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Ribosomal Proteins Control Tumor Suppressor Pathways in Response to Nucleolar Stress

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Ribosome biogenesis includes the making and processing of ribosomal RNAs, the biosynthesis of ribosomal proteins from their mRNAs in the cytosol and their transport to the nucleolus to assemble pre-ribosomal particles. Several stresses including cellular senescence reduce nucleolar rRNA synthesis and maturation increasing the availability of ribosome-free ribosomal proteins. Several ribosomal proteins can activate the p53 tumor suppressor pathway but cells without p53 can still arrest their proliferation in response to an imbalance between ribosomal proteins and mature rRNA production. Recent results on senescence-associated ribogenesis defects (SARD) show that the ribosomal protein S14 (RPS14 or uS11) can act as a CDK4/6 inhibitor linking ribosome biogenesis defects to the main engine of cell cycle progression. This work offers new insights into the regulation of the cell cycle and suggests novel avenues to design anticancer drugs.

1. Introduction

Ribosomes are made from rRNA and ribosomal proteins. Most of the rRNA is transcribed in the nucleolus from multiple copies of genes coding for precursors transcripts that assemble into pre-ribosomal particles while undergoing several maturation reactions. This process requires relocation of ribosomal proteins from their synthesis in the cytosol to the nucleolus and hundreds of factors including non-ribosomal proteins, small nucleolar RNAs and the 5S rRNA which is transcribed by RNA polymerase III in the nucleoplasm.[1] Ribosome biogenesis is coordinated during cell growth to ensure stoichiometric amounts of ribosomal components. The TOR pathway is a central regulator of ribosome biogenesis at multiple levels. TOR links nutrient availability to cell growth and ribosome synthesis.[2–4] TOR is activated in multiple human cancers where it drives ribosome biogenesis, which is necessary for the unlimited growth of cancer cells.[5] Another major regulator or ribosome biogenesis in cancer cells is the transcription factor HSF1 which coordinates the transcription of proteins and RNAs required for translation with many other anabolic process.[6,7] Despite the clear link between production of ribosomes and cancer, some ribosomal proteins can trigger anti-cancer responses. Here, we review the evidence and molecular mechanisms of the tumor suppressor activity of ribosomal proteins and discuss how this research can lead to innovative anti-cancer therapies. Additional non-ribosomal functions of ribosomal proteins were already discussed in a review by Zhou et al.[8] and are therefore not the focus of the present review. For more information on old and new systems for naming ribosomal proteins, we refer our reader to a review by Ban et al.[9]

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2. Dysfunctional Ribosome Biogenesis: Four Models Leading to Cancer

Mutations in several genes coding for ribosomal proteins (RPGs) have been associated to cancer. The Diamond–Blackfan anemia (DBA) is a congenital ribosomopathy characterized by bone marrow failure and a 5.4-fold increase in overall cancer incidence. Additionally, DBA patients have a much higher risk to develop myelodysplastic syndrome (287-fold), AML (28-fold), colon cancer (36-fold), osteogenic sarcoma (33-fold), and female genital cancers (12-fold).[10] Mutations in RPL11 (uL5), RPL15 (eL15), RPL26 (uL24), RPL31 (eL31), RPL36A (eL42), RPL5 (uL18), RPS7 (eS7), RPS10 (eS10), RPS17 (eS17), RPS19 (eS19), RPS24 (eS24), or RPS26 (eS26) are linked to DBA.[11–15] Analysis of pre-rRNA precursors in cells from patients with these mutations and knockdown of RPG expression in cell culture indicate that DBA mutations affect rRNA processing. Defects in the maturation of rRNA trigger a cellular stress response to which erythrocyte precursors seem to be highly sensitive, explaining the anemia phenotype.[16] However, how a dysfunctional RNA biogenesis leads to cancer predisposition is not very clear since cancer cells need abundant ribosomes for their growth. Four models have been proposed.

The first model is based on the activation of p53 by ribosome biogenesis defects and nucleolar stress caused by DBA mutations.[16,17] p53 activation creates a selective pressure for suppressor mutations in the p53 pathway explaining the cancer predisposition in DBA patients (**Figure 1**).[17,18] This model cannot explain why mice heterozygous for RPL5 (uL18) and RPS24 (eS24) develop soft tissue sarcoma with intact p53.[19]

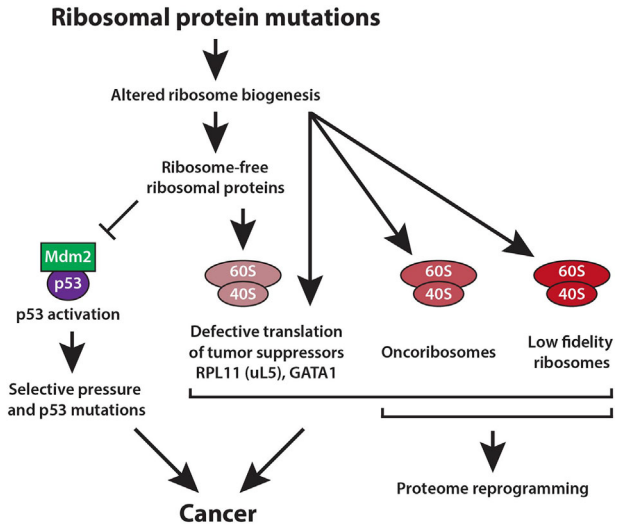

Figure 1. Models explaining the cancer-prone phenotype in Diamond–Blackfan Anemia (DBA). The first model is based on p53 tumor suppressor activation after nucleolar stresses. The second model is based on the ability of ribosome-free ribosomal proteins to activate the tumor suppressor p53 and affect proper translation. The third and fourth models implicate synthesis of specialized ribosomes (oncoribosomes) translating oncogenic mRNAs or synthesis of defective ribosomes with decreased translational fidelity.

A second model is also based on the ability of RPL11 (uL5) and other ribosomal proteins to activate p53 and is supported by a mouse model where partial loss of RPL11 (uL5) recapitulates DBA and compromised p53 activation after nucleolar stress (Figure 1).[20] However, most proteins mutated in DBA do not activate p53. Hence, for this model to be valid, DBA mutations should all converge in defective production of RPL11 (uL5) and other ribosomal proteins required for p53 activation. This is indeed plausible because DBA mutations can impair translation. This has been shown for GATA1 mRNA,[21] indicating messenger-specific defects in translation that could also involve ribosomal proteins required for p53 expression.

A third model proposes that altered ribosome biogenesis leads to the production of specialized ribosomes (oncoribosomes) that translate better oncogenic mRNAs (Figure 1). This idea is supported by studies showing that differential ribosomal proteins composition confers translation selectivity to ribosomes.[22] For example, RPS26 (eS26), one of the proteins mutated in DBA, regulates the translation of multiple well-translated mRNAs by recognizing their Kozak sequence. RPS26 (eS26) deficient ribosomes preferentially translate mRNAs in stress pathways that can confer an advantage to tumor cells.[23]

A fourth model is based on studies in yeast showing that suppression of mutations leading to ribosome biogenesis defects may release defective ribosomes into the translationally active pool decreasing translational fidelity.[18] Little is known about the role of translational fidelity in the origin of human cancers. Diaz and co-workers reported that p53 increases translational fidelity by repressing fibrillarin, a protein that controls rRNA methylation.[24] In this view, tumors in DBA patients would result from low fidelity translation that reprograms the proteome toward a cancer prone phenotype (Figure 1).

3. Ribosomal Protein Gene Mutations in Cancer: Causes or Consequences?

The findings linking ribosomal proteins mutations to DBA sparked the search for additional roles of ribosomal proteins in cancer both in model organisms and cancer patients. Early work in zebra fish unexpectedly revealed that many ribosomal protein genes are haploinsufficient tumor suppressors.[25] More recently, RPL36 (eL36) was revealed as a tumor suppressor in a KRAS-driven model of pancreatic cancer in this organism.[26] In Drosophila, mutations in RPS6 (eS6) lead to growth and hyperproliferation of lymph glands.[27] In mammals, RPS6 (eS6) is phosphorylated by the TOR-activated kinases S6Ks.[28] Mice expressing an RPS6 (eS6) that cannot be phosphorylated by S6Ks are protected from KRAS-driven pancreatic cancer and have enhanced p53 activation.[29] These results suggest a tumor suppressor role for RPS6 (eS6) that is antagonized by PI3K-TOR signaling.

RPL22 (eL22) is another candidate ribosomal protein tumor suppressor. Studies with Epstein Barr virus revealed that RPL22 (eL22) binds small nuclear RNAs called EBER (Epstein Barr encoded RNAs)[30] which support the proliferation of cells infected by this virus.[31] Partial loss of RPL22 (eL22) accelerated lymphomagenesis in mice[32] and its gene is monoallelically inactivated in patients with T-ALL.[33] Inactivation of RPL22 (eL22) triggers the expression of the stemness factor Lin28B via NF-kB signaling[33] but how exactly RPL22 (eL22) represses the NF-kB pathway remains unresolved. RPL22 (eL22) blocks Mdm2-p53 interaction and synergizes with the complex RPL5 (uL18)/RPL11 (uL5) to activate p53.[34] In pediatric T-ALL, exome sequencing also identified mutations in RPL5 (uL18) and RPL10 (uL16).[35] The T-ALL mutant RPL10 R98S (uL16 R98S) drives IRES-dependent BCL2-translation consistent with the idea that altered translation of specific mRNAs underlies cancer predisposition in cells with mutant ribosomal protein genes.[36] Intriguingly, mouse lymphoid cells engineered to express RPL10 R98S (uL16 R98S) express higher levels of genes in the JAK-STAT pathway and exhibit a hyperstimulation of this pathway upon cytokine stimulation.[37]

The 5q- syndrome is a subtype of myeloproliferative disease associated to somatic heterozygous loss of RPS14 (uS11).[38] As in DBA, loss of RPS14 (uS11) triggers defects in ribosome biogenesis leading to p53 activation.[38,39] However, these traits should prevent cell proliferation. Perhaps, other defects associated to the loss of RPS14 (uS11) may explain the tumor prone phenotype in the 5q- syndrome (see below).

In CLL, whole exome sequencing identified frequent RPS15 (uS19) mutations.[40] RPS15 (uS19) interacts with Mdm2/Mdmx but mutant RPS15 (uS19) is defective in p53 activation.[41] RPS15 (uS19) is required for ribosome biogenesis. Translation of RPS15 (uS19) and RPS28 (eS28) mRNAs is regulated by tRNA-derived small RNA fragments (tsRNAs). Inactivation of the tsRNA LeuCAG3'tsRNA decreases RPS15 (uS19) and RPS28 (eS28) translation and blocks ribosome biogenesis.[42]

Exome sequencing identified frameshifting mutations of RPL5 (uL18) in glioblastoma.[43] De Keersmaecker and co-workers identified heterozygous mutations in RPL5 (uL18) in multiple tumor types at frequencies between 11 and 34%.[44] RPL5 (uL18) together with RPL11 (uL5) activates p53 in response

to nucleolar stress but other functions of RPL5 (uL18) were suspected because its knockdown was equally tumorigenic in p53 wild type and p53 mutant cell lines.[44] The same strategy led to the finding of germline mutations in RPS20 (uS10) in colorectal cancer, also in association to defective ribosome biogenesis.[45]

4. Ribosomal Protein Gene Expression: Up or Down Regulated in Cancer?

Analysis of cancer genome data revealed that 43% of human tumors show hemizygous RPG deletions[17] consistent with the idea that RPGs are haploinsufficient tumor suppressors. Mutations and hemizygous deletions of RPGs in cancer suggest that some ribosomal proteins must be poorly expressed in cancers as well. We used Oncomine to investigate the expression of each RPG in human cancers. In most tumor types, ribosomal proteins are highly expressed when compared to normal tissues but many studies found downregulation of ribosomal proteins. Intriguingly, RPS14 (uS11), RPS15 (uS19), and RPS12 (eS12) in the small subunit and RPL3 (uL3), RPL26 (uL24), RPL15 (eL15), and RPL37 (eL37) in the large subunit were more often downregulated than upregulated (**Figure 2** and 3). These data suggest that ribosomal protein expression reflects the active ribosome biogenesis process typical of growing tumors but also indicate that downregulation of some ribosomal proteins may confer specific advantages to tumor cells. A highly intriguing observation in this dataset is that in breast cancers the expression of many ribosomal proteins for both subunits is often downregulated (**Figure 4** and 5).

5. Ribosomal Proteins and p53 Stabilization: An Established Paradigm

The best understood mechanism coupling nucleolar stress to tumor suppression involves a complex between the ribosomal proteins RPL5 (uL18)-RPL11 (uL5) and the 5SrRNA.[46,47] This ribonucleoprotein complex accumulates in the nucleoplasm upon a decrease in ribosome biogenesis gaining access to Mdm2, leading to p53 stabilization[46,47] and in some conditions to cellular senescence.[48] Many ribosome-free ribosomal proteins are degraded upon inhibition of rRNA biogenesis but RPL5 (uL18) and RPL11 (uL5) form a complex that protects them from the ubiquitin proteasome system.[49] The release of RPL11 (uL5) from the nucleolus is facilitated by the loss of Pict1, a factor that retains the ribosomal protein in the nucleolus.[50] Intriguingly, nucleolar stress induces the degradation of Pict1 via the proteasome but independently of ubiquitination.[51] The key motif that allows recognition of Pict1 by the proteasome remains to be identified. The localization of RPL11 (uL5) in the nucleoplasm is also controlled by Neddylation. A decrease in RPL11 (uL5) Neddylation localizes the protein to the nucleoplasm to activate p53.[52] SUMOylation of RPL11 (uL5) decreases its Neddylation contributing to p53 activation in response to nucleolar stress.[53] Recently, nucleolar oxidation was linked to p53 activation during nucleolar stress. In particular, S-glutathionylation of nucleophosmin (NPM1) triggered its

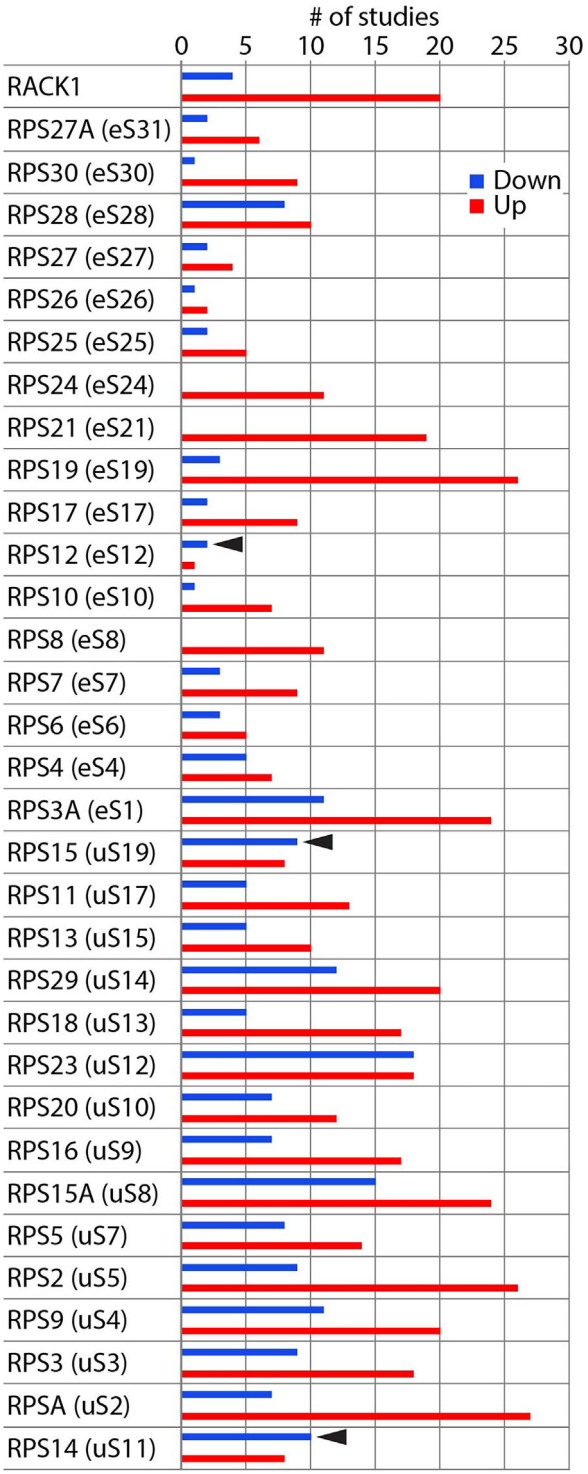

Figure 2. Expression of small subunit RPGs in human cancers. A summary of microarray studies in bladder, brain and CNS, breast, cervical, colorectal, esophageal, gastric, head and neck, kidney, liver, lung, ovarian, pancreatic and prostate cancers as well as in leukemia, lymphoma, melanoma, myeloma, and sarcoma available in Oncomine and using the following settings: threshold *P*-value: 0.01; fold change: 2. Black arrowheads indicate downregulated ribosomal protein mRNAs.

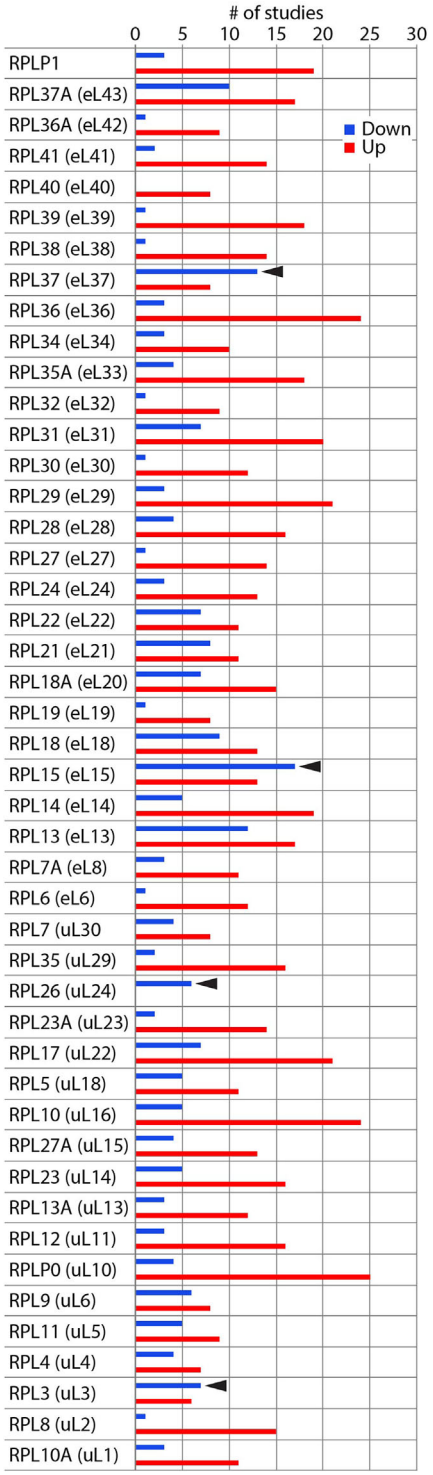

Figure 3. Expression of large subunit RPGs in human cancers. A summary of microarray studies available in Oncomine as for Figure 2. Black arrowheads indicate downregulated ribosomal protein mRNAs.

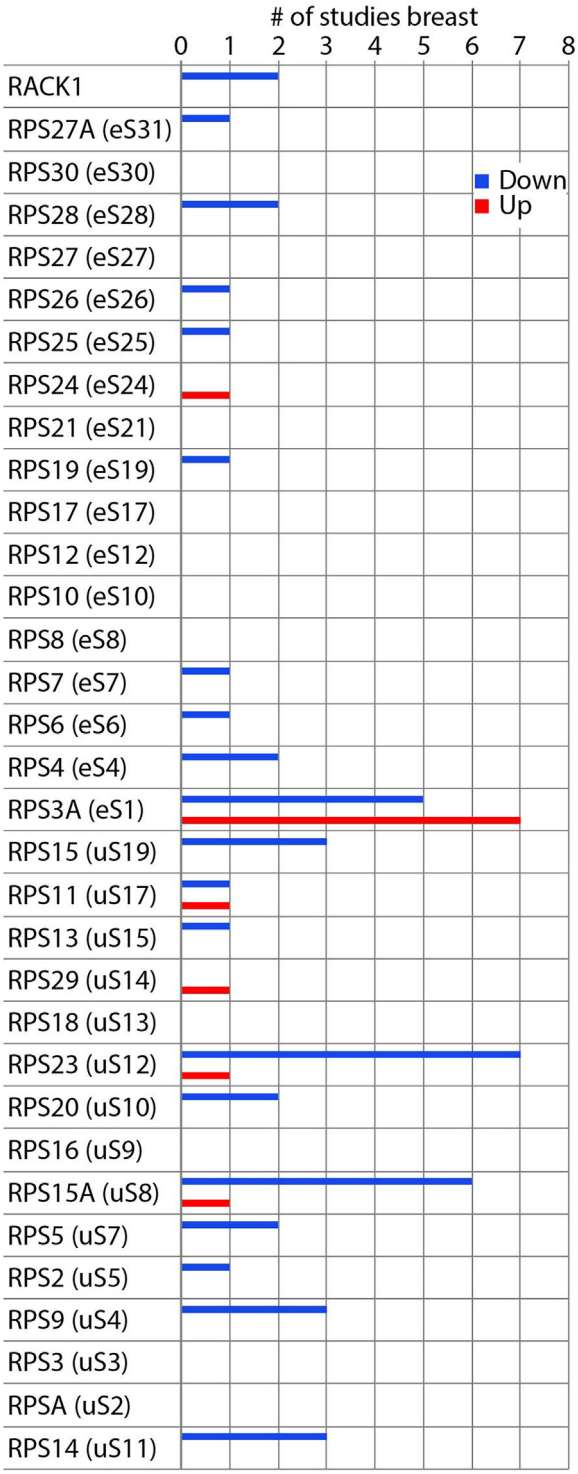

Figure 4. Expression of small subunit RPGs in breast cancers. A summary of microarray studies in breast cancers available in Oncomine and using the following settings: threshold *P*-value: 0.01; fold change: 2.

dissociation from RNA in the nucleolus allowing its translocation to the nucleoplasm and inhibition of Mdm2-p53 interaction.[54] Mdm2 binds to RPL11 (uL5) via an acidic domain and two zinc fingers mimicking 28S rRNA.[55] The proline-rich AKT substrate of 40 kDa (PRAS40) and the glutamate-rich WD40 repeat containing 1 protein (GRWD1) negatively regulate the RPL11 (uL5)-MDM2-p53 pathway and suppresses induction of p53 by nucleolar stress.[56,57]

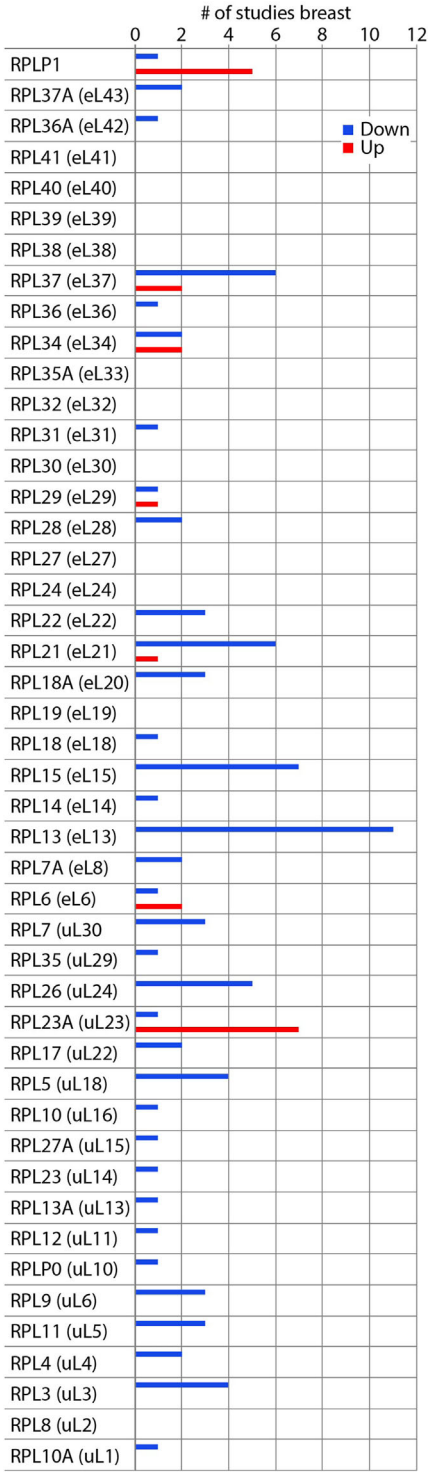

Figure 5. Expression of large subunit RPGs in breast cancers. A summary of microarrays studies in breast cancers available in Oncomine as for Figure 4.

The in vivo relevance of the RPL5 (uL18)/RPL11 (uL5) p53 activation pathway was elegantly demonstrated in a mouse model expressing an Mdm2 variant that cannot bind RPL11 (uL5). These mice are more susceptible to Myc-induced lymphomas.[58] Also the splicing factor SRSF1 interacts with RPL5 (uL18) to disrupt Mdm2 functions and activate p53 linking the spliceosome to the nucleolar stress pathway.[59] Other RPs are able to bind Mdm2 and activate p53. However, Fumagalli et al.[60] showed that only RPL11 (uL5) and RPL5 (uL18) are required for p53 activation since when they are depleted other ribosomal proteins cannot mediate p53 activation upon nucleolar stress. Similarly, Lafontaine and co-workers found that depletion of RPL11 (uL5) or RPL5 (uL18) impaired p53 accumulation in response to depletion of any one of the 24 ribosomal proteins whose inactivation led to p53 accumulation.[61] In conclusion, although these experiments do not deny a role for all the ribosomal proteins with ability to inhibit Mdm2, they do point that RPL11 (uL5) and RPL5 (uL18) are the major players at least in the experimental conditions where nucleolar stress have been linked to p53 so far.

6. RPS14 and CDK Inhibition: A New Paradigm

The decrease in proliferation in response to defects in ribosome biogenesis or nucleolar stress does not always require the p53 tumor suppressor pathway. In fact, in flies, inactivation of the RNA polymerase I cofactor Transcription Factor IA (TIF-IA) arrested cell growth and reduced rRNA synthesis. However, while in mouse cells loss of TIF-IA activated p53, in Drosophila, p53 was not required for the growth arrest phenotype.[62] In yeast, where there is no p53, defects in ribosome biogenesis directly inhibit the passage through Start, a point in G1 that commits cells to DNA replication and the S phase. The yeast homologue of the retinoblastoma protein (RB) called Whi5 mediates this checkpoint.[63] In human cancer cell lines, which often bear p53 mutations, inhibition of ribosome biogenesis trigger antiproliferative responses that have been difficult to explain so far.[64–69] Finally, ribosome biogenesis defects characterize cellular senescence and inhibition of ribosome biogenesis factors can trigger the process. Intriguingly, the senescence response to ribosome biogenesis defects is p53 independent but can be inhibited by genetic treatments that inactivate the retinoblastoma tumor suppressor (RB).[70] RB blocks the cell cycle by binding the E2F family of transcription factors. Cell cycle progression requires a release of E2Fs from RB. This is achieved via RB phosphorylation by the CDK2-cyclin E and the CDK4/6-cyclin D complexes. To arrest the cycle these complexes should be inhibited by a large family of CDK inhibitors or CKIs.[71] During OIS, the CKIs p21 and p16 have been shown to inhibit the CDK complexes but their tumor suppressor functions can be compensated by other mechanisms because individual inactivation of these proteins does not block OIS.[72–76] Similarly, inactivation of p16INK4a or p21 did not bypass senescence triggered by ribosome biogenesis defects nor RB-mediated E2F-targets repression.[70] The ribosomal protein RPS14 (uS11) was found associated to CDK4-cyclin D complexes in senescent cells and its expression at moderate levels was able to inhibit CDK4 and RB phosphorylation. In vitro kinase assays demonstrated that RPS14 (uS11) is a direct inhibitor of the CDK4-cyclin D complex but not of the CDK1-cyclin B complex.[70] These results support a new model linking ribosome

biogenesis to cell cycle control where a ribosome-free ribosomal protein acts as a CKI while others acts as p53 activators (**Figure 6**). Of note, RPS14 (US11) can also inhibit Mdm2 and activate p53[77] indicating that this ribosomal protein is endowed with the ability to activate the two major tumor suppressor pathways in mammalian cells. The structure of RPS14 in complex with CDK4-cyclin D or Mdm2 should shed light into the mechanisms of tumor suppression by this ribosomal protein.

Additional functions of ribosomal proteins that can contribute to p53-independent tumor suppression were reviewed before[78] and include modulation of E2Fs,[65] MYC,[79] and NF-κB[80,81] transcription factors. Both RPS14 (uS11) and RPL11 (uL5), two ribosomal proteins that accumulate in the ribosome-free fraction of cells upon nucleolar stress, bind and inhibit MYC transcriptional activity.[79,82] They can also decrease MYC expression by recruiting miRNAs to the 3′UTR of the MYC mRNA.[82,83] MYC controls the synthesis of rRNA by RNA polymerase I,[84,85] suggesting that its inhibition by ribosome-free RPS14 (uS11) and RPL11 (uL5) could explain the shut down in rRNA transcription observed after nucleolar stress and cellular senescence.[70] The regulation of NF-κB by ribosomal proteins is complex since RPS3 (uS3) increases its activity[80] while RPL3 (uL3)[81] and RPL22 (eL22)[33] act as inhibitors. In the context of senescence, RPS3 (uS3) could contribute to the senescence associated secretory phenotype that requires NF-κB[86] whereas RPL22 (eL22) could attenuate this response. Of note, since ribosomal proteins are essential and very abundant, they constitute an ultimate fail-safe mechanism to prevent cancer cell proliferation.

7. Pharmacological Modulation of the Tumor Suppressor Activity of Ribosomal Proteins

It has been argued that cancer cells are more sensitive to treatments that impair ribosome biogenesis due to their increased demand for ribosomes and the fact that cancer

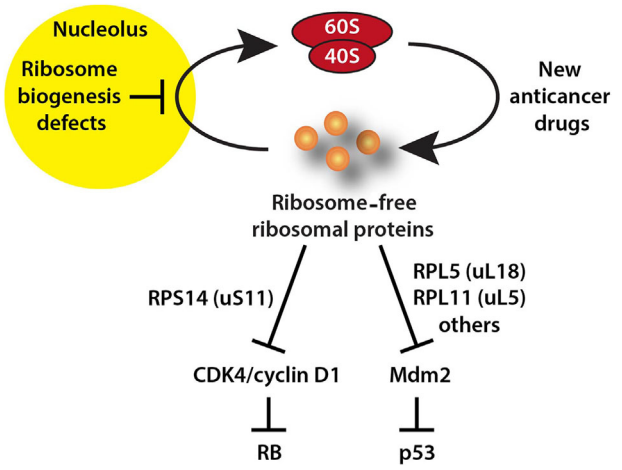

Figure 6. Ribosome-free ribosomal proteins (RPs) link ribosome biogenesis to tumor suppressor pathways. Drugs acting on ribosome biogenesis or releasing RPs from the large pool of ribosomes may trigger these antitumor responses in cancer cells.

mutations increase ribosome biogenesis.[87] Current cancer chemotherapy inhibits ribosome biogenesis potentially activating tumor suppressor pathways that involve ribosome-free ribosomal proteins.[88] Some anticancer drugs work at least in part by releasing ribosomal proteins from the nucleolus triggering tumor suppressor responses. 5-FU (5-fluorouracil) and low doses of Act D (actinomycin D) increase the fraction of ribosome-free RPL5 (uL18), RPL11 (uL5), RPL23 (uL14), and RPS27 (eS27) which block Mdm2 and activate p53.[89–91] Act D also leads to accumulation of ribosome-free RPL3 (uL3) that increases p21 transcription and stability via hyperactivation of ERK and phosphorylation of Sp1, a transcriptional activator of p21.[92,93] Oxaliplatin, in contrast to other platinum containing chemotherapeutics, kills cancer cells by inhibition of ribosome biogenesis.[94] It will be interesting to investigate whether ribosome-free ribosomal proteins play a role in the anticancer effects of oxaliplatin. Another interesting group of compounds that inhibit ribosome biogenesis are alkaloids from Amaryllidaceae, which have been used as folk medicines to treat several diseases including cancer. These alkaloids inhibit the early steps of rRNA processing as well as the biogenesis of the large ribosomal subunit and trigger a p53 response in tumor cells.[95] Any therapy engaging ribosome-free ribosomal proteins must take into account the short half-life of free ribosomal proteins.[96] Proteasome inhibitors may potentiate the function of ribosome-free ribosomal proteins by allowing their accumulation.[97] On the other hand, TOR inhibitors can blunt antitumor responses of nucleolar stress by reducing the synthesis of ribosomal proteins. Hence, combining TOR inhibitors with drugs that work via inhibition of ribosome biogenesis may reduce their effectiveness.[98]

Drugs inhibiting enzymes required for ribosome biogenesis may trigger efficient anti-cancer response by restoring the p53 and RB tumor suppressor pathways and other growth inhibitory functions of ribosomal proteins. Of note, targeting small nucleolar RNAs U3 and U8 triggered a potent p53 response in breast and lung cancer cells mediated by RPL5 (uL18) and RPL11 (uL5).[99] These RNAs interact with their targets in rRNA processing by base pairing and are susceptible to inhibition by antisense nucleic acids.[99] It would be interesting to investigate if inhibition of U3 or U8 small nuclear RNAs leads to inhibition of CDK4 via RPS14 (uS11). Since tumors contain abundant ribosomes, agents that can selectively release tumor suppressor ribosomal proteins from the ribosomes could be also considered for cancer therapy (Figure 6). A new generation of ribosome drugs may engage these ancient pathways to treat cancer. In fact, cellular senescence, an anticancer response, takes advantage of ribosomal proteins to activate both p53 and RB tumor suppressor pathways.[70]

8. Conclusions

Ribosomes are the protein factories of the cell. Their biogenesis is a complex and energy requiring process that is coupled to cell needs including cell proliferation, protein secretion, and turnover. This coordination is a highly conserved process that evolved early during evolution to increase cell fitness. At the molecular level, there are specific signals that supress ribosome

biogenesis when cell proliferation is inhibited. The tumor suppressors p53, ARF and RB link the DNA damage response and cell cycle control to ribosome biogenesis by repression of RNA polymerase I activity.[100–103] This reversible checkpoint pathway is important for cell homeostasis, but more lasting responses are needed upon the threat of malignant transformation. We reviewed here the evidence for triggering cellular tumor suppressor responses such as apoptosis and senescence upon the accumulation of ribosome-free ribosomal proteins in cells experiencing oncogenic stress. Ribosomal proteins can now be linked to tumor suppression via activation of p53,[46,47] but also inhibition of E2F, MYC, NF-κB[65,79–81] and the cell cycle engine kinases CDK4/6.[70]

Ribosomal proteins were originally viewed as complements for rRNA in ribosomes but are now emerging as mediators of a variety of checkpoint pathways that link ribosome biogenesis to the cell cycle and other cellular functions.[104] Assuming that the first ribosomes were made of RNA, then it is likely that ribosomal proteins evolved from pre-existing proteins in ancient cells. Hence it should not come as a surprise that ribosomal proteins exert multiple functions outside ribosomes. RNA binding proteins playing a role in ribosome biogenesis might have been the first ribosomal proteins. Consistent with this idea, many ribosomal proteins, in particular those present in all three domains of life, play a role in ribosome assembly.[105] The characterization of the structural motifs that mediate all non-ribosomal functions of ribosomal proteins will offer insights to explain the evolution of anticancer responses and new targets to develop new anticancer drugs.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

cancer, CDK4, RB, ribosomal proteins, ribosome biogenesis, RPS14, senescence

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