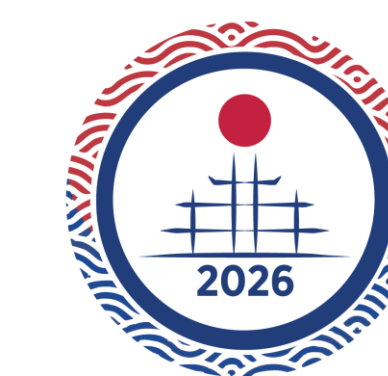




P3.120: A Classical ASCL1/NKX2-1 Subtype and an Unrecognized SOX11-associated Axis Suppressing Immunogenicity in Neuroendocrine Lung Cancer

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INTRODUCTION

Heterogeneity of neuroendocrine (NE) differentiation in pulmonary high-grade NE carcinoma, mainly small-cell lung cancer (SCLC), has been recently explored based on the expression of lineage factors such as ASCL1, NEUROD1 and POU2F3. However, molecular classification determined by them is not settled and NE differentiation among lung cancers is more heterogeneous.

Profiling of large clusters of putative enhancers in close genomic proximity, termed super-enhancers is a powerful tool to identify novel cancer cell lineages governed by specific transcriptional regulators (Sato et al. *Cancer Res*, 2019, etc.).

In this study, we elucidated the heterogeneity of NE differentiation by super-enhancer profiling of a wide range of lung cancer with NE components, mainly large-cell neuroendocrine carcinoma (LCNEC).

METHODS

We investigated super-enhancer profiles of 24 formalin-fixed paraffin-embedded tumor tissues from patients with primary lung cancer containing LCNEC components. Associations between epigenomic profiles and NE-related factors were examined.

The functional significance of SOX11 was evaluated by transcriptomic analysis following CRISPR-Cas9-mediated SOX11 deletion in an NE lung cancer cell line, together with analyses of human LCNEC/SCLC tumor and organoid datasets.

REFERENCES & ACKNOWLEDGEMENTS

References

Sato T, et al. *Lung Cancer*, 2026 Sato T, et al. *Cancer Res*, 2019



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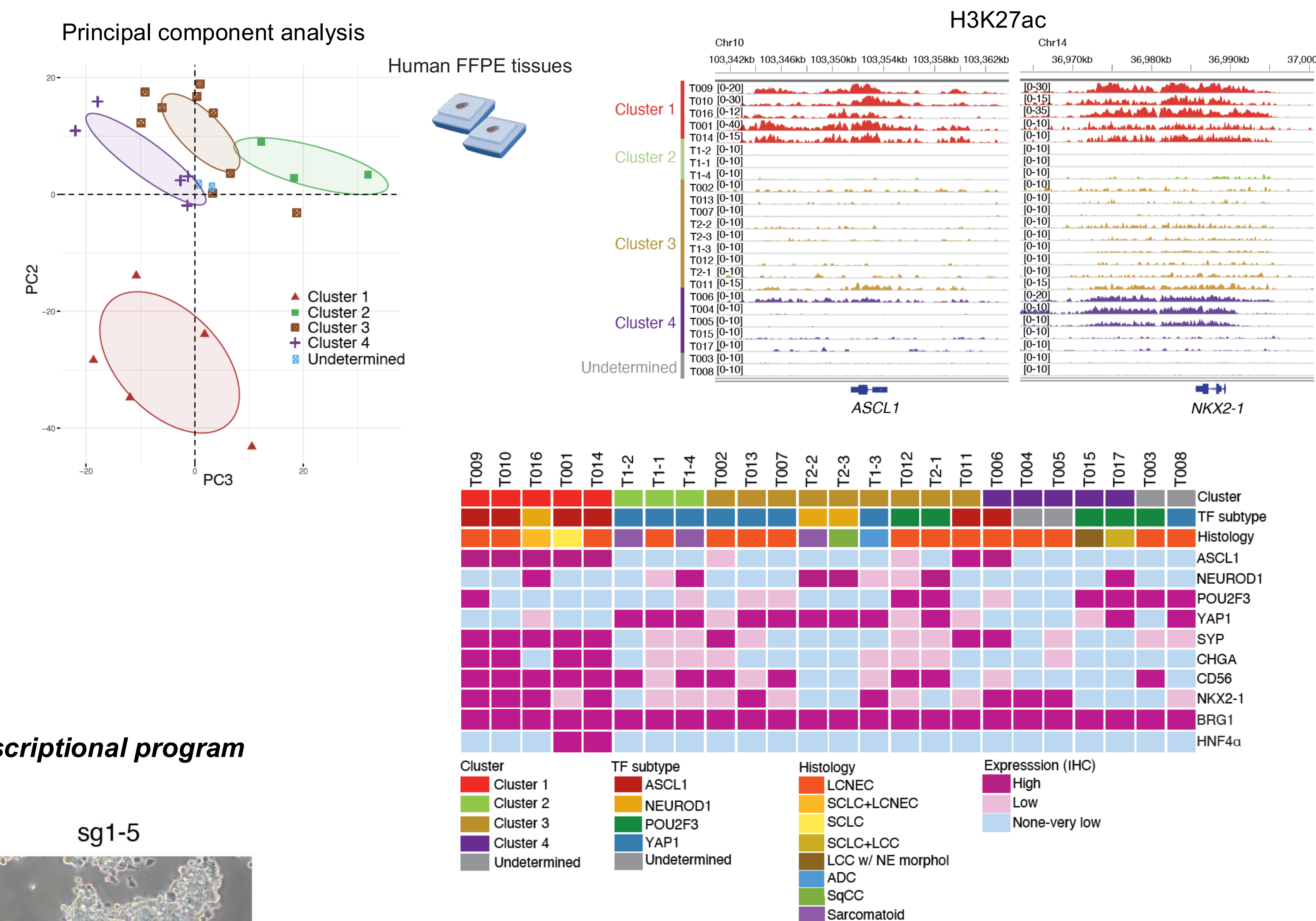
The authors used ChatGPT to assist in improving the quality of English writing.

DISCUSSION AND CONCLUSION

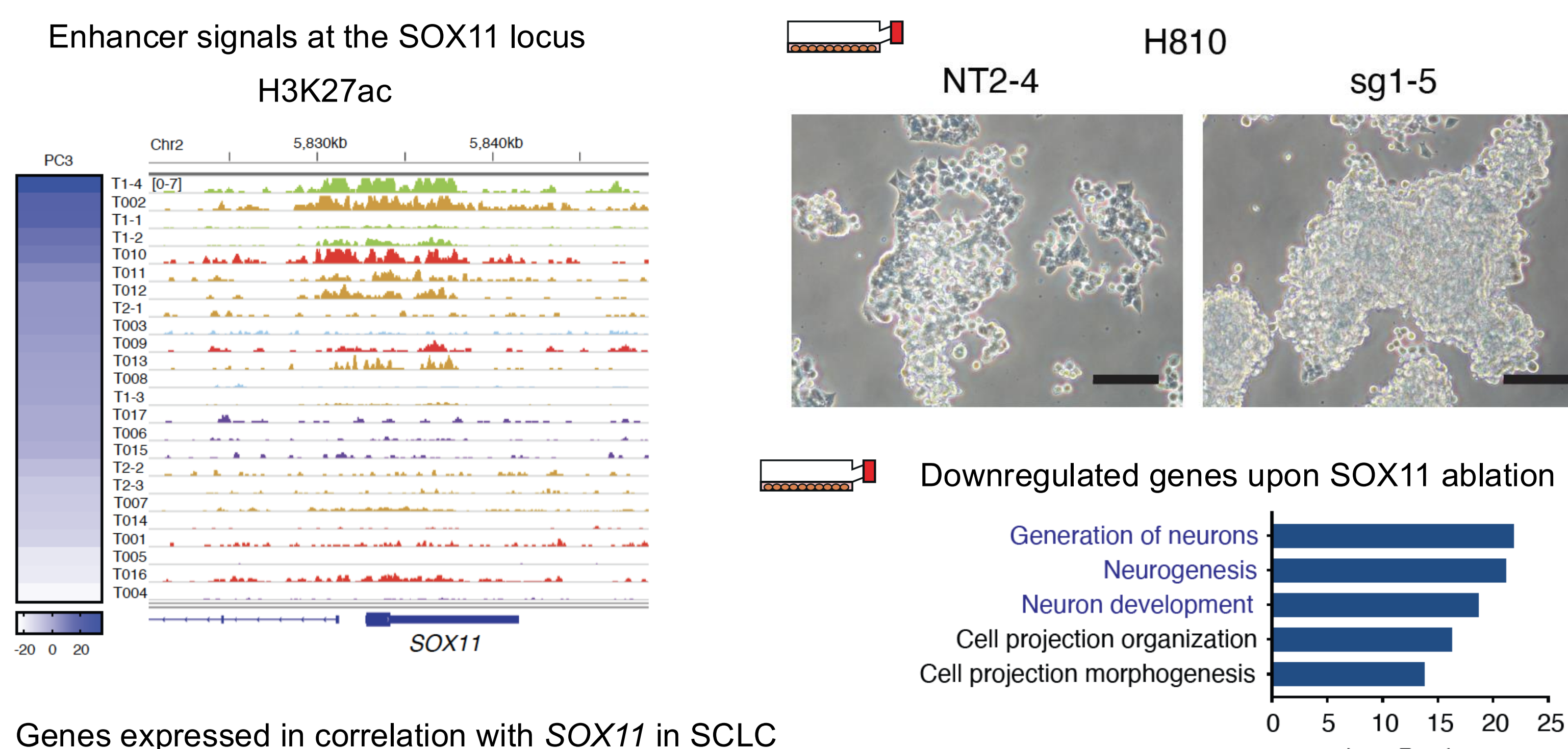
- Epigenomic profiling revealed **heterogeneous differentiation states** beyond conventional lineage factor-based classification of NE lung cancers.
- A **classical NE ASCL1/NKX2-1 subtype** was identified, characterized by typical NE features.
- **SOX11 defined a distinct neuronal differentiation axis**, largely independent of the ASCL1/NKX2-1 axis.
- SOX11 was associated with **reduced tumor immunogenicity**, including suppression of MHC class I expression.
- These findings suggest a link between **lineage states and tumor immunogenicity** in NE lung cancers.
- Further studies using **syngeneic mouse models** will clarify how SOX11-associated lineage states shape the tumor immune microenvironment and response to immunotherapy.

RESULTS

Super-enhancer profiling identifies distinct NE differentiation states including ASCL1/NKX2-1 subtype



SOX11 determines a 'neuronal' axis and regulates a 'neuronal' transcriptional program



SOX11 suppresses immunogenicity in NE lung cancer cells

