

P3.291: Apoptotic Caspase Limit Drug-Induced Inflammatory Response in Small-cell Lung Cancer (SCLC)

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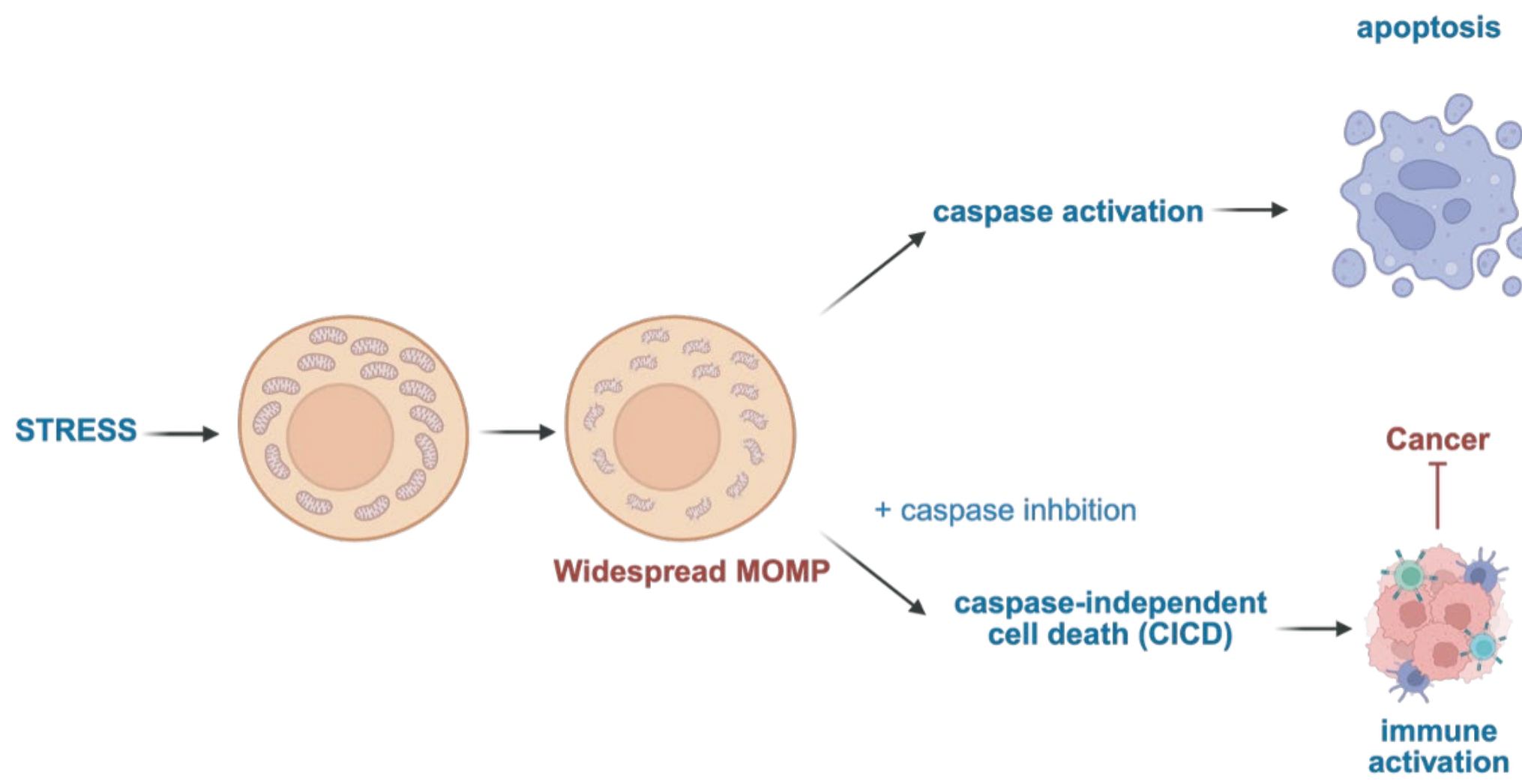
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INTRODUCTION

SCLC

- SCLC accounts for ~ 15% of all lung cancer cases
 - Tumours grow back quickly as resistant tumours after initial chemotherapy
 - Poor response to immunotherapy due to highly immunosuppressive environment
- There is a need for the characterization of molecular vulnerabilities to identify druggable targets

Caspase-independent cell death (CICD)



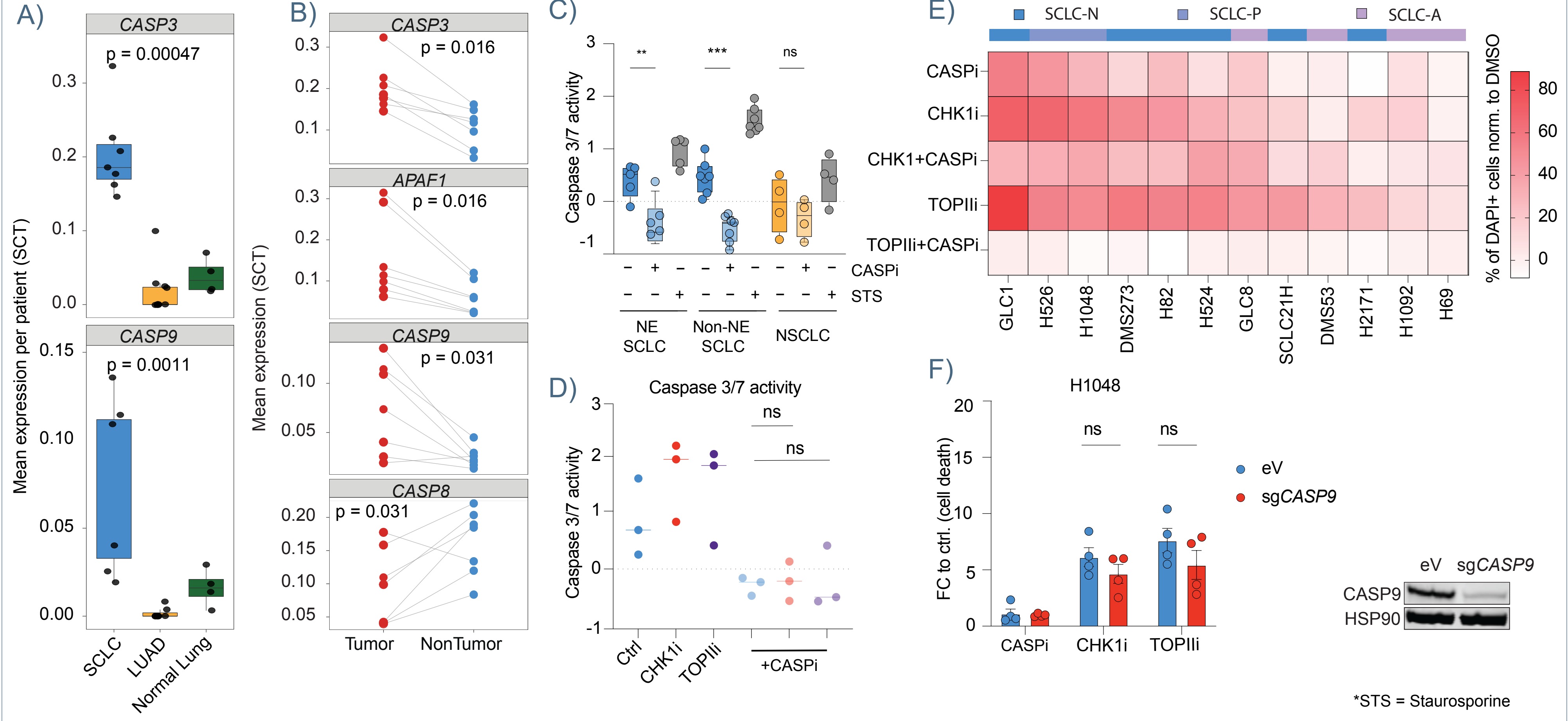
- genotoxic stress induces mitochondrial permeabilization, mitochondria release factors triggering caspase activation
 - contents released by the cells cannot be cleared under caspase inhibition and lead to immun cell activation
- Harnessing CICD in SCLC might increase immunogenicity and facilitate immune infiltration in immunologically cold SCLC tumours

EXPERIMENTAL STRATEGY

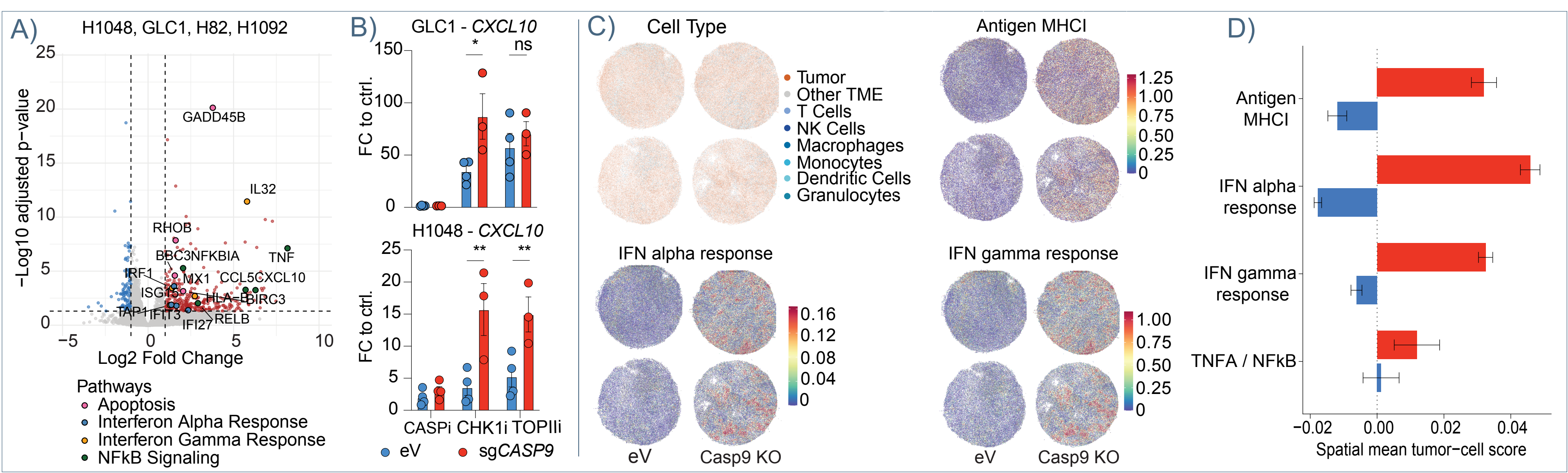
- Can we induce CICD in SCLC cell lines?
Caspase GLO assay, Flow cytometric analysis
- Can CICD induce inflammation in SCLC?
3' UTR-Sequencing qPCR, Spatial Transcriptomics
- 3+4) How is CICD-induced inflammation in SCLC triggered?
Immunofluorescence, Western Blot

RESULTS

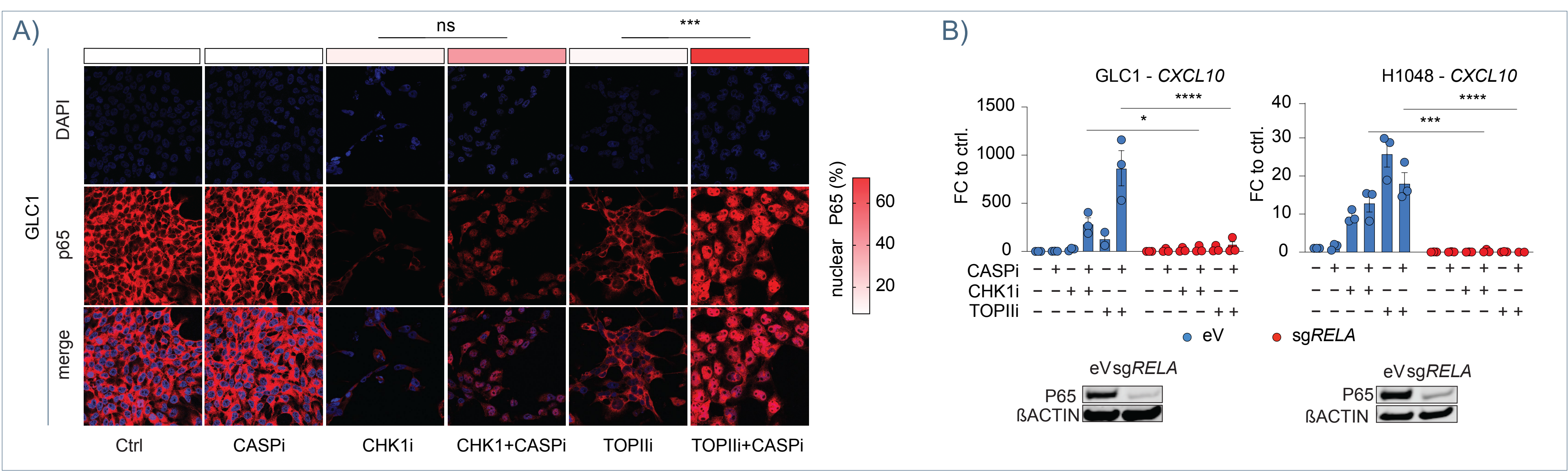
1) SCLC cells exhibit increased caspase activity and undergo CICD under therapeutic stress in combination with caspase inhibition



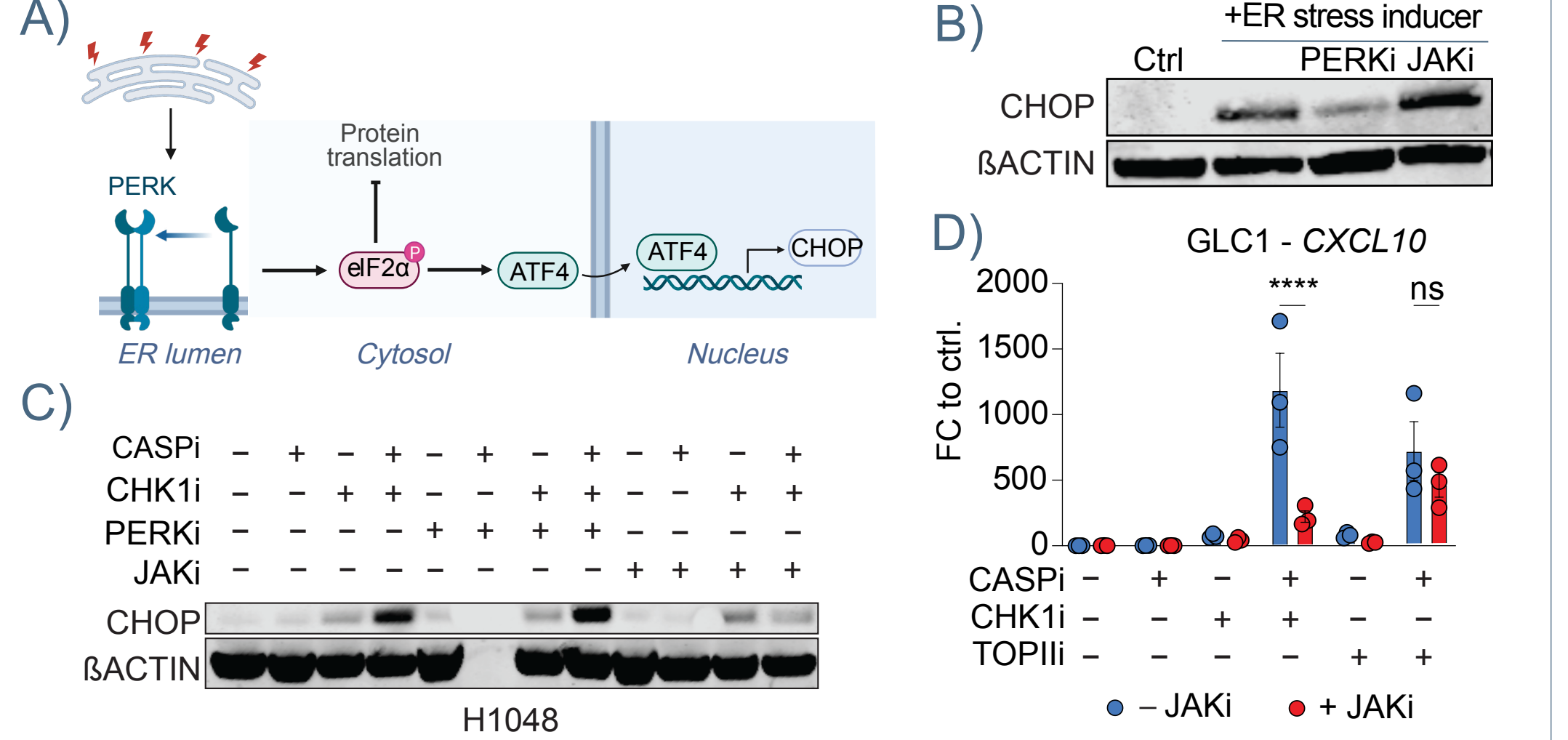
2) Upregulation of inflammatory pathways under therapeutic stress in combination with caspase inhibition in vitro and in vivo



3) NF-κB induction drives the upregulation of immune signalling under therapeutic stress



4) Unfolded-Protein-Response (UPR) might mediate inflammatory response during CICD



DISCUSSION AND CONCLUSION

- SCLC tumours express increased intrinsic apoptotic and decreased extrinsic apoptotic factors
 - CICD-induced inflammation might increase immune cell attraction in syngeneic mouse models
 - Prolonged UPR might induce inflammatory response as well as delayed cell death by CHOP
 - Inflammatory response as well as CHOP levels are decreased by JAKi
- Combining therapeutic stress with caspase inhibition might increase efficacy of immunotherapy in immunological cold SCLC tumours
- Resistant tumours might respond well as CICD relies on intrinsic apoptotic factors rather than extrinsic

REFERENCES & ACKNOWLEDGEMENTS

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