

Conference Abstracts

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Polymerase θ as a Target for Synthetic Lethality in APOBEC3A-high Cancer

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Abstract

Background

APOBEC3 cytidine deaminase enzymes are major drivers of cancer evolution, genomic instability, tumor heterogeneity and therapeutic resistance, yet no therapy selectively targets tumors with APOBEC3 activity. We investigated how APOBEC3A-induced double-strand breaks (DSBs) are repaired and whether this creates a therapeutically targetable vulnerability in APOBEC3A-high urothelial tumor.

Methods

We used doxycycline-inducible APOBEC3A expressing bladder cancer cells, fluorescent DSB repair reporters, DNA fiber assay, biochemical binding and competition assays, genomic analyses of clinical tumor samples and TCGA database, amplicon sequencing of CRISPR-Cas9 induced genomic DSB, genetic POLQ depletion by shPOLQ, pharmacologic Pol θ inhibition with ART558 and ART6043, clonogenic assays, and studies in preclinical xenograft mice models to define the mechanism of APOBEC3A DSB repair and synthetic lethality both in vitro and in vivo.

Results

APOBEC3A induction caused replication-fork stalling, replication-associated DNA damage,

DSBs and S-phase arrest. Mechanistically, APOBEC3A competed with replication protein A (RPA) for single-stranded DNA overhangs, exposing microhomologous sequences and shifting repair from homologous recombination (HR) towards Pol θ -dependent theta-mediated end-joining (TMEJ). Genomic analyses of clinical tumors demonstrated spatial proximity among APOBEC3 mutational footprints and microhomology-mediated deletions (MMDs), and association with TMEJ-associated chromosomal instability signatures. At an endogenous CRISPR-Cas9 break site at HPRT1 exon 3, APOBEC3A increased co-occurring APOBEC-signature substitutions and MMDs on the same sequencing reads. Genetic POLQ depletion increased persistent γ H2AX foci upon APOBEC3A induction. APOBEC3A expression also increased POLQ mRNA level over time. Small-molecule Pol θ inhibitors preferentially reduced viability and clonogenic survival in APOBEC3A-active cells. Finally, in xenograft NSG/nude mice, genetic and pharmacological Pol θ inhibition suppressed APOBEC3A-expressing tumor growth and increased markers of DNA damage, replication stress and apoptosis, supporting synthetic lethality in vivo.

Conclusion

APOBEC3A limits RPA-mediated protection of single-stranded DNA and exposes microhomologies at DSBs, which are repaired by Polθ-dependent TMEJ. These findings establish a mechanistic link between APOBEC3A-mediated ssDNA remodeling, TMEJ pathway engagement,

and therapeutic sensitivity in urothelial cancer. The heightened dependence of APOBEC3A-active tumors on Polθ supports Polθ inhibition as a rational therapeutic strategy and provides a basis for evaluating APOBEC3A activity or APOBEC mutational signatures as biomarkers for patient selection.

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