

FBXO11 loss Is a Novel Determinant of PARP Inhibitor Resistance in Small Cell Lung Cancer

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Background

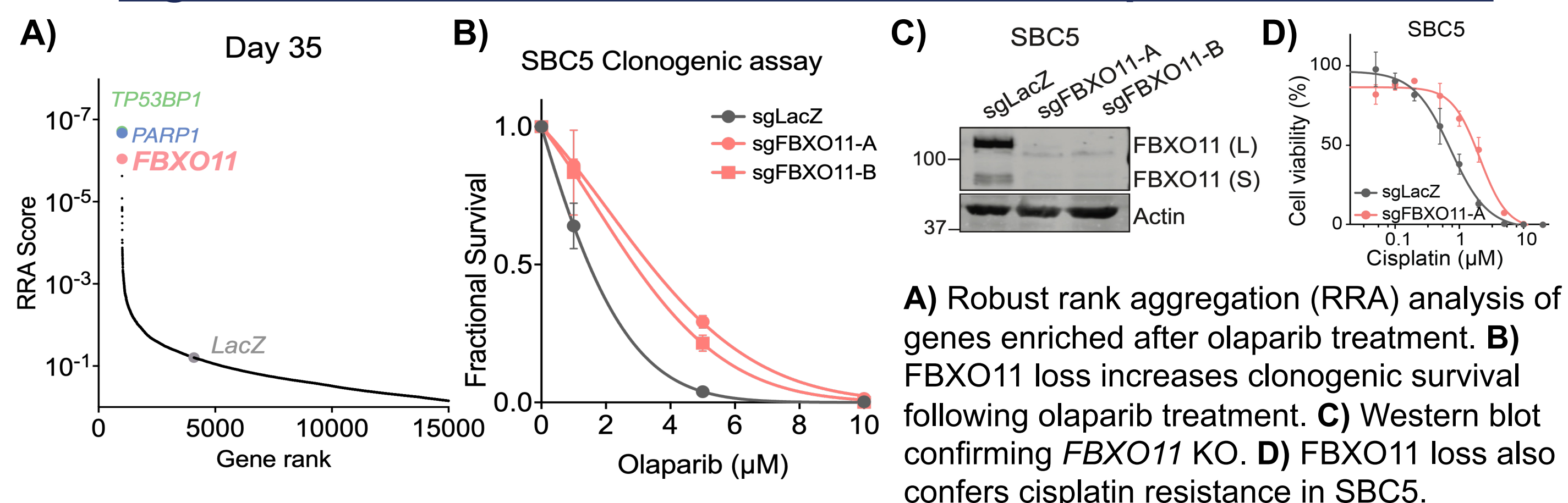
- Small cell lung cancer (SCLC) is an aggressive neuroendocrine malignancy characterized by rapid disease progression and a high rate of relapse following initial chemotherapy.
- Poly(ADP-ribose) polymerase inhibitors (PARPi) have emerged as a promising therapeutic strategy for SCLC based on its high levels of replication stress and DNA damage; however, clinical responses have been modest, and predictive biomarkers and mechanisms of resistance remain poorly understood.
- To identify genetic determinants of PARPi response, we performed a genome-wide CRISPR knockout (KO) screen in SCLC cells treated with olaparib. *FBXO11* loss emerged as a top determinant of PARP inhibitor resistance.
- FBXO11* encodes the substrate recognition component of the SCF E3 ubiquitin ligase complex, but its role in regulating therapeutic response in SCLC has not been defined. Here, we investigate the molecular mechanism by which *FBXO11* loss promotes resistance to PARP inhibitors and platinum chemotherapy and evaluate its potential clinical relevance as a biomarker of treatment resistance.

Methods

- Genome-wide CRISPR-KO screen**
 - SBC5-Cas9 cells
 - TKO.v1 library (~17,661 genes)
 - ± olaparib (5 µM)
 - NGS → MAGeCK analysis
- Isogenic SCLC models & function assays**
 - sgLacZ (control) and sgFBXO11 SCLC cell lines
 - Cell viability assay
 - Clonogenic assay
 - γH2AX staining, comet assay, apoptosis
- Multi-omic profiling to identify substrates**
 - 3 pairs of isogenic sgFBXO11 SCLC cell lines
 - LC-MS and RNA-seq to identify FBXO11 substrates
- Mechanistic validation**
 - shRNA-mediated knockdown & drug response
 - protein stability
 - proximity ligation assay
 - ubiquitylation assay
- Clinical cohort analyses**
 - FBXO11 copy number and RNA expression in patients at baseline and relapse

Results

Figure 1. FBXO11 loss confers PARPi and cisplatin resistance



Results

Figure 2. FBXO11 loss attenuates PARPi and cisplatin-induced DNA damage and cell death

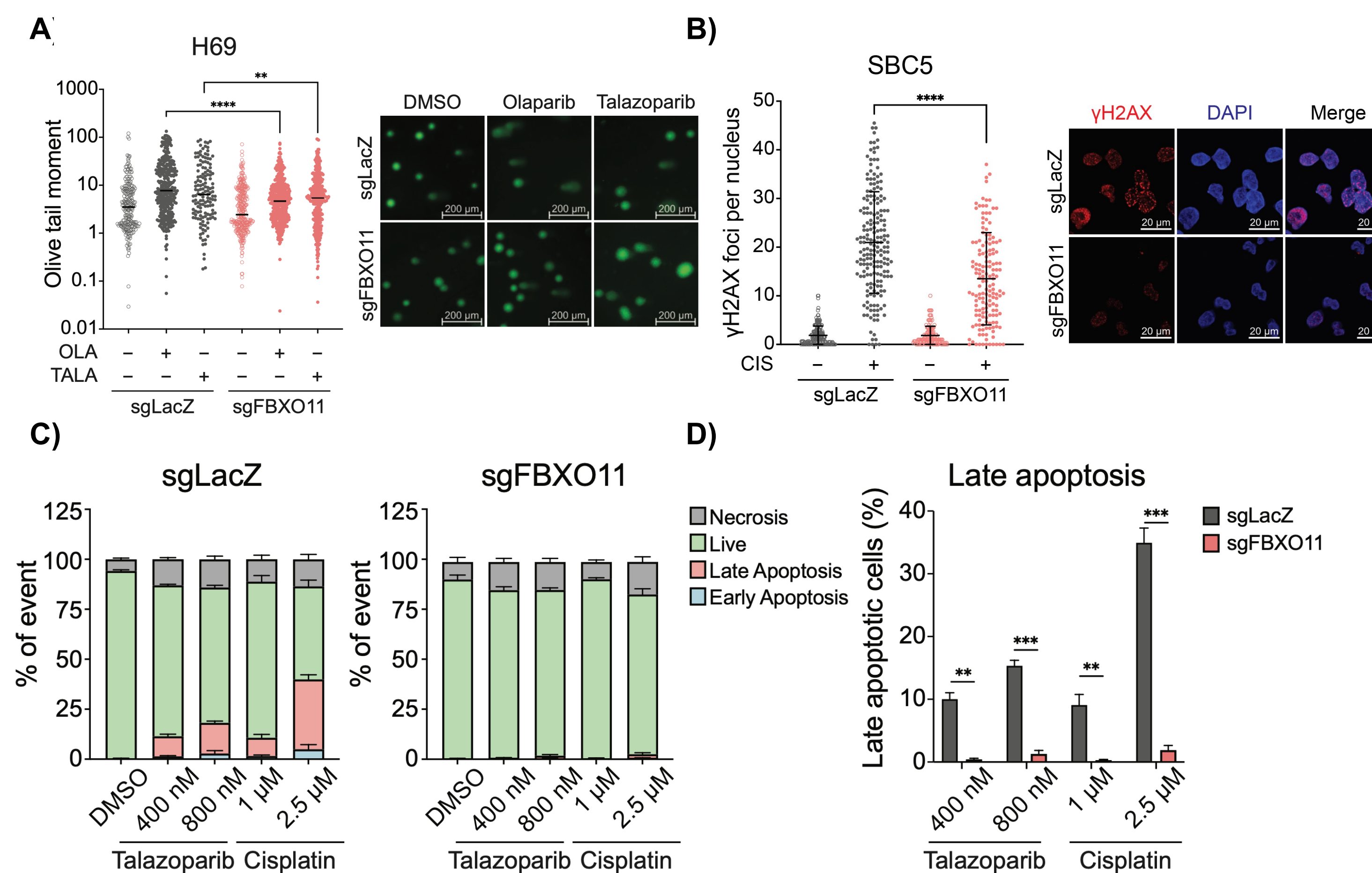
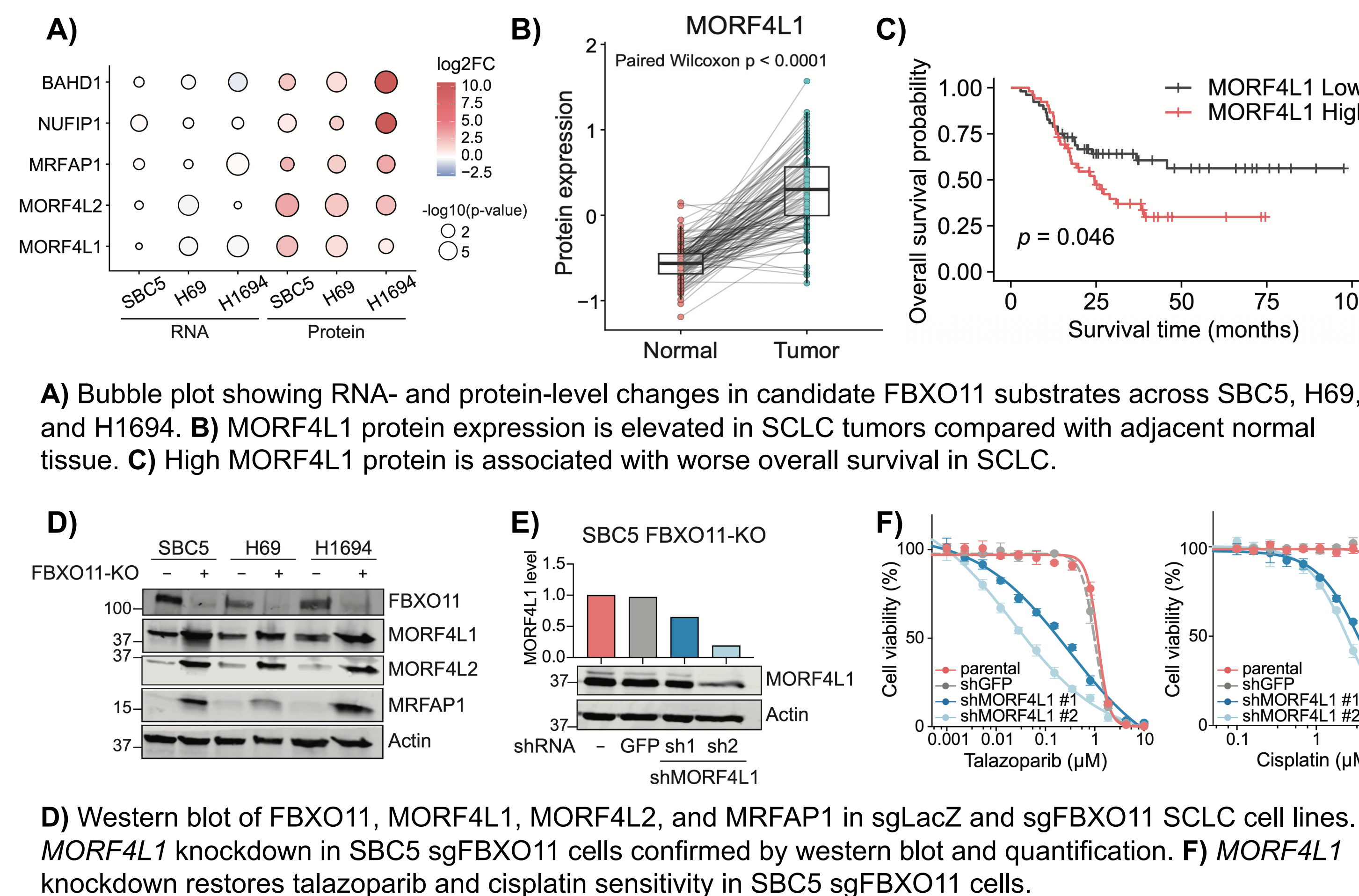
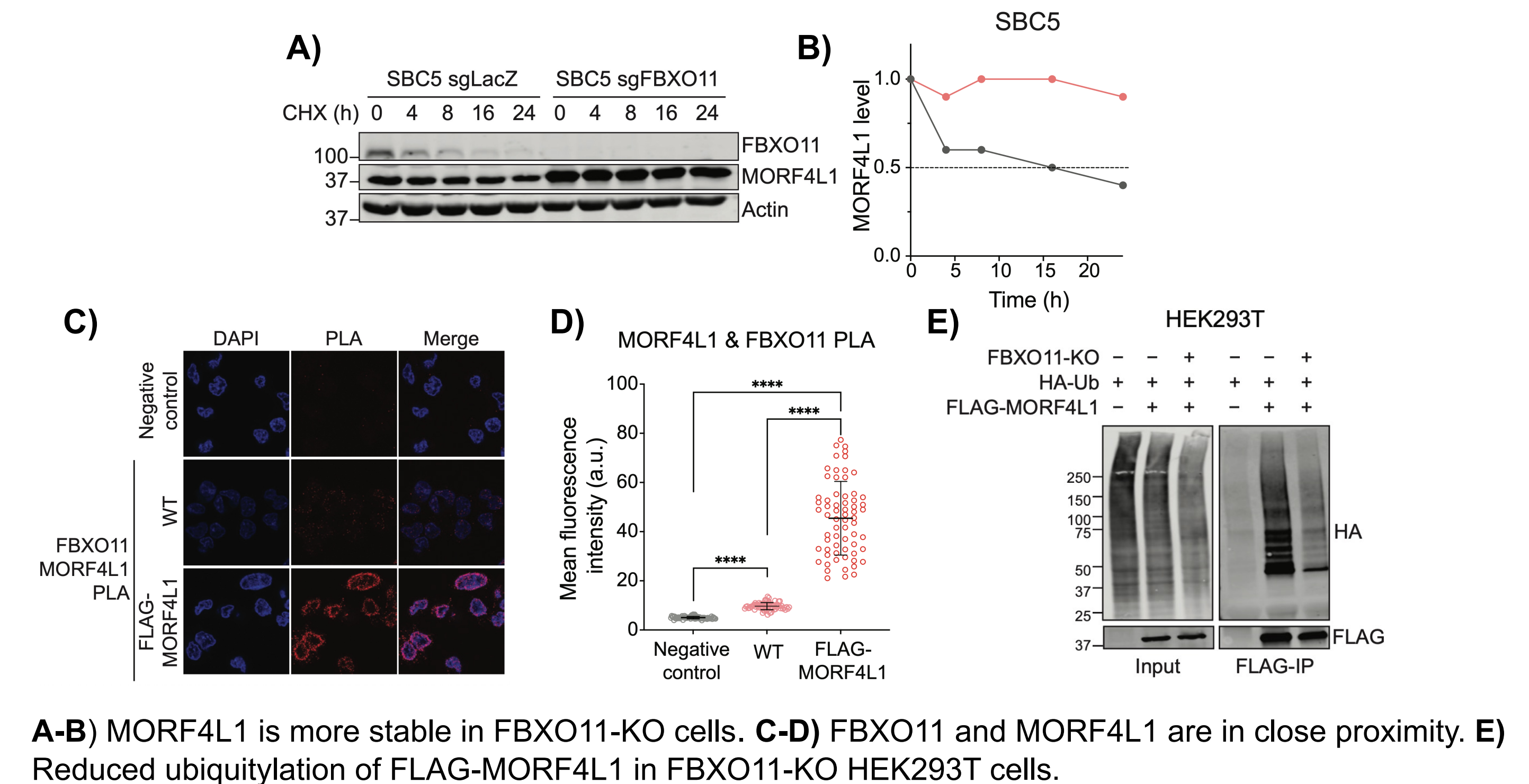


Figure 3. MORF4L1 upregulation mediates FBXO11 loss-driven drug resistance



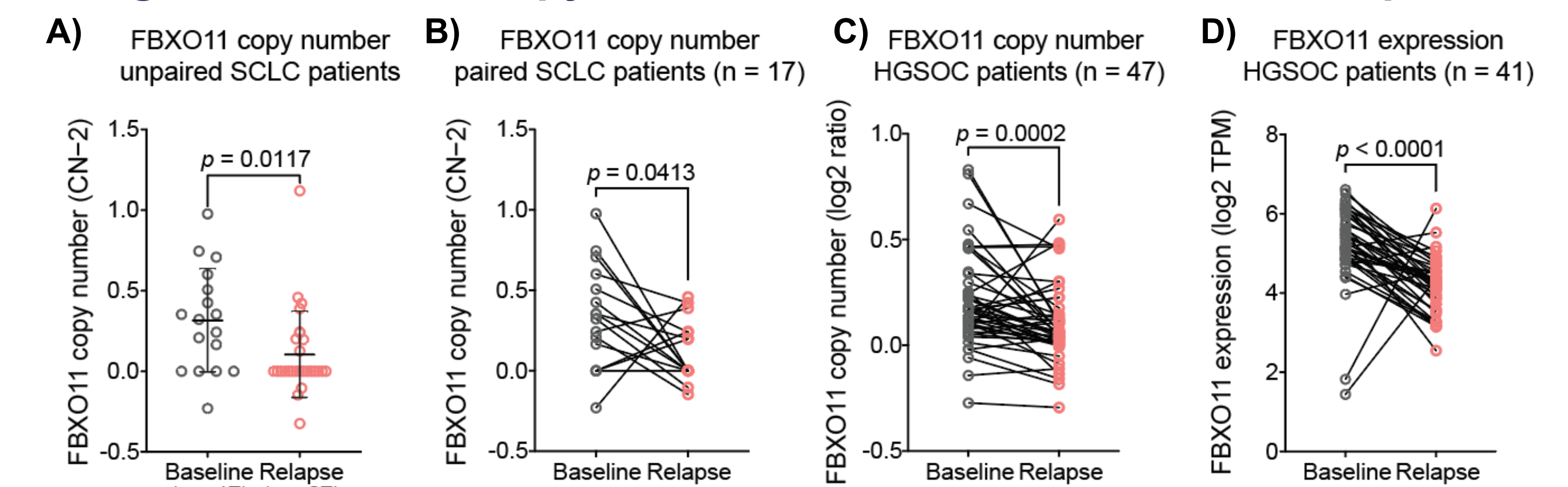
Results

Figure 4. MORF4L1 is a putative FBXO11 substrate

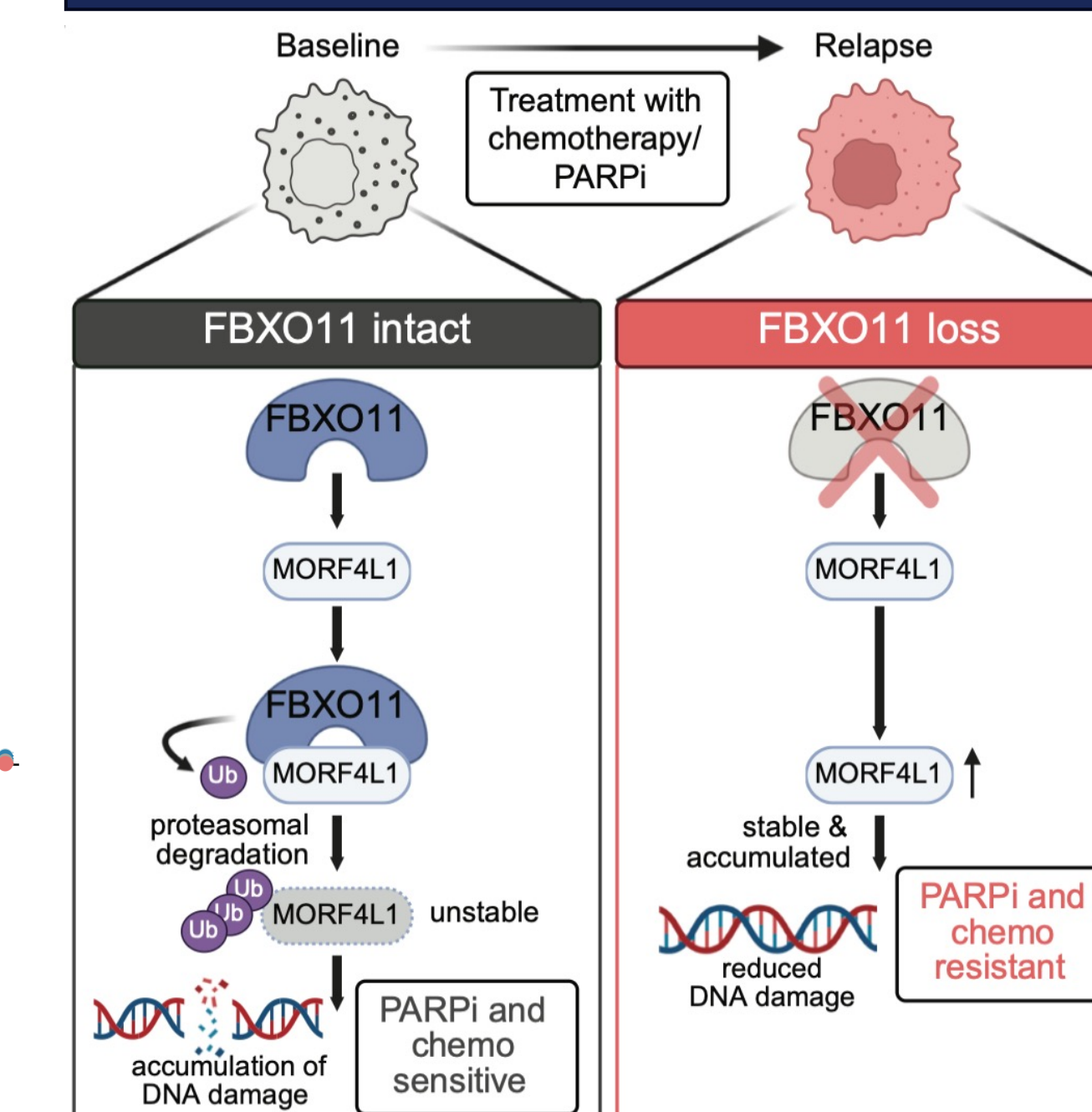


Results

Figure 5. FBXO11 copy-number loss is associated with relapse



Conclusion & future directions



Conclusion

- FBXO11 loss confers PARPi and cisplatin resistance in SCLC by stabilizing MORF4L1.

Future directions

- Evaluate the utility of FBXO11 and/or MORF4L1 as biomarkers of response.
- Identify therapeutic vulnerabilities of FBXO11-low, MORF4L1-high tumors