



UMEÅ UNIVERSITY

Umeå University Medical Dissertations New Series no. 2411

Functional Characterization of RNA Modifying Enzymes in Breast Cancer

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Academic dissertation

Which, with the due permission of the Vice-Chancellor of Umeå University for the examination for the Degree of Doctor of Philosophy, is presented for public defence in Major Groove, Norrlands universitetssjukhus on Friday, 24 April, 2026 at 09:00.

The thesis will be defended in English.

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Umeå University
Department of Molecular Biology
Wallenberg Center for Molecular
Medicine

Document type

Doctoral thesis

Date of publication

2 April 2026

Author

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Title

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Abstract

RNA modifications constitute an important layer of post-transcriptional gene regulation, yet their collective contribution to breast cancer progression remains poorly understood. While individual epitranscriptomic marks have been implicated in tumorigenesis, how distinct RNA modifications and their regulators converge to shape aggressive cancer phenotypes is largely unexplored. Here, we investigate the coordinated roles of RNA modification pathways in breast cancer, with a focus on triple-negative breast cancer (TNBC). By analyzing expression patterns of 49 mRNA modification regulators in the SCAN-B breast cancer cohort, we identify subtype-specific epitranscriptomic signatures and reveal coordinated upregulation of multiple RNA modification pathways – including m⁶A, m⁵C, pseudouridine, and RNA editing – in TNBC. Several regulators within these pathways are associated with poor patient survival, and co-occurrence of m⁵C- and pseudouridine-related factors suggests a shared regulatory module linked to enhanced translational activity. We further demonstrate that dynamic m⁶A regulation contributes to TNBC adaptation under hypoxic stress. Using single-nucleotide-resolution m⁶A mapping combined with translation and mRNA stability profiling, we show that hypoxia-induced m⁶A deposition within coding regions is associated with ribosome collision and increased transcript stability, challenging the prevailing view of m⁶A as a predominantly destabilizing modification. In parallel, we uncover non-canonical functions of the m⁶A methyltransferase METTL3, showing that cytoplasmic METTL3 promotes vesicle trafficking and invasive behavior independently of its catalytic activity through interaction with the exocyst component EXOC7. Finally, we identify a role for ribosomal RNA 2'-O-methylation in TNBC aggressiveness, demonstrating that fibrillarin-dependent ribosome remodeling selectively regulates oncogenic translation programs. Together, these findings reveal that coordinated RNA modification pathways and non-traditional functions of epitranscriptomic regulators converge to drive translational reprogramming and aggressive behavior in breast cancer.

Keywords: RNA modifications, m⁶A, METTL3, hypoxia, exocytosis, translation, breast cancer.

Language

English

ISBN

978-91-8070-933-0 (print)
978-91-8070-934-7 (pdf)

ISSN

0346-6612

Number of pages

48+ 4 papers