**Ribosomal Lesions Promote Oncogenic Mutagenesis**

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**Abstract**

Ribosomopathies are congenital disorders caused by mutations in ribosomal proteins (RP) or assembly factors and are characterized by cellular hypoproliferation at an early stage. Paradoxically, many of these disorders have an elevated risk to progress to hyperproliferative cancer at a later stage. In addition, somatic RP mutations have recently been identified in various cancer types, for example, the recurrent RPL10-R98S mutation in T-cell acute lymphoblastic leukemia (T-ALL) and RPS15 mutations in chronic lymphocytic leukemia (CLL). We previously showed that RPL10-R98S promotes expression of oncogenes, but also induces a proliferative defect due to elevated oxidative stress. In this study, we demonstrate that this proliferation defect is eventually rescued by RPL10-R98S mouse lymphoid cells that acquire 5-fold more secondary mutations than RPL10-WT cells. The presence of RPL10-R98S and other RP mutations also correlated with a higher mutational load in patients with T-ALL, with an enrichment in NOTCH1-activating lesions. RPL10-R98S–associated cellular oxidative stress promoted DNA damage and impaired cell growth. Expression of NOTCH1 eliminated these phenotypes in RPL10-R98S cells, in part via downregulation of PKC-θ, with no effect on RPL10-WT cells. Patients with RP-mutant CLL also demonstrated a higher mutational burden, enriched for mutations that may diminish oxidative stress. We propose that oxidative stress due to ribosome dysfunction causes hypoproliferation and cellular insufficiency in ribosomopathies and RP-mutant cancer. This drives surviving cells, potentiated by genomic instability, to acquire rescuing mutations, which ultimately promote transition to hyperproliferation.

**Significance:** Ribosomal lesions cause oxidative stress and increase mutagenesis, promoting acquisition of rescuing mutations that stimulate proliferation.

**Introduction**

Impaired ribosome assembly and/or function stemming from mutations in ribosomal protein (RP) or ribosome assembly genes cause congenital disorders called ribosomopathies [e.g., Diamond–Blackfan Anemia (DBA) and Shwachman–Diamond Syndrome (SDS)]. Despite the presence of identical ribosomal mutations in every cell, ribosomopathies display tissue-specific hypoproliferative phenotypes, which particularly affect the hematopoietic system. Intriguingly, these disorders also carry an increased risk of developing cancer later in life, particularly acute myeloid leukemia (AML) and myelodysplastic syndrome (1). This paradoxical transition from cellular hypoproliferation to hyperproliferation is reminiscent of a known phenomenon first observed in 1967. Here, William Dameshek described that patients who initially develop a hypoproliferative disease, such as aplastic anemia, tend to be at higher risk of hyperproliferative diseases, such as acute leukemia (2). Ribosomopathies are thus examples of the longstanding and unsolved “Dameshek’s Riddle.” On the basis of data obtained in yeast, we have previously proposed that compensatory mutations might be rescuing the proliferation defects imposed by ribosomal mutations over time (3). Recurrent somatic mutations in RP genes (RPS15, RPL5, RPL10, RPL11, and RPL22) have recently also been discovered in various solid tumor types including breast cancer, glioblastoma, and melanoma, as well as in hematopoietic cancers such as T-cell acute lymphoblastic leukemia (T-ALL), chronic lymphocytic leukemia (CLL), and multiple myeloma (1). Of these, the R98S mutation in ribosomal protein L10 (RPL10-R98S) is the most recurrent known missense mutation, present in 8% of pediatric T-ALL (4). RPL10 (also called Ul6) is an essential protein near the ribosomal catalytic core, and we have previously shown that the R98S mutation interferes with ribosome function and cell proliferation (4-6). Moreover, RPL10 interacts with the ribosome maturation protein SBDS during ribosome assembly, and SBDS mutations cause similar hypoproliferative defects in SDS (7). In this study, we explored the paradoxical transition from hypoproliferation and investigated how an initial ribosomal defect that restricts cell proliferation, exemplified by the RPL10-R98S mutation, can ultimately have an oncogenic impact.
Materials and Methods

Cell culture

Breeding and usage of transgenic Rpl10<sup>RK1</sup> <sup>R98S</sup> and control animals for cell isolations were approved by the local ethics committee (P145/2014). Ba/F3 cells were obtained from Leibniz-Institute DSMZ. Cells were not authenticated but all cell cultures were confirmed to be free of *Mycoplasma* contamination. The NOTCH1-ICN construct has been described previously (8). Viable cell counts were obtained using a Guava EasyCyte (Merck Millipore). Flow cytometry analysis of CellROX (Thermo Fisher Scientific, catalog no. C10422) and Phospho-H2AX (Cell Signaling Technology, catalog no. 9718S) to detect reactive oxygen species (ROS) and DNA damage, respectively, was performed using a MACSQuant VYB (Miltenyi Biotec) or BD FACSBox and FlowJo software.

**Ba/F3 cells.** Generation and culturing of isogenic cell lines expressing RPL10-R98S and RPL10-WT has been described previously (6). As long as the cells were cultured, stable expression of RPL10-R98S was confirmed on a weekly basis by cDNA sequencing of the RPL10-R98S locus as reported previously (6). Cells were transduced with NOTCH1-ICN-ires-GFP, NOTCH1-L1601P-APEST-IRES-GFP, or empty IRES-GFP vector, sorted for GFP, and treated with 10 μmol/L of the NOTCH1 transcriptional complex inhibitor SAHM1 or DMSO. Cells were plated at a density of 100,000/mL and counted after 48 hours.

**Lineage-negative cells.** Generation and culturing of lineage-negative (lin<sup>-</sup>) cells on semisolid media was recently reported (9). Briefly, isolation of lin<sup>-</sup> cells from the bone marrow of 6- to 8-week-old transgenic MX1-Cre Rpl10<sup>RK1</sup> <sup>R98S</sup> and from MX1-Cre control mice was performed using an EasySep Mouse Hematopoietic Progenitor Cell Enrichment Kit (StemCell Technologies). Isolated cells were retrovirally transduced with NOTCH1-ICN-ires-GFP, NOTCH1-L1601P-APEST-IRES-GFP, or empty IRES-GFP vector, sorted for GFP, and plated at 2 × 10<sup>5</sup> cells/mL in Methocult with recombinant cytokines (GFM3534, StemCell Technologies), supplemented with 10 μmol/L SAHM1 or DMSO. The cells were replated after 12 days, and cell count measurements and flow cytometry stainings carried out at the second replating are shown in the figures. For experiments involving the antioxidant N-acetyl-cysteine (NAC), lin<sup>-</sup> cells were suspended in liquid cystine-rich media, and cultured for 3 hours in the presence or absence of 20 μmol/L NAC (Sigma) followed by analysis by flow cytometry or Western blotting.

**Pro-T cells.** Cell cultures were established as described previously (10) from CD2-Cre Rpl10<sup>RK1</sup> <sup>R98S</sup> and Rpl10<sup>RK1</sup> <sup>R98S</sup> control mice. Briefly, isolated lin<sup>-</sup> cells were seeded onto 12-well cell culture plates that were coated with DLA/Fc fusion protein in the presence of murine stem cell factor and IL7 (Final concentration 20 ng/μL, StemCell Technologies). After 2 to 3 weeks, the differentiation of lin<sup>-</sup> cells into T-cell progenitors with a retained DN2-DN3 phenotype was confirmed by flow cytometry analysis of CD25, CD44, and CD117 markers.

**Western blotting analysis**

Standard Western blotting analysis was carried out as reported previously (9) using primary antibodies targeting Phospho-H2AX (Cell Signaling Technology, catalog no. 9718), catalase (Cell Signaling Technology, catalog no. 14097), and PKC-θ (Cell Signaling Technology, catalog no. 13643), and a secondary Goat Anti-Rabbit IgG-HRP antibody (Thermo Fisher Scientific). Proteins were visualized using chemiluminescence on an Azure C600 (Azure Biosystems). Quantification was performed using LI-COR Image Studio Lite software version 5.2. Vinculin (Sigma Aldrich) was used to normalize for protein input.

**Exome sequencing and patient data analysis**

Exome sequencing of Ba/F3 cell clones was performed by BGI-Tech using Agilent SureSelect exome capture and Illumina sequencing. Three independent clones were analyzed. The SNPs and INDELs unique to each clone were first identified. These gene sets were subsequently subjected to several filtering steps to exclude silent and germline mutations, and those mutations falling in intragenic regions. The variant allele frequencies (VAF) of RPL10-R98S and NOTCH1-activating lesions from the Cools (11) and Mulighan (12) T-ALL cohorts were calculated by dividing the number of reads of the specific allele in the tumor sample by the total number of reads in that tumor sample. For male patients, VAF values of RPL10-R98S were divided by 2 to correct for the X-chromosome location of this gene. VAFs higher than 0.6 were divided by 2 to allow comparison of heterozygous and homozygous mutations.

**Mutational signature analysis**

Mutational signature analysis as described by Alexandrov and colleagues (13) was performed using the R package “mutSignatures” and was applied on the Mullighan T-ALL whole-exome sequencing dataset (12), after dividing the samples into three groups according to RP mutation status (RP-R, RPL10-R98S, other RP-mutant). The first two signatures were used because analysis of the lowest root mean squared error (RMSE) indicated that the lowest RMSE was obtained by taking 1 or 2 signatures for each group, and because the first two signatures could explain all the mutations for each group. The first and second mutational signatures were thus used to compare the three groups using a Wilcoxon rank-sum test.

**Statistical analysis**

The statistical tests that were used are indicated in the figure legends.

**Results**

The T-ALL–associated RPL10-R98S mutation is one of the best described somatic ribosomal mutations in cancer. Confirming previous observations (4), introduction of the RPL10-R98S mutation into lymphoid Ba/F3 mouse cells, a well-established hematopoietic model for oncogenic studies, caused a proliferation defect compared with WT cells (Fig. 1A, left). However, consistent with previous research in an RPL10-R98S yeast model (5), this proliferative defect disappeared after culturing the cells for 5 additional weeks (Fig. 1A, middle). We confirmed that this proliferative recovery of RPL10-R98S Ba/F3 cells was not due to loss of expression of the RPL10-R98S mutation, and performed exome sequencing of one RPL10-WT and two RPL10-R98S Ba/F3 cell clones collected after this additional culturing period to gain insights into the proliferation rescue. Exome sequencing revealed an approximately 5-fold higher mutational load in the mutant...
cells (average of 368 vs. 72 mutations, Fig. 1A, right). These mutations were evenly distributed among a variety of cellular pathways in WT cells, but clustered into pathways of signal transduction, immune system, and metabolism in RPL10-R98S cells (Fig. 1A, right). These results prompted us to explore a potential mutagenic phenotype in ribosome-mutant T-ALL. To this end, we surveyed available T-ALL targeted resequencing data (11; Cools cohort) of genes known to be recurrently mutated in T-ALL (T-ALL genes). Notably, patients with T-ALL carrying RPL10-R98S, as well as mutations in other RPs, presented approximately twice as many mutations in T-ALL genes, with an average of 10.1 mutations for all RP-mutant cases versus 5.2 mutations for RP-WT cases (Fig. 1B). Lesions in other T-ALL genes with similar incidences as the RPL10-R98S defect in pediatric T-ALL, such as IL7R and EZH2, did not correlate with an increased number of mutations (5.8 and 4.9 average number of mutations, respectively). These findings were further confirmed by analysis of a recent whole-exome sequencing dataset from 264 pediatric patients with T-ALL (12; Mullighan cohort). In this comprehensive study, patients with RP-mutant T-ALL displayed an approximately 37% higher total mutational load compared with patients with RP-WT T-ALL (Fig. 1C).

To better understand the mutagenic processes in RP-mutant T-ALL, we applied a mutational signature analysis on the Mullighan dataset as described previously (13). Two signatures were selected for analysis (see Materials and Methods), and RPL10-R98S samples displayed a significant difference for signature 1 compared with RP-WT samples (Fig. 2A). We described previously that RPL10-R98S elevates oxidative stress in mouse cell models, and that reduction of reactive oxygen species (ROS) levels by means of an antioxidant can rescue the proliferation defect of RPL10-R98S cells (9). Furthermore, oxidative stress is known to induce DNA damage, which can in turn promote mutagenesis. In agreement with these findings, the mutational signature of RPL10-R98S patient samples mainly consists of C:G>T:A transversion mutations (Fig. 2A, left bars in signature 1 indicated by a star).

Figure 1. RP lesions increase the mutagenic burden in T-ALL. A, Left and middle, growth curves of Ba/F3 cell clones expressing RPL10-R98S or RPL10-WT at different timepoints. Right, number of mutations as determined by exome sequencing on three cell clones (one RPL10-WT and two RPL10-R98S) from the left panel of Fig. 1A. The percentages in the reactome pathways correspond to the fraction of mutated genes in the RPL10-R98S clones belonging to the mentioned reactome pathway. B, The number of mutations in genes known to be recurrently mutated in T-ALL (T-ALL genes) in RP-mutant versus RP-WT T-ALL patient samples, mined from targeted resequencing data (11). The RPL10-R98S category includes patients with RPL10-R98S as the only RP mutation. The “other RP-mutant” category includes patients with mutations in RPL5, RPL22, or in multiple RPs including RPL10-R98S. Mean values are indicated by a green line and the corresponding green number. C, The number of mutations in RP-mutant versus RP-WT T-ALL, mined from patient whole exome data (12). The RPL10-R98S category includes patients with RPL10-R98S as the only RP mutation. The “other RP-mutant” category includes a patient with the RPL10-Q123P mutation, and patients with mutations in RPL4, RPL5, RPL9, RPL11, RPL22, RPS3, RPS13, or in multiple RPs. Mean values are indicated by a green line. P values were calculated using a t test after accounting for equality of variances using an F test (B and C; *, P ≤ 0.05; **, P ≤ 0.01; ***, P ≤ 0.001).
black rectangle), which correspond to mutations that have been linked to oxidative DNA damage (14). Signature 2 also shows a 14-fold higher probability for this mutational type in RPL10-R98S samples as compared with RP-WT samples. These findings thus underscore that mutational processes in RPL10-R98S samples differ from those in RP-WT T-ALL, and that oxidative DNA damage is a major mutational cause in RPL10-R98S leukemia.

We next investigated whether RP-mutant cases are enriched for mutations in particular genes. After accounting for multiple testing (Benjamini–Hochberg correction) in the Cools cohort, the top 3 genes mutated at higher incidences in patients with RP-mutant T-ALL, and particularly in RPL10-R98S cases, consisted of the transcription factors BCL11B, NOTCH1, and FBXW7 (P = 0.08 each). The last two belong to the NOTCH1-signaling pathway, and activating mutations in NOTCH1 or inactivating mutations in its inhibitor FBXW7 were significantly enriched in RP-mutant cases (Fig. 2B). This was confirmed in the Mullighan cohort, revealing a 100% cooccurrence of NOTCH1 mutation, we introduced the transcriptionally active form of NOTCH1 (Intracellular NOTCH1 - ICN) into three RPL10-R98S and RPL10-WT cell models. First, expression of ICN rescued the proliferation defect of RPL10-R98S Ba/F3 cells (Fig. 3A), which was reversed by addition of the NOTCH1 transcriptional complex inhibitor SAHM1. Second, we isolated lin− hematopoietic stem cells from RPL10-R98S and RPL10-WT knock-in mice (7) and cultured them on cytokine-rich semisolid medium. Here, although the proliferation of both mutant and WT cells benefited from ICN expression, RPL10-R98S cells displayed a markedly increased proliferative benefit compared with cells isolated from WT mice (Fig. 3B). Finally, we generated NOTCH1 ligand (Delta-like 4, DL4) dependent pro-T cultures from RPL10-R98S and WT lin−/C0 cells. Such pro-T-cell lines approximate the stage of T-cell differentiation at which T-ALL cells are blocked. Pro-T cells generated from RPL10-R98S lin− cells displayed a proliferative advantage compared with cultures generated from WT lin− cells in this NOTCH1-stimulated system. A more pronounced proliferative decline of the mutant cells was moreover observed upon DL4 removal (Supplementary Fig. S1). These data from three independent, genetically defined cellular models suggest that NOTCH1 cooperates with RPL10-R98S to accelerate cellular proliferation.

We explored the molecular mechanism of the RPL10-R98S - NOTCH1 cooperation by employing a clinically relevant
mutant form of NOTCH1 that is recurrently found in patients with T-ALL (NOTCH1-L1601P-DEST). Expression of this active form of NOTCH1 also strongly promoted growth in RPL10-R98S lin− cells (Fig. 3C). In agreement with the mutational signature analysis as well as previous observations (9), RPL10-R98S induced elevated ROS levels in these cells. Furthermore, analysis of the phosphorylated form of histone H2A.X, a marker of double-strand DNA breaks, demonstrated that the higher RPL10-R98S linked ROS levels were associated with enhanced DNA damage. Importantly, expression of NOTCH1-L1601P-DEST or ICN reduced the oxidative stress and DNA damage in RPL10-R98S but not in WT lin− cells (Fig. 3D; Supplementary Fig. S2, left). To confirm the causative role of oxidative stress on DNA damage in RPL10-R98S cells, we treated lin− cells with the antioxidant NAC followed by ROS and DNA damage staining as above. Similar to NOTCH1, this NAC treatment decreased ROS and DNA damage levels in RPL10-R98S cells (Supplementary Fig. S3).

Discussion

We employed the RPL10-R98S mutation found in T-ALL as a tool to investigate the oncogenic mechanisms of a ribosome-mutant cancer. This mutation also mimics the cellular transition...
of hypo-to hyperproliferation of ribosomopathies in cell culture and is functionally linked to SBDS, which is in turn mutated in the ribosomopathy SDS, characterized by elevated cancer incidences. In addition to being a model of recurrent somatic ribosomal lesions in cancer, RPL10-R98S thus offers an appropriate and useful system to also model the oncogenic transition of ribosomopathies.

Our results allow the generation of a model linking Dameshek’s Riddle in congenital ribosomopathies and the growing list of somatic ribosome defects in cancer (Fig. 4). RP mutations first cause insufficient functional ribosomes to be produced, which affects hematopoietic cells in particular, for reasons that are only beginning to emerge (e.g., specialized ribosome composition in hematopoietic tissue). This causes early hematopoietic insufficiency, with the surviving and ribosome-defective cells facing high oxidative stress, DNA damage, and pressure to select for compensatory mutations, which can rescue the oxidative stress and associated proliferation defect. Of note, only ribosomopathies associated with hematopoietic deficiencies progress to cancer. For example, DBA and SDS are characterized by early anemia and bone marrow failure, and a high risk to develop predominantly hematologic cancers, such as AML, later in life. In contrast, Treacher Collins Syndrome does not display any hematopoietic abnormalities and is not correlated with increased cancer risk (1). Fanconi anemia is another congenital disorder, without RP mutations, that initially presents with anemia followed by a higher risk of progression to AML. The genes affected in Fanconi anemia have important roles in DNA repair, and the elevated cancer risk in this disease was partly attributed to faulty DNA repair (15).

Intriguingly, other RP-mutant T-ALL samples outside of RPL10-R98S did not show a signature mainly driven by oxidative stress in our analysis. This suggests that other types of stress may cause the elevated mutation rate seen in these samples. However, emerging literature support a more general connection between ribosomal lesions, oxidative stress, and mutagenesis. For example, a mouse model of the ribosomopathy SDS was shown to be characterized by oxidative stress and activation of DNA damage responses in hematopoietic cells (16). Furthermore, oxidative stress–induced DNA damage has recently been described in DBA samples (17). Finally, increased oxidative stress was shown to be involved in accelerating DNA damage and mutagenesis in myeloid cells (18). By inducing oxidative stress, RP lesions may thus act as promoters of DNA damage in RP-mutant diseases. In addition, ribosomal RNA has been shown to be a target for oxidative nucleobase damage, which interferes with ribosome function (19). This oxidative “snowball” effect might even further enhance a mutagenic phenotype of RP lesions.

A larger mutagenic pool is expected to increase the cellular oncogenic potential. Fittingly, we observed an approximately 2-fold higher load of known T-ALL mutations in RP-mutant T-ALL compared with patients with WT ribosomes (Fig. 1B and C). One such mutation type affects the NOTCH1 pathway and our data support that cells expressing RPL10-R98S, and likely other RP mutations (Fig. 2B and C), display elevated dependence on NOTCH1. This dependence might stem from the ability of NOTCH1 to protect ribosome-mutant cells from increased generation of ROS. We have previously shown that RPL10-R98S ribosomes are functionally rewired and lead to the overexpression of oncogenes such as JAK–STAT signaling mediators and the antiapoptotic factor BCL-2 (6, 9). However, this alone seems insufficient to drive cellular transformation, as increased ROS levels interfere with cellular proliferation. Selecting for mutations that diminish oxidative stress could remove a major
impediment toward achieving transformation. To this end, NOTCH1 has known roles in modulating the cellular responses to high oxidative stress. In particular, NOTCH1 signaling has been shown to reduce ROS production by elevating catalase levels (20) and by repression of protein kinase C ε (PKC-ε), which in turn represses ROS accumulation (21). Although we did not observe NOTCH1-induced changes in catalase levels, lin-^ RPL10-R98S cells displayed a more significant reduction of PKC-ε levels upon expression of NOTCH1 (Supplementary Fig. S2), thereby corroborating this previously proposed mechanism of ROS repression via NOTCH1. Our model assumes that RPL10-R98S precedes the NOTCH1-rescuing mutations. Although determining the exact mutational order at the preleukemic stage is not possible, analysis of the variant allelic frequencies in the Cools and Mullighan T-ALL cohorts indicates that NOTCH1-activating mutations are acquired after RPL10-R98S in the majority of cases (Supplementary Fig. S4). In addition to NOTCH1, a recent genomic study also described frequent cooccurrence of translocations driving overexpression of the transcription factor NKX2-1 with RP-mutations in T-ALL (12). Because we focused on point mutations and INDELS in our studies (4, 11) and not on translocations, this association was not picked up in our analyses. Investigating the relationship between RP mutations and overexpression of NKX2-1 can be an important aim for future studies.

Recurrent ribosomal mutations in CLL have also been described, with mutations in ribosomal protein S15 (RPS15) reported as early clonal events with poor prognosis (22, 23). We analyzed an available CLL whole-exome dataset (22) and also observed an approximately 30% higher mutational burden in RP-mutant CLL (Supplementary Fig. S5). Although RP mutations did not correlate with NOTCH1 lesions here, an enrichment of TP53 aberrations in RPS15-mutant CLL was previously reported (23). Moreover, a recent study described the acquisition of TP53 mutations in patients with the ribosomopathy SDS as early events in the transformation to AML (24). A mouse model of SDS further displayed oxidative stress and activation of DNA damage responses in hematopoietic cells (16). The role of TP53 inactivation in RP-mutant CLL and SDS is unclear, but it may also alleviate oxidative stress as TP53 activation upon a cellular burden (i.e., ribosome assembly defects) is known to promote oxidative stress.

Hematopoietic cancers depend on multiple mutagenic events. We suggest that hematopoietic RP lesions act as intrinsic cellular stressors that make transformation more accessible by predisposing cells to acquire mutations that alleviate RP lesion–associated stress and stimulate cellular proliferation. These findings provide novel perspectives for prognosis and treatment of RP-mutant patients. For example, our data indicate that patients with RP-mutant T-ALL might particularly benefit from NOTCH1-targeted therapy. Moreover, tumor mutational burden was recently demonstrated as a biomarker of response to checkpoint inhibitor immunotherapy, with higher mutational burdens corresponding to higher response rates in a variety of cancers (25). Immunotherapy therefore represents a compelling targeted therapy opportunity for RP-mutant patients, a number that keeps on growing.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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