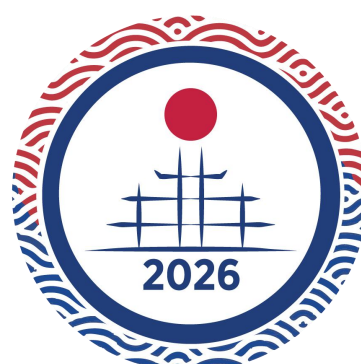




Combination of Topoisomerase Inhibitors with KRAS G12C Inhibitors Overcomes Resistance in KRAS G12C-Mutant NSCLC

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INTRODUCTION

KRAS is one of the most frequently mutated oncogenes in solid tumors, with KRAS G12C mutations occurring in approximately 8–13% of non-small cell lung cancer (NSCLC). Although KRAS G12C inhibitors such as sotorasib and adagrasib have demonstrated promising clinical efficacy, acquired resistance remains a major challenge. Therefore, identifying effective combination strategies is critical to improving therapeutic outcomes.

METHODS

Design:

A high-throughput drug screening platform was utilized to discover compounds synergizing with AMG510 in KRAS G12C-mutant H358 NSCLC cells. Drug synergy was evaluated by Chou-Talalay combination index (CI) analysis. RNA-seq was performed to dissect transcriptomic alterations triggered by single-agent and combinatorial treatment. Colony-formation assays and time-course western blots were applied to verify key phenotypes and DNA-damage-related signaling events.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- Topoisomerase inhibitors were identified as potent synergistic partners with KRAS G12C inhibitors in KRAS G12C mutant NSCLC cells.
- Topoisomerase inhibitors based combination markedly amplifies DNA-damage response and apoptotic signaling relative to monotherapy.

Future Direction for Research

- Further work will dissect shared or distinct mechanisms of two topoisomerase-inhibitor combinations with KRAS G12C-inhibitors, followed by in vivo efficacy-safety evaluation to identify translationally feasible strategies for overcoming KRAS G12C inhibitor resistance.

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Artificial Intelligence (AI) Use Disclaimer

AI-assisted language refinement was applied for manuscript and slide text editing. No AI-generated experimental data or images were used in this poster. The following AI tool was utilized: ChatGPT. All scientific content, experimental interpretation and conclusions were generated and validated by the authors.

RESULTS

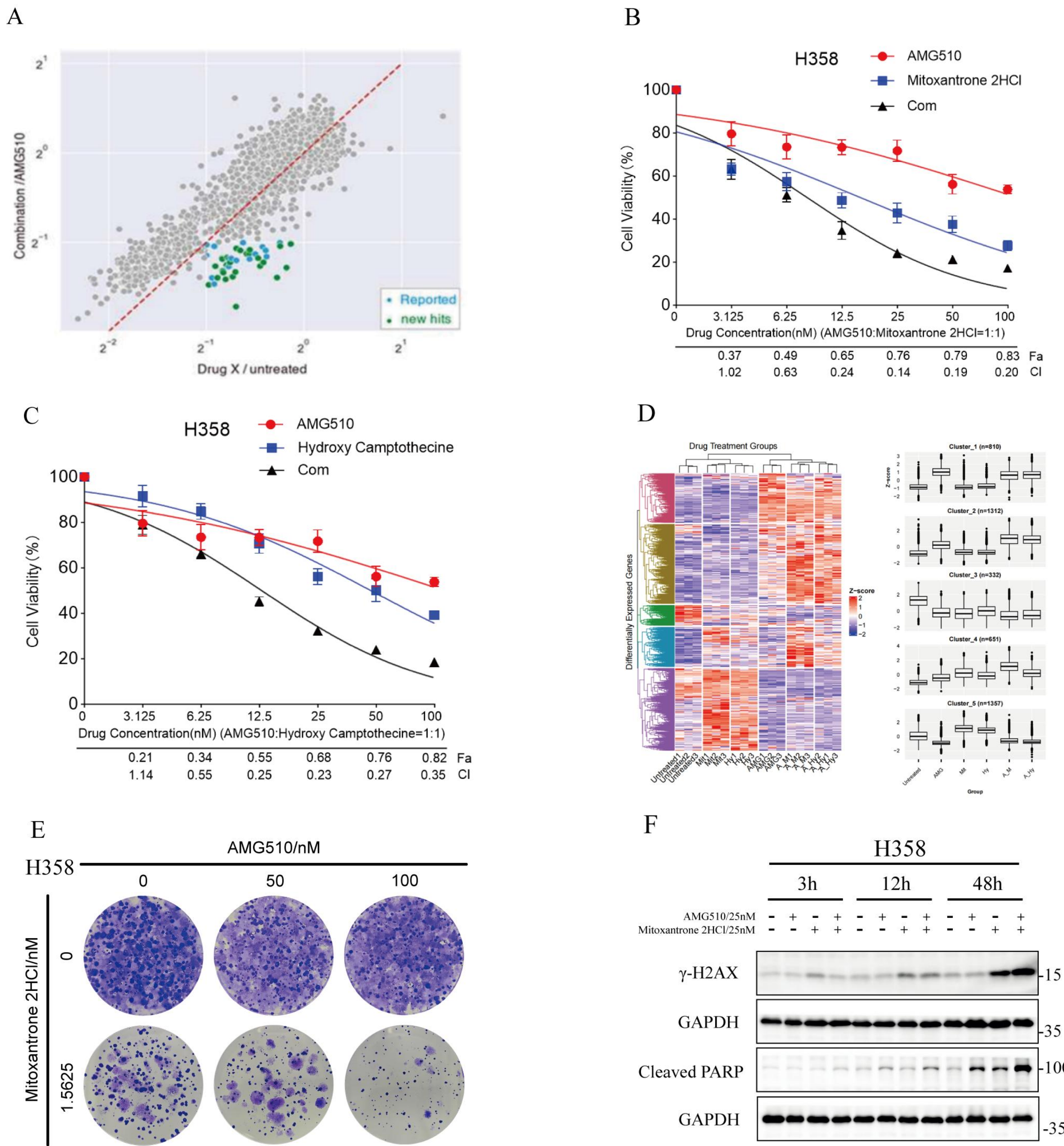


Figure 1. Topoisomerase inhibitors represent promising combination partners for KRAS G12C inhibitors in H358 NSCLC cells. (A) High-throughput drug screening identifies topoisomerase inhibitors as AMG510 sensitizers. (B-C) Cell viability and Fa-CI synergy curves for AMG510 combined with mitoxantrone 2HCl (B) and hydroxycamptothecin (C). (D) Transcriptome profiling of H358 cells upon single-agent and combination treatment. (E) Colony-formation assay showing long-term proliferative inhibition by AMG510 plus mitoxantrone 2HCl. (F) Time-course western blot analysis of DNA-damage-related markers following combined treatment with AMG510 and mitoxantrone 2HCl.