Acquired ribosomopathies in leukemia and solid tumors

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A mutation in the gene encoding the small subunit-associated ribosomal protein RPS19, leading to RPS19 haploinsufficiency, is one of the ribosomal protein gene defects responsible for the rare inherited bone marrow failure syndrome Diamond-Blackfan anemia (DBA). Additional inherited and acquired defects in ribosomal proteins (RPs) continue to be identified and are the basis for a new class of diseases called the ribosomopathies. Acquired RPS14 haploinsufficiency has been found to be causative of the bone marrow failure found in 5q– myelodysplastic syndromes. Both under- and overexpression of RPs have also been implicated in several malignancies. This review will describe the somatic ribosomopathies that have been found to be associated with a variety of solid tumors as well as leukemia and will review cancers in which over- or underexpression of these proteins seem to be associated with outcome.

Learning Objectives

- To review the leukemias and solid tumors found to have an acquired ribosomal protein defect
- To review the solid tumors in which over- and underexpression of ribosomal proteins seem to be associated with outcome

Introduction

Each ribosome that constitutes the cellular translational machinery is composed of a small (40S) subunit consisting of an 18S RNA and 33 ribosomal proteins (RPs) and a large (60S) subunit with a 5S RNA, a 28S RNA, a 5.8S RNA, and 46 RPs. This complex of structural ribosomal RNAs and associated proteins is carefully regulated and omnipresent. Thus, the initial discovery in 1997 by Gustavsson et al[1] that Diamond-Blackfan anemia (DBA), a rare inherited bone marrow failure syndrome, was the result of a defect in the gene encoding the small subunit-associated ribosomal protein RPS19 was met with considerable skepticism. DBA now stands as the founding member of the class of disorders known as ribosomopathies, and pathogenic mutations have been described in at least 19 other RP genes.[2-11] In DBA, these mutated RP genes are estimated to be inherited in an autosomal dominant manner in about half the cases, the remaining cases being de novo mutations. DBA has also recently been clarified as a cancer predisposition syndrome.[12] Patients with DBA are predisposed to a variety of solid tumors as well as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Adult patients in particular have a significantly increased risk of luminal gastrointestinal cancers.[13] Notably, there seems to be no genotypic predilection to MDS, AML, or solid tumors, which suggests that cancers result from downstream events and are not related to the specific RP haploinsufficiency. Another inherited ribosomopathy, Shwachman-Diamond syndrome (SDS), results most commonly from mutations in *SBDS* leading to faulty ribosome subunit joining.[14] SDS generally presents with neutropenia but other cytopenias and pancytopenia are not uncommon. Solid tumors are rarely reported in SDS,[15] but the disorder clearly predisposes to MDS and AML, although the exact mechanisms remain unknown.[16]

In 2006, Ebert et al[17] reported that the 5q– syndrome, a subtype of MDS, was the result of an acquired somatic *RPS14* deletion. Although typically presenting in the seventh decade of life, 5q– syndrome was soon thereafter reported in 2 children with anemia who had been misdiagnosed as having DBA.[18] Over the past 10 years, somatic RP mutations have been found in a variety of cancers in patients without evidence of DBA or signs of another inherited bone marrow failure syndrome. Somatic mutations in genes encoding RPs seem to be a common feature of many cancers, suggesting their importance in oncogenesis.[19] Furthermore, over- and underexpression of some of the RPs are present in a variety of malignancies and have been postulated to be predictive of outcome.[20] This article summarizes the recent published findings relevant to acquired ribosomopathies (Table 1) and suggests areas of future inquiry. We describe how aberrations in RP expression that act by overexpression as oncogenes or by haploinsufficiency as possible tumor suppressors serve as heretofore underappreciated drivers of malignancy. The concordance of inactivating RP mutations with TP53 inactivation suggests that the latter is an interdicting mutation to the selective pressure of diminished translational capacity, nucleolar stress, and growth retardation as a consequence of RP loss of function.

MDS and leukemia

An acquired deletion of the short arm of chromosome 5 has been known to lead to MDS, which may subsequently progress to AML in some patients. In particular, the 5q– syndrome has been noted mostly, but not exclusively, in women older than age 75 years who present with macrocytic anemia and erythroid hypoplasia and have a recurrent somatic 1.5-Mb commonly deleted region (CDR) in 5q.[21] Ebert et al[17] used short hairpin RNAs to target each of the 40 genes

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Table 1. Cancer types and associated RP mutations or deletions

Cancer type	RP mutation/deletion	Reference
T-cell acute lymphoblastic leukemia	*RPL5*, *RPL10*, *RPL11*, *RPL22*	27, 31
Chronic lymphoblastic leukemia	*RPS15*, *RPSA*, *RPS20*	32, 33
5q- syndrome	*RPS14*	19
Glioblastoma multiforme	*RPL5*	34, 35
Gastric adenocarcinoma	*RPSA*, *RPS5*, *RPL22*	35, 41, 42
Endometrial carcinoma	*RPS20*, *RPL22*	35, 37, 39
Melanoma	*RPL5*, *RPL11*, *RPS27*	35, 36
Breast cancer	*RPL5*	35

within the CDR and identified RPS14 haploinsufficiency as the predominant cause of erythroid hypoplasia in 5q– syndrome. Roles for CSNK1A1 and microRNA-145/146a have also been demonstrated to contribute to the overall phenotype.[22] Unique to this situation and not specifically related to RP haploinsufficiency, deletions in the common deleted region (CDR) in 5q– that also result in IRAK/TRAF activation may play a role in malignant transformation.[23] Interestingly, *RPS14* deletions have not been identified in patients with DBA, but a growing number of other RP gene germline deletions have been noted.

Since Ebert's seminal contribution, several hematologic malignancy–associated RP mutations have been identified. RPL22 has been shown to be essential in T-cell development through the T-cell receptor signaling pathway.[24] In fact, a murine *Rpl22* knockout blocked the development of αβ-lineage T cells selectively by activating a p53-dependent checkpoint.[25] Rao et al[26] identified mutations of *RPL22* that led to monoallelic inactivation in 4 (~10%) of 47 patients with T-cell acute lymphoblastic leukemia (T-ALL). Two of these 4 patients had induction failure, and 1 responded to chemotherapy but then relapsed. In this limited population, of the 9 patients with induction failure, 2 (22%) had deletions involving the region of *RPL22*. Of the 38 patients who achieved induction remission, only 2 had a deletion containing the *RPL22* gene. On further investigation, 6 (~30%) of 19 T-ALL cell lines and 1 of 20 primary patient samples taken at relapse had a deletion in *RPL22* that resulted in a frameshift and a subsequent truncated RPL22 protein. Haploinsufficiency of RPL22 in these patients portended aggressive disease, which prompted these authors to postulate that RPL22 is a tumor suppressor. The authors then showed that RPL22 inactivation resulted in an increase in LIN28B, which had previously been demonstrated to be a direct transcriptional target of NF-κB. The increase in LIN28B had been shown to be associated with an increase in cell proliferation and tumor growth.[27] Subsequently in 2013, De Keersmaecker et al[28] reported somatic RP gene mutations and deletions in *RPL5*, *RPL10*, and *RPL22* in 20% of children with acute T-ALL with *RPL10* R98S, a missense mutation, found exclusively in 7.9% of the pediatric patients with T-ALL. Defects in *RPL11* were also found, but less frequently.

Landau and colleagues[29] identified an *RPS15* mutation as a novel driver mutation of chronic lymphoblastic leukemia (CLL) through whole-exome sequencing of 278 patient and germline samples and 2 other previously published whole-exome sequencing cohorts. *RPS15* was recurrently mutated in 23 of the patients sequenced (4.3%), and these mutations were associated with a shorter progression-free survival. This was further confirmed by an analysis of another group of 41 patients from Europe[30] in whom *RPS15* mutations were found pretreatment (17.1%) and at relapse (19.5%). Of the 8 patients, 3 had additional mutations in TP53 and 3 had deletions in 11q. Similar to the whole cohort, 6 patients (75%) achieved complete remission and 5 patients (63%) relapsed within 3 years of diagnosis. Targeted resequencing of RPS15 performed on a larger CLL cohort revealed that 6% of patients had mutations. *RPS15* mutations were also noted exclusively in the more aggressive forms of CLL. Concurrent mutations in TP53 were found more commonly in patients with *RPS15*-mutated CLL vs patients with nonmutated *RPS15* CLL (36% vs 18%; $P < .01$). Overall survival was poor for patients with *RPS15* mutations and even worse for patients with concurrent *RPS15* and *TP53* mutations. In addition, of the patients without *RPS15* mutations, 3 had *RPSA* and *RPS20* mutations.

Solid tumors

RPL5 has been found to be mutated in glioblastoma multiforme (GBM) and other tumors.[31] Further investigation of The Cancer Genome Atlas (TCGA) database by Fancello and colleagues[32] identified 5 RP genes that were mutated in 4 different cancer types: *RPL5* in cutaneous melanoma and GBM, *RPL11* also in cutaneous melanoma, *RPS5* in gastric adenocarcinoma, *RPS20* in uterine corpus endometrial carcinoma, and *RPSA* also in gastric adenocarcinoma. Precise analysis of *RPL5* mutations has documented heterozygous deletions in GBM (11%), melanoma (28%), and breast cancer (34%) samples associated with lower *RPL5* expression. The possible role of *RPL5* as a tumor suppressor gene in GBM was noted, and underexpression of RPL5 was associated with lower overall survival in these patients. Regarding cutaneous melanoma, a previously reported recurrent mutation has been noted in the 5′ untranslated region of *RPS27* in about 10% of samples, and it was the most frequent mutation in the melanoma samples studied.[33]

Mutations in *RPL22* have also been discovered in 10.9% of uterine corpus or endometrioid endometrial carcinoma through the efforts of TCGA, which used sequencing to document somatic variants across different tumor types.[34] Loss of DNA mismatch repair and subsequent tumor microsatellite instability (MSI) are found in 30% of these types of endometrial cancers.[35] Further characterization of *RPL22* mutations in these tumors found a heterozygous nucleotide deletion in 116 (52%) of 226 tumors.[36] Interestingly, in smaller cohorts, only the MSI-high tumors carried this mutation, and it was not seen in any MSI-stable tumors. In this study, the females with the *RPL22* mutations were older than mutation-negative females but had similar progression-free survival. The significance of this mutation in the progression of these tumors and its relevance with other known mutations such as *PTEN* and *TP53* are areas that need to be investigated.

Gastric cancer is also known to have MSI. A study by Nagarajan et al[37] revealed recurrent deletions of *RPL22* in 64% of MSI-positive gastric cancer tumors, but no mutations were found in MSI-negative tumors. A subsequent report on MSI-unstable endometrial and colorectal tumors confirmed a heterozygous *RPL22* mutation in 50% and 77% of tumors, respectively, further implicating this gene in MSI cancers.[38]

Under- and overexpression of RPs in tumor tissues

Yang et al[39] demonstrated downregulation of RPL22 messenger RNA (mRNA) and protein levels in non–small-cell lung cancer tissue compared with levels found in normal controls. RPL15 underexpression with lower mRNA and protein levels has been reported in pancreatic ductal adenocarcinoma tumor tissue compared with noncancerous tissues.[40] Correlation with tumor characteristics in 2 cohorts of patients revealed association of low levels of RPL15 expression with poor histology and vascular invasion. Positive correlation was also noted with increased overall patient survival in those with high levels of RPL15 expression in the tumor. Further

investigation with RPL15 short interfering RNAs (siRNAs) showed that RPL15 overexpression blocked the invasiveness of the pancreatic cancer cells. In a murine model, RPL15 overexpression led to fewer pulmonary metastases than in controls.

Yong et al[41] reviewed the data from the TCGA database and from primary, secondary, and recurrent GBM tumor specimens to identify RPS11, RPS20, and VEGF-A as possible markers for prognosis. Overexpression of RPS11 in all GBM tumors was associated with more than a fourfold increase in death; overexpression of RPS20 had a twofold increase. This hazard rate remained the same if only primary GBMs were analyzed. However, in secondary GBMs (those who had progressed from low-grade gliomas) only increased expression of RPS11 was found to be associated with poor prognosis; in recurrent tumors, overexpression of RPS20 was more predictive of poor survival. In the TCGA database with 578 GBM reported, patients with high *RPS11* or *RPS20* mRNA expression had a 20% increased hazard of death when compared with patients with low-level expression. However, patients with both RPS11 and RPS20 overexpression had a 43% increase in the hazard of death when compared with those with low levels of both. These authors further postulate that RPS11 and RPS20 may be therapeutic targets.

Investigators have also compared patients' gastric cancer tumor tissue with non-tumor tissue and found increased expression of RPL15 in the tumors compared with the normal gastric tissue from controls, but this did not correlate with cancer stage.[42] This overexpression was also seen in different gastric cancer cell lines. The authors demonstrated siRNA knockdown of *RPL15* leading to decrease in tumor size in mice, thus deeming RPL15 a potential therapeutic target. Overexpression of full-length *RPL15* complementary DNA has also been noted in esophageal tumors.[43] Kasai and colleagues[44] studied expression profiles of many RPs in human normal colorectal mucosa and colorectal adenocarcinoma cells. They found that RPS11 and RPL7 were significantly overexpressed in the cancer cells but 10 other RPs were underexpressed. RPL13 was found to be overexpressed in 28% of gastric cancer, 41% of colorectal cancer, and 20% of liver cancer tissues compared with normal tissue.[45] Inhibition of *RPL13* by siRNA transfection showed reduction in cancer cell growth. *RPL13* mRNA overexpression correlated with advanced stage in gastric cancer and in colorectal cancer, but it was not statistically significant in the latter, and with no other pathologic or clinical features.

RP genes were found to be both up- and downregulated in human hepatocellular carcinoma (HCC).[46] Further investigations were performed on RPL36 because of its overexpression in hepatoma cell lines.[47] Overexpression of RPL36 was noted in human HCC tumor tissue compared with the adjacent non-tumor tissue. Interestingly, high RPL36 levels correlated with hepatic synthetic function and lower α-fetoprotein levels whereas low RPL36 levels were noted with increased portal vein invasion and higher stage of HCC. In fact, patients with high levels in their tumors were found to have longer survival. Thus, according to these findings, levels of RPL36 may be decreased with tumor progression and could be used as a marker of disease state.

Overexpression of RPL39 (along with MLF2) was found in breast cancer stem cells derived from patient biopsies and lung metastases from these patients.[48] Overexpression was also associated with cell migration and proliferation, and treatment with *RPL39* siRNA showed significant decrease in tumor volume. The gain-of-function mutation found in RPL39 was not found in the primary tumors in the TCGA database but was present in more than 10% of the lung metastases. Clinically, patients with this mutation had a significantly shorter median time to relapse compared with those without this mutation.

RPL19 has been reported to also be overexpressed in malignant prostate cancer cell lines, 4.9 to 6.7-fold higher than in benign prostate cancer cell lines.[49] This was recapitulated in malignant and benign human prostate tissues. In fact, when assessed with regard to the grade of the malignancy, intensity of RPL19 staining positively correlated with the higher grade of the tumor. Kaplan-Meier analysis confirmed that patients who expressed higher levels of RPL19 in the tumor had significantly poorer survival, thus making this a possible tumor marker in the future.

Conclusion

Strong evidence now exists that overexpression of RPs that results in disrupted translation can be an oncogenic driver that confers malignant growth potential to tissues with such acquired mutations. It also seems certain that RP haploinsufficiency, both germline (DBA) and somatic (5q– syndrome and other cancers), creates a selective pressure predisposing to malignancy. The importance of RP hemizygosity as a driver of malignancy is strongly supported by the observation that 43% of several tumor specimens and cancer cell lines are RP haploinsufficient.[19] Furthermore, the strong association of somatic acquired RP hemizygosity with inactivating mutations of TP53, as described by Ajore et al,[50] imply that the TP53 inactivation may result from inactivating interdicting mutations in TP53 as a consequence of the growth suppressive properties of RP haploinsufficiency. We suspect that although the notion is hypothetical, altered translation of tissue-specific transcripts acting as either oncogenes or tumor suppressors will be identified as drivers of oncogenesis as a consequence of RP haploinsufficiency. RP haploinsufficiency almost certainly also results in selective expression of preferred transcripts perhaps by favoring canonical translation over internal ribosome entry site–mediated translation. Whether this mechanism is functional in malignancy in a tissue-specific manner is currently unknown.

Both over- and underexpression of RPs suggest that they are potential therapeutic targets. The role of RP genes, presumably as both oncogenes and tumor suppressors, is an emerging science. There is much to be learned about how aberrations in the translational machinery and its components can lead to the development of both hematologic and nonhematologic cancers. It seems probable that influencing RP expression will emerge as an important therapeutic target strategy.

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