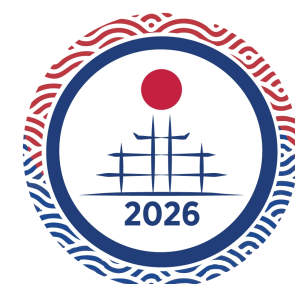




P3.075. Genetically Prioritized Antidiabetic Drug Targets in Lung Cancer: Mendelian Randomization and Functional Validation

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INTRODUCTION

Background: Metabolic dysregulation contributes to lung carcinogenesis, but target-level therapeutic relevance for antidiabetic drugs remains unclear.
Objective: Identify genetically supported antidiabetic targets linked to lung cancer risk and prioritize translationally relevant candidates.
Translational gap: Pair genetic direction with functional validation before repurposing.

METHODS

Drug-target instruments: cis-eQTL instruments for antidiabetic drug-target genes.
Outcome GWAS: TRICL lung cancer summary statistics: 29,863 cases and 55,586 controls.
MR framework: Two-sample Mendelian randomization with heterogeneity, pleiotropy and leave-one-out checks.
Sensitivity checks: Robustness assessed using heterogeneity, pleiotropy and leave-one-out analyses.
Functional follow-up: PheWAS, pathway/PPI, mutation and immune-infiltration analyses plus A549 migration assays.

Analysis workflow

cis-eQTL

MR screen

Multiomic analysis

A549 validation

KEYS

Study question: Can genetically proxied modulation of antidiabetic drug targets identify lung cancer-relevant biology?
Interpretation frame: MR signals were interpreted together with pathway, tumor microenvironment and cell-migration evidence rather than as standalone genetic associations.
Practical output: Prioritized candidate targets for metabolism-directed biomarker and repurposing studies.

Key messages
Target-level screen: The analysis moves from drug classes to genetically proxied drug-target genes.
Translational prioritization: Genetic signals were integrated with tumor biology and A549 migration assays.
Poster focus: Emphasize target direction, linked drug and functional follow-up rather than exhaustive MR diagnostics.

Keywords

Mendelian randomization

Drug repurposing

Lung cancer

INTERPRETATION

Actionable take-away
Integrated genetic and functional evidence nominates antidiabetic drug-target biology as relevant to lung cancer risk.
Biologic lead
SERPINE1 emerged as a candidate mediator of context-dependent troglitazone response.
Next step
Validate target-gene mechanisms in larger molecularly annotated cohorts and experimental models.

LIMITATIONS

Caution: MR estimates represent genetically proxied target modulation, not direct treatment effects.
Validation: Functional and clinical validation should prioritize SERPINE1 and targets with consistent genetic and biologic support.
Clinical relevance: Findings may inform metabolism-directed biomarker studies and drug-repurposing hypotheses.

IMPLICATIONS

Biomarker development: Prioritize metabolism-directed biomarkers at the drug-target level rather than treating antidiabetic exposure as one uniform class.
Repurposing logic: Protective and risk-increasing directions are target-specific, so linked drugs should be interpreted alongside gene function.
Validation priority: SERPINE1 and migration phenotypes provide the clearest immediate experimental follow-up.

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RESULTS

