



NSUN2-mediated tRNA m5C methylation maintains oncogenic translation and cisplatin resistance in LUAD by stabilizing cell-cycle codon-biased tRNAs

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INTRODUCTION

Lung adenocarcinoma (LUAD) remains a leading cause of cancer mortality, and platinum chemotherapy is still essential for patients without actionable driver mutations. Yet durable benefit is limited because many tumors are intrinsically resistant or rapidly acquire resistance to cisplatin. Beyond DNA repair and apoptosis escape, resistant cells may survive by rewiring translation, allowing selective proteins to be produced during drug stress. NSUN2 is a cytosine-5 RNA methyltransferase that installs m5C on tRNAs, a modification linked to tRNA stability and protein synthesis. This study asks whether NSUN2-mediated tRNA methylation creates a translational program that protects LUAD cells from cisplatin.

METHODS

Candidate resistance genes were nominated by integrating public neoadjuvant chemotherapy datasets, cisplatin-resistant cell-line transcriptomes, and large LUAD cohorts with survival information. A ten-target barcoded CRISPR knockout library was then tested in orthotopic A549 lung tumors treated with cisplatin to identify genes required for resistant tumor persistence. NSUN2 function was validated in A549-DDP and PC9-DDP models using CRISPR/Cas9 knockout, wild-type rescue, and the catalytic-dead K190M mutant. The methylation mechanism was examined with global m5C dot blotting, published iCLIP-seq, and tRNA-m5C-seq, while tRNA-seq, charged tRNA profiling, and tRF-seq measured tRNA stability and fragmentation. Ribo-seq, OP-puro labeling, polysome profiling, apoptosis assays, cell-cycle analysis, and in vivo treatment experiments connected RNA methylation to translation, proliferation, and cisplatin response. Clinical relevance was evaluated in neoadjuvant specimens, the JSSZL LUAD cohort, TCGA, GTEx, and pan-cancer survival analyses. All assays used paired controls, independent biological replicates, and statistical testing to connect molecular changes with treatment response.

DISCUSSION

These findings place NSUN2 upstream of a tRNA-centered translational resistance program in LUAD. In resistant cells, NSUN2 deposits m5C at key positions on selected tRNAs, helping them remain intact rather than being cleaved into tRNA-derived fragments. This stabilizing effect preserves charged tRNA pools and supports ribosome occupancy on transcripts enriched for cognate codons, especially genes controlling protein synthesis and cell-cycle progression. When NSUN2 is lost, global translation declines, G2/M, MYC, MTORC1, ribosome, proteasome, and cell-cycle pathways are suppressed, and cells shift toward a state that is more vulnerable to cisplatin. The catalytic-dead K190M rescue failure argues that methyltransferase activity, rather than NSUN2 expression alone, is essential. Clinically, high NSUN2 in non-responders and its association with poor OS/PFS support its potential as both biomarker and target. Because palbociclib enhances cisplatin efficacy in this model, cell-cycle modulation may provide a practical route to exploit NSUN2-dependent vulnerability. Together, these data broaden the view of chemotherapy resistance from a DNA-damage problem to a translation-control problem. They also explain why cell-cycle blockade can cooperate with cisplatin: it attacks the proliferative state that NSUN2 helps preserve. This makes NSUN2 a mechanistic bridge between RNA modification and treatment selection for resistant LUAD models and clinical stratification.

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CONCLUSION

Collectively, this study nominates NSUN2 as a central driver of cisplatin resistance in lung adenocarcinoma and defines a mechanistic axis linking tRNA methylation, selective translation, and cell-cycle persistence. Multi-layered genomic screening first prioritized NSUN2 from resistance-associated genes, and functional CRISPR experiments showed that NSUN2 loss sensitizes resistant LUAD cells and tumors to cisplatin. Mechanistically, NSUN2-dependent m5C maintains the stability of six codon-biased tRNAs, including Asp-GTC, Ser-TGA, Thr-CGT, Thr-TGT, Val-AAC, and Val-CAC, limiting stress-induced tRF generation and preserving charged tRNA availability. These stable tRNAs help sustain ribosome occupancy and protein synthesis programs enriched for cell-cycle and oncogenic translation pathways. When NSUN2 is removed, mature tRNAs decline, tRFs accumulate, translation output falls, and resistant cells become less able to maintain proliferative cycling under platinum pressure. The inability of the catalytic-dead NSUN2(K190M) mutant to restore resistance confirms that m5C methyltransferase activity is required for this phenotype. Clinical samples further show higher NSUN2 expression in chemotherapy non-responders, association with advanced disease, and worse survival, supporting its value as a biomarker of platinum resistance. The model also suggests therapeutic opportunities: direct NSUN2-pathway inhibition, biomarker-guided patient selection, and rational combinations of cisplatin with cell-cycle modulators such as palbociclib.

By connecting epitranscriptomic tRNA control to chemotherapy failure, NSUN2 provides a targetable framework for overcoming platinum-resistant LUAD. Importantly, this mechanism is not a general increase in protein production alone; it is a codon-biased survival strategy that keeps specific cell-cycle transcripts translated when cisplatin imposes genotoxic stress. Three clinical and molecular observations converge on the same point: resistant tumors retain NSUN2, NSUN2 preserves tRNA integrity, and preserved tRNAs maintain a proliferative translation state. Therefore, future work should define NSUN2-high patient subsets, develop pharmacologic inhibitors or degraders, and test whether NSUN2 status predicts benefit from platinum combinations in prospective biomarker-guided LUAD trials and preclinical resistance models urgently.

