240, and Ser-244.[257] In addition, casein kinase 1 (CK1) mediates the phosphorylation of S6 on Ser-247.[257] The phosphorylation of S6 is an important event that regulates cell growth in mammals. In quiescent mammalian cells, S6 phosphorylation is enhanced in the presence of mitogenic stimulation, growth factors, transforming agents, and

carcinogenic chemicals, etc., while rapid dephosphorylation is caused by contact inhibition, nutrient starvation, heat shock or cellular stress.[258] The overall outcome of S6 phosphorylation is to potentiate its mRNA cap-binding activity, but the physiological function of S6 phosphorylation remains enigmatic. Knock-in mice with mutations in all five phosphorylatable sites have been produced, and have provided further insights into the phosphorylation events.[54,233] As a key player in glucose homeostasis in mice, S6 phosphorylation is necessary for regulating this process in some cell types (pancreatic β-cells and MEFs), but is expendable for the translational control of 5'-TOP mRNAs.[58,259] In addition, S6 phosphorylation-deficient mice suffer from muscle weakness, which is thought to reflect impaired growth and reduced energy.[260] Of note, mice lacking all five phosphorylatable sites in S6 develop fewer pancreatic cancer precursor lesions induced by DMBA (7,12-dimethylbenz(a)anthracene) or mutant K-ras.[261] It was demonstrated that S6 phosphorylation attenuates K-ras-induced DNA damage and p53-mediated tumor suppression,[261] indicating that the phosphorylation of S6 is important for the initiation of pancreatic cancer.

4). RP Sumoylation—The small ubiquitin-like modifier (SUMO)-mediated post-translational modification has an important regulatory role in many cellular functions, including cell cycle progression, DNA repair, and transcription.[262] The nucleolar SUMO-specific protease 3, SENP3, is associated with several RPs (S4, S8, S11, and S18),[263] but the functional roles of this modification are not fully understood. S3 is also a target for SUMO-1, and sumolyated S3 has increased stability compared to the unmodified protein,[264] suggesting that sumoylation may represent another mechanism to protect RPs from proteolysis.

F. RPs, miRNAs and Nucleolar Stress

There is increasing evidence supporting the role of miRNAs in the regulation of the functions of RPs. It has been shown that L11 controls c-myc mRNA turnover *via* recruiting the miRISC (miRNA-induced silencing complex) in response to ribosomal stress.[241] L11 can downregulate c-myc at the mRNA levels by binding to its 3'UTR, and recruits both miR-24 and the miRISC argonaute 2 (Ago2) core component to that region.[241] The silencing of Ago2 abolishes this effect, while L11 knockdown rescues cells from miR-24-mediated c-myc mRNA reduction.[241] Nucleolar stress-inducing agents, such as 5-FU or Act D, can enhance the associations of L11 with c-myc mRNA, miR-24, and Ago2. Recently, S14 has been suggested to induce c-Myc mRNA decay through the recruitment of Ago2 and miR-145, indicating that the association with the miRISC is probably a common feature of RPs that is related to regulating their mRNA stability and protein level and activity.[92]

Recent studies with RNA interference screening assays have suggested that reduced expression of RP genes (including L11) leads to the dissociation of miRNA complexes from target mRNAs, increasing the stability of the miRNA-targeted mRNAs, their polysome association and subsequent translation.[265] These miRNAs co-sediment with ribosomes, and RP gene knockdown decreases their levels in monosomes, while increasing their target mRNAs in the polysomes. Chemical induction of nucleolar stress phenocopies RP gene knockdown, and this suggests that reduced RP gene expression regulates miRNA function

through p53-dependent pathways. These findings indicate that the levels of RPs modulate miRNA-mediated repression of translation initiation, which provides a novel mechanism for the role of RPs in regulating protein translation and cell proliferation.

G. Crosstalk Between Nucleolar Stress and Other Stress Pathways

DNA damage can initiate nucleolar stress, but the mechanisms underlying this effect are not well known. A recent report suggested that genotoxic insults, such as UV (ultraviolet) irradiation and cytotoxic drugs (such as cisplatin), cause proteasome-mediated destruction of L37 in the nucleoplasm and L11-dependent stabilization of p53.[149,266] These observations are validated by the fact that high levels of L37 decrease the p53-mediated DNA damage response. Thus, DNA damage-induced L37 degradation may be the link between DNA damage and the ribosomal stress pathway.[149,266]

In contrast, the tumor suppressor, ARF, senses oncogenic insults (such as Ras and c-Myc) and activates p53. It directly binds to L11, along with MDM2 and p53; suppressing MDM2 and enhancing the transcriptional activities of p53 and inducing cell cycle arrest.[267] Silencing L11 attenuates ARF-induced cell cycle arrest and reduces p53 accumulation, demonstrating that ARF activates p53 by inducing nucleolar stress, which suggests that the ARF-MDM2-p53 and L11-MDM2-p53 pathways are functionally connected.

5. RIBOSOMAL PROTEINS AND THE PATHOGENESIS OF HUMAN DISEASES

Since RPs play a crucial role in the synthesis of proteins, which form the building blocks of tissues, disruptions in genes encoding RPs affect organogenesis, erythropoiesis and other physiological functions. Deficiencies in RPs lead to defects at distinct steps in ribosome biogenesis, resulting in a variety of disorders that affect different organs/systems. In the following sections, the discussion will be focused on the pathogenesis and therapeutic implications of these RP-associated disorders. The animal models used to study the roles of individual RPs in genetic diseases and ribosomopathies are described in Table II.

A. Developmental Disorders

Proper ribosome biogenesis maintains normal protein translation, which is essential for normal cellular functions. Therefore, the proteins required for ribosome assembly are vigorously and ubiquitously expressed. During times of rapid proliferation, such as embryonic development, the demand for functional ribosomes becomes even greater. Indeed, several studies in model organisms have underscored the importance of RPs during development.[272] For instance, the disruptions of RP genes in *Drosophila* contribute to the “Minute” phenotype, which is characterized by slow development, absent or short bristles, poor fertility, and recessive lethality; these gene deficiencies lead to growth retardation by impairing the overall protein synthesis capacity of the ribosome.[272] Knockdown of a large cohort of RP genes in developing zebrafish has demonstrated a variety of axis defects and abnormalities in the central nervous system (CNS) that can be attributed to the loss of individual RPs.[162] For example, the knockdown of S15 leads to an enlarged fourth ventricle, and knockdown of S3, S5, S29, and L35a lead to brain deformities, while extreme body

trunk abnormalities are seen in organisms with S29 knockdown.[162] Meanwhile, in S7-deficient zebrafish embryos, p53 is activated, leading to apoptosis, cell cycle arrest, and impaired hematopoiesis.[162] The matrix metalloproteinase (MMP) family genes are also activated in S7 mutants, indicating that there might also be improper migration of cells, further causing abnormal development.[162] Concomitant knockdown of the p53 protein only partially reversed the abnormal phenotype, indicating that both p53-dependent and -independent mechanisms are involved in the onset of these developmental disorders.[162]

Homozygous mutations in RPs cause gross developmental defects and generally result in embryonic lethality.[273] In zebrafish with RP mutations, defects in the endoderm-derived tissues are frequently noted in homozygous embryos.[232] L23a and L6 are expressed in exocrine pancreatic progenitor cells and are essential for normal pancreas development. The haploinsufficiency of RP genes disrupts ribosome assembly, triggering ribosomal stress and inducing a p53-dependent cellular stress response.[123] Surprisingly, in both L23 and L6 mutant embryos, the simultaneous knockdown of p53 is unable to restore the normal growth of pancreatic progenitor cells, suggesting that L23a and L6 have p53-independent roles in the physiological development of the pancreas. Altered liver and gut development in RPL mutants have also been reported, suggesting that developing endodermal tissues express high levels of RPL genes, and are very sensitive to the disruption of RPL gene function.[123] It has been suggested that high levels of proliferation among pancreatic, liver, and gut progenitor cells may render these tissues highly sensitive to RPL disruption.[123] Each of these affected tissues ultimately generate large numbers of adult cells, which are characterized by high-level protein synthesis and secretion, and the associated requirement for well-developed rough endoplasmic reticulum in these adult cell types, further making them susceptible to dysfunction in association with ribosome defects.[123]

In higher organisms such as mammals, mutations in RPs are typically associated with a wide array of specific abnormalities.[274] One example comprises the tail-short (Ts) laboratory mice, which possess short, kinky tails and numerous skeletal abnormalities.[274] L38 located within the Ts locus is altered in these mutants.[274] Similarly, a deletion within L24 has been identified in mouse “Belly spot and tail (Bst)” mutants, which exhibit a kinked tail with a ventral midline spot.[246] The expression of wild-type transgenes of L24 rescue these abnormalities.[268]

Heterozygous targeted mutant S6 mice exhibit embryonic lethality,[83] while the mice with heterozygous targeted mutations of L22 or L29 can survive.[15,271] On the other hand, homozygous targeted mutations of L22 cause αβ T-cell-specific developmental defects.[15] Mice heterozygous for mutations in S19, S20, or L27a exhibit epidermal hyperpigmentation and anemia, along with decreases in body size, while the heterozygosity of L27a also causes cerebellar ataxia.[103,275] The abnormal phenotypes of these heterozygous mutations can be rescued by the concomitant removal of one copy of *TP53*.[162] S19-null mice are embryonic lethal prior to implantation, but mice heterozygous for the disrupted S19 allele have normal growth and organ development.[105] The disruption of S7 results in reduced body size, skeletal malformations, mid-ventral white spotting (from severe developmental abnormalities in melanoblasts), and eye malformations, which can be attenuated by simultaneous *TP53* deletion.[88] Interestingly, S7 mutant mice do not show anemia,[88] an

abnormality commonly associated with RP mutations in humans. These observations support the existence of distinct functions of the RPs, and possible species-associated differences in their functions.[6] S6, S7, S19, S20, and L27a are all critical for epidermal cell development;[88,103,268,269,270] S7, L24, and L38 play essential roles in skeletal and neural development,[88,269,276] and S14, S19, and S20 are necessary for hematopoiesis.[95,103]

RPs may also play an important role in the maintenance of cognitive functions.[277–279] High L10 levels are observed in the murine hippocampus, a key site in the brain for promoting memory and learning. Interestingly, in humans, this gene is located at chromosome Xq28, an autism candidate region.[278] Autism comprises a complex group of behavioral disorders characterized by impaired language and social skills. Indeed, two non-synonymous mutations of L10, L206M and H213Q have been detected in four males with autism.[278] However, a larger study in human subjects has not found any causative mutations of L10 with respect to the susceptibility to autism.[277–279]

In model organisms, the phenotypes associated with RP mutation(s) appear to occur via three distinct mechanisms: 1) global protein synthesis suppression; 2) suppression of specific protein synthesis; and 3) extraribosomal functions. Diminished global protein synthesis has been identified in the $L24^{Bst/+}$ phenotype, while $S7^{Mtu/+}$ mice present with defective 18S rRNA preprocessing in the brain and liver, without any decrease in global protein synthesis.[276] In $S7^{Mtu/+}$ mice, there is impaired rRNA preprocessing along with p53 activation, indicating the intimidate association of p53 with the genesis and progression of RP-related disorders.[88] Due to the essential and ubiquitous nature of RPs, it is believed that even slight disruptions in their functions can result in a wide range of developmental disorders.[280]

B. Cardiovascular and Metabolic Disorders

Several RPs have been implicated in the development and progression of cardiovascular diseases.[281–283] For instance, the Minute syndrome in *Drosophila*, which is associated with RP haploinsufficiency, also affects the heart.[281–283] The cardiomyopathy associated with the Minute syndrome is caused by haploinsufficiency for genes encoding cytoplasmic RPs. Specifically, the heart-specific knockdown of S15a severely impairs the cardiac function in adult *Drosophila*.[283] RPs also have a role in the vascular system. For example, L17 acts as a vascular smooth muscle cell growth inhibitor and limits carotid intima thickening in mice.[135] L17 expression inhibits the growth of vascular smooth muscle cells by arresting the cells at the G0/G1 phase.[135] L17 is paralogous to the L23 protein, and L23 is known to activate p53 by inhibiting MDM2 in response to nucleolar stress. Thus, L17 may also act as a cell cycle inhibitor through p53 activation, although no evidence of its role in the p53 pathway has been reported.

Transgenic knock-in mice in which all five phosphorylatable serines for the S6 protein were substituted with alanines exhibit impaired pancreatic β-cell function and glucose homeostasis, along with muscle weakness.[58,257,259] Pancreatic insufficiency is also manifested as an inability to secrete enough insulin, and thus, these mice have faulty glucose utilization. Interestingly, the global protein synthesis rate in MEFs derived from S6 P−/− mice is significantly higher than that in cells derived from wild-type mice.[58] These

observations suggest that S6 phosphorylation may be a positive regulator of the cell size and whole body glucose homeostasis, while being a negative regulator of global protein synthesis. However, the underlying mechanisms are not fully understood.

S6K, a S6 kinase, is intimately associated with several cardiovascular and metabolic functions. S6K is a major downstream target of mTOR (mammalian target of rapamycin).[284] The mTOR signaling network regulates cell proliferation, growth, and survival, and is involved in metabolic regulation and tumor transformation. S6K is known to be rapidly and strongly activated after myocardial infarction, leading to pathological cardiac remodeling through myocardial infarction-enhanced Akt signaling.[285] S6K1 (S6 kinase 1) is implicated in the pathogenesis of Type 2 diabetes, as S6K1 knockdown in mice leads to hypoinsulinemia.[286] Similarly, rats treated with S6K1 antisense oligonucleotides exhibit reduced body weight gain and appetite, improved glucose utilization, and reduced fasting insulin levels.[286] The depletion of hepatic S6K1 in *db/db* mice using S6K1 shRNA results in the downregulation of SREBP1c (sterol regulatory element binding protein-1c) gene expression in the liver, along with reduced hepatic and serum triglyceride concentrations.[287] The deletion of S6K1 leads to an increased life span and resistance to aging-related disorders, such as motor dysfunction, bone disorders, and loss of insulin sensitivity.[288] S6K1 inhibition also reduces adiposity, which inversely correlates with longevity in mice. Regular exercise in adolescent rats reduces the basal phosphorylation levels of S6 *via* a decrease in S6K1.[288] However, as discussed earlier, S6K is also implicated in the mitogenic and nutrient-responsive PI3K-mTOR pathway, and S6K controls cell growth by regulating ribosome biogenesis at the translational level. Several of its effects may therefore not be directly related to S6 phosphorylation, but to a more general control of global protein synthesis *via* its effects on ribosome synthesis.

The disruption of one L13a allele confers resistance to lipid-induced oxidative apoptosis in CHO (Chinese hamster ovary) cells, indicating that L13a may be a potential therapeutic target for the treatment of hyperlipidemia-associated conditions.[289] A recent study demonstrated that knockdown of L13a in macrophages abolished the translational termination of inflammatory chemokines.[133] Interestingly, unlike S19 or S24, the depletion of L13a does not impair ribosome biogenesis or overall protein synthesis in human monocytes.[290] Considering the fact that inflammation and lipidemic conditions are intimately linked, it is worthwhile to further investigate the specific role(s) of L13a in the progression of inflammatory conditions such as atherosclerosis.

C. Ribosomopathies

Ribosome dysfunction causes specific pathological conditions called ribosomopathies, a collection of rare genetic disorders characterized by macrocytic anemia in association with growth retardation and developmental abnormalities.[23] Although ribosomes are active in all cell types, the predominant phenotype of ribosomopathy is a failure of erythropoiesis.[29] A better understanding of the pathogenesis of ribosomopathies would help develop approaches to their early diagnosis and treatment.

1). Diamond Blackfan Anemia (DBA)—DBA is a congenital erythroid aplasia characterized by defective erythropoiesis, physical abnormalities such as short stature and cardiac defects, as well as an increased risk for cancer.[24,291] It usually presents in infancy, with lethargy and pallor being the most common clinical symptoms.[24] Approximately half of the DBA patients carry mutations and deletions in RP genes, such as those encoding S19,[24] S24,[292] S17,[97–99] L5,[293,294] L11,[293,294] L26,[295] L35a,[148] S7,[294] S10,[296] S26,[296] or S15[297]. The mutations observed in the RPs include nonsense, missense, frameshift, and splice site mutations. Mutations in S19, the most common mutations found in DBA, lead to defective pre-rRNA processing of the 18S rRNA, and reduce the 40S ribosomal subunit production.[298] S19 deficiency in zebrafish results in a phenotype resembling DBA, with the suppression of neural differentiation through p53 and ΔNp63 deregulation.[299] ΔNp63 is required for the specification of the non-neural ectoderm; its upregulation leads to craniofacial abnormalities during gastrulation. The induction of p53 causes p21 accumulation and subsequent cell cycle arrest in erythroid progenitor cells, leading to hypoproliferative anemia.[102] Clinical evidence also suggests that mutations in the large ribosomal unit proteins are linked to specific physical abnormalities observed in DBA patients.[148,293,294] L5 is associated with higher incidences of cleft lip/palate and cardiac anomalies associated with DBA, while isolated thumb abnormalities may be linked to L11 mutations.[293,294] The haploinsufficiency of RPL proteins reduces the amount of 60S ribosome and the mature 80S ribosome, probably contributing to the bone marrow failure and potential cancer predisposition in DBA patients.[148] The deletion of L11 in the zebrafish model causes defects in hematopoiesis[193] and embryonic development[192] through a p53-depedent mechanism.

2). 5q- Syndrome—The 5q- syndrome, a unique subtype of myelodysplastic syndrome (MDS) with del (5q) as the sole cytogenetic abnormality, is manifested as severe macrocytic anemia, normal/high platelets with dysplastic micromegakaryocytes, and rare progression to acute myeloid leukemia (AML), in contrast to other types of MDS.[300] S14 haploinsufficiency has been identified as the major genetic abnormality in 5q-syndrome patients.[25] S14 deficiency causes erythroid defects, with relative preservation of the other lineages. Conversely, the overexpression of S14 in bone marrow $CD34^+$ cells from 5q-syndrome patients rescues their erythroid differentiation.[25] S14 deficiency blocks the processing of 18S rRNA in human erythroleukaemia cells[25] and recapitulates the macrocytic anemia of 5q- syndrome in mice.[95] The deletion of miR-145/146a is responsible for other hematological phenotypes, such as thrombocytosis and megakaryocytic defects.[301] The loss of S14 induces and activates p53, leading to p21-mediated cell cycle arrest and destruction of erythroid progenitor cells.[95,102,302]

3). Treacher Collins Syndrome—Treacher Collins syndrome (TCS) is a congenital autosomal dominant disorder associated with craniofacial development, including hypoplasia of the facial bones, particularly the lower mandible and cheek; abnormalities of the eyes; and alterations of the external ears.[303] To date, more than 200 mutations, including deletions, insertions, nonsense mutations, and alternative splicing have been reported,[304] all of them leading to a truncated Treacle protein.[304] The Treacle protein is a putative nucleolar phosphoprotein that plays a role in rDNA transcription and 18S pre-rRNA methylation. All

TCS patients are heterozygous for a *Tcof1* (Treacher Collins-Franceschetti syndrome 1) mutation; and the disease manifestations are due to haploinsufficiency, not dominant negative effects. Intensive investigations in murine models have shown that *Tcof1* is essential for the formation and proliferation of neural crest cells.[305] In *Tcof1*$^{+/-}$ mice, the haploinsufficiency of *Tcof1* disturbs ribosome biogenesis, resulting in p53-dependent apoptosis and cell cycle arrest in neuroepithelial cells.[303] The surviving population proliferates more slowly than *Tcof1* wildtype cells, further decreasing the number of neural crest cells, which leads to the characteristic hypoplasia seen in TCS.[303] Since the Treacle protein is involved in ribosome synthesis and processing, a non-functional variants implies that there is likely a lack of mature ribosomes. This may be the reason for both the apoptosis and the slow growth rate. Supporting this idea, fewer mature ribosomes are also observed in the neuroepithelium of *Tcof1*$^{+/-}$ mice.[303] However, the reason for the specific defects in the neuroepithelium is still unclear, since TCOF1 is expressed in various other tissues.

4). Shwachman Diamond Syndrome—Shwachman diamond syndrome (SDS) is a rare autosomal recessive disorder manifested as bone marrow failure, skeletal deformities, and exocrine pancreatic hypoplasia.[306–308] Patients exhibit a predisposition to leukemia, and the symptoms are typically manifested in early infancy, including fat malabsorption, growth failure, and fat soluble vitamin deficiency (vitamins A, D, E and K).[306–308] The most common hematological aberration observed is neutropenia. Up to 90% of the SDS patients exhibit biallelic mutations in the SBDS gene (named after Drs. Shwachman, Bodian and Diamond, who first described the syndrome) which is involved in ribosome synthesis and processing.[308–310] Low expression of many RP genes, including S9, S20, L6, L15, L22, L23 and L29, and genes involved in rRNA and mRNA processing, is observed in SDS patients.[23] An increase in Fas-mediated apoptosis is also seen, presumably leading to bone marrow failure.[311] A recent study demonstrated the possibility that pancreatic tumors may be associated with SDS, thereby broadening the clinical phenotype of the disease.[312] *In vivo* SDS models based on mammals, insects, and fish replicate the genetic and/or developmental aspects of ribosomopathies, and have led to the identification of pathways and candidate molecules that are important in the pathogenesis of the diseases.

D. Cancer

Impairments of ribosome biogenesis and protein translation have been shown to be associated with cancer.[2,18,29,304] Disruption of one or several steps that control ribosome and protein synthesis can affect cell cycle progression and cell growth, leading to malignant transformation.[2] In various cellular, animal, and clinical models, ribosome protein synthesis, as well as ribosome translation initiation, has been shown to be regulated by both oncogenes and tumor suppressor genes.[2,18,29,304] Although clinical studies on the relationship between RP expression and human cancers are still limited, the available data indicate that the up- or downregulation of RPs can be seen in a variety of human cancers. In this section, we will focus on several representative pathways that demonstrate the importance of the RPs in cancer development and progression (Fig. 5).

The oncogene and transcription factor Myc modifies several genes that are necessary for ribosomal assembly.[29,313] Its overexpression drives the ribosome and protein biosynthesis in

tumor cells, thereby initiating tumorigenesis *via* increased cell growth and proliferation.[241,314] Myc facilitates rRNA transcription[315] and processing[316] and the production of other tralslation appartus compontents, including RPs.[241] The direct link between Myc and RPs in carcinogenesis has been demonstrated using transgenic mouse models, which showed that the loss of one allele of L24 or L38 decreases the incidence of *Eμ-Myc*-driven lymphomagenesis and delays tumor onset.[317] B lymphocytes heterozygous for L24 and overexpressing Myc show normal rates of total protein synthesis.[317] It has been speculated that the haploinsufficiency of the L24 gene antagonizes Myc's ability to induce tumors by inhibiting the translation of cyclin-dependent kinase 11 during mitosis and blocking the switch from CAP to IRES (internal ribosomal entry site)–dependent translation. However, when two alleles of L24 are present along with Myc overexpression, there is a considerable increase in protein synthesis during mitosis. Thus, even a moderate decrease in the expression of a single RP gene can hinder the ability of Myc to initiate tumorigenesis.[317] In contrast, Pol I and Pol III transcription are repressed by p53 and retinoblastoma (Rb).[234,318] In cancer cells that harbor inactivating mutations in p53 and Rb, deregulation of Pol I and Pol III activity can lead to tumorigenesis (Fig. 5A).[318]

The extraribosomal functions of RPs may be critically invovled in carcinogenesis. Many RPs were identified as haploinsufficient tumor suppressors in a cancer screening study in a zebrafish model.[319] Heterozygous mutations in several RP genes (those encoding L35, S15a, S8, L36, L7, S7, L13, S29, and L23a) led to an increased risk of developing MPNSTs, a rare tumor type, in laboratory strains of zebrafish. These nerve sheath tumors are unable to efficiently synthesize p53 protein, even in the presence of p53 mRNA. Interestingly, a homozygous loss-of-function point mutation in the *TP53* gene also leads to the same tumor type in zebrafish.[232] Therefore, it is possible that an appropriate amount of RP expression is necessary for p53 activation and signaling;[232] and haploinsufficiency of RPs may lead to disruption of this tumor suppressor pathway, ultimately leading to carcinogenesis.

How these RPs act as tumor suppressors, or in certain cases, as tumor-causing or promoting genes is unknown. The main function of the RPs is ribosome assembly and the maintenance of the efficiency and accuracy of translation. Defects in the RPs themselves will lead to impaired protein synthesis, and as such, the level of critical tumor suppressors may be decreased below a threshold level. This may lead to the cell not being protected from genotoxic and other insults, which can ultimately cause malignant transformation. Mutations or loss of certain RPs may dramatically affect the level or function of their binding partners (either tumor suppressors or oncogenes). A recent study provided direct evidence of the extraribosomal function of RPs in preventing cancer, demonstarting that inactivation of L22 predisposes cells to transformmation *in vitro* and leukemogenesis *in vivo*, and that the loss of L22 induces stemness factor Lin28B expression through a NFκB-dependent mechanism.[136] Lin28B has been shown to increase cell proliferation and promote tumor growth,[320,321] suggesting the involvement of a novel L22-NFκB-Lin28B signaling pathway in the development of T-ALL (T-acute lymphoblastic leukemia).[320,321]

The involvement of RPs in the regulation of the MDM2-p53 pathway is also linked to carcinogenesis and cancer progression (Fig. 5B). For example, the C305F missense mutation in the central zinc finger domain of MDM2 disrupts the interaction of MDM2 with L11 and

L5, inhibiting its nuclear transport and proteasomal degradation, and promoting p53 degradation.[322] In fact, transgenic mice with the MDM2 C305F mutant retain the normal p53 response to DNA damage, but do not show the p53 response to nucleolar stress.[323] Indeed, perturbations in the RP-MDM2 interaction significantly increase the rate of *Eμ-Myc*-induced lymphomagenesis.[323] Furthermore, the p53 response induced by nucleolar stress does not require $p19^{ARF}$, suggesting that an RPs-MDM2-p53 interaction mediates an ARF-independent c-Myc-activated tumor suppression pathway.[323]

In addition to the p53 signaling pathway, RPs also influence tumorigenesis *via* the regulation of other important molecules. For example, S13 overexpression promotes multidrug resistance and decreases drug-induced apoptosis in gastric cancer cells.[91] S13 downregulates p27 expression and CDK2 kinase activity, thus promoting the G1 to S phase transition, whereas S13 knockdown leads to the G1 arrest of gastric cancer cells.[91] Similarly, L6 and L23 enhance the resistance to multiple chemotherapeutic agents. Downregulation of L6 reverses multidrug resistance (MDR) and sensitizes cells to adriamycin-induced apoptosis.[121] Additionally, L23 enhances glutathione S transferase (GST) activity and the intracellular glutathione content in the cells.[324]

RPs have also been shown to contribute to radioresistance.[76] In non-small cell lung cancer cells, ionizing radiation (IR) led to casein kinase 2α (CK2α)-mediated phosphorylation of S3, which induced the dissociation of the S3-TRAF2 complex and led to NFκB activation, resulting in a significant upregulation of prosurvival genes (cIAP1, cIAP2, and survivin).[76] Another interesting observation is that the phosphorylation of S6 is increased in pancreatic acinar cells upon challenge with DMBA, a carcinogen, or transgenic expression of mutant K-ras.[261] The development of pancreatic cancer precursor lesions is greatly reduced in $S6P^{-/-}$ mice, which are incapable of S6 phosphorylation.[261]

6. THE POTENTIAL VALUE OF RIBOSOMAL PROTEINS IN THE DIAGNOSIS AND TREATMENT OF HUMAN DISEASES

RPs constitute the functionally active part of the ribosome, in addition to acting as a scaffold that keeps proteins in position for optimal functioning. However, it is now clear that the RPs often perform auxiliary functions and act as “sentinels for self-evaluation of cellular health”.[6] Thus, it is not surprising that even slight disruptions in RPs can lead to a wide array of pathologies. Due to their involvement in pathways that are tightly linked to cell growth, proliferation, and metabolism, RPs may serve as promising diagnostic and prognostic biomarkers and therapeutic targets for human diseases. In the following section, we focus on the implications of RPs in various disease states and their potential for diagnosing disease and as targets for treatment.

A. Ribosomal Proteins as Cancer Biomarkers

Differential expression of several RP genes is observed in different human disorders, especially in genetic diseases and cancer (Table III). It is known that aberrant ribosome synthesis contributes to increased cellular proliferation, but whether the differential

expression of RPs is a causative factor or simply an associated feature in enhanced cell proliferation is unclear.

Differential display (DD) analyses demonstrated that the S8, L12, L23a, L27 and L30 mRNA levels are enhanced in human hepatocellular carcinoma (HCC) tissue samples and cell lines.[325] Immunohistochemical analyses suggested that L36 is expressed in 75% of HCC patients, but is not detected in corresponding non-tumor liver tissues. The L36 level is higher in the early stages of cancer, and L36 expression is associated with a better overall survival, suggesting that it may represent an independent prognostic factor for HCC.[326] L36a mRNA is preferentially overexpressed in 85% of HCC tissues and in all eight HCC cell lines in a previous study.[8] The overexpression of L36a enhances colony formation and cell proliferation.[8]

L15 expression is markedly upregulated in gastric cancer cell lines and tissues.[158] Inhibition of L15 expression suppresses gastric cancer cell growth *in vitro* and reduces tumorigenicity *in vivo*.[158] S13 expression is also upregulated in human gastric cancer.[91] S13 knockdown inhibits gastric cancer cell growth, with significant G1 cell cycle arrest, probably through the upregulation of p27.[91] L6 is overexpressed in adriamycin-resistant SGC7901 gastric cancer cells.[120] Similarly, L6 is also upregulated in gastric cancer tissues compared to normal gastric mucosa,[120] and contributes to increased cell growth *via* cyclin E upregulation.[120] Patients with low levels of L6 have better survival than those with higher levels, suggesting that L6 may be a potential prognostic biomarker for gastric cancer patients.[120] The upregulation of L13 mRNA expression was observed in 10 of 36 (28%) gastric cancer tissue samples, and the upregulation of the L13 gene was associated with the clinical stage of the disease.[327]

The expression of RPs in colorectal cancer (CRC) differs from that seen in the normal mucosa.[328] The RP genes overexpressed in CRC include the large subunit protein, L5, and the small subunit proteins, S3, S6, S8, and S12.[329] Another study demonstrated differential expression of 12 RPs (Sa, S8, S11, S12, S18, S24, L7, L13a, L18, L28, L32, and L35a) in CRC compared with paired normal colonic mucosa.[330] S11 and L7 were highly expressed, and all other ribosomal proteins were markedly decreased, in CRC tissue samples.[330] Fecal L19 expression is associated with advanced tumor stages and addictive to serum CEA (carcinoembryonic antigen), and can be used to predict the prognosis of CRC patients.[331] A fluorescent mRNA differential display analysis also identified several RPs (L10a, L44, S11, and S19) that are remarkably upregulated in human colon carcinoma.[332] The upregulation of L13 mRNA expression was observed in 19 of 46 (41%) colorectal cancer tissue samples compared to adjacent normal tissue samples. Knocking down L13 expression using small interfering RNA (siRNA) results in a dramatic attenuation of colon cancer cell growth *in vitro* and decreased tumorigenicity *in vivo*.[327] In contrast, recent evidence suggests that increased levels of S27L in either feces or cancer tissue are associated with a better prognosis. Thus, assessing the RP levels can be useful as a predictive index for disease progression and can enable the personalization of therapies, particularly in intermediate-stage CRC patients.[333]

Another tumor type exhibiting differential RP expression is prostate cancer, wherein the mRNA levels of L19 are elevated, contributing to reduced patient survival.[334] The siRNA-mediated L19 knockdown abolishes aggressive phenotypes of the disease.[335] Thus, L19 may serve as both a prognostic marker and a valid therapeutic target for prostate cancer. S2 is overexpressed in malignant prostate cancer cell lines and tissues, and has been reported to be a novel diagnostic marker for prostate cancer.[336,337]

Decreased expression of L14[338] and overexpression of L15[339] in esophageal cancer have previously been suggested. Additionally, hyperphosphorylation of S6 and an increased phosphorylated S6/S6 (pS6/S6) ratio were seen in esophageal squamous cell carcinoma patients, and were associated with a reduced disease-free survival.[340] Importantly, knockdown of S6 and S6K1 increased cell death *via* the downregulation of cyclin D1, and also suppressed cell migration and invasion *via* the downregulation of ERK/JNK phosphorylation in esophageal cancer cells.[340] These findings suggest that pS6 and the ratio of pS6/S6 are closely related to tumor progression and have prognostic significance in esophageal squamous cell carcinoma.[340]

The RPs appear to have roles in a wide variety of other cancer types as well. For example, the expression levels of L22 mRNA and protein have been shown to be significantly downregulated in NSCLC patients.[341] In addition, high pS6 expression was suggested to be a negative prognostic factor for lung adenocarcinoma, because it was associated with the time-to-metastasis in patients with early stage lung adenocarcinoma.[169] pS6 is also overexpressed in brain metastatic lesions of lung cancer.[169] The downregulation of L41 mRNA was detected in 75% of primary breast cancers.[150] Downregulation of L7a is associated with a poorer survival of osteocarcinoma patients with lung metastasis.[342] The S6 protein is highly expressed in diffuse large B cell lymphomas (DLBCL), and knockdown of S6 leads to decreased proliferation of these cells in culture.[343] L23 mRNA is overexpressed in higher-risk MDS patients, and elevated L23 expression is inversely associated with apoptosis in $CD34^+$ bone marrow cells. The L23 level can serve as an independent prognostic indicator, regardless of the patient age, IPSS (international prognostic scoring system) score, or hemoglobin level. Thus, a higher level of L23 predicts disease progression and poor survival.[344] A recent study indicated that high levels of X-linked RPS4 (RPS4X) correlated with reduced disease progression and a decreased risk of death in patients with high-grade serous epithelial ovarian cancer. Indeed, depletion of RPS4X reduces the cell growth rate and increases the resistance to cisplatin in ovarian cancer cell lines.[345]

B. Ribosomal Proteins as Molecular Targets for Drug Discovery and Development

Considering that aberrant ribosome biogenesis and protein translation are associated with cell growth and cell proliferation, hematological and neurological disorders, and an increased risk of cancer and other chronic diseases, it would be reasonable to target the components of the ribosome biogenesis and the translation machinery that are deregulated in specific disease states in order to develop novel targeted therapies. Below, we will discuss a few examples to illustrate the potential of RPs as novel drug targets.

1). Gene Therapy and Pharmacotherapy for Ribosomopathies—Because many DBA patients exhibit a deficiency in S19, gene therapy has been attempted using lentiviral vectors containing the S19 gene transduced into the bone marrow $CD34^+$ cells from DBA patients.[346] The enforced expression of the S19 transgene improves the proliferation of S19 mutant $CD34^+$ cells and enhances the erythroid development of S19-deficient hematopoietic progenitors, suggesting the feasibility of gene therapy for S19-deficient DBA. Furthermore, a high level of S19 expression is required for correction of the erythroid development, and transplantation of unsorted S19-transduced $CD34^+$ cells from mobilized peripheral blood led to successful gene therapy effects *in vivo*.[346] These results indicate that targeted therapies modulating specific RPs in disease states may represent a new approach to treatment of this type of ribosomopathy.

The induction and activation of the p53 pathway are common in human disorders of defective ribosome biogenesis, such as DBA[102] and 5q- syndrome.[302] Lenalidomide (Len), a thalidomide derivative, stabilizes MDM2 and accelerates p53 degradation.[347] Len treatment leads to increased phosphorylation of MDM2 on Ser-166/186, and disturbs the binding of S14, resulting in suppressed MDM2 autoubiquitination, restoring the function of MDM2 in 5q- syndrome, and overcoming the p53 activation.[347] Thus, the inhibition of p53 in patients with ribosomopathies seems to be a promising therapeutic concept, since the typical disease phenotype arises due to improper p53 activation, which leads to the apoptosis of hematopoietic progenitor cells. However, it is important to note that long-term p53 inactivation may lead to an increased risk of various cancers. The inactivation of upstream regulators of p53, such as MDM2-interacting RPs (*i.e.*, L11) could be possible alternatives to reduce this risk.[348]

2). Treatment of Neurological Disorders—S3 plays crucial roles in oxidative stress and DNA repair. Based on the protein transduction domain, PEP-1, researchers have developed a novel construct, PEP-1-S3, which has been shown to protect against experimental cerebral ischemic damage.[349] In addition, the PEP-1-S3 construct could protect dopaminergic neurons from oxidative stress in an MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced mouse model of Parkinsonism.[350] PEP-1-S3 could be efficiently delivered to the *substantia nigra*, where it significantly inhibited the generation of reactive oxygen species (ROS) and DNA fragmentation, and improved cell survival. This observed neuroprotection was related to the antiapoptotic activity of PEP-1-S3, which suggests that it might represent a novel therapy for Parkinson's disease.

3). Therapy for Inflammatory Diseases—Considering that S19 plays a role in the inflammatory response by binding to the pro-inflammatory cytokine macrophage migration inhibitory factor (MIF),[104] researchers have sought to establish whether recombinant S19 can exert anti-inflammatory effects in a mouse model of anti-GBM (glomerular basement membrane) glomerulonephritis (GN), in which MIF is known to play an important role. GBM-GN mice treated with S19 showed the absence of glomerular crescents, glomerular necrosis, renal dysfunction and/or proteinuria. Interestingly, S19 was shown to block the upregulation of MIF and CD74 and inactivate ERK and NFκB signaling, thereby inhibiting

macrophage and T-cell infiltration, Th1 and Th17 responses, and the expression of pro-inflammatory cytokines.[351]

4). Inhibition of rRNA Transcription and RP Expression for Cancer Therapy— Uncontrolled ribosome synthesis due to increased rRNA transcription by Pol I leads to increased cellular proliferation and cancer. An orally active small molecule, CX-5461, targets rRNA transcription and selectively kills B-lymphoma cells with little effect on the wild-type population.[352] CX-5461 selectively inhibits only Pol I-driven transcription, causing nucleolar disruption and subsequent activation of the p53-dependent apoptotic signaling pathway. Additionally, CX-5461 inhibits rRNA synthesis and induces both autophagy and senescence, but not apoptosis, *via* a p53-independent mechanism in solid tumor cells.[353] Thus, selectively inhibiting rRNA transcription could serve as a promising therapeutic strategy for cancer, in both hematological and solid tumors.[353] Another small molecule compound, CX-3543, also inhibited Pol I transcription and induced apoptosis in cancer cells by causing the selective disruption of the nucleolin/rDNA complex.[354]

Silencing RP expression by RNAi techniques has been shown to inhibit the proliferation of human pancreatic,[144] gastric,[119] and prostate[335] cancer cells both *in vitro* and *in vivo*. DNAZYM-1P, a 'ribozyme-like' oligonucleotide, has recently been developed to target the overexpression of S2. DNAZYM-1P decreased the S2 expression in malignant prostate cells with little effect on normal cells. DNAZYM-1P inhibited cell growth and induced apoptosis in prostate cancer cells. *In vivo*, DNAZYM-1P blocked tumor growth and metastasis, and eventually eradicated tumors. Moreover, DNAZYM-1P improved the disease-free survival of tumor-bearing mice in a dose-dependent manner.[337]

Another interesting study reported that recombinant L23a and L31 proteins cloned from the giant panda possessed anticancer activities, as shown by their ability to retard the growth and proliferation of human laryngeal carcinoma, Hep-2, and human hepatoma, HepG-2, cells.[145,146]

5). Modulation of the RPs-MDM2-p53 Pathway for Cancer Therapy—More recently, experimental cancer therapy targeting the S7-MDM2-p53 pathway has been reported.[328] This study employed recombinant LZ-8 (rLZ-8) to inhibit precursor ribosomal RNA synthesis, and was shown to reduce polysome formation, triggering nucleolar stress and resulting in an increased binding of S7 to MDM2, leading to p53 activation.[355] LZ-8, an immunomodulatory protein, was derived from the medicinal mushroom *Ganoderma lucidum* (*Reishi or Ling Zhi*). As noted above, rLZ-8 treatment activates p53, leading to p21 expression, G1 arrest, and the inhibition of cell growth in a p53-dependent manner. It also suppressed the growth of xenograft tumors in mice.[355] In another report,[356] adenovirus-mediated delivery of L23 was shown to inhibit the proliferation of gastric cancer cells harboring wildtype p53 *in vitro* and *in vivo*. Exogenous L23 stabilizes and activates p53 though the inhibition of the MDM2-p53 interaction, inducing cell cycle arrest and apoptosis.[356]

7. MITOCHONDRIAL RIBOSOMAL PROTEINS –A BRIEF DISCUSSION

This review has focused mainly on the cytoplasmic ribosomal proteins. However, the mitochondria have their own protein synthesis machinery. Mammalian mitochondrial ribosomes (55S) consist of small (28S) and large (39S) subunits.[357,358] The 55S ribosome contains more than 75 mitochondrial ribosomal proteins (MRPs), encoded by nuclear genes that are imported into the mitochondria, where they are assembled into the mitochondrial ribosome. The small subunit of this ribosome contains 29 proteins, whereas the large subunit has about 50 proteins.

As expected, MRPs play key roles in the ribosomal structure and assembly, and also in mitochondrial protein translation. Knockdown of MRPs caused mitonuclear protein imbalances and impaired mitochondrial respiration. Similar to the cytoplasmic RPs, MRPs also possess several extra-ribosomal functions unrelated to mitochondrial translation. Several MRPs (MRPS29,[359,360] MRPS30,[361,362] MRPL37,[363] MRPL41,[364]) have also been reported play a role in apoptosis. For example, MRPL41 physically interacts with Bcl-2, which may contribute to its pro-apoptotic activities.[364] Studies also reported that MRPL41 stabilizes the p53 protein to induce apoptosis.[365] Interestingly, MRPL41 also causes p53-independent G1 phase cell cycle arrest *via* stabilization of p27.[365] MRPL41 has also been shown to stabilize p21 and arrest cells in the G1 phase under conditions of serum starvation.[366]

MRPL41 is downregulated in breast and kidney cancer cell lines/tissues, suggesting that it may have tumor-suppressor properties.[367] The overexpression of the MRPS36 retards cell proliferation *via* the induction of p21 expression and phosphorylation of p53.[368] Contrarily, the overexpression of the MRPS18-2 protein leads to the immortalization and dedifferentiation of primary rat embryonic fibroblasts, thus indicating that it has a potential role in tumorigenesis.[369] MRPL59 (CRIF1, CR6-interacting factor 1) has been identified as a transcription co-factor that interacts with Gadd45 and negatively regulates cell growth and cell cycle progression.[370] MRPL58 (ICT1, immature colon carcinoma transcript 1) is essential for cell viability. Knockdown MRPL58 inhibits cell proliferation and decreases the mitochondrial membrane potential and mass, and also decreases the cytochrome c oxidase activity.[371]

Recently, Chinese researchers have established a link between the overexpression of MRPS12 and the proliferation and migration of gastric cancer cells.[372] Studies have also identified MRPs with major mutations leading to mitochondrial translation deficiencies and lethality. Abnormal expression of MRPs is also observed in various cancers, such as gliomas, breast cancer, squamous cell carcinoma, and osteosarcoma.[370,373,374] For example, the expression of MRPL59 is dramatically reduced in adrenal adenoma and papillary thyroid cancer.[370] SNPs in the MRPS30 gene were shown to correlate with breast cancer in both Caucasian and Chinese populations, especially in the older subjects.[373,374]

8. CONCLUSIONS AND FUTURE DIRECTIONS

Our understanding of the ribosome and RPs based on information obtained during the past two decades has considerably improved. RPs were initially thought to be “housekeeping” genes, but are now considered to have diverse extraribosomal functions, including roles in cellular functions ranging from cell cycle progression to cell death, to malignant transformation and cellular metabolism. Another important extraribosomal function includes the surveillance of ribosome synthesis. Importantly, an aberration or deregulation in any of these processes may drive malignant transformation and lead to an abnormal cellular phenotype.[375] The discovery of extraribosomal functions of the ribosomal components adds an additional layer of complexity to the relationship between dysregulated ribosome biogenesis and disease states such as cancer. In fact, it is difficult to distinguish the primary from secondary effects of mutant RPs. Critically, one must appreciate that the nucleolar proteome is not static, but exhibits dynamic responses when stimulated with physiological and pathological stresses, such as nutrient and growth factor starvation. These environmental factors regulate the nucleolar localization and trafficking of many proteins through controlled sequestration and release. Disturbances in the normal nucleolar function and structure lead to disruption of this regulation, and as a consequence, affect multiple cellular functions. In fact, several pathways that modulate Pol I transcription during ribosome biogenesis/protein synthesis are subject to regulation by the nucleolus. Thus, the nucleolus is both a target of cancer signaling, and also an upstream regulator of pathways important for normal cell growth and function. There is frequent cross-talk between the components of the ribosome, especially the ribosomal proteins, and other signaling pathways; these proteins undergo numerous modifications in response to stress and physiological demands.[376]

The disruption of ribosome biogenesis is an important causal factor in the induction of ribosomal stress. It affects the ultimate fate of the cell, and may result in cell cycle arrest or apoptosis *via* a p53-mediated pathway. Indeed, numerous reports have emphasized the importance of the RPs-MDM2-p53 interplay, which helps to maintain the integrity of ribosome biogenesis, and ultimately, normal cellular development and function. Studies on human ribosomopathies, as well as animal models, have highlighted the role of the p53 pathway in the clinical manifestations of many human ribosomal disorders, such as DBA and 5q-syndrome. It appears that p53 activation is a common cellular response, but the consequences of this response vary in different cell types, probably due to the differences in the tissue-specific activation of p53’s downstream targets.

The fact that the dysregulation of p53 is an important causal factor in more than half of human cancers, and the involvement of ribosomal stress in the activation and regulation of p53 in relation to cell cycle control, makes studies of the RP-MDM2-p53 pathways pivotal to understanding the mechanisms of carcinogenesis, and for the development of novel treatments for cancer. We have already discussed how several RPs, such as L11, L5, L23, L26, L6, etc., modulate the MDM2-p53 pathway, in some cases playing redundant roles. Owing to the large number of RPs and their similar functions, one should be careful when evaluating the roles of RPs as molecular biomarkers and therapeutic targets for human disease.

Further investigations will be required to reveal the regulatory network associated with this signaling cascade. For instance, the exact mechanisms that control RP shuttling between the nucleolus and nucleoplasm after ribosomal stress are not clear. The interacting partners for MDM2-binding RPs have also not yet been identified. In addition, RPs are short-lived proteins that need to be post-translationally modified to ensure their stability and nuclear transport. The modifications of RPs that are involved in the RPs-MDM2-p53 pathway deserve further exploration. Interestingly, the HBx (Hepatitis B virus X) oncoprotein confers nucleolar stress-induced p53 expression by disrupting the interaction between L11 and MDM2,[377] suggesting the possible inactivation of the L11-MDM2-p53 pathway by the HBx oncoprotein in hepatocellular carcinogenesis. However, the relationship between defective ribosome biogenesis and cancer is complicated and not fully understood. The altered expression of some RPs seems to be a common feature in many cancers, however, it is unclear whether increased ribosome activity due to increased cellular proliferation leads to RP overexpression, or whether these RPs are actually responsible for the cell transformation. Although changes in RP levels have been suggested as potential biomarkers for cancer prognosis, most of these studies were descriptive and lacked mechanistic insights. Further studies will therefore be needed to reveal the functional roles of distinct sets of RPs that are deregulated in specific cancer types.

Furthermore, it is not clear how the MDM2-binding RPs modulate MDM2's E3 ubiquitin ligase activity. For example, it is unclear whether MDM2-binding RPs function individually or as a subribosomal complex in response to nucleolar stress. The emerging findings indicate that the pathways linking ribosome defects and p53 signaling are more complicated than previously considered, and it is most likely that multiple players are involved in these interactions. Finally, how individual RPs perform non-redundant roles in each stage of the ribosomal stress response is also a topic that needs to be addressed.

More recent evidence suggests that the RP-associated p53 induction in response to ribosomal stress is independent of the RPs-MDM2 interaction. A direct link between RP deficiency and impaired p53 protein synthesis has been established in the absence of MDM2.[123,228] In addition, p53-independent cell cycle arrest mechanisms in response to ribosome biogenesis have also been described. Moreover, the role of RPs in regulating proteins other than p53 may reflect their diverse extraribosomal functions, and represent distinct outcomes of ribosomal stress. Therefore, future studies are needed to explore the putative extraribosomal functions of RPs in regulating p53-independent pathways.

The differential expression of RPs in several cancer types makes them attractive candidates that may serve as noninvasive biomarkers for cancer. Ribosome biogenesis appears to be an attractive target for cancer prevention or therapy. Supporting this possibility, the activation of p53 by nucleolar stress has been shown during the treatment of B-cell lymphoma in mice. The newly appreciated RPs-MDM2-p53 pathway also offers an opportunity for anticancer drug development. For example, it is now recognized that targeting both MDM2 and MDMX presents a more effective approach towards p53 activation and subsequent tumor growth suppression.[378] An ideal anticancer drug candidate would be a small molecule that could bind to the zinc finger domain of MDM2 and prevent its interaction with p53 in a manner similar to L11. This hypothetical molecule could potentially activate p53 by

deactivating both MDM2 and MDMX, since turning on the nucleolar stress-RP-p53 pathway can simultaneously deactivate both MDM2 and MDMX. Thus, designing lead compounds that mimic the ability of RPs to bind to MDM2 could open a door for the future development of novel therapeutic agents.

In addition, RPs have a role in the metabolic control of the cell, mainly *via* the S6 kinase/mTOR signaling pathways. RPs are also critical in organogenesis; it will be important to investigate their roles in organ growth, metabolic control, and interactions with growth factors in order to obtain a better understanding of their roles in maintaining homeostasis.

Considering that RPs are associated with numerous signaling pathways and regulate, as well as are regulated by, various genetic and epigenetic factors, future studies are needed to explore the role of RPs under normal and pathological conditions with respect to both the p53-dependent and –independent pathways. It is hoped that a better understanding of these intricate pathways and the complex interplay between RPs and various signaling pathways will provide new strategies for the diagnosis, prevention, treatment and monitoring of RP-associated human diseases.

ACKNOWLEDGEMENTS

The contents of the paper are solely the responsibility of the authors, and do not necessarily represent the official views of the National Institutes of Health or other funding agencies. R.Z. was supported by NIH grants R01 CA112029, R01 CA121211, and R01 CA186662. We thank the current and former members of our laboratories for their contributions to the publications cited in this work. We thank Dr. Jiang-Jiang Qin and Mr. Sukesh Voruganti for helpful discussions during the preparation of this manuscript. The research field of ribosomal proteins reviewed in this article is rapidly expanding; we apologize for not being able to cite all of the references published in the recent years, due to space limitations.

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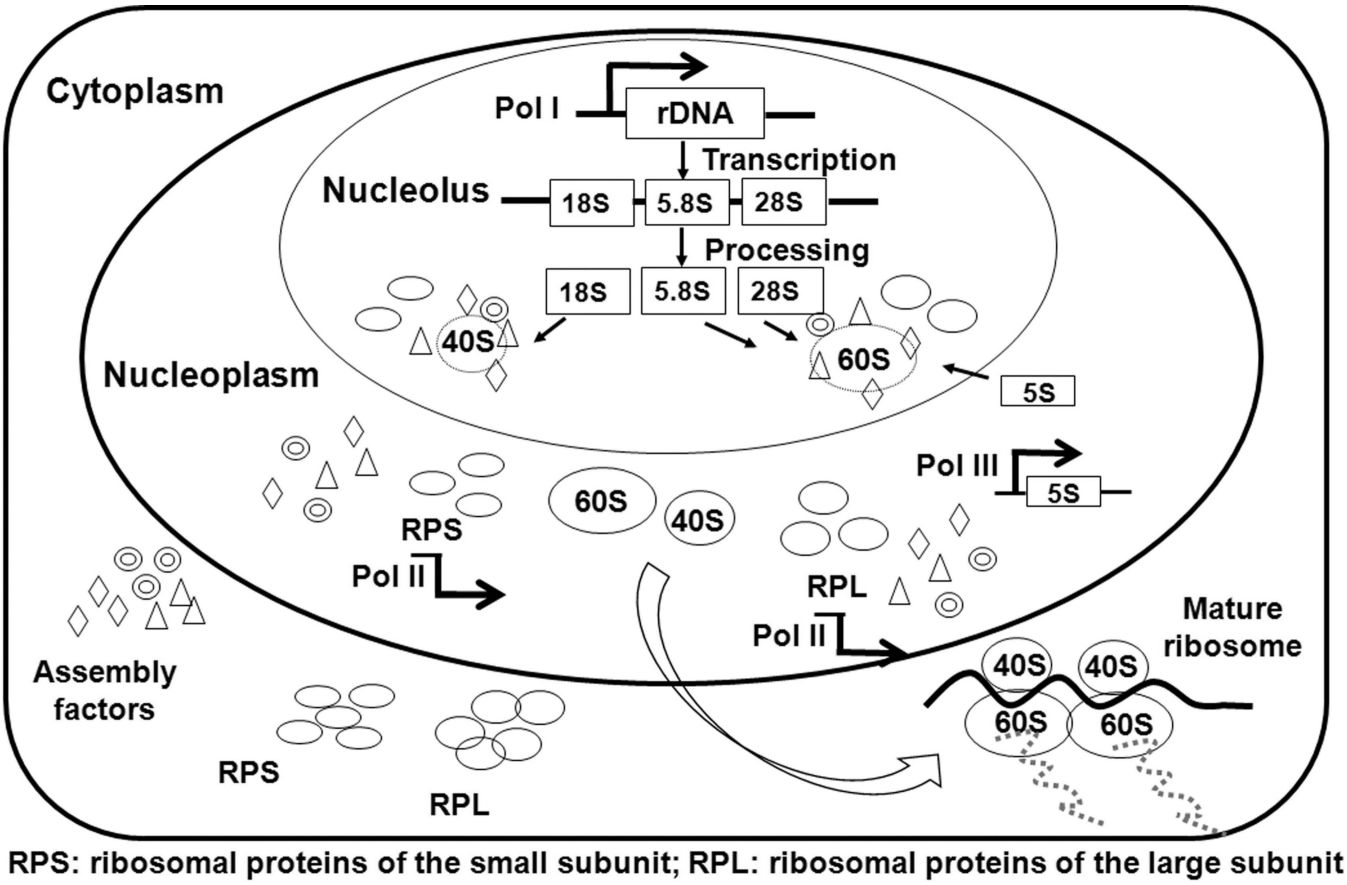

Figure 1. The process of ribosome biogenesis

Ribosome synthesis is a dynamic and coordinated multistep process. All three types of RNA polymerases and several hundred accessory factors participate in this process, which occurs throughout the cell. The ribosomal RNA genes are transcribed by RNA polymerase I (Pol I) into a single rRNA precursor within the nucleolus, which is subsequently cleaved and modified by several accessory factors to yield 18S, 5.8S, and 28S rRNA. The 5S rRNA gene is transcribed separately in the nucleoplasm by RNA polymerase III (Pol III). The RP genes are transcribed in the nucleoplasm by RNA polymerase II (Pol II), and these transcripts are exported to the cytoplasm for translation. The RPs and 5S RNA are imported to the nucleolus, where they assemble with rRNAs to form the small (40S) and large (60S) subunits. These preassembled subunits are then exported to the cytoplasm, where they undergo additional maturation to form the mature (80S) ribosome.

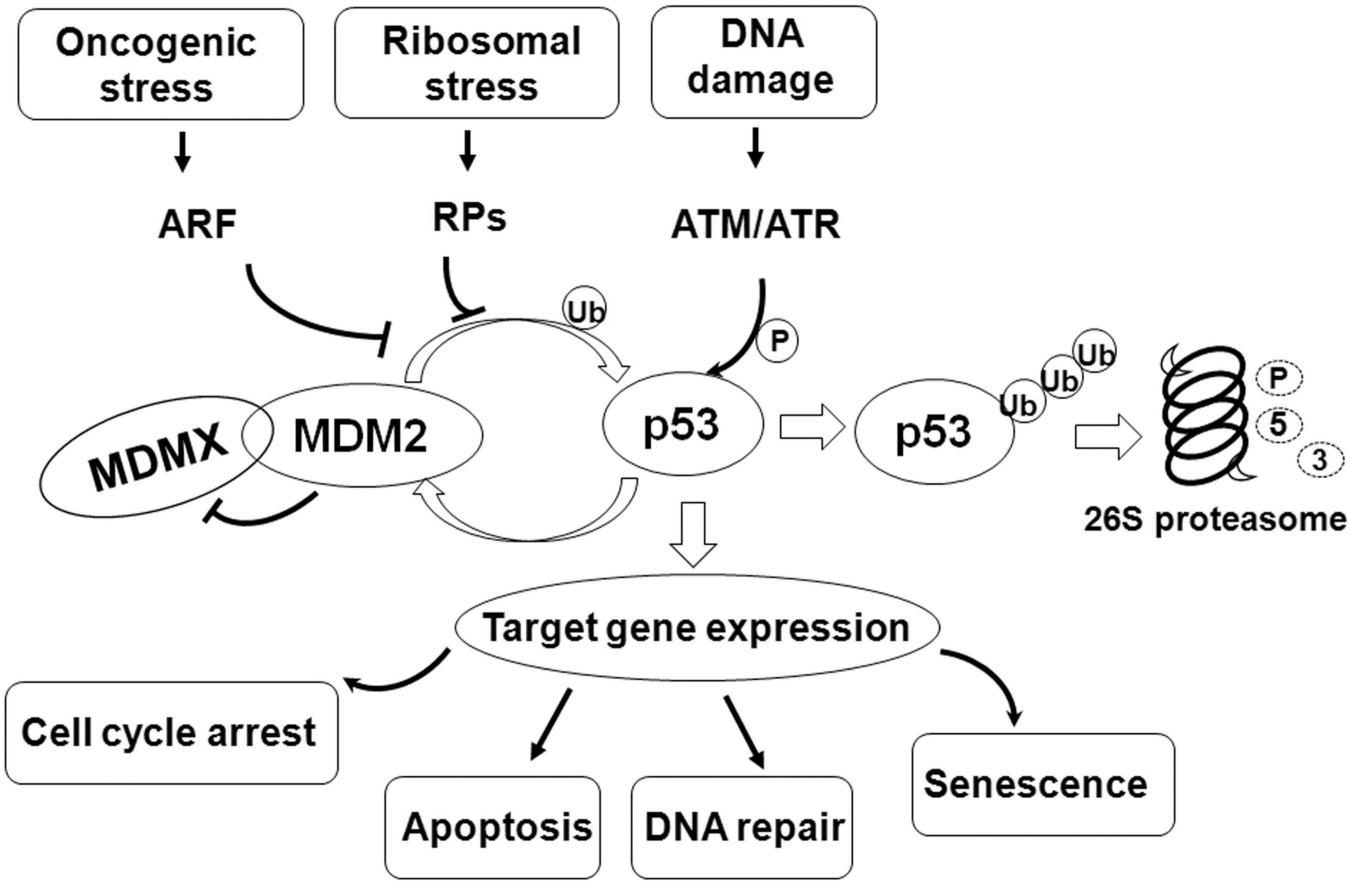

Figure 2. The MDM2-p53 signaling pathway

The p53 tumor suppressor coordinates a complicated network of signaling pathways to prevent aberrant cell growth and proliferation. Under normal conditions, the p53 protein expression is tightly regulated and maintained at a low level by murine double minute 2 (MDM2) and MDMX. MDM2 has E3 ligase activity, and mediates the attachment of a ubiquitin (Ub) moiety to p53, which targets it for proteasomal degradation. MDM2 also binds p53 and inhibits its transcriptional activity. MDMX lacks the E3 ligase, but forms a heterodimeric complex with MDM2 to stimulate MDM2-mediated p53 degradation. MDMX also suppresses the transcriptional activity of p53 through its direct interaction with p53. In turn, p53 controls the transcription of MDM2 through a negative feedback loop. MDM2 also targets MDMX for ubiquitination and proteosomal degradation. In response to stress stimuli, the inhibitory effects on p53 are removed through distinct mechanisms, allowing p53 to be activated. For instance, exposures to radiation (ionizing and ultraviolet light) and DNA-damaging agents activate several kinases, such as ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3 related (ATR), which modify the phosphorylation states of p53, MDMX, and MDM2, leading to conformational changes in these proteins that block their interactions, resulting in p53 stabilization. Oncogenic signals stimulate the production of alternative reading frame (ARF), which binds to MDM2 and stabilizes p53. Defective ribosome biogenesis causes the release of several RPs, which bind to MDM2 and suppress its E3 ligase activity, resulting in p53 accumulation and activation. The consequence of p53 protein activation is the transactivation of several downstream genes. Depending on the cell

type and the stressors, the outcome can be cell cycle arrest, apoptosis, DNA repair, or senescence.

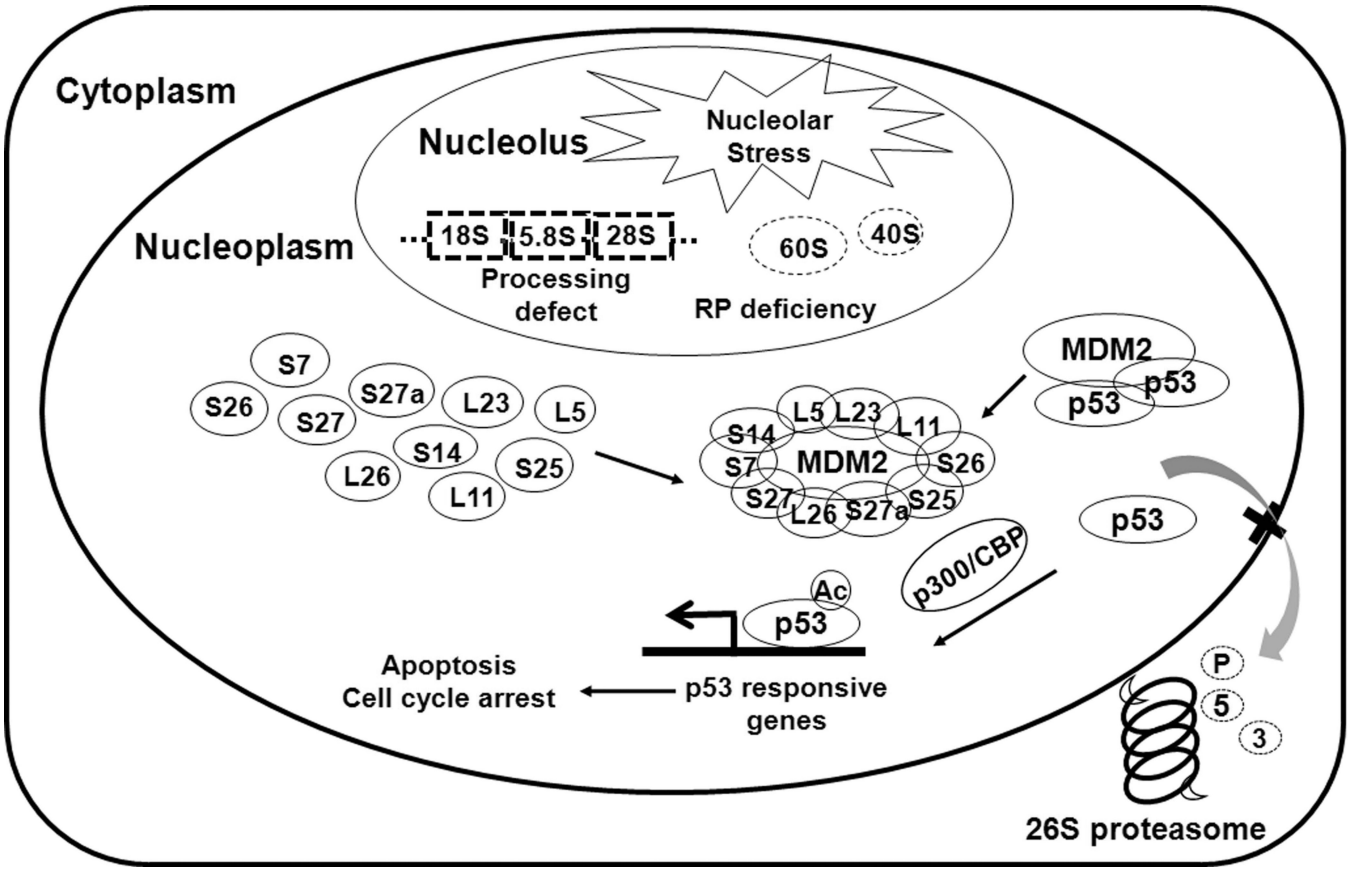

Figure 3. The RPs-MDM2-p53 interplay in nucleolar stress

Defects in ribosome biogenesis due to impairment of rRNA synthesis or processing, nucleolar protein deficiency, or due to malfunctions trigger nucleolar stress (also called ribosomal stress). In response to nucleolar stress, a subset of RPs is released from the nucleolus to the nucleoplasm, where they bind to MDM2 and inhibit the MDM2-mediated ubiquitination and degradation of p53, leading to the stabilization and activation of p53. The RPs-MDM2-p53 interplay provides a surveillance mechanism to monitor the integrity of ribosome biogenesis and coordinate cell growth and proliferation.

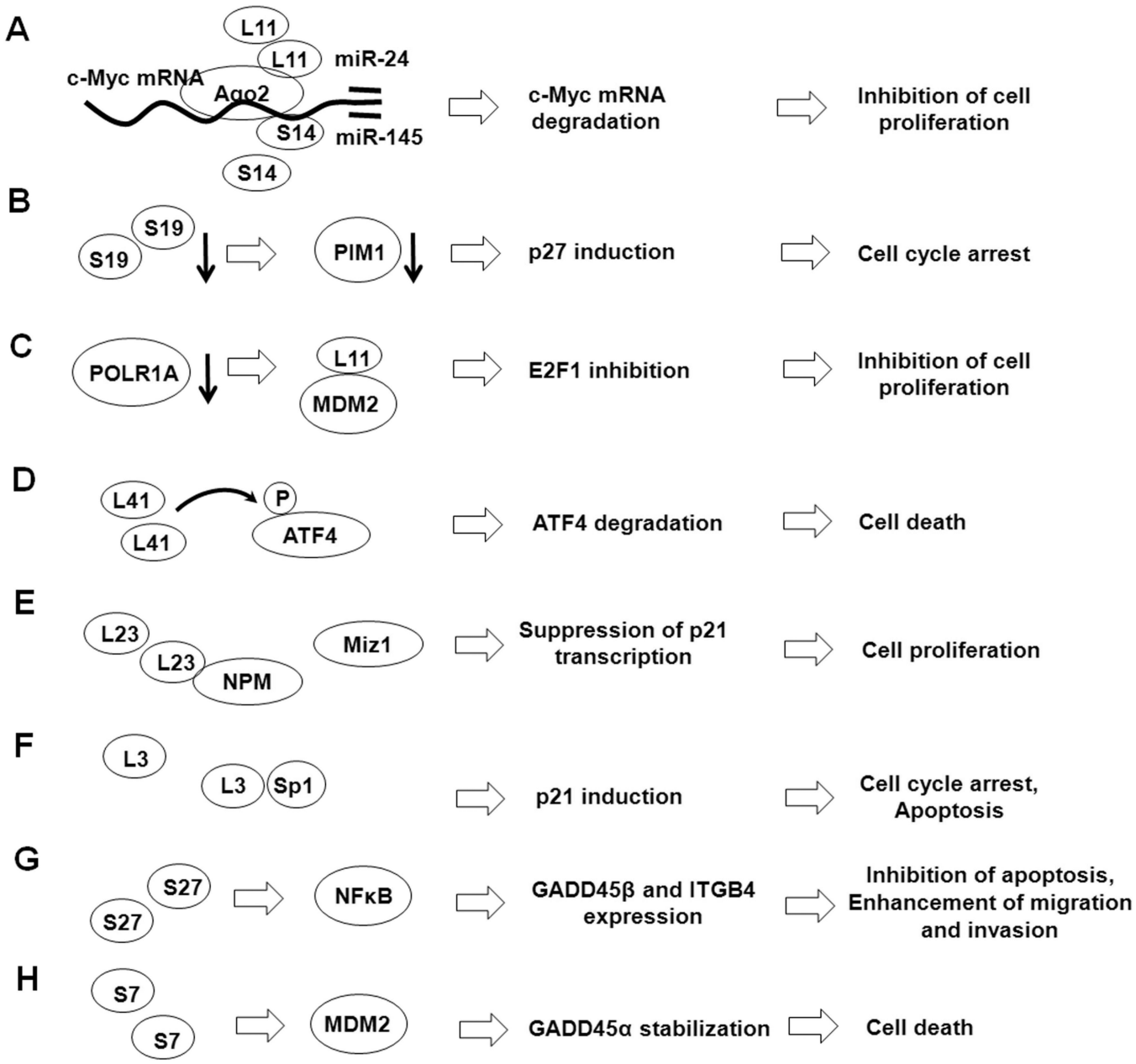

Figure 4. The p53-independent functions of RPs

The roles of RPs in regulating cellular functions also involve p53-independent mechanisms. (A) L11 and S14 bind to c-Myc mRNA and recruit Ago-2 and miRNAs, resulting in the degradation of c-Myc mRNA. (B) S19 deficiency causes PIM1 degradation and p27 accumulation, resulting in the inhibition of cell cycle progression. (C) Knockdown of POLR1A activates the L11-MDM2 interaction and inhibits the MDM2-mediated stabilization of E2F1. (D) L41 mediates the phosphorylation and translocation of ATF4 and induces the proteosomal degradation of ATF4. (E) L23 binds to NPM, the essential co-activator of Miz1 involved in regulating p21 transcription, leading to increased cell proliferation. (F) L3 mediates p21 upregulation through its interaction with Sp1. (G) S27 regulates GADD45β and ITGB4 through NFκB signaling to inhibit apoptosis and promote

cell migration and invasion. (H) The S7-MDM2 interaction stabilizes GADD45α and induces cell death.

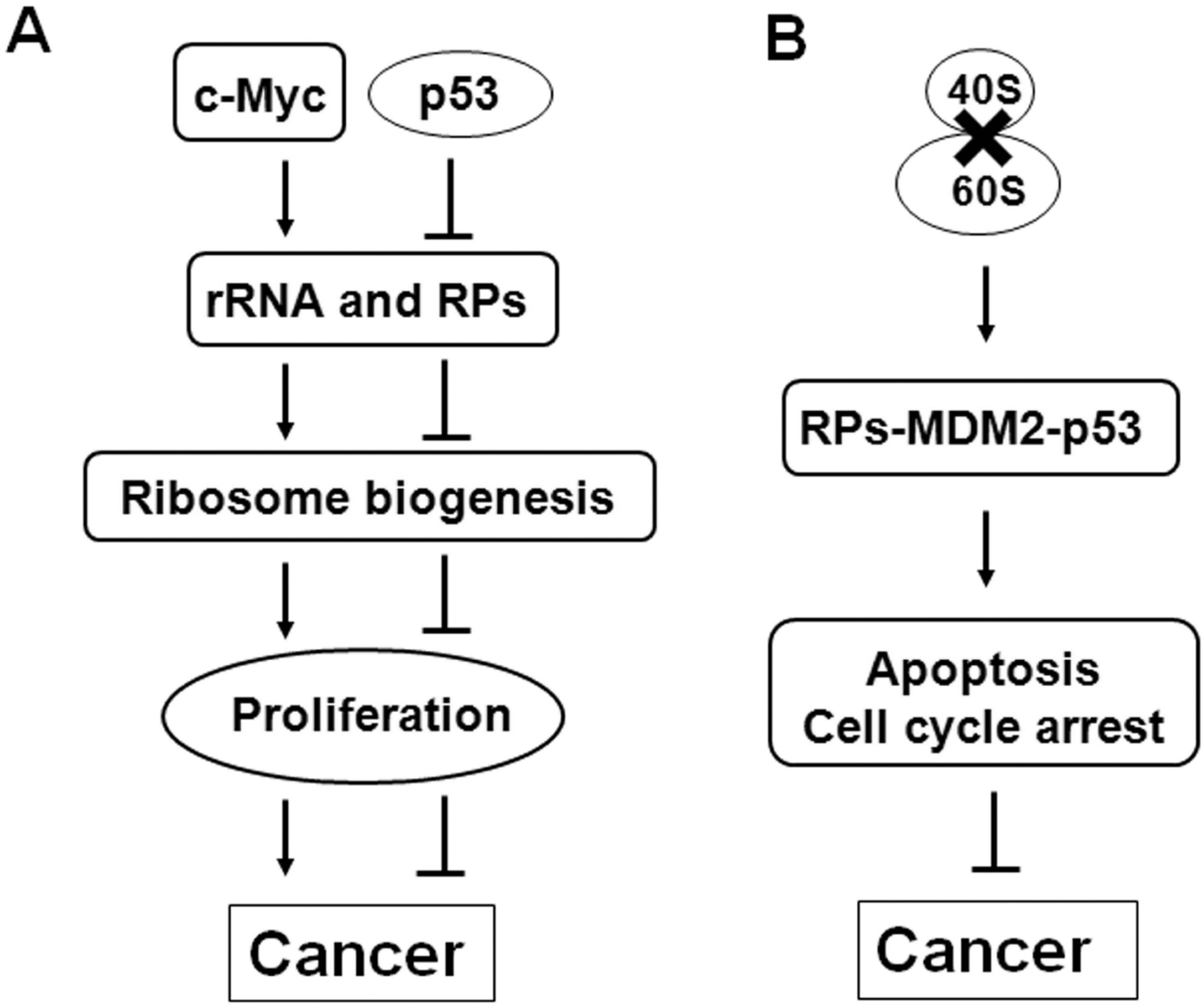

Figure 5. Proposed models of the roles of RPs in cancer

The ribosomal and extraribosomal functions of RPs are involved in carcinogenesis, cancer progression, and metastasis. (A) Aberrant ribosome biogenesis due to oncogene activation (such as c-Myc) causes uncontrolled cell growth and proliferation, increasing the risk of malignant transformation and carcinogenesis. On the contrary, p53 negatively regulates rRNA synthesis and ribosome biogenesis, protecting the cells from transformation and carcinogenesis. (B) The impairment of RPs-MDM2-p53 is linked to cancer progression. A MDM2 mutation in the central zinc finger (C305F) disrupts its interaction with L11, and significantly accelerates *Eμ-Myc*-induced lymphomagenesis in mice.

Table I

Extraribosomal Functions of Ribosomal Proteins

RP	Extraribosomal function(s)	Mechanism(s)	Ref.
Sa	Spleen development	Not studied	68
S2	PRMT3 enzyme complex subunit	Not studied	69
S3	DNA repair NFκB signaling Apoptosis Radioresistance	Interacts with both MDM2 and p53 and stabilizes p53 Interacts with DNA base excision repair proteins (8-oxoG) Induces apoptosis via JNK activation; NF-κB complex subunit Interacts with E2F1 and upregulates Bim	70–77
S3a	Apoptosis Cell transformation Cell differentiation Drug sensitivity	Interacts with CHOP	69–80
S4	Cell proliferation	Cysteine protease activity	81
S5	Cell cycle Cell differentiation	S5 downregulates the CDK-2/4/6 levels	82
S6	Apoptosis Cell proliferation Glucose metabolism	S6 depletion activates the p53 pathway through L11	9,23,58,83,84
S7	Cell cycle Apoptosis Cellular development	Interacts with MDM2 and stabilizes p53 S7 knockdown activates p53 in zebrafish S7 protects GADD45α from MDM2-mediated ubiquitination and degradation	85–88
S8	Cell survival	Interacts with CDK11p46 and sensitizes cells to Fas ligand-induced apoptosis	89
S9	Cell proliferation Cell differentiation	S9 depletion activates the p53 pathway	7,90
S13	Cell proliferation	S13 downregulates p27 expression and CDK2 kinase activity	91
S14	Cell cycle Apoptosis	S14 interacts with MDM2 and stabilizes p53 S14 depletion activates the p53 pathway S14 negatively regulates c-Myc activity	92–95
S15	Cell cycle	Interacts with MDM2 and stabilizes p53	96
S17	Possible cellular development	Not studied	97–99
S19	Cell differentiation Immunoregulation Embryonic development	S19 knockout impairs erythropoiesis and stimulates epidermal melanocytosis S19 interacts with macrophage migration inhibitory factor (MIF) and inhibits its function Homozygous disruption causes embryonic lethality in mice, possibly related to p53 activation	25,100–105
S20	Cell cycle Cellular development	S20 knockout leads to epidermal melanocytosis due to p53-mediated Kit ligand expression Interacts with MDM2 and stabilizes p53	96, 100–103
S25	Cell cycle Apoptosis	S25 interacts with MDM2 and stabilizes p53	106,107
S26	Cell cycle Apoptosis	S26 interacts with MDM2 and stabilizes p53 S26 enhances the p53–p300 association	108
S27	Cell proliferation Apoptosis Cell migration and invasion	S27 interacts with MDM2 and stabilizes p53 S27 regulates NF-κB -Gadd45β signaling S27 regulates integrin β4 expression	109–111
S27a	Cell cycle Apoptosis	S27a interacts with MDM2 and stabilizes p53	112
S29	Apoptosis Chemosensitization	Downregulation of apoptosis inhibitors and upregulation of apoptosis inducers	113,114

RP	Extraribosomal function(s)	Mechanism(s)	Ref.
L3	Cell Cycle Apoptosis Cellular development	L3 upregulates p21 through the interaction with Sp1 L3 deletion impairs the expansion of pancreatic progenitor cells in zebrafish, independent of p53	115,116
L5	Cell cycle Apoptosis	Interacts with MDM2 and stabilizes p53	117,118
L6	Cell proliferation Chemoresistance	Upregulates MDR proteins, GST activity/intracellular GSH, and cyclin E (gastric cancer) Interacts with MDM2 and stabilizes p53 (under ribosomal stress) Involved in normal pancreas development	119–123
L7	Cell cycle Apoptosis	Not studied	124
L8	Apoptosis Cell proliferation Cellular development	L8 deletion impairs development, inhibits cell proliferation and induces apoptosis in Drosophila	125,126
L11	Cell cycle Apoptosis	L11 interacts with MDM2 and stabilizes p53 Deletion of L11 activates p53 in zebrafish L11 negatively regulates the c-Myc level and activity	4,26,127–130
L13a	Immunoregulation	Inhibits the production of chemokines	131–133
L15	Cell proliferation	Interacts with the IFN-stimulated antiviral protein, p56	134
L17	Cell proliferation	Inhibits vascular smooth muscle cell growth	135
L22	Cellular development Cell transformation	Depletion of L22 increases p53 protein synthesis in αβ T cells L22 inactivation induces Lin28B expression through NFκB	15,136
L23	Cell cycle Apoptosis Cell invasion	Interacts with MDM2 and stabilizes p53 L23 depletion stabilizes p53 Sequesters nucleophosmin from Miz1	137–139
L26	Cell cycle Apoptosis	Interacts with MDM2 and stabilizes p53 Regulates p53 translation upon DNA damage	140,141
L29	Cell proliferation Cellular development Angiogenesis	L29 depletion activates p53	142–144
L31	Cell Proliferation	Not studied	145,146
L35a	Cell survival Drug resistance	Not studied; overexpression contributes to drug resistance	147,149
L36a	Cell proliferation	Not studied	8
L37	Cell cycle	L37 interacts with MDM2 and stabilizes p53 L37 depletion activates p53 through L11	96,150
L41	Cell survival Cell cycle Cell transformation	L41 phosphorylates and degrades ATF4	151,152
P1	Cell transformation	P1 upregulates E2F1 and cyclin E	153

Table II

Animal Models Used to Investigate RPs and Ribosomopathies

RP	Species	Alteration	Phenotype	Mechanism	Ref.
S6	Mouse	Conditional deletion (+/−) in liver cells	Cell cycle blockade in hepatocytes	Inhibits cyclin E mRNA expression	9
S6	Mouse	Conditional deletion (+/−) in T cells	Cell cycle arrest in T cells	p53 pathway activation	194
S6	Mouse	Deletion (+/−) in growing oocytes	Perigastrulation lethality	p53 pathway activation	83
S6	Mouse	Phosphorylation site mutation	Smaller size, decreased pancreatic insulin secretion, and impaired glucose tolerance	Not studied	58
S7	Mouse	ENU screening for mutation	Decreased body size, skeletal anomalies, midventral white spotting, and eye and central nervous system malformations	p53 pathway activation	88
S14	Mouse	Conditional deletion (+/−) in hematopoietic progenitor cells	Hematopoietic progenitor cell deficiencies	p53 pathway activation	102
S19	Mouse	Deletion (−/−)	Zygotes do not develop to normal blastocysts	Not studied	105
S20	Mouse	Mutation (Dsk+/−)	Increased pigmentation, erythrocyte hypoplasia	p53 stabilization stimulates Kit ligand expression	103
S7	Zebrafish	Morpholino knockdown	Apoptosis, cell cycle arrest, impaired hematopoiesis	Activation of the p53 pathway and MMP family genes	161
S19	Zebrafish	Morpholino knockdown	Erythropoietic failure	Activation of p53 family members (p53/ ΔNp63/TAp73)	191
S29	Zebrafish	Morpholino knockdown	Erythropoietic failure	Not studied	162
L22	Mouse	Deletion (−/−)	Impaired αβ T cell development	Induction of p53 protein synthesis	15
L24	Mouse	Mutation in C57BLKS Bst/+ mice	p53 pathway activated	p53 pathway activation	268,269
L27a	Mouse	Mutation in sooty foot ataxia (SFA) mice	Epidermal hyperpigmentation	p53 pathway activation	270
L29	Mouse	Deletion (−/−)	Mild growth retardation	Decrease in global protein synthesis	271
L11	Zebrafish	Morpholino knockdown	Defects in the development of hematopoietic stem cells (HSCs) and the maintenance of erythroid cells	p53 pathway activation	192
L38	Zebrafish	Morpholino knockdown	Shorter body trunk	Not studied	162

Table III

Ribosomal Protein Expression and Human Cancers

Cancer Type	RP(s)	Alteration	Implications for disease	Ref.
Liver cancer	S8, L12, L23a, L27, L30, L36, L36a	Upregulation	Increased L36 expression is associated with better survival	8,325,326
Gastric cancer	L15, S13, L6, L13	Upregulation	Upregulation is associated with increased cell proliferation, drug resistance, and poor survival	91,120,158,327
Colorectal cancer	L13, S11, L7, L10a, L44, S19, L19 (feces), S27L (cancer tissues and feces)	Upregulation	Fecal L19 expression is associated with advanced disease while elevated S27L expression correlates with a better prognosis	327–333
	Sa, S8, S12, S18, S24, L13a, L18, L28, L32, and L35a	Downregulation	Downregulation is associated with the ribosomes of the mucosal epithelia	
Prostate cancer	S2, L19	Upregulation	Elevated L19 expression is associated with advanced disease	334–337
Esophageal cancer	L14, L15, pS6	Downregulation (L14); Upregulation (L15, pS6)	Elevated levels of pS6 are associated with shorter survival and an adverse prognosis	338–340
Lung cancer	L22, pS6	Downregulation (L22); Upregulation (pS6)	Higher pS6 expression is associated with a shorter metastasis-free survival	169,341
Breast cancer	L41	Downregulation	L41 downregulation is related to malignant transformation	150
Osteosarcoma	L7a	Downregulation	Downregulation of L7a is associated with poor survival of osteosarcoma patients with lung metastasis	342
Leukemia Lymphoma	S6, L23	Upregulation	Elevated levels of L23 are associated with poor survival	343,344
Ovarian cancer	S4X	Upregulation	High expression of RPS4X is associated with a lower risk of death and later disease progression	345