RIBOSOMAL LESIONS PROMOTE ONCOGENIC MUTAGENESIS

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Abstract: S150

Type: Presidential Symposium

Presentation during EHA23: On Friday, June 15, 2018 from 16:00 - 16:15

Location: Room A1

Background

Ribosomopathies are congenital disorders with mutations in ribosomal proteins (RPs) or assembly factors, characterized by cellular hypo-proliferation which particularly affects blood lineages. Intriguingly, ribosomopathies with hematopoietic insufficiency carry an increased risk to develop cancer, such as AML, later in life. The transition from hypo- to hyper-proliferation fits within an unexplained paradox known as Dameshek's Riddle (Dameshek, *Blood* 1967). Somatically acquired RP mutations have recently also been described, primarily in blood cancers such as T-ALL and CLL. Of these, the R98S mutation in ribosomal protein L10 (RPL10 R98S) is the most recurrent missense mutation, found in 8% of pediatric T-ALL. We have previously shown that this mutation interferes with ribosome function and cell proliferation. Moreover, RPL10 interacts with the SBDS protein during ribosome assembly, and *SBDS* mutations cause similar cellular defects in the ribosomopathy Shwachman-Diamond Syndrome (SDS).

Aims

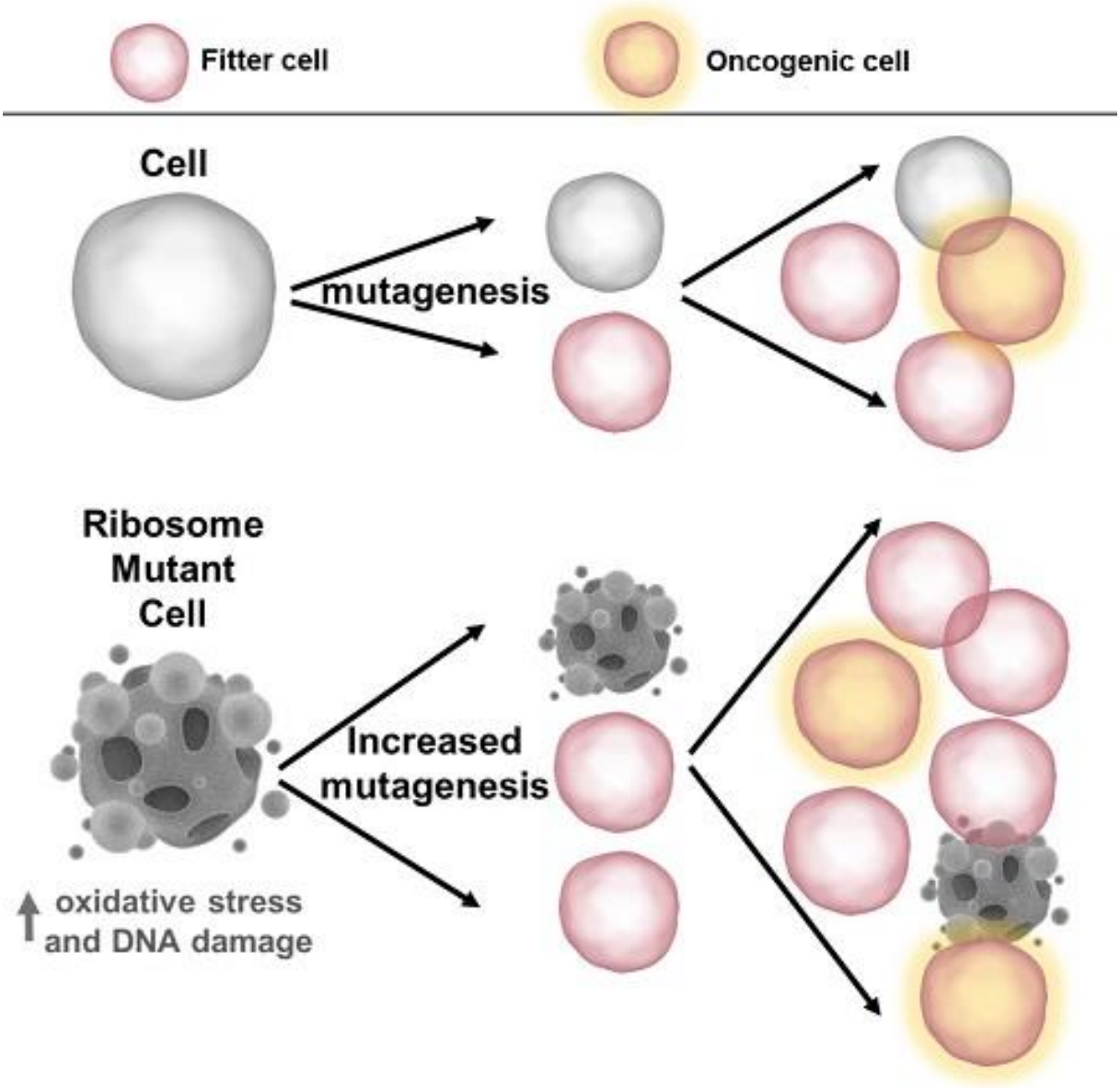
To investigate how an early ribosomal mutation, exemplified by RPL10 R98S which negatively affects cell proliferation, can ultimately have an oncogenic impact.

Methods

Analysis of isogenic models expressing RPL10 R98S or WT including Ba/F3, lineage-negative cells from transgenic Rpl10-R98S and control mice, and pro-T cell cultures. NOTCH1-hyperactivation was attained by DL4 stimulation or expression of active NOTCH1 forms (NOTCH1-ICN or NOTCH1-L1601P-ΔPEST found in T-ALL patients).

Results

RPL10 R98S induced a proliferation deficiency in lymphoid mouse cells, which was rescued with time by acquisition of additional mutations. Specifically, exome sequencing revealed that RPL10 R98S promoted a ~5-fold higher acquisition of additional mutations compared to WT. Analysis of two sets of previously generated T-ALL exomes (De Keersmaecker, *Nat. Genet*. 2013; Liu, *Nat. Genet*. 2017) revealed a ~2-fold higher load of mutations and oncogenic drivers in patients with RPL10 R98S or other RP mutations compared to patients with WT ribosomes. Further, RP-mutant patients from both cohorts displayed a significant enrichment for NOTCH1 pathway activating lesions. NOTCH1 expression rescued the proliferation defect of RPL10 R98S cell lines, which was reversible with NOTCH1 inhibition. In particular, RPL10 R98S specifically increased oxidative stress levels, which in turn promoted DNA damage, and both of these phenotypes were eliminated by NOTCH1 expression. Analysis of CLL patient exomes (Landau, *Nature*2015) also demonstrated a higher mutational burden in cases with RP lesions (i.e. RPS15), and an enrichment in TP53 aberrations in RP mutant CLL cases. A recent study moreover described the acquisition of TP53 mutations in SDS patients as early events in the transformation to AML (Xia, *Blood* 2018). The role of TP53 mutations in RP mutant CLL and SDS is unclear, but it may also alleviate oxidative stress as TP53 activation upon cellular burden (i.e. ribosome assembly defects) is known to promote oxidative stress.



Conclusion

We propose that RP lesions in ribosomopathies and cancer cause ribosome dysfunction-driven oxidative stress and consequently DNA damage, hypo-proliferation and hematopoietic insufficiency. This drives surviving blood cells to acquire rescuing mutations which, potentiated by genomic instability, leads to a larger mutagenic pool. RP mutations may thus act as intrinsic cellular stressors that make transformation more accessible by opening the oncogenic window in disease-specific pathways. This in turn opens the window for novel prognosis and therapy potential for RP mutant patients.

Session topic: 1. Acute lymphoblastic leukemia – Biology & Translational Research