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RESEARCH HIGHLIGHT

Targeting mRNA translation aberrations: A novel approach for therapy in chronic lymphocytic leukemia

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1 | mRNA TRANSLATION IS AFFECTED IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) AT VARIOUS LEVELS

mRNA translation dynamics enable tight regulation of protein expression and rapid stress adaptation; however, its contribution to oncogenesis is overlooked compared to genetic and epigenetic aberrations. Aberrations in mRNA translation are a common feature of cancer and are established as a therapeutic vulnerability. There is growing evidence of dysregulated protein synthesis in CLL. For instance, the Ribosomal Protein S15 (RPS15) coding gene, a part of the 40S ribosomal subunit, is frequently mutated in CLL, leading to altered translation fidelity and efficacy, and associated with poorer prognosis [1, 2] (Figure 1A). Reduced expression of Dyskerin, a modifier of ribosomal RNAs (rRNAs) critical for translation fidelity, is associated with translatome changes [3]. CLL subgroups with mutations/expression changes in ribosomal proteins and complexes could be further classified as "ribosomopathies". In these conditions, evolution from hypo- to hyperproliferative phenotypes is likely aided by a shift towards an oncogenic translatome and the acquisition of rescue mutations, explaining higher frequencies of cancer [4]. Whether the same mechanisms occur in RPS15-mutated CLL requires further investigation.

Alongside translational program defects triggered by ribosomal protein mutations, increased protein synthesis is observed in CLL. The lymph node (LN) microenvironment drives intense proliferation through diverse pathways. Interestingly, CLL cells in patient LNs exhibit an enriched mRNA translation signature compared to circulating cells [5]. Stimulation of CLL cells markedly raises global translation rate via heightened Eukaryotic translation Initiation Factor 4A (eIF4A) and eIF4G1 expression, coupled with reduced Programmed Cell Death 4 (PDCD4) levels, an eIF4A inhibitor (Figure 1B). Furthermore, elevated expression of certain factors impacts translation rate. The Zeta chain of T cell receptor-associated protein kinase 70 (ZAP-70), highly expressed in aggressive CLL cases, interacts with ribosomal proteins and translation initiation factors, sustaining high translation of genes involved

Abbreviations: CLL, Chronic Lymphocytic Leukemia; DMDAPatA, DesMethyl DesAmino Pateamine A; eIF4A, Eukaryotic translation Initiation Factor 4A; ETS-1, E26 Transformation Specific 1; LN, Lymph Node; MAPK, Mitogen-Activated Protein Kinase; MYC, MYeloCytomatosis oncogene; NF-KB, Nuclear Factor Kappa light chain enhancer of activated B cells; PDCD4, Programmed Cell Death 4; PHB, prohibitin; RAF, Rapidly Accelerated Fibrosarcoma; RAS, RAt Sarcoma virus; RPS15, Ribosomal Protein S15; rRNA, ribosomal RNA; SILAC, Stable Isotope Labeling with Amino acids in Cell culture; TCL1, T-Cell Leukemia 1; Treg, regulatory T cells; ZAP-70, Zeta chain of T cell receptor-associated protein kinase 70.

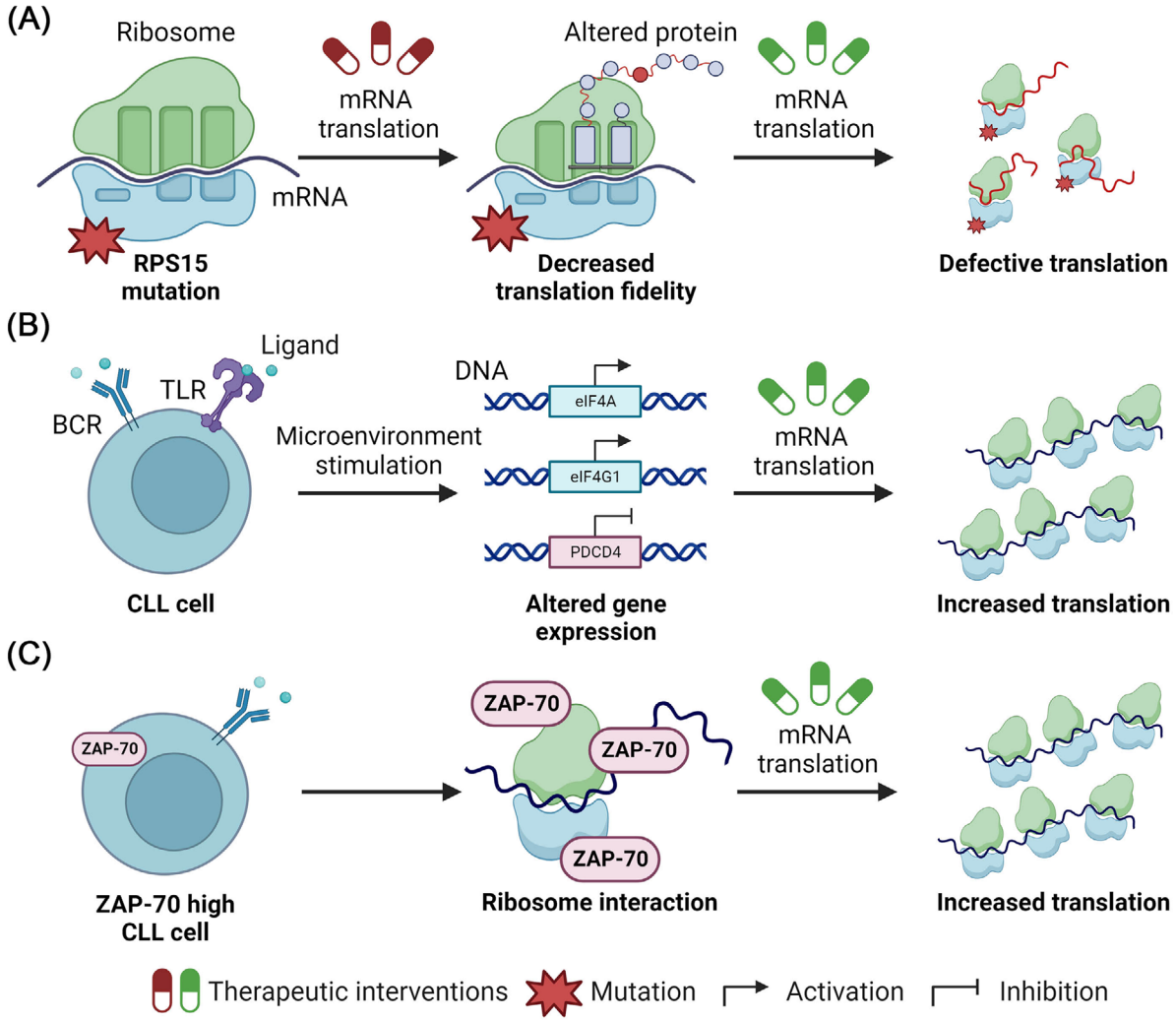

FIGURE 1 Aberrations in mRNA translation in CLL. Different cellular mechanisms contribute to altered translation in CLL cells compared to non-leukemic B cells. mRNA translation could be targeted with different therapeutic approaches (*e.g.*, targeting of the mutated ribosome, inhibition of translation initiation) as a novel treatment for CLL. (A) Defective translation caused by mutations in RPS15 and affected translation fidelity. (B) Activation of signaling pathways linked to the microenvironment (*e.g.*, downstream of the BCR or TLR) alters gene expression and leads to increased translation rates in CLL cells. (C) Intrinsic factors such as ZAP-70 are involved in several pathways of abnormal translation in CLL. Figure created with Biorender.

Abbreviations: BCR: B-Cell Receptor; CLL: Chronic Lymphocytic Leukemia; eIF4A: Eukaryotic translation Initiation Factor 4A; PDCD4: Programmed Cell Death 4; RPS15: Ribosomal Protein S15; TLR: Toll-Like Receptor; ZAP-70: Zeta chain of T cell receptor-Associated Protein kinase 70.

in cell survival [6] (Figure 1C). In their study [7], using pulsed Stable Isotope Labeling with Amino acids in Cell culture (SILAC) assay, Largeot *et al.* identified the mRNAs affected by the increased translation upon stimulation of CLL patient cells. Gene ontology analysis revealed a positive loop, with proteins involved in mRNA translation and also in apoptosis regulation and cytokine signaling. In addition, they revealed that both human and murine CLL cells display a high translation rate compared to B cells from healthy donors and also to B cells found in the blood of patients and in the murine splenic microenvironment. In addition, increased expression of translation-related genes is associated with increased disease progression and poor survival in a cohort of CLL patients [7], confirming the clinical significance of this process.

2 | TARGETING OF ABERRANT TRANSLATION IN CLL CELLS

These findings reveal potential therapeutic strategies targeting mRNA translation abnormalities in CLL. In RPS15-mutated CLL cases, strategies could be developed to expand on existing approaches for ribosomopathies.

Structural variations between mutated and wild-type ribosomal proteins allow the design of specific small molecules targeting these mutations [4]. Moreover, since ribosomal protein mutations modify the translational program, inhibiting translation could also impede the oncogenic progression. Translation inhibitors have been developed to target elevated mRNA translation in cancers, some showing promising results in CLL treatment. These compounds primarily target the translation initiation machinery, globally inhibiting translation while affecting mRNA translational programs. Examples include DesMethyl DesAmino Pateamine A (DMDAPatA) targeting eIF4A; 4EGI-1 blocking eIF4E and eIF4G interaction; and flavagline family members (*e.g.*, silvestrol, rocaglamide, FL3) targeting eIF4A or prohibitins (PHBs). Notably, these agents hinder various processes in the CLL pathogenesis, such as reducing translation of overexpressed anti-apoptotic proteins inducing apoptosis [8, 9], potentially decreasing elevated expression of oncogenes including MYeloCytomatosis oncogene (MYC) [10].

In their recent study, Largeot *et al.* reaffirmed the potential of targeting mRNA translation in CLL. Upon FL3 treatment, apoptosis primarily affected CLL cells, with a lesser impact on healthy B cells [7]. This could be linked to higher expression of translation initiation factors in CLL cells compared to healthy B cells. Alternatively, CLL cells may depend on a different translation initiation machinery readily targeted by FL3. Multi-omics analysis of FL3-treated CLL cells further confirmed reduced translation of several oncogenes, including MYC and Nuclear Factor Kappa light chain enhancer of activated B cells (NF-KB), as well as other oncogenes not previously linked to CLL such as E26 Transformation Specific 1 (ETS-1). Metabolomic profiling revealed that MYC loss is at least partially responsible for the observed metabolic changes upon mRNA translation inhibition. While limited evidence existed for translation inhibition's impact on CLL development in vivo, this study demonstrated FL3's efficacy in controlling CLL development, alone or combined with immune checkpoint blockade, using the Eμ-T-Cell Leukemia 1 (TCL1) adoptive transfer model. Subsequent profiling of splenic cell populations showed decreased translational activity in FL3-treated mice. Notably, treatment primarily reduced CLL cells and regulatory T cells (Treg) translation, highlighting varied susceptibilities of distinct immune populations to mRNA translation inhibition.

A crucial breakthrough by Largeot *et al.* is the elucidation of the mechanism of action of FL3. In contrast to prior findings in other cancer models, FL3 did not inhibit translation via the RAt Sarcoma virus-Rapidly Accelerated Fibrosarcoma-Mitogen-Activated Protein Kinase (RAS-RAF-MAPK) signaling pathway. In the CLL context, PHBs interact directly with the translation initiation machinery. FL3, through its binding to PHBs, disrupts the translation initiation machinery, inhibiting mRNA translation [7]. This discovery holds significance in unraveling the complexity of mRNA translation initiation and uncovering novel players in this process. This new knowledge offers potential for developing targeted therapies that may alter the interaction between PHBs and the eIF4F complex. Additionally, it may shed light on potential resistance mechanisms to FL3 treatment.

In summary, targeting mRNA translation may be a promising avenue to explore for CLL treatment. Although the development of translation inhibitors is advancing, their clinical application is limited and ongoing clinical trials will reveal their implementation in this setting. Combining therapies may yield better results, warranting further investigations for optimal combinations. Other explorations aimed at the role of mRNA translation inhibition in CLL transformation into Richter syndrome, which is in part driven by MYC and resistant to standard therapies, are anticipated.

DECLARATIONS

AUTHORSHIP CONTRIBUTION

All authors wrote the main text, prepared the figure and revised the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

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Not applicable.

CONSENT FOR PUBLICATION

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