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REVIEW ARTICLE

Toward an understanding of cancer-associated ribosomal protein mutations

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Abstract

Ribosomal proteins (RPs) are essential structural and functional components of the ribosome, and their disruption during embryogenesis generally results in embryonic lethality. Nevertheless, cancer genomes frequently harbor somatic missense mutations and gene deletions in RP genes in patterns that suggest selective advantages, often linked to inactivation of the tumor suppressor protein p53 pathway. This review discusses the landscape of RP mutations in cancer and their mechanistic consequences. RP mutations are detected across multiple malignancies, including glioblastoma, melanoma, T-cell acute lymphoblastic leukemia, as well as in congenital ribosomopathies, such as Diamond-Blackfan anemia, which confer an elevated lifetime risk of developing cancer. Cancer-associated RP mutations disturb ribosome homeostasis, compromise translational fidelity, and trigger proteotoxic and ribosomal stress, yet without halting tumor growth. Some RP mutants occupy structurally sensitive positions within the ribosome, altering mRNA selectivity and quality control. In turn, cancer cells may adapt through compensatory mechanisms, including the upregulation of RP paralogs, activation of proteostasis regulators, and rewiring of stress response pathways. Rather than a loss-of-function event, an RP mutation may create a persistent ribosomal disequilibrium that fundamentally alters cellular functions. Such changes in a cancer cell could generate interesting therapeutic vulnerabilities and targets, such as dependence on stress signaling, proteasome activity, or RP paralog expression.

Keywords: Ribosome biogenesis; Ribosomal protein; p53; Cancer; Ribosomal stress

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1. Introduction

Ribosomes are indispensable for cell growth, translating the genetic code into functional proteins. In human cells, ribosomal proteins (RPs) constitute 4–6% of the total protein mass. Thousands of ribosomes are produced every minute and are usually present at levels of 1–5 million/cell.[1-4] A higher ribosome content is often observed in rapidly growing cells. The structure of the human 80S ribosome has been solved, revealing the complexity and details of this molecular machine with a mass of 4.3 MDa.[5] Ribosome biogenesis (RiBi) is well regulated from ribosomal RNA (rRNA) synthesis and RP expression to subunit assembly and nuclear export to ensure that cells maintain sufficient translational capacity without triggering proteotoxic stress.[6-8] In rapidly dividing cancer cells, which frequently harbor genetic alterations, including the loss of whole chromosomes containing *RP* genes, this balance is likely to be disrupted.[9,10] In

addition to large-scale chromosomal losses, more specific changes in RPs, such as recurrent point mutations, have also been implicated in cancer development.[11] Genome sequencing efforts revealed *RP* gene alterations across a range of malignancies.[12,13] These mutations have structural, functional, and regulatory effects that can alter the ribosome stoichiometry/homeostasis, impair translation, change the cellular proteome, and inactivate tumor suppressors.[14,15]

It has become evident over the past decades that RPs also have functions beyond their canonical role in translation. They influence cellular processes, including cell cycle regulation, mRNA splicing, apoptosis, and DNA damage response.[16] In this review, focus is laid on deletions and missense mutations in RPs, and how these create vulnerabilities and force adaptations in the cancer cells. While certain RP mutants have been extensively investigated and widely discussed in the literature, they have been underexplored in the context of fundamental ribosome biology and cellular homeostasis in human cells.[11,14,15,17] It is argued herein that RP mutations not only impair mRNA translation but also force cancer cells toward specific compensatory strategies to survive and sustain proliferation.

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2. Fundamental facts of RiBi and RPs

RiBi is a complex, energy-intensive process that primarily takes place in the nucleolus and involves the coordinated transcription, processing, and assembly of rRNA and RPs.[18] The eukaryotic ribosome consists of around 80 RPs and four rRNAs. Much of the knowledge about RiBi in eukaryotes comes from studies in yeast. At the same time, many ribosome core components are conserved in humans; the mammalian RiBi process exhibits greater complexity in terms of associated RiBi factors.[2,5,6,19,20] In principle, the assembly proceeds in a stepwise fashion along a trajectory. The nucleolus is the primary location of rRNA synthesis, where RNA polymerase I transcribes the 47S rRNA precursor, which is subsequently processed into the 18S, 5.8S, and 28S rRNAs. Separately, RNA polymerase III transcribes the 5S rRNA, and RNA polymerase II transcribes *RP* genes and RiBi helper factors.[2,19] The rRNA transcript undergoes various modifications, including pseudouridylation and methylation, mediated in part by small nucleolar ribonucleoproteins; these rRNA modifications function in stability and fine-tune the function of the ribosome. In yeast, experimental evidence shows that RiBi is regulated at the transcriptional level and that there is extensive coordination of *RP* gene and rRNA transcription.[8,21] RPs are synthesized in the cytoplasm and transported into the nucleus via importins. A subset of RPs associate with chaperones and assembly factors before integrating into pre-ribosomal subunits.[22,23] The 40S subunit harbors 18S rRNA and the small RP proteins, whereas the 60S subunit incorporates 28S, 5.8S, and 5S rRNAs along with large RP proteins. The ribosomal precursor particles are then transported out into the cytoplasm through the nuclear pore complex, where some final maturation steps occur, including removal of assembly factors.[2] Functionally, the 40S subunit is responsible for mRNA binding, start codon recognition, followed by interaction with initiation factors, and it ensures decoding fidelity by checking correct codon-anticodon pairing in the A site of the ribosome. The 60S ribosomal subunit catalyzes peptide bond formation and elongation, and it facilitates polypeptide exit through the ribosomal tunnel and interacts with elongation and termination factors.[24,25]

Central regions of the core ribosomal RPs are highly conserved across species at both DNA and protein levels, reflecting evolutionary pressure to preserve the fundamental ribosomal structure and function. However, in higher eukaryotes, some RPs have evolved flexible extensions (expansion segments) outside the centrally conserved domains.[26] RPs are often critical building blocks within the ribosomes, but the majority of RPs are essential for the proper processing of rRNA and subunit export. From 2005 to 2015, several studies systematically depleted RPs using siRNA, revealing defects in rRNA maturation, subunit export, and nucleolar architecture, and RP loss frequently induced p53 accumulation.[27-30] Moreover, in comprehensive genetic screens, cellular proteins and modules were identified as crucial for proper 40S and 60S biogenesis.[31,32] An interesting feature of RPs is that they are produced in surplus, and then imported into the nucleus at a high rate, but degraded by the proteasome if not needed.[33-37] At least in yeast, this degradation is a regulated process that occurs in a cotranslational manner.[37] The studies in yeast support the idea that RiBi is highly co-regulated. In contrast, in normal and cancerous human cells, there appears to be considerably more "wasting" of metabolic resources with RPs produced in excess.[38] In summary, producing ribosomes is a major biosynthetic activity in growing, proliferating cells; it is a regulated and balanced process sensitive to disruption, playing a role in human cancer development through various mechanisms.[39,40]

3. The landscape of RP mutations in human ribosomopathies and cancer

In human cancers, recurrent mutations have been identified in both classical driver genes and in more unexpected ones, which have fundamentally changed our view of cancer. For example, *IDH1/IDH2* in gliomas and mismatch-repair genes, including *MSH2* and *MSH6*, in colorectal and endometrial cancers, as well as histone H3 isoform mutations in pediatric malignant brain tumors.[41-43] This underscores how mutations in essential chromatin, metabolic, and DNA repair regulators can shape tumor evolution besides the more classical ones, such as *TP53* and *BRCA1/2*.[44] Against this broader range of cancer-associated mutations, *RP* genes were also considered unlikely contributors to tumorigenesis for a long time, but have now also been found to be mutated, including in the tumor types mentioned above. However, this assumption of essentiality and static behavior has been challenged over the years by a series of discoveries. First, in 1999, mutations in *RPS19* (eS19) were identified in individuals with Diamond–Blackfan anemia (DBA).[45] This was unexpected, but apparently some mutations can be tolerated. It was later found that multiple other *RP* genes were mutated in DBA.[46,47] Thus, alterations in *RP* genes can be survivable. However, this comes with a cost; a higher risk of developing cancer is seen in DBA.[48] DBA is not a single disease entity but belongs to a group of diseases collectively known as ribosomopathies, which contribute to a diverse group of hematologic and developmental disorders. Ribosomopathies are characterized by bone marrow failure and developmental abnormalities with considerable differences in penetrance (also depending on the type of RP mutation), as well as an elevated risk of developing cancer.[49,50] Ribosomopathies are often caused by mutations in RPs, defective rRNA processing, decreased RNA polymerase I activity, or loss of upstream regulatory factors controlling these activities.[49]

Second, approximately a decade after the discovery of human congenital mutations in *RP* genes, somatic mutations associated with human cancer were identified. Large-scale cancer genome analyses revealed that a subset of *RP* genes is recurrently mutated in specific tumor types.[51-54] These were not distributed randomly across all the *RP* genes. For example, *RPL5* (uL18) haploinsufficiency emerged as one of the most common RP defects. Heterozygous deletion or missense mutation of *RPL5* occurs in 10–20% of glioblastomas, melanomas, and breast cancers.[55-57] Low *RPL5* expression correlates with poor survival, and knockdown of *RPL5* in breast cancer cells accelerated growth in mouse xenografts, suggesting a tumor-suppressive role.[57] *RPL22* (eL22) frameshift mutations are observed in approximately 25% of colorectal and endometrial cancers, often those with high microsatellite instability, as well as gastric cancers. Approximately 7–9% of T-cell acute lymphoblastic leukemias (T-ALLs) display *RPL22* loss,[53,54,58,59] whereas mutations in *RPL10* (uL16) also occur in approximately 8% cases.[51] Similarly, chronic lymphocytic leukemia (CLL) exhibits *RPS15* (uS19) mutations in 5–10% of patients, correlating with aggressive disease progression.[60] Other less common alterations, including *RPS5* (uS7) mutations and rare germline variants in *RPS20* (uS10), are suspected in familial colorectal cancer.[61,62] A recurrent but not highly frequent mutation in the 5' untranslated regions (5'UTR) of *RPS27* (eS27) has also been identified in malignant melanomas.[63] The consequences of these rare alterations in RPs remain poorly understood, and it is unclear if they contribute to cancer.

Third, over the past decade, the concept of ribosome heterogeneity has grown stronger.[64-68] The concept has been debated, and numerous pitfalls in the interpretation and definition of heterogeneity have been identified.[64,69,70] As one important example, the testis expresses specialized *RPL39L*-containing ribosomes that are functionally distinct from *RPL39* (eL39)-containing ribosomes in other tissues.[71] In relation to ribosome heterogeneity, it has been noted that cancers may express RP variants.[12,72] Cancers often acquire aneuploidies or focal copy-number variants that impact *RP* gene dosage. Whole-chromosome losses (monosomies) can delete multiple *RP* genes simultaneously.[9] Because RPs are essential in most cases, and some display features of haploinsufficiency depending on cell context and species, this imposes a significant challenge to the cell. Focal *RP* gene deletions are common in hematologic malignancies, and one example is the myelodysplastic syndrome, 5q-syndrome, which deletes *RPS14* (uS11) and causes anemia via defective RiBi.[73] In a 2017 analysis, Ajore *et al.*[13] reported that *RP* gene deletions occurred in 43% of the 10,744 cancer specimens and cell lines, and it was noted that *RP* genes are conserved with respect to the lack of homozygous deletions. Thus, it was considered that many changes in *RP* genes are sub-clonal or heterozygous, assuming that the complete loss of the corresponding *RP* genes would be detrimental for the cell. However, this was partly challenged in a more recent analysis, suggesting that bi-allelic *RP* gene losses can be found, though it may be explained by functional redundancy, expression of paralogues, or even pseudogenes as back-ups. In The Cancer Genome Atlas (TCGA) pan-cancer analysis, Panda *et al.*[12] reported widespread single- and occasional double-copy losses of *RP* genes across tumor types. Thus, single-copy losses of many *RP* genes are widespread and often affect multiple *RP* genes

in a tumor. A study in glioma indicates that ribosomes in certain hypoxic core regions of the tumor may be entirely devoid of RP, large subunit (RPL) 22 protein and also its back-up paralog RPL22L1.[74] In another study, using mouse models of hepatoblastoma and hepatocellular carcinoma, researchers observed a loss of the normal stoichiometry of RP transcripts and RPs, accompanied by the accumulation of unincorporated, partially processed rRNA—resembling the ribosomopathy setting.[75] Moreover, in hepatocellular carcinoma, a subset of *RP* gene mutations was found to be identical to those reported in ribosomopathies. This led to the interesting idea that certain cancers possess ribosomopathy-like features.[75]

Copy-number gains of *RP* genes have been observed (e.g., *RPL23A* [uL23] amplification in uterine cancer[57]), although their impact is less studied. Beyond genetic changes, dysregulated mRNA expression of *RP* genes has also been described and, in a few studies, linked to tumor development and progression. Tumors have expression patterns of RPs that differ from those observed in corresponding normal tissues, and sometimes correlate with pathological and clinical parameters, including survival.[12,76-78] In one study, elevated expression of *RPL15* (eL15) has been detected in gastric cancer tissues and cell lines, promoting cellular proliferation.[79] Notably, *RP* genes and mRNA translation factors were enriched in an *in vivo* genome-wide clustered regularly interspaced short palindromic repeats (CRISPR) screen using circulating tumor cells from patients with breast cancer.[80] Here, *RPL15* was noted, and its overexpression increased metastasis and enhanced translation of other RPs and cell cycle proteins.[80] The findings on *RPL15* are interesting and surprising, given that excess RPs often are degraded if not needed. There are other examples than *RPL15* that do not seem to follow the standard rules.

4. RP mutations in cancer development

The traditional view held that RPs were passive players in protein synthesis. The current view, however, recognizes RPs as active regulators of translation, tumor suppression, cellular stress responses, and other functions.[17,81-83] The idea that RP mutations often negatively affect RiBi, which can contribute to cancer, may seem paradoxical given that ribosomes are essential for protein synthesis and cell growth. In fact, disruption of ribosome assembly can impair leukemia development in a mouse model, also in a p53-independent context.[84] Yet, RP mutations or losses in cancer do not simply stop protein production. This is expected, as inhibition of RP translation would be strongly counter-selected and thus absent in cancer. This shift in the view of ribosomes and protein synthesis has redirected the field toward targeting RiBi and ribosomes, exploring the concept of the oncoribosome, and investigating specialized modes of translation in cancer.[11,14]

Several experimentally supported hypotheses have emerged to explain how RP mutations can contribute to cancer development. These hypotheses may not be mutually exclusive, and for RP mutations, it is unlikely that a single hypothesis can be applied in all scenarios. These cancer-promoting events include selective pressure to mutate p53, increased translation of oncogenes, generation of reactive oxygen species and DNA damage, metabolic changes, cell competition, and transcriptional rewiring. To begin with, the selective pressures acting on RP mutations in cancer are different from those in congenital ribosomopathies. Rather than causing hypoproliferation, several cancer mutations can be selected for their ability to fine-tune translational control and provide some immediate benefit for the cancer cell. This is likely to occur in other genomic alterations and p53 mutations. Notably, many recurrently mutated RPs occupy regulatory or structurally sensitive positions within the ribosome, such as the inter-subunit interface, the decoding center, or the exit tunnel.[85] At these positions, even subtle amino acid substitutions can affect translation by altering mRNA selectivity, nascent chain folding, or ribosome-associated quality control. Such alterations generate selective pressure for adaptive changes through transcriptional rewiring, stress tolerance pathways, or clonal diversification. Multiple distinct scenarios are likely at play, each potentially relevant to cancer development in different contexts.

It is also essential to consider several fundamental aspects of the specific RP mutant in question. First, is the expressed mutant RP stable and incorporated into mature ribosomes, and if so, does it contribute to the pool of actively translating ribosomes? Some RP mutants may misfold, aggregate, or be rapidly degraded, potentially causing proteotoxic stress. In contrast, other RP mutants that retain partial functionality might be incorporated into ribosomes, leading to widespread incorporation and potentially altering ribosome function in a biologically meaningful way. In other scenarios, the acute loss of one or both RP alleles may deprive the cell of an essential ribosomal component, prompting a compensatory response. Second, will the cancer cell maintain ribosome output by upregulating compensatory mechanisms, or will the total number of ribosomes decline? If ribosome levels are reduced, competition among mRNAs for translation could intensify. Indeed, the absolute number of ribosomes per cell may be critical in certain tissues, such as the hematopoietic tissues. In humans, this is exemplified by DBA, where ribosome composition remains intact, but

reduced ribosome abundance impairs translation of specific mRNAs.[86,87]

Patients diagnosed with DBA often have a predisposition to cancer, especially leukemia, soft tissue cancers, or gastrointestinal cancers.[48,88] The two-hit model suggests that the first hit (RP mutation) leads to reduced ribosome function and impaired cell proliferation, causing a bottleneck in development. The second hit is a compensatory mutation or oncogenic mutation, which could also be an inactivation of a tumor suppressor gene (e.g., *TP53*), allowing surviving cells to overcome an initial growth defect and acquire pro-oncogenic properties.[15,50] This model may explain why early ribosome dysfunction can paradoxically lead to increased cancer risk later in life (Figure 1). At an early stage in cancer evolution, loss of RPs induces

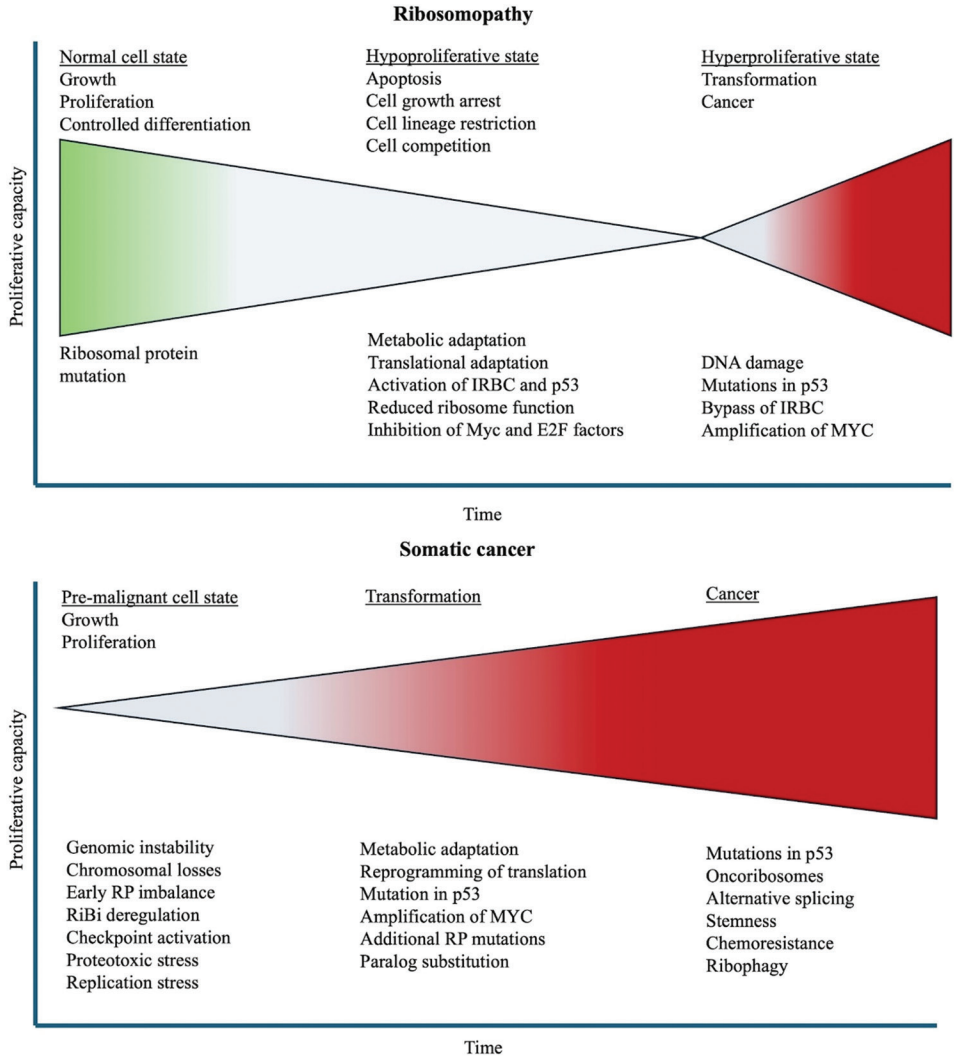

Figure 1. Ribosomal protein (RP) mutations in cancer development. (A) In normal cells, ribosome biogenesis (RiBi) supports balanced growth, proliferation, and regulated differentiation. RPs mutations in congenital ribosomopathies disrupt this balance, leading to a hypoproliferative state marked by apoptosis, cell lineage restriction, and cell competition. This is often mediated by the activation of the impaired RiBi checkpoint (IRBC) and p53, leading to reduced ribosome output and repression of proliferative drivers, such as the myelocytomatosis (MYC) oncogene and E2F1. Over time, adaptations may allow rare mutant clones to survive and accumulate additional genetic changes. These include p53 mutations, MYC amplification, or bypass of IRBC, which can drive progression to a hyperproliferative, transformed state of cancer. (B) In contrast, somatic cancers typically arise from pre-malignant cells already undergoing unchecked proliferation and experiencing genomic instability. Early RP imbalance, missense mutation, or RiBi deregulation may further activate cellular stress responses, including proteotoxic stress. As transformation progresses, several adaptations, such as metabolic rewiring, translational changes, p53 loss, MYC amplification, or acquisition of additional RP mutations (e.g., in RPL5), occur. These changes support clonal evolution toward full high-grade malignancy. In advanced cancers, ribosome-related alterations may contribute to tumor aggressiveness through several mechanisms, such as oncoribosome formation, aberrant splicing, stemness, and chemoresistance. Image created by the author.

ribosomal stress and activates p53, such that only clones that silence p53 or its downstream network can survive. Congenital RP mutations, as seen in ribosomopathies, such as DBA or 5q-syndrome, typically cause tissue-specific defects and activate p53-dependent checkpoints during development. In contrast, somatic RP mutations in cancer arise later in life. They are often sudden and sub-clonal, allowing cells to bypass early growth arrest due to pre-existing changes in p53. This temporal difference suggests that congenital RP mutations trigger surveillance mechanisms before malignant transformation, whereas somatic RP mutations may exploit or disable such surveillance pathways, or arise after critical mutations occur in these pathways, thereby accelerating tumor evolution (Figure 1).

5. Ribosome assembly defects and p53 activation

Tumors frequently harbor RP dosage imbalances resulting from whole-chromosome aneuploidy, focal deletions, point mutations, or epigenetic alterations. These imbalances disrupt RiBi and mRNA translation, leading to cellular stress and exerting selective pressure on cancer cells to adapt. It was reported that upon loss of *Rps6* (eS6) in mouse liver cells, the cells' protein synthesis could continue (from pre-existing ribosomes). However, cell proliferation was stopped due to the triggering of a cell cycle checkpoint.[89] Ribosomal stress, also known as nucleolar stress, arises when RiBi is disrupted, whether by mutations, chemotherapeutic agents, or excessive oncogenic signaling, leading to the activation of both p53-dependent and independent pathways.[90-93] p53 is a central regulator of cellular stress responses, including DNA damage, oxidative stress, oncogene activation, and ribosomal dysfunction.[94] When ribosome assembly is stalled due to the loss of an RP, p53 is stabilized and activated. It has been reported that even modest disturbances in RiBi can lead to assembly bottlenecks, accumulation of orphan RPs (RPs that do not become incorporated or bound to any ribosome), or ribosomal and proteotoxic stress responses that feed into the p53 network. Consequently, *RP* gene deletions in tumors are often coupled to *TP53* mutation or gene loss.[13,56,58] In contrast, p53 activation typically induces genes such as *CDKN1A* (encoding p21, which triggers cell-cycle arrest) or pro-apoptotic genes, such as *BBC3* (Puma) and *PMAIP1* (Noxa), halting proliferation or triggering cell death. In addition, p53 also regulates differentiation, senescence, and other cell fates.[95-97] It can directly influence numerous genes, particularly in stress response, but loss of p53 will result in profound impacts on the transcriptome and downstream pathways. These transcriptional responses vary depending on the type of stress and cellular context.[97] It should also be mentioned that there are other surveillance systems of the mature ribosome function that monitor translational elongation and overall quality of the ribosome work (e.g., ribotoxic stress responses and ribosome quality control).[98,99] It will be of interest to see how these surveillance systems are integrated with the p53-checkpoint and other aspects of RP alterations in cancer.

Hemizygous deletions of *RP* genes are rather common in cancer but underrepresented in *TP53*-intact tumors, suggesting that functional p53 imposes negative selection against RP loss.[13] In *TP53*-mutant tumors, no such selection is observed.[13] As another example, *RPS12* (eS12) is reduced in diffuse large B-cell lymphomas, particularly in the context of p53 loss of function.[100] In several mouse models, RP haploinsufficiency activates a p53-dependent checkpoint that restricts development or survival. For example, suppression of *RPS14* expression in primary human erythroid progenitors recapitulates the 5q-phenotype, underscoring the role of p53 activation.[101] A mouse model of human 5q-syndrome confirmed that this phenotype is p53-dependent.[102] Likewise, *Rps19* and *Rps20* mutants in mouse "dark skin/Dsk" models activate p53, inducing KIT ligand and epidermal melanocytosis, while also impairing erythropoiesis and growth.[103] Loss of one *Rps6* allele triggers a p53-dependent checkpoint during gastrulation, causing embryonic lethality.[104] Complete *Rps6* deletion blocks T-cell development, whereas heterozygosity impairs peripheral T-cell survival; both effects are p53-dependent.[105] Reduced *Rpl27a* (eL43) also enhances p53 activity *in vivo* and delays tumor development.[103]

In an engineered human cell line model, CRISPR/Cas9-mediated *TP53* deletion in RPE1 cells allowed isolation of clones missing single chromosomes. These monosomic clones showed reduced RNA and RP content as well as impaired protein synthesis.[9] In the monosomic RPE1 clones, total RNA decreased to 70–80% of the control levels, consistent with reduced *RP* gene dose and additional stress-induced effects. Thus, even single-copy RP loss impairs translation in monosomic cells.[9]

In summary, a subset of early-stage tumors acquires RP copy-number variations that disrupt ribosome assembly and activate the ribosomal stress response. Data from TCGA, engineered monosomies, CRISPR screens, and animal models consistently demonstrate that altered RP dosage leads to impaired RiBi, p53 activation, proteotoxic stress, ribosomal stress, and changes in mRNA translation.[9,13,76,101,102,106-108]

6. Activation of the impaired RiBi checkpoint

Chromosomal instability is a hallmark of cancer, which involves abnormal chromosome number or structure that can impact RP expression. It was hypothesized several years ago that RPs have evolved an additional specific surveillance role, functioning as sensors of genomic imbalance by engaging the mouse double minute 2 homolog (MDM2)-p53.[109] When RP expression becomes unbalanced due to genomic instability, excess free RPs can accumulate, triggering p53 activation, which may serve as a secondary safeguard against propagation of genomically unstable cells.[109] Whether such a putative mechanism is operational and relevant to cancer remains unclear.

Under normal conditions, p53 is maintained at low levels through its negative regulators, MDM2 and mouse double minute 4 homolog (MDM4), which promote p53 degradation via ubiquitination (Figure 2). MDM2 is an E3 ubiquitin ligase that targets p53 for proteasomal degradation,[110] while MDM4 does not have E3 ligase activity but inhibits p53 transcriptional activity. RPs themselves act as critical sensors and transducers of ribosomal stress, relaying it to the p53 pathway.[111,112] Thus, RPs can serve as both sources and sensors of ribosome dysfunction.

Among the RPs involved in p53 regulation, RPL5, RPL11, and RPL22 are particularly important (Figure 2). A central component of this checkpoint is the 5S ribonucleoprotein complex (5S RNP), which, in its most basic form, consists of 5S rRNA bound to RPL5 and RPL11. 5S RNP is incorporated into assembling ribosomes, but when RiBi is impaired, excess 5S RNP accumulates in the nucleus and binds to the central acidic domain of MDM2.[113-116] This interaction causes conformational changes that inhibit MDM2's function, preventing p53 degradation. Several biochemical studies reported p53 activation through the binding of RPL5, RPL11, and other RPs onto MDM2.[117-122] A structural study conducted by Zheng *et al.*[123] further confirms this interaction by resolving the MDM2-RPL11 complex at 2.4 Å, revealing how RPL11 docks onto MDM2 central acidic and zinc finger domains, mimicking 28S rRNA. In addition, Estrada *et al.*[113] resolved the cryo-electron microscopic structures of the nascent 5S RNP complex, providing further structural context. Studies on siRNA knockdown also underscore the importance of RPL5 and RPL11; depleting either protein attenuates p53 stabilization under ribosomal stress, whereas in general, knockdown of other RPs does not.[124-126]

Additional regulators of the impaired RiBi checkpoint (IRBC) have been identified. For example, recently

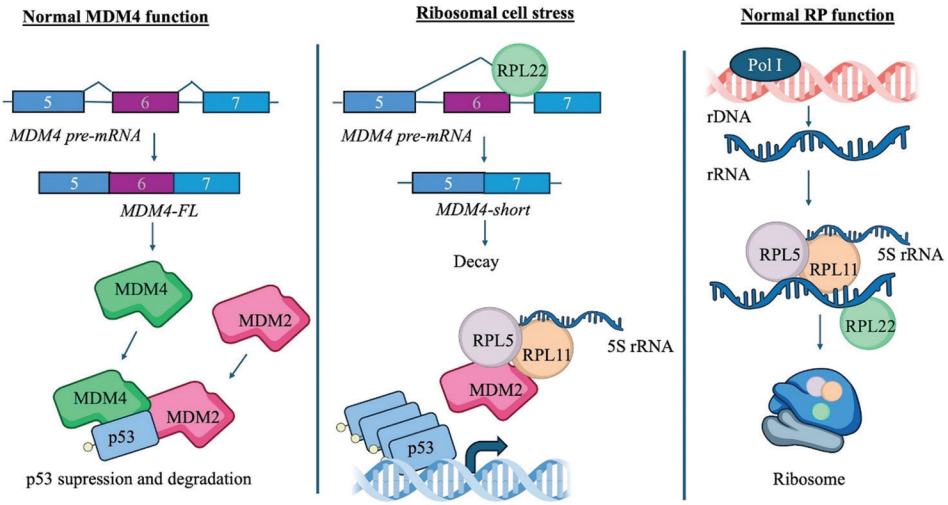

Figure 2. Regulation of p53 through ribosomal stress. Under normal conditions (left), p53 activity is restrained by the coordinated action of its negative regulators, mouse double minute 2 homolog (MDM2) and mouse double minute 4 homolog (MDM4). The full-length *MDM4* (*MDM4*-FL), generated by inclusion of exon 6 in the *MDM4* pre-messenger ribonucleic acid (mRNA), binds and inhibits p53, often in cooperation with MDM2, which also targets p53 for ubiquitin-mediated degradation. However, in response to ribosomal stress, this balance is disrupted (middle). One key mechanism involves the alternative splicing of *MDM4* pre-mRNA. Ribosomal protein (RP), large subunit (RPL) 22 binds to intron 6 of *MDM4* pre-mRNA and promotes exon 6 skipping, resulting in the production of a shortened *MDM4* transcript (*MDM4*-short). This variant lacks critical domains for p53 inhibition and is rapidly degraded, relieving *MDM4*-mediated suppression of p53. In parallel, free RPs RPL5 and RPL11 form a complex with 5S ribonucleic acid (rRNA). This 5S ribonucleoprotein complex binds and sequesters MDM2, blocking its E3 ligase activity and allowing p53 to accumulate and activate its downstream targets. In normal conditions (right), RPL5, RPL11, and RPL22 are co-assembled into ribosomal subunits following rRNA transcription by RNA polymerase I. Upon stress, these components are instead diverted from ribosome production to p53 activation (middle), linking nucleolar integrity and ribosome homeostasis directly to tumor suppression. Image created by the author.

identified surfeit locus protein 2 (SURF2) was found to be associated with free 5S RNP. SURF2 acts as a buffer, limiting 5S RNP's inhibition of MDM2.[127] Overexpressing SURF2 renders cells resistant to ribosomal stress, whereas its depletion enhances p53 activation. Other components, such as Huntingtin, elongation factor 3, protein phosphatase 2A, target of rapamycin (TOR) 1 repeat-containing 3, and La/Sjogren syndrome antigen B, associate with 5S RNP, suggesting a potentially complex regulation of the IRBC.[127] Mutations in the MDM2 zinc finger that disrupt RPL5/RPL11 binding accelerate tumorigenesis in myelocytomatosis oncogene (MYC)-driven cancer.[92] Clinically, individuals with DBA, who carry germline mutations in *RPL5* and *RPL11*, have an elevated risk of developing cancer.[48] Moreover, numerous cancers harbor heterozygous deletions or missense mutations in *RPL5*, particularly in tumors with intact p53.[56,57] This anti-correlation suggests that impairing the checkpoint can compensate for disabling p53. In contrast, *RPL11* is rarely mutated, implying that tumors preferentially target *RPL5* or bypass p53 directly. Indeed, mutations in the MDM2 zinc finger are extremely rare in patients, although they are used experimentally to probe this pathway.[92] If mutations impair RP function, p53 activation may be insufficient, allowing cells with DNA damage or oncogenic mutations to survive and proliferate, creating a permissive environment for tumor development.[128,129]

Besides the 5S RNP pathway, RPL22 regulates p53 via an independent mechanism. RPL22 binds *MDM4* pre-mRNA and promotes an alternative splicing event that produces a shorter, not fully functional isoform of *MDM4*.[58,130] Under conditions of ribosomal stress, RPL22 translocates to the nucleoplasm, binding *MDM4* pre-mRNA through the recognition of a set of specific stem-loop sequences.[130] This binding forces exon 6 skipping, generating the short MDM4-S isoform.[131,132] As MDM4-S lacks the domains needed to effectively inhibit p53, exon 6 skipping removes the brake on p53. Loss of *RPL22* thus facilitates the expression of the *MDM4* oncogene. RPL22 also represses its own paralog, *RPL22L1*.[58,130,133] RPL22 binding to *RPL22L1* pre-mRNA induces a cryptic exon, leading to a nonsense isoform of *RPL22L1*. When RPL22 is lost, *RPL22L1* expression increases, and high RPL22L1 correlates with *MDM4*-FL upregulation. RPL22L1 can substitute for RPL22 in the ribosome. However, RPL22L1 does not promote the same splicing events. RPL22 may broadly link ribosome assembly to alternative splicing programs, with MDM4 as a critical p53-relevant output.

In the context of defect detections by p53 in the small subunit during RiBi, it was noted that disruption of 40S biogenesis can cause selective upregulation and translation of 5'-terminal oligopyrimidine tract mRNAs, including *RPL11* (of the 60S), which then inhibits MDM2.[126] This response is independent of global translation and occurs despite ongoing 60S ribosome production. However, it has also recently been shown that small subunit defects impair late 60S maturation and export due to an early coupling event that takes place during the biogenesis of both subunits.[134]

Taken together, in the setting of ribosomal stress, p53 is activated through at least two complementary pathways. RPL5/RPL11 stabilizes p53 by preventing its degradation, whereas RPL22 relieves p53 from MDM4 inhibition.[135] Several other RPs have been described to bind MDM2, affecting MDM2's E3 ligase activity or modulating p53 mRNA translation, and several RPs can also serve as substrates for MDM2 E3 ligase function.[56,118,136-140] Comprehensive lists of RP-MDM2-p53 interactions were summarized in previous studies.[18,111,112]

7. Translational selectivity in RP mutant cancers

For global translation attenuation due to decreased ribosome expression or stress responses that shut down translation, RP mutations can alter or reprogram selective mRNA translation because mRNAs are not fully dependent on ribosome function. Some mRNAs, particularly those with complex 5' UTRs, appear to require a fully functional ribosome for translation. For example, tumor suppressor *p53* mRNAs have structural complexity in the 5' UTRs, rendering them more dependent on an intact ribosome and subject to regulatory mechanisms.[141] Mutations in RPs can also lead to both selective advantages and disadvantages simultaneously for certain mRNAs. One example is RPL10-R98S, positioned near the peptidyl transferase center; this arginine-to-serine substitution alters ribosomal conformational dynamics, affecting translational fidelity and codon-specific pausing. This substitution results in a selective reduction in the translation of transcripts enriched in proline codons, rewiring the proteome in ways that may promote the progression of leukemia.[142] The reduction in translation occurs without collapsing global protein synthesis, suggesting that mutant ribosomes retain partial functionality sufficient to support growth and cause a significant phenotypic change. The mutant has also been linked to the elevation in reactive oxygen species and mitochondrial dysfunction. Cells with the R98S mutation upregulate the anti-apoptotic protein B-cell lymphoma-2 through internal ribosome entry site-dependent translation, enhancing cell survival.[143] A rare novel RPL10 mutation, Q123R, has been identified in pediatric T-ALL patients (case report).[144] This mutation is associated with

defects in protein synthesis. RPL10 mutations, though infrequent, have also been observed in multiple myeloma clustering at specific hotspots distinct from those in T-ALL.[145] These mutations do not significantly impair RiBi but may subtly affect ribosomal function. *RPS15* mutations in CLL cluster at the interface between the ribosomal subunit and mRNA, likely compromising fidelity of start site selection or mRNA surveillance.[146,147] This shows that cancer-associated ribosomes are likely to be functionally distinct from normal ribosomes.

8. Alternative routes to cancer in the context of RP loss

Several RPs have extraribosomal functions beyond protein synthesis, including transcription and splicing, the DNA damage response, and cell cycle control.[16] Mutations in RPs can disrupt these roles, contributing to genomic instability and tumorigenesis. Due to p53's importance, research has been focused on the role of p53-dependent effects. However, there are numerous p53-independent effects and regulators of ribosomal/nucleolar stress responses.[148-151] The Wnt signaling pathway is likely to be involved, as well as various mechanisms in controlling autophagy processes.[152] Another example is that RPs influence the retinoblastoma (RB) 1 pathway, a critical regulator of the cell cycle that prevents premature progression. RPL11 and RPL5 have been implicated in RB1 regulation, influencing E2 promoter-binding factor (E2F) transcription factor activity.[153] RPL23 (uL14) has also been shown to inhibit MDM2 *in vitro*, indirectly promoting RB1 stabilization.[118] RB pathway alterations are common in cancers with ribosomal stress signatures, and loss of RB1 function in ribosome-defective tumors can drive proliferation despite p53 activation. Other examples include RPS14 and RPL22 interacting with and inhibiting cyclin-dependent kinases (CDK) 4 and CDK6.[150,154] Moreover, knockdown of nucleolar small ubiquitin-like modifier (SUMO) isopeptidases, SENP3 and SENP5, downregulates CDK6, disrupting normal RB/E2F control of cell cycle progression.[149]

The MYC oncogene is a central oncogenic factor influenced by RP function and a prime suspect in the context of RiBi. Indeed, both RPL5 and RPL11 have been reported to negatively regulate MYC expression and function.[155,156] Although this regulation has received less attention than RP-mediated control of p53, it is biologically plausible, given MYC's master role in coordinating and driving RiBi.[157-160] Excess MYC activity is also known to activate the IRBC.[92,93] Taken together, loss of RP function could negatively impact multiple normal functions in the cell, including p53 and those related to the control of cell cycle (RB1/E2F/CDKs), and RiBi (MYC). This may explain why mutations in essential RP proteins can be tolerated.

9. Lessons learned from animal models

Important insights into the role of RPs in cancer have emerged from non-mammalian model organisms. In the fruit fly, *Drosophila melanogaster*, loss of a single *RP* gene copy typically results in the minute phenotype characterized by slow growth and small bristles.[161] However, in certain contexts, RP reductions can paradoxically promote tissue overgrowth. These effects may be non-cell-autonomous, driven by extrinsic mechanisms, such as reduced synthesis of steroid hormones, which delays developmental timing and thereby induces overgrowth of tissues and organs, resulting in a benign abnormal cell mass.[162] However, most $RP^{+/-}$ cells in flies are eliminated by neighboring wild-type cells through a process known as cell competition.[163] Nevertheless, at least one specific RP alteration has tumor suppressor-like effects, and it is the *lethal(1)air8* (air8) locus, which encodes RPS6. Loss-of-function air8 mutants display overgrowth of the larval lymph glands (the fly hematopoietic organs), overproduction of blood cells, and melanotic tumors.[164] Thus, RPS6 acts as a tumor suppressor in *Drosophila* hematopoiesis. Outside of this tissue, $RP^{+/-}$ clones do not form tumors but are instead eliminated through cell competition. RP haploinsufficiency in flies triggers a stress response centered on the transcription factor Xrp1.[165] Xrp1 is induced and drives an integrated stress response, causing eukaryotic translation initiation factor 2α (eIF2α) phosphorylation and a global reduction in protein synthesis. Importantly, loss of Xrp1 restores normal growth and translation in $RP^{+/-}$ cells, indicating that the growth defect is largely Xrp1-mediated. This Xrp1-mediated stress response resembles the p53-dependent checkpoint observed in vertebrates.[163,166] In flies, however, the role of p53 appears minimal, and Xrp1 acts as the principal stress-induced transcription factor. Other studies have indicated the importance of proteotoxic stress, suggesting that the aggregation of RPs, rather than a decrease in translation, is of importance in marking cells that are to be outcompeted, and such proteotoxic stress can be alleviated by inhibition of TOR in *Drosophila*.[108,167] A subsequent study confirmed the important role of Xrp1 for both cell competition and decreased translation.[168]

In zebrafish, a previous study has shown that malignant peripheral nerve sheath tumors (MPNSTs) arise in animals heterozygous for *RP* genes, supporting the idea that RPs can function as haplo-insufficient tumor suppressors in fish.[169] The researchers proposed that "Many *RP* genes might also be cancer genes in humans, where their role in tumorigenesis could easily have escaped detection up to now."[169(p1)] Nearly all RP-mutant zebrafish lines with high tumor incidence showed developmental defects, such as

slow growth and reduced body size, suggesting a global defect in protein synthesis precedes tumorigenesis. In early stages, $RP^{+/-}$ cells exhibit reduced growth and activate p53-dependent checkpoints. Ultimately, however, emerging tumors do not express the p53 protein. MacInnes *et al.*[170] demonstrated that MPNST cells from $RP^{+/-}$ lines had wild-type p53 mRNA but failed to produce p53 protein even after DNA damage, suggesting that insufficient RP levels impair *p53* translation, a defect that appears critical for tumor formation. In general terms, RP haploinsufficiency likely creates selective pressure for loss of p53, mirroring mechanisms seen in human cancer. Moreover, Lai *et al.*[171] reported that $RP^{+/-}$ larvae had reduced global translation and that RP-deficient cells were eliminated via cell competition.

Overall, both *Drosophila* and zebrafish models demonstrate that reduced RP dosage activates ribosomal stress pathways, involving p53 in vertebrates and Xrp1 in flies, which can be tumor-suppressive unless bypassed, and reduces global translation, despite similar ribosome numbers per cell. However, cell competition has not been well studied in early stages of human cancer development, although it is a re-emerging concept and has been investigated in other aspects of human cell biology.[172] There is no direct human ortholog of Drosophila Xrp1. Activating transcription factor 4 (ATF4) has been suggested as a partial functional analog; however, it has not been established. It has recently been observed that *ATF4* is downregulated in human cells following a decrease in RPs, in a p53-independent manner.[173]

10. Compensatory responses to RP mutations in cancer

Previous studies on Xrp1 in *Drosophila*, as well as ATF4 and p53 in mammals, highlight a broader theme: How cancer cells with RP mutations adapt through diverse compensatory mechanisms. RiBi is tightly regulated by growth-related signaling pathways, such as mechanistic TOR (mTOR), which controls rRNA synthesis and translation.[157-160,174] Hyperactivation of mTOR, a hallmark of numerous cancers, increases ribosome production and protein synthesis. Similarly, MYC enhances RiBi by stimulating transcription of rRNA, RiBi factors, and *RP* genes. MYC amplification is common in aggressive cancers and often correlates with elevated translational capacity. It is plausible that cancer cells harboring RP mutations may become dependent on MYC and/or active mTOR.

Cells with RP mutations may also display integrated stress response, unfolded protein response, and heat shock factor (HSF) pathway activity to cope with the consequences of defective ribosome assembly. For instance, HSF1, a regulator of proteostasis, is influenced by RP synthesis. In yeast, newly synthesized RPs modulate HSF1 activity to protect against proteotoxic stress during ribosome assembly.[175] Most studies on this topic have been conducted in yeast and *Drosophila*, while the extent to which these findings can be applied to human cells remains unclear. Nevertheless, in humans, RP mutations or deletions may activate compensatory pathways that promote MYC overexpression[176] and selective pressure to inactivate p53 or related tumor suppressors.[177] Functional studies align with this notion. In mice, heterozygous RP loss has been shown to cooperate with oncogenes, such as MYC. Mice lacking one allele of *Rpl11* or *Rpl22* develop normally but exhibit accelerated lymphoma upon oncogene activation.[59,178,179] Loss of a single *Rpl5* or *Rps24* (eS24) allele leads to sarcomas.[180] Barna *et al.*[181] showed that reducing *Rpl24* (eL24) expression in MYC-driven lymphoid precursors normalized translation and prevented malignant transformation.

As mentioned, cells can actively buffer RP imbalances at the protein level, and excess ribosomal subunits tend to be rapidly turned over by the proteasome. In the RPE1 monosomies, for instance, attempts to overexpress RPL21 (eL21) failed because the proteosome rapidly degraded the excess RPs.[9] This fits with other studies showing that free RPs are degraded if unincorporated.[33,35,182] Cells struggle to cope with a change in ribosome stoichiometry. For example, losing one *RP* gene copy impairs RiBi and protein synthesis, whereas gaining extra *RP* gene copies floods the proteome with RPs that are degraded. It has been shown that the net effect in aneuploid cells is chronic proteotoxic stress, and that may expand the endoplasmic reticulum and lysosomal compartments to activate the unfolded protein response.[108,167,183,184] In other words, extra chromosome-derived protein could become a burden on quality-control systems, and aneuploidy-induced unfolded protein response and proteasomal activity are required to maintain homeostasis. Specifically in this setting, orphan wild-type or mutant RPs can lead to proteasomal overload and/or aggregation.

RP mutations are not passive defects; they actively disrupt ribosome stoichiometry, creating a state that is only tolerable through specific adaptations. Cells must resolve the imbalance between ribosome subunit production, translational demand, and quality control. It can do so by activating stress pathways, such as those controlling eIF2α phosphorylation or the IRBC. Over time, tumors may evade these checkpoints by inactivating *TP53*, stabilizing MDM4, or increasing proteasomal degradation of orphan RPs. This creates a selective landscape in which only subclones capable of buffering ribosomal stress

can survive. Such adaptations may include alternative splicing (RPL22) or induction of ribophagy (Figure 1). RP mutations also influence tumoral heterogeneity because altered translational output can amplify transcriptional noise, promoting divergent cell fates even within genetically identical populations. Thus, RP mutations not only contribute to tumor initiation but also shape clonal evolution and therapy resistance by generating a persistent state of ribosome imbalance, conceptually analogous to how low-level replication stress induces genomic instability without causing mitotic catastrophe (Figure 1).

One intriguing strategy in RP mutant tumors is the modification of ribosome composition through the substitution of paralogs.[72] Several RPs have paralogs and gene duplicates arising from ancient duplication events (e.g., RPL22, in Figure 3A), which retain structural similarity but differ in regulatory control, tissue-specific expression, or exhibit subtle changes in functional properties.[72,185] A recent example is the RPL22-RPL22L1 axis, as was already introduced in relation to MDM4 and p53. Loss of RPL22 leads to compensatory upregulation of RPL22L1.[130,133,186] Although RPL22L1 rescues RiBi, it diverges functionally, as it alters RNA binding and influences alternative splicing in ways different from RPL22. At least some cancer cell lines that rely on RPL22L1 exhibit paralog dependency, making them selectively vulnerable to its inhibition[135] (Figure 3B), an opportunity akin to synthetic lethality paradigms seen in breast cancer susceptibility gene/poly(ADP-ribose) polymerase (PARP) or AT-rich interaction domain 1A/AT-rich interaction domain 1B-mutant contexts.[187] That is, loss of RPL22L1 is hypothesized to be detrimental for the cell in the context where RPL22 is already non-functional. However, if RPL22L1 is lost, cells can still manage with RPL22 if it remains functional (Figure 3B).

Other RP paralogs may display similar divergence and context-specific roles. *RPL39L*, highly expressed in embryonic and cancer cells, is linked to aggressive phenotypes in hepatocellular carcinoma and glioblastoma.[188-190] RPL10-L, enriched in embryonic stem cells, may support stem-like programs in cancer, whereas RP S4 X-linked/RP S4 Y-linked and RPL7 (uL30)/RPL7-L1 exhibit sex-specific or lineage-specific expression, with implications for disease susceptibility and tumor progression.[191] Thus, ribosomal heterogeneity via paralog substitution could enable cancer cells to survive ribosomal stress or RP mutations, but at the cost of new dependencies. Future studies should investigate paralog usage across tumor types in greater detail, as this is likely a common phenomenon in tumors.

11. Therapeutic considerations for cancer in the context of RP alterations

RP-p53 pathways affect cellular sensitivity to agents that disrupt RiBi, such as actinomycin D, 5-fluorouracil, or PARP inhibitors.[192-196] Several studies show that many of these drugs depend on RPL5 and RPL11 to effectively activate p53.[73,112-116] For instance, the PARP inhibitor Olaparib blocks rRNA synthesis, enhancing RPL5/RPL11 binding to MDM2 and stabilizing p53.[197] Similarly, Ishihara *et al.*[198] demonstrated that RPL11 depletion renders p53wild-type cancer cells markedly resistant to etoposide and doxorubicin, due to failure in p53

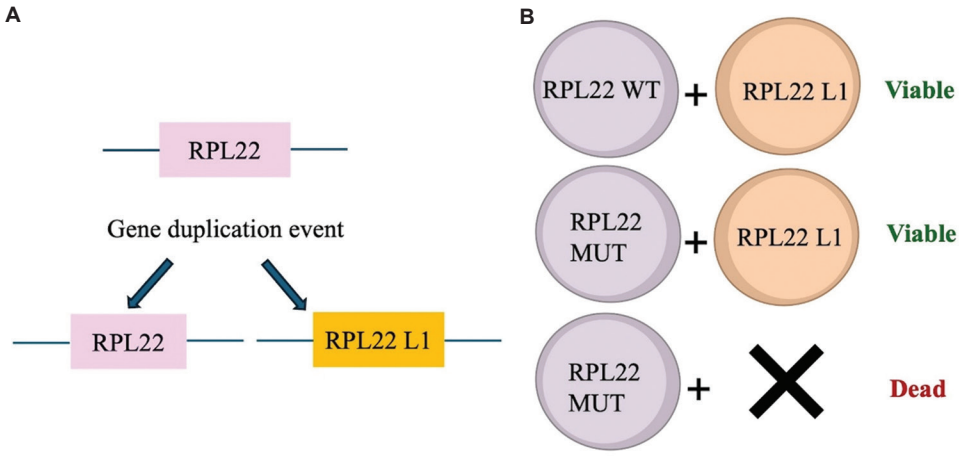

Figure 3. Functional redundancy and synthetic lethality between ribosomal protein, large subunit (RPL) 22 and RPL22L1. (A) Schematic of the gene duplication event that gave rise to the paralogous ribosomal proteins, RPL22 and RPL22L1. (B) Genetic interaction matrix illustrating hypothetical cell viability outcomes upon different combinations of RPL22 and RPL22L1. Cells with a single loss or mutation of either RPL22 (WT [wild type] or MUT [mutant]) or RPL22L1 remain viable, indicating functional compensation. However, simultaneous loss of both RPL22 (due to mutation) and RPL22L1 leads to cell death, revealing a lethal interaction. Image created by the author.

stabilization. The RPL22-MDM4 circuit similarly affects drug responses, and Weinstein *et al.*[58] found that the loss of RPL22 confers resistance to RiBi targeting agents. Without RPL22, MDM4 remains elevated. Therefore, inhibiting MDM2 is unable to fully activate p53. Tumors deficient in RPL22 might be sensitive to drugs targeting MDM4 or to nucleolar stress inducers.[58,130,199] Conversely, RPL22-mutant cancers could resist MDM2 inhibitors, such as Nutlin-3a, as shown by Weinstein *et al.*[58] Given dependency on proteostasis, according to several studies, RP-deficient tumors may exhibit enhanced sensitivity to proteasome or heat shock protein 90 inhibitors.[200] Similarly, mTOR-addicted RP-mutant cancers could be targeted using clinically available inhibitors.[108] It would also be of interest to explore if RP-mutant cells are sensitive to translation inhibitors, including homoharringtonine, also known as omacetaxine.[201] RP mutation recurrent sites or loss of RPs may serve as predictive biomarkers for chemotherapy resistance, as in multiple myeloma.[202,203] Moreover, RPL22 status may influence sensitivity to RiBi inhibitors.[130] The RP mutations in *RPL10* and *RPS15* found in T-ALL, CLL, and other cancers may serve as patient stratification markers to indicate tumors that are more likely to benefit from translation inhibitors or stress-response modulators.[51,60,145,204] Transcriptomic profiling of *RP* genes and paralog usage may indicate prognostic markers. For instance, *RPL39L* expression correlates with glioblastoma aggressiveness.[190]

12. Conclusion

RP alterations, including missense mutations, deletions, or overexpression, in cancer are not neutral events but actively drive tumor phenotype formation and clonal evolution. RP alterations are tolerated in cancer due to their partial functionality, preserving enough ribosome output to sustain growth while altering translation to the benefit of the cancer cell. These alterations may disrupt RiBi, alter translational fidelity, and provoke proteotoxic and ribosomal stress, but not necessarily all at the same time. In response to this, the cancer cells likely must change, disabling p53 checkpoints, engaging MYC, or substituting for ribosomal paralogs. The new cell state imposed by RP alterations is likely to create dependencies, such as reliance on paralogs (e.g., RPL22L1), proteostasis regulators (e.g., HSF1), or to inactivate the ribosome surveillance machinery (p53). These vulnerabilities could be exploited in future therapy. Strategies that reactivate ribosomal stress checkpoints, inhibit compensatory regulators (MYC inhibitors), or exploit ribosome-induced proteotoxic stress (proteasome inhibitors) could be tested. Future work should prioritize the investigation of the various stress responses in relation to RiBi and ribosome function. Moreover, the mechanism of RP mutations that affects the tumor microenvironment and immune recognition has not been discussed in this review, which needs to be taken into account.[205] An in-depth understanding of how RP mutations alter the transcriptional and translational landscape in cancer remains fundamentally important.

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