EDITORIAL

Dysregulated Ribosome Biogenesis in Colorectal Cancer: The Emerging Role of Fibrillarin

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For decades, cancer research has primarily focused on genetic abnormalities, aberrant signaling pathways, and epigenetic changes as the principal drivers of malignant transformation. However, a shift has recently been noted, and researchers have begun to pay attention to a largely overlooked aspect of cancer biology: dysregulated ribosome biogenesis. Multiple transcriptional and posttranscriptional events are involved in the intricate, strictly regulated process of ribosome biogenesis, which is accompanied by stringent quality-control checkpoints that ensure the precise assembly of functional ribosomes. This pathway becomes hyperactivated in cancer to meet the high protein synthetic demands of tumor cells through enhanced ribosome biogenesis and remodeling of the translational machinery. In this context, fibrillarin (FBL), the catalytic ribosomal RNA (rRNA) 2′-O-methyltransferase of box C/D snoRNP complexes, has emerged as a critical regulator of ribosome biogenesis and function, as well as an important mediator of cellular transformation. FBL-mediated alterations in rRNA methylation are thought to promote preferential translation of cancer-associated mRNAs and the synthesis of oncogenic proteins.[1]

Ribosomes are assembled within the nucleolus through the tightly regulated process of ribosome biogenesis, involving rRNA transcription, processing, chemical modification, and ribosomal protein assembly. FBL, a nucleolar protein, has a conserved catalytic rRNA 2′-O-methyltransferase domain, which is crucial in various stages of ribosomal biogenesis, including site-specific rRNA methylation, ribosome assembly, structural stability, and translational fidelity.[2] With the growing understanding of the ribosomal epitranscriptome, rRNA modifications are now recognized as dynamic regulators of translational specificity and tumor development rather than passive structural marks.

FBL participates in numerous physiological and pathological processes, in addition to its traditional role in ribosome synthesis. Neuronal differentiation, stem cell maintenance, embryonic development, and nucleolar architectural preservation all depend on FBL.[3] According to experimental research, FBL deficiency is linked to smaller nucleoli and nuclei, as well as longer lifespans, indicating a role in regulating ageing and cellular longevity. On the other hand, dysregulated protein homeostasis has been linked to elevated FBL expression in mature oocytes throughout ageing.[3,4]

Several viruses also use FBL to aid in viral RNA processing and replication due to its nucleolar localization and RNA-binding properties.[5] Additionally, anti-FBL antibodies are highly specific serological indicators of systemic sclerosis, especially in patients with diffuse cutaneous disease and internal organ involvement, highlighting the role of FBL as an autoantigen. When taken as a whole, these findings demonstrate the various biological roles of FBL, which go far beyond ribosome biogenesis and include development, ageing, viral pathogenesis, autoimmunity, and cancer.[4]

Aberrant rRNA 2′-O-methylation patterns, together with transcriptional and genetic alterations in FBL, have increasingly been recognized as important regulators of cancer development and progression (Fig. 1).[6] Emerging evidence indicates that rRNA 2′-O-methylation is not a constitutive structural mark but rather a dynamic epitranscriptomic modification. The cell's repertoire of proteins is shaped by these methylation events, which also affect ribosome assembly, structural stability, translational fidelity, and codon decoding efficiency. Functionally distinct ribosomes known as oncoribosomes can be produced by aberrant FBL-mediated rRNA methylation. These ribosomes preferentially translate transcripts related to cellular stress responses, metabolic adaptation, proliferation, and survival. This emerging concept helps explain how dysregulated FBL activity contributes to colorectal cancer (CRC) progression and offers a mechanistic framework connecting modified ribosome biogenesis with translational reprogramming. CRC is characterized by prominent nucleolar enlargement and increased protein synthetic demand, making dysregulated ribosome biogenesis a particularly relevant hallmark of disease progression.

The enlarged and dysregulated nucleoli are hallmarks of cancer cells with increased ribosome biogenesis and high metabolic demands. FBL is a crucial regulator of ribosome biogenesis and a major contributor to tumorigenesis in several cancers, including CRC.[7] Aberrant FBL expression promotes the selective translation of oncogenic transcripts by altering ribosome structure, translational fidelity, and rRNA

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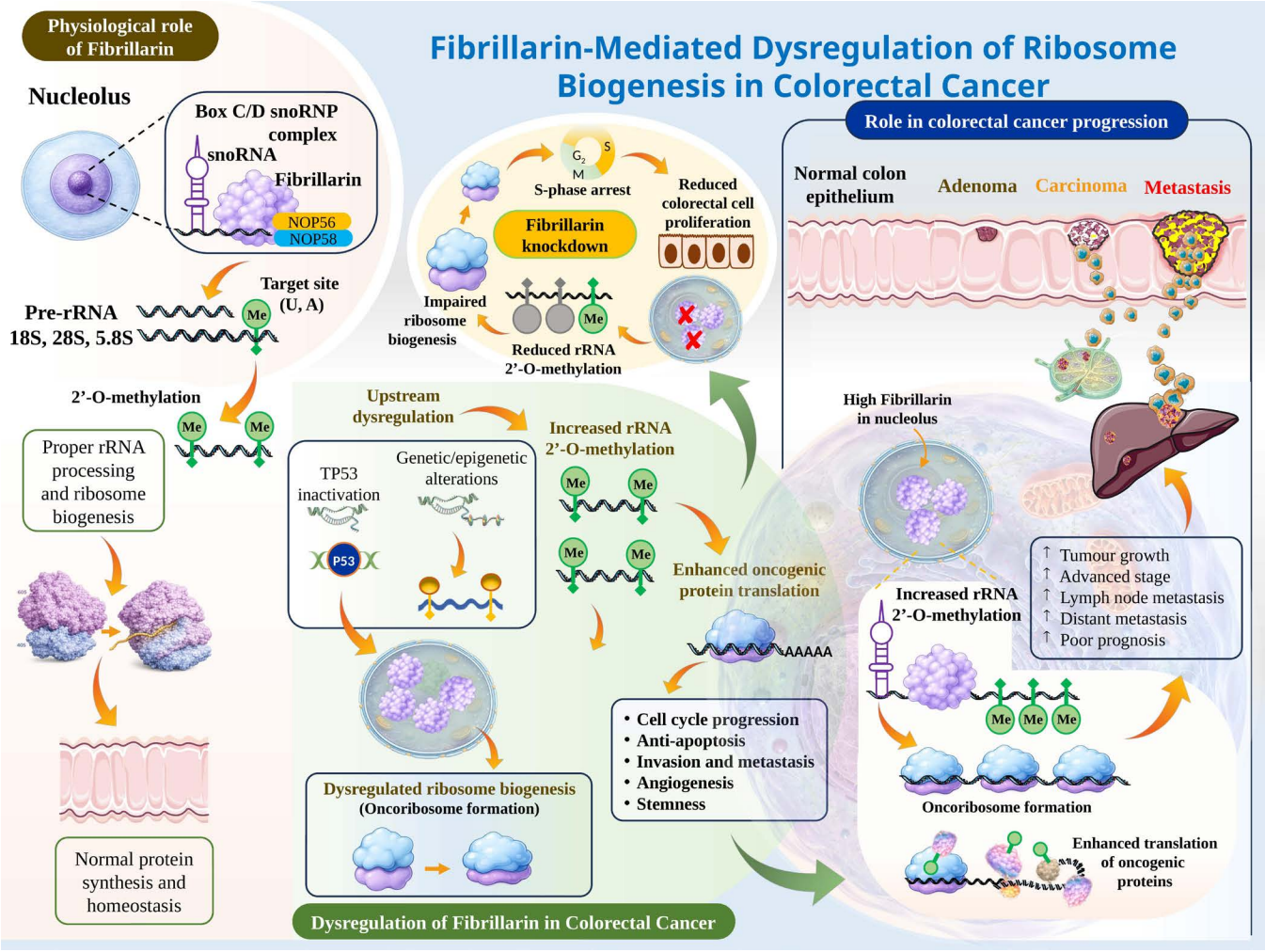

Fig. 1: Fibrillarin-mediated dysregulation of ribosome biogenesis in CRC. Under physiological conditions, FBL, the catalytic component of the box C/D snoRNP complex, directs site-specific rRNA 2′-O-methylation and supports proper ribosome biogenesis and protein synthesis. In CRC, FBL overexpression promotes rRNA hypermethylation, dysregulated ribosome biogenesis, and oncoribosome formation, resulting in enhanced synthesis of oncogenic proteins and tumor progression. Conversely, FBL knockdown reduces rRNA 2′-O-methylation, impairs ribosome biogenesis, induces S-phase arrest, and suppresses CRC cell proliferation

methylation, thereby enhancing cancer cell proliferation. In certain malignancies, such as colorectal, endometrial, breast, and prostate cancers, elevated FBL levels have been associated with tumor aggressiveness and poor clinical outcomes. Experiments have demonstrated that FBL depletion inhibits tumor growth both *in vitro* and *in vivo*, suggesting its potential as a therapeutic target.[8] Mechanistically, FBL is tightly controlled by the tumor suppressor p53, which directly suppresses FBL transcription; on the other hand, p53 inactivation leads to increased FBL expression and enhanced ribosome biogenesis. Additionally, FBL interacts with pathways linked to cancer, such as the SNORD60–PIK3CA–PI3K/AKT/mTOR axis in endometrial carcinoma, where knockdown of SNORD60 or FBL attenuates PI3K/AKT/mTOR signaling and suppresses tumor progression.[9] Aberrant FBL expression has been reported in breast, hepatocellular carcinoma, prostate, lung, ovarian cancers, hematological malignancies, and glioma, where it contributes to altered ribosome biogenesis, enhanced tumor cell proliferation, and poor clinical outcomes.

Against this evolving understanding of ribosome biology, the study featured in this issue, "RTL-P Analysis Reveals the Molecular Role of rRNA 2′-O-Me Modification in FBL-deficient Colorectal Cancer Cells," provides important mechanistic evidence demonstrating how FBL-dependent rRNA methylation contributes to CRC cell proliferation. The authors show that depleting FBL in HCT-116 CRC cells significantly inhibits cellular proliferation, induces S-phase cell-cycle arrest, and reduces rRNA 2′-O-methylation at multiple sites within the 18S and 28S rRNAs.[10] Although limited to an *in vitro* model, the study emphasizes the significance of the ribosomal epitranscriptome in tumor biology. It explains how FBL-mediated rRNA methylation contributes to CRC biology and reinforces the emerging concept that abnormal ribosome biogenesis is not just a byproduct of malignant transformation but also an active driver of tumor growth. However, there are still several unresolved issues, such as the downstream translational programs that FBL controls, the function of FBL-mediated ribosome remodeling in metastasis and treatment resistance, and its possible utility as a prognostic biomarker.

Collectively, the emerging evidence positions FBL as a central regulator of cancer-associated ribosome biogenesis rather than merely a housekeeping nucleolar protein. By showing that FBL depletion lowers rRNA 2′-O-methylation, impairs ribosome biogenesis, and suppresses CRC cell proliferation through S-phase arrest, the study featured in this issue offers additional mechanistic support. These results support the idea that abnormal ribosome biogenesis actively contributes to colorectal carcinogenesis, even though they need to be confirmed in more cellular and *in vivo* models. Future research should integrate ribosome profiling, epitranscriptomics, patient-derived models, and *in vivo* validation to identify the downstream translational programs regulated by FBL and ascertain whether targeting FBL-dependent ribosome remodeling can be translated into effective precision therapies for CRC. Since interest in cancer epitranscriptomics and specialized ribosomes continues to grow, FBL is emerging as a desirable biomarker and therapeutic target, thus presenting new opportunities to leverage ribosome biology for precision oncology.

Artificial Intelligence Disclosure Statement

The authors used ChatGPT (OpenAI) solely to improve the grammar, language, and readability of the manuscript. The authors independently verified all scientific content, approved the final version of the manuscript, and assume full responsibility for its originality, accuracy, and integrity.

Author Contributions

YK conducted the literature search and prepared the draft of the manuscript. AB provided valuable input for the manuscript. All authors reviewed and approved the final version of the manuscript.

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