Targeted Nucleotide Quantification Supports Mechanism Discovery of Gemcitabine Resistance

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Our role: Creative Proteomics provided targeted nucleotide quantification by LC-MRM/MS to support analysis of intracellular nucleotide-related changes relevant to gemcitabine response and resistance.

Background & Significance

Gemcitabine is a nucleotide prodrug that requires intracellular activation to exert its effects. In diffuse large B-cell lymphoma, resistance remains a major challenge and cannot be fully understood through static expression changes alone. In this study, functional proteomics mapped dynamic resistance programs, while intracellular nucleotide-state information provided a key complementary layer for interpreting drug response.

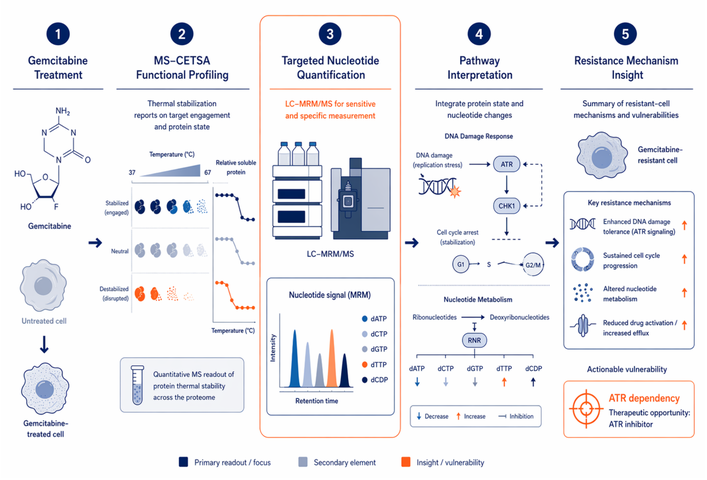
Research Gap

Most resistance studies rely on genomics or transcriptomics, which do not directly capture drug-induced biochemical changes. For gemcitabine, intracellular nucleotide context remains an important missing layer in resistance interpretation.

Study Objective

To define how gemcitabine-sensitive and gemcitabine-resistant DLBCL cells diverge over time at the biochemical level, identify DNA repair programs associated with resistance, and reveal actionable nodes that may restore drug sensitivity.

Workflow



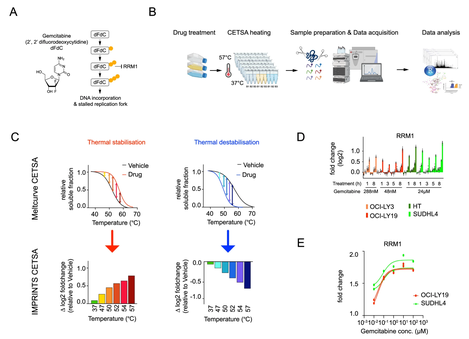
Key Findings

Shared early response confirms canonical gemcitabine action

Both cell states showed early responses consistent with RNR inhibition and DNA-damage signaling.

This indicates that resistance was not simply due to loss of initial drug action.

Early biochemical responses were broadly shared before later divergence emerged.



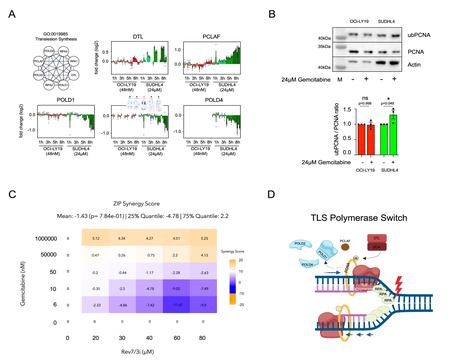
Gemcitabine induced shared early biochemical responses in sensitive and resistant cells.

Resistant cells transition into a distinct DNA-repair adaptive state

Sensitive cells progressed toward apoptotic response patterns.

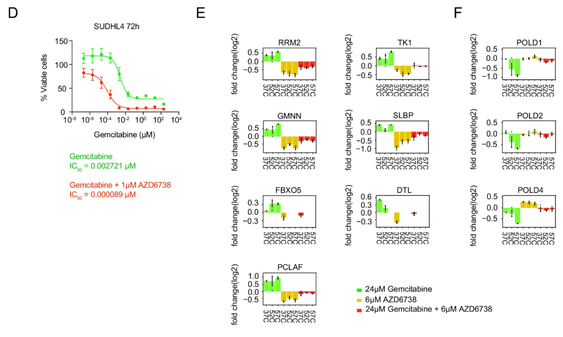
Resistant cells instead transitioned into a distinct state with checkpoint opening and translesion DNA synthesis (TLS).

These findings support adaptive pathway rewiring as a key feature of resistance.



Resistant cells adopted a late DNA repair–adaptive state characterized by checkpoint and TLS-associated responses.

ATR-linked repair programs create an actionable vulnerability



ATR-linked repair programs supported resistance and revealed an actionable vulnerability.

Resistant cells induced an Auxiliary DNA Damage Repair program that supported replication under damage stress.

ATR inhibition attenuated this adaptive response.

This helped re-establish gemcitabine sensitivity, identifying ATR as a tractable resistance node.

For Research Use Only. Not for use in diagnostic procedures.

Our Contribution (Creative Proteomics)

Targeted nucleotide quantification by LC-MRM/MS, supporting measurement of intracellular nucleotide-related changes relevant to gemcitabine metabolism, response, and resistance interpretation.

What This Service Helps Solve

- Quantify intracellular nucleotide-related biochemical changes under drug treatment
- Support interpretation of nucleotide-prodrug response mechanisms
- Complement proteomics readouts with targeted metabolite-level evidence
- Strengthen pathway-level conclusions in resistance and DNA repair studies

Why This Service Matters

Gemcitabine is a nucleotide prodrug, and intracellular nucleotide-related measurements provide critical biochemical context for interpreting drug response and resistance. Targeted nucleotide quantification helps connect drug metabolism, cellular adaptation, and resistance-associated pathway changes in mechanism-focused studies.

Why Choose Creative Proteomics

- 300+ peer-reviewed publications supported
- 1200+ metabolomics projects delivered
- >90% of datasets with QC median RSD < 15% in pooled QC workflows
- Targeted LC-MRM/MS workflows for quantitative nucleotide analysis
- Multi-omics capability spanning targeted metabolite analysis and proteomics support
- Publication-ready deliverables for downstream reporting and figure preparation

Working on nucleotide-drug response, resistance adaptation, or DNA repair biology?

Creative Proteomics provides targeted LC-MRM/MS quantification and complementary proteomics-enabled support for mechanism-focused oncology studies.

Contact us to discuss a customized analytical strategy for your next project.

Web: www.creative-proteomics.com

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