



Introduction

Small cell lung cancer (SCLC) is an aggressive neuroendocrine malignancy with limited durable responses to current therapies. Despite its high tumor mutational burden, many SCLC tumors remain poorly recognized by cytotoxic T cells because of reduced MHC class I antigen presentation. Previous work from our laboratory demonstrated that SCLC cells can undergo lineage plasticity and transition from a neuroendocrine (NE), MHC-I-low state to a non-neuroendocrine (nonNE), MHC-I-high state with increased immune visibility.

Methods

We integrated ChIP-seq, RNA-seq, and ribosome profiling in isogenic H69 models to identify concordantly activated genes and the pathways associated with loss of epigenetic repression.

We then generated nonNE-like states from NEUROD1⁺ SCLC cells (H446, H1694, and DMS273) using epigenetic or growth factor treatments and examined changes in morphology, NEUROD1, and HLA-I expression. Pathways commonly increased across nonNE models were identified, and shared surface targets emerging during the ASCL1⁺-to-nonNE transition were validated by flow cytometry and in patient sample spatial transcriptomics data. Immune activation was assessed using interferon/STING readouts and T-cell recognition assays, together with CTA/OFA induction as a potential contributor to immunogenicity.

Conclusions

- SCLC cells can transition from the neuroendocrine state through several routes, including epigenetic treatment and growth-factor exposure.

- Loss of NE identity was generally accompanied by increased ECM remodeling, EMT, inflammatory signaling, antigen presentation, and surface-target expression.
- Epigenetic priming also enhanced interferon signaling, CXCL10 secretion, STING responsiveness, and T-cell-mediated cytotoxicity.

- In parallel, multiple CTA/OFA genes were induced and may provide an additional source of tumor immunogenicity.

- NE-to-nonNE plasticity creates distinct and potentially targetable immune vulnerabilities, while providing stable isogenic models for studying immune-responsive states in SCLC.

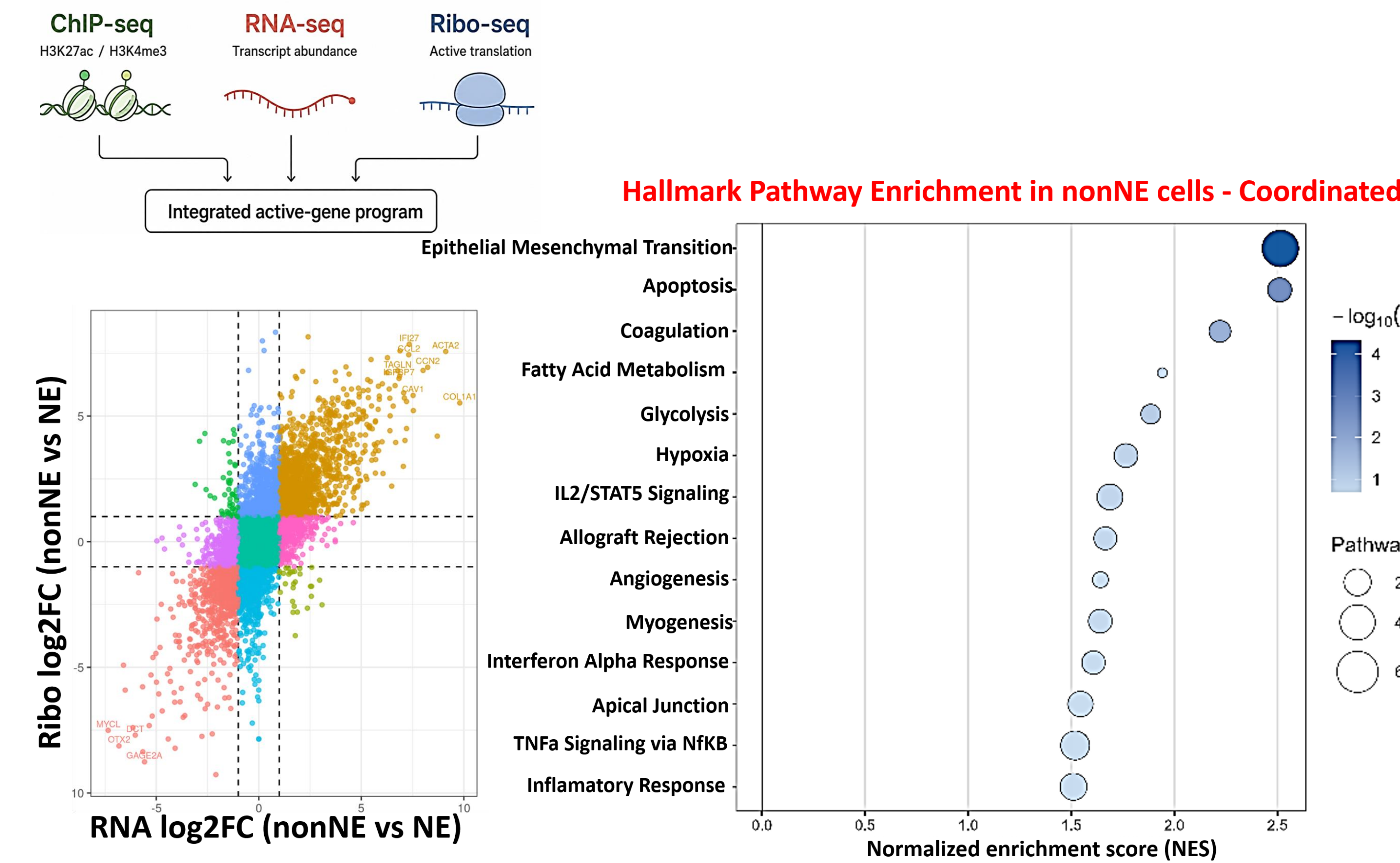
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AI Disclosure: Schematic illustrations and the QR-linked resource page were created with assistance from OpenAI's ChatGPT. All scientific content was reviewed and edited by the authors.



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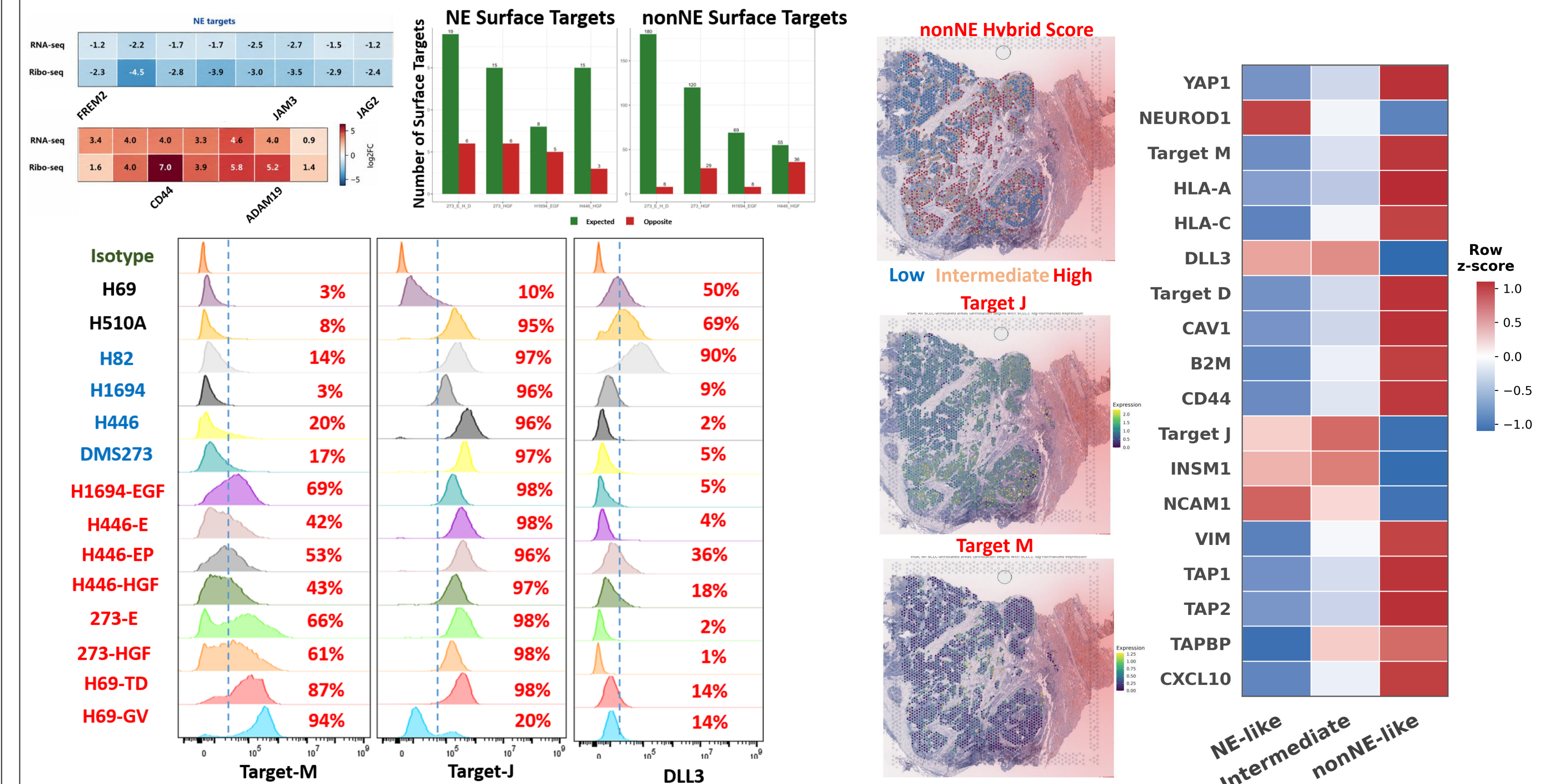
Coordinated nonNE programs converge on EMT and inflammatory hallmarks



RNA-Riboseq concordance analysis shows that nonNE/HLA-I positive states include genes that rise coordinately at both transcript and ribosome levels, alongside a distinct set with disproportionate ribosome-associated gain. These patterns suggest selective post-transcriptional reinforcement beyond transcription alone.

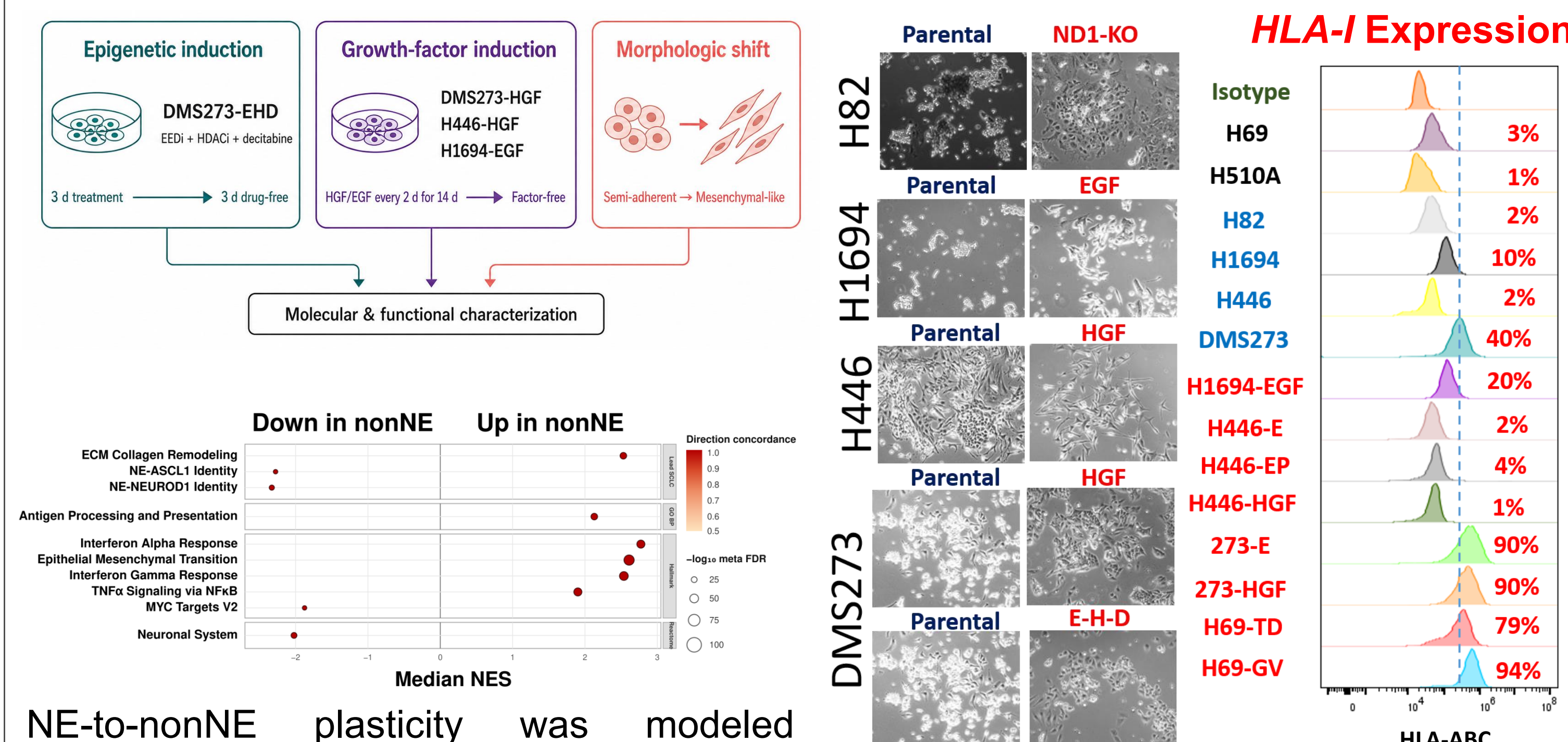
NE-to-nonNE Plasticity Reshapes Target and Immune-Expression Programs

NE-to-nonNE transition is accompanied by loss of neuroendocrine identity and coordinated induction of mesenchymal targets and antigen-presentation genes

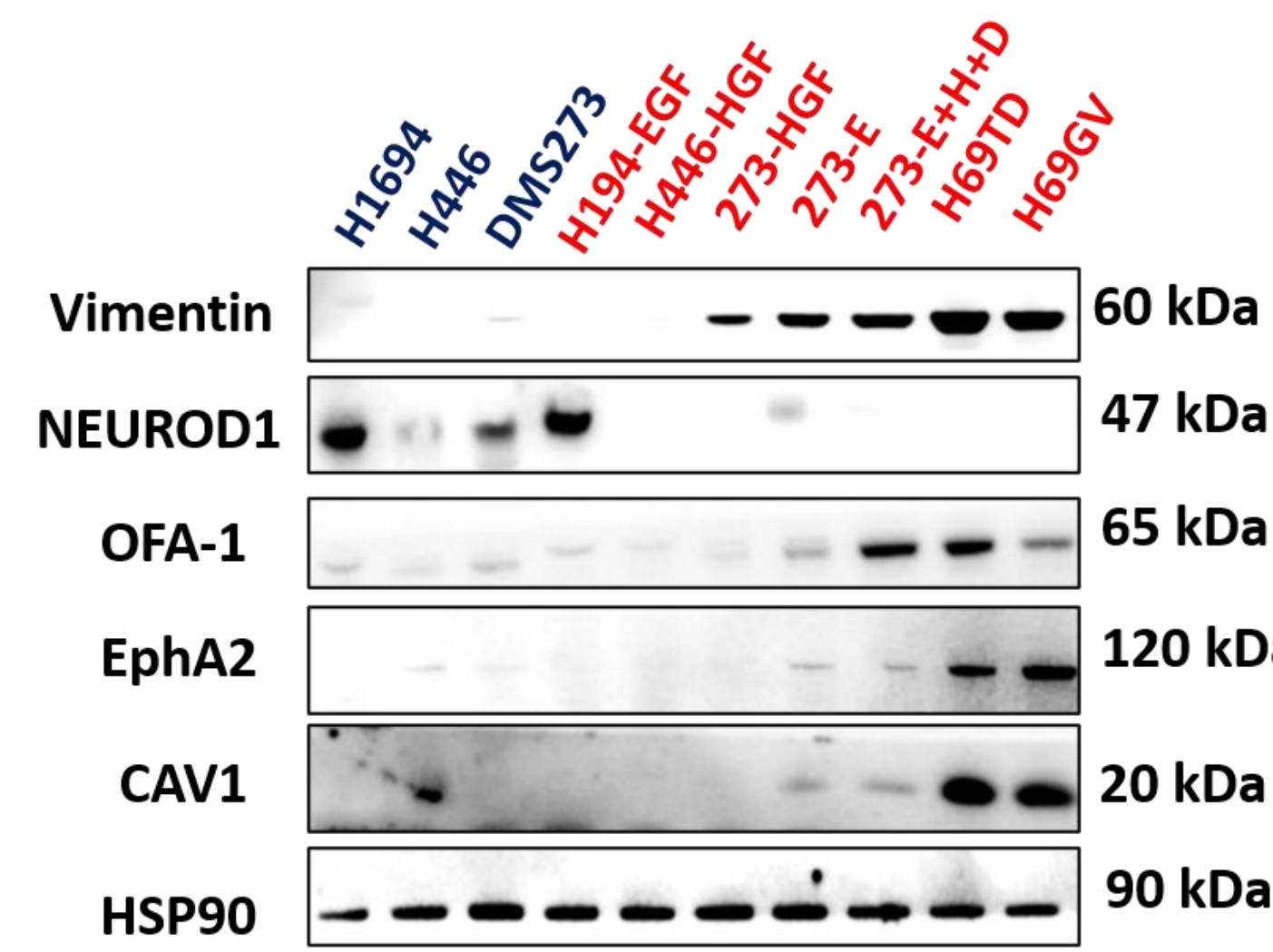


Integrated transcriptomic, translational, flow-cytometric, and spatial analyses reveal coordinated but heterogeneous NE-to-nonNE remodeling. NE-associated targets are reduced, whereas mesenchymal, antigen-presentation, and selected surface-target programs increase in nonNE-like states.

NEUROD1+ cell-derived plasticity models

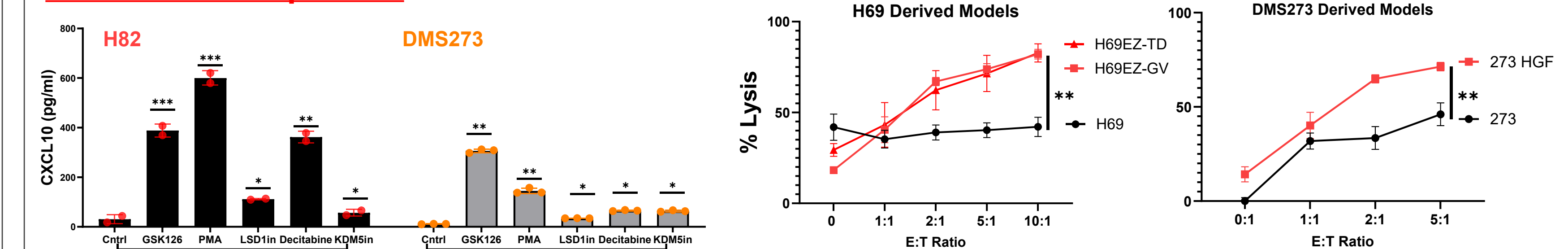


NE-to-nonNE plasticity was modeled through epigenetic treatment, growth-factor exposure, and morphological selection. These transitions were characterized by loss of NE identity and enrichment of ECM remodeling, EMT, inflammatory signaling, and antigen-presentation pathways. Although HLA-I induction was heterogeneous, selected nonNE derivatives—particularly DMS273-E/HGF and H69-TD/GV—showed a marked increase in surface HLA-I expression, supported by protein-level validation.

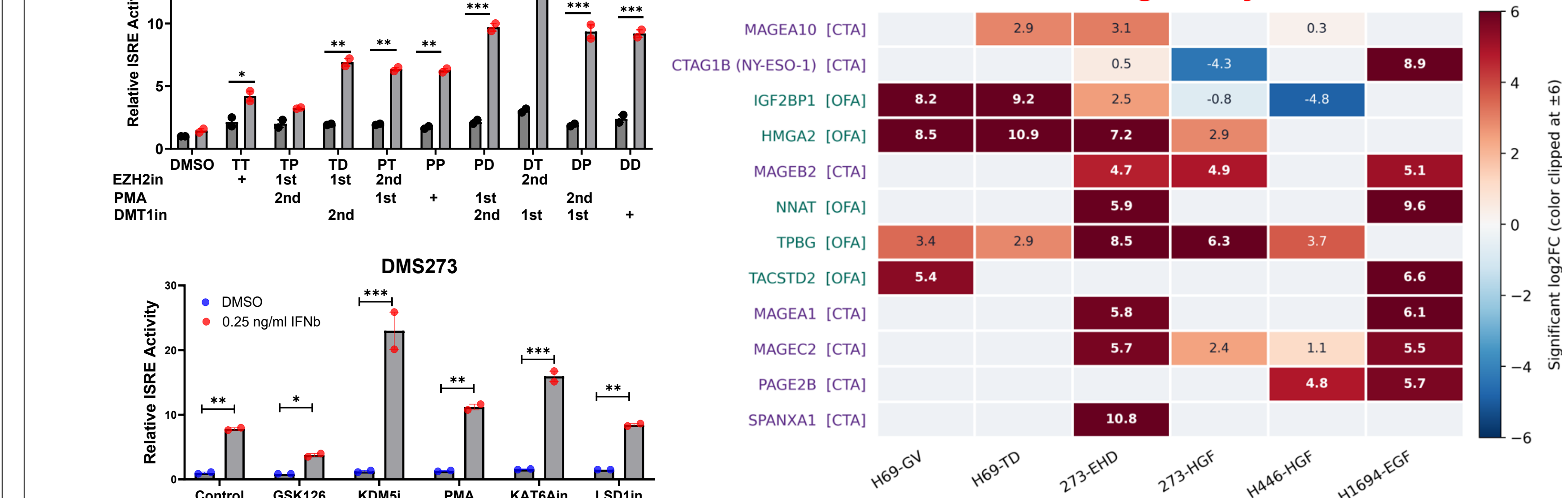


Epigenetic Priming and nonNE Plasticity Enhance Immune Responsiveness in SCLC

Epigenetic Priming Enhances Interferon and STING Responses **nonNE Transition Increases Sensitivity to T-cell Killing**



Induction of CTA/OFA Programs May Enhance Tumor Immunogenicity



Epigenetic modulation enhanced interferon signaling, CXCL10 secretion, and sensitivity to STING agonism. Epigenetic and growth factor-driven transitions also induced multiple CTA/OFA genes, potentially increasing tumor immunogenicity. Consistently, nonNE-like DMS273-HGF cells showed greater T-cell-mediated growth inhibition than parental cells.