(PS122) CYTOPLASMIC LOCALIZATION OF QKI MEDIATES THERAPUETIC RESISTANCE AND IMMUNE EVASION

Topic: 03. Acute myeloid leukemia - Biology & translational research

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Background

The combination of the BCL2 inhibitor venetoclax with hypomethylating agents has transformed treatment for elderly patients with acute myeloid leukemia (AML) who cannot tolerate the mainstay chemotherapy regimens. However, long-term treatment response remains a major hurdle with primary resistance and relapse occurring in ~50% of patients, highlighting the need to identify molecular mechanisms driving therapeutic failure to combat them. Increasing evidence suggests that differentiation state and post-transcriptional gene regulation, including RNA modifications, influence treatment response, yet RNA regulatory pathways contributing to venetoclax resistance remain poorly understood.

Aims

To identify RNA-binding protein–mediated mechanisms of venetoclax resistance in AML and evaluate therapeutic strategies to overcome this resistance.

Methods

An RNA-binding protein–focused CRISPR activation screen was performed in MOLM13 AML cells to identify regulators of venetoclax response. Functional studies using genetic deletion and isoform-specific overexpression were conducted to assess QKI function using in vitro (MOLM13, MV4-11, Kasumi-1, & NKM1) and in vivo assays (NSG mice injected with MOLM13 AML cells). Transcriptomic profiling and analysis of AML patient datasets (BeatAML) were performed to identify downstream targets and clinical associations. Drug sensitivity and combination assays were used to evaluate therapeutic responses and potential synergistic strategies. Additionally, AML cells and PBMC-derived immune cell co-cultures followed by flow cytometry assays were used to assess novel immunotherapies in AML.

Results

We identified the m7G reader protein Quaking (QKI) as a key post-transcriptional driver of venetoclax resistance. Genetic deletion of QKI sensitized AML cells to venetoclax alone and in combination with 5-azacytidine in vitro and in vivo. QKI is alternatively spliced into four isoforms with distinct subcellular localization. QKI-5 is predominantly nuclear, whereas QKI-6, QKI-7, and QKI-7b localize to the cytoplasm. Overexpression of cytoplasmic isoforms promoted resistance, demonstrating an isoform-specific effect mediated by subcellular localization. Mechanistically, we identified ZFP36L1, a regulator of monocytic differentiation associated with venetoclax resistance, as a direct target of cytoplasmic QKI but not nuclear QKI and the m7G writer METTL1. Indeed, we show that cytoplasmic QKI's interaction with ZFP36L1 is m7G dependent. Transcriptomic analyses further revealed that QKI regulates the immune checkpoint molecule CD276 (B7-H3), which was significantly upregulated in AML patient samples, specifically in the monocytic lineage. Targeting CD276 using the monoclonal antibody enoblituzumab demonstrated strong synergy with venetoclax in eliminating AML cells.

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Summary/Conclusion

These findings identify cytoplasmic QKI as a key regulator of differentiation-associated venetoclax resistance and immune evasion in AML and support targeting CD276 as a rational therapeutic strategy to overcome therapy resistance.

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