Digital Pathology Uncovers Multi-Omic Hallmarks of Lung Cancer in Histopathology Images

Abstract #2252

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STUDY BACKGROUND

- The hallmarks of cancer (HOC) describe the core characteristics and complexity underlying cancer progression. As our understanding of cancer has grown, the number of HOC has increased from six (1) to ten (2) to fourteen (3).
- While some HOC (e.g., inflammation and angiogenesis) can be visualized directly in pathological specimens such as cancer tissue, others are best understood via next-generation sequencing (NGS)-derived signatures. Given that most diagnostic, prognostic, and treatment decisions are made using pathology slides, there is a need to understand the relationship between hallmark-associated signatures and their presentation in the cancer tissue, including in the tumor microenvironment (TME).
- Digital pathology enables the quantification of tumor morphology, potentially revealing the underlying properties of a cancer. Conversely, the advent of pathology-based biomarkers necessitates linking morphological biomarkers to the conceptual scaffolding provided by cancer hallmarks.
- Here, we used a digital pathology approach to gain a deeper understanding of the relationships between the TME and HOC in non-small cell lung cancer (NSCLC).

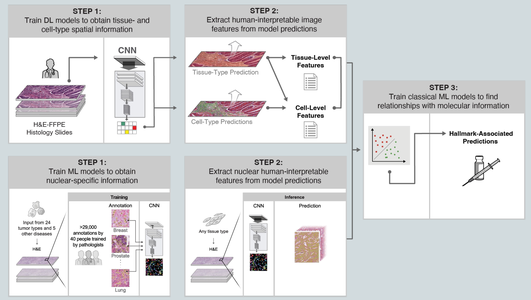

Figure 1. Workflow for extracting human-interpretable features (HIFs) from hematoxylin and eosin (H&E)-stained images. HIFs were extracted from cells and tissue regions (top), as well as nuclei (bottom). ML-based models were then trained to associate these HIFs with genomic signatures associated with cancer hallmarks. Methodology for cell and tissue models described in (4). Process for nuclei models described in (5).

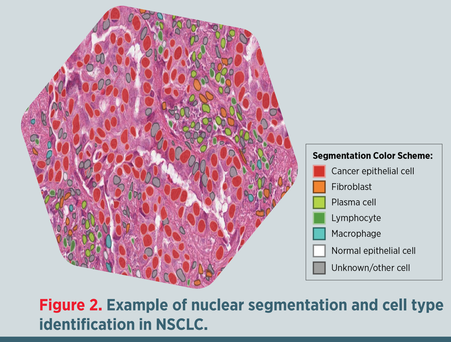

Figure 2. Example of nuclear segmentation and cell type identification in NSCLC.

METHODS

Extraction of features from tissue and cell models.
The overall study workflow is summarized in Figure 1. ML-based model was used to segment nuclei and assign a cell class to each nucleus from the cell model predictions (Figure 2). Additional ML-based models were trained to identify and quantify cells (neoplastic and non-neoplastic; Figure 3A) and regions of tissue (Figure 3B) within the TME and were deployed on 884 hematoxylin and eosin (H&E)-stained whole-slide images (WSIs) from the TCGA LUAD and LUSC datasets. Human-interpretable features (HIFs) quantifying tissue areas and cell presence in tumor regions were computed to summarize the TME for each WSI. We quantified the morphology of each nucleus and summarized these features across each WSI to generate nuclear HIFs. To quantify the relationship between pathology HIFs and hallmarks, we used a set of immune and mutational signatures derived from TCGA-derived whole-exome sequencing and bulk RNA-seq (6), from which SNV smoking signature and tumor mutation burden (TMB) were calculated using deconstructSigs (7) and direct mutation counts, respectively.

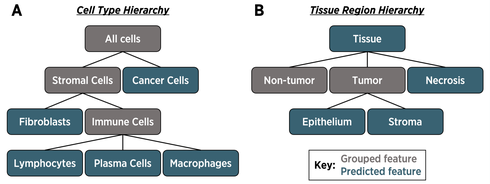

Figure 3. Summary of features identified by A) cell and B) tissue models used in this study.

Statistical analysis.
To identify correlations between HOCs and HIFs, Spearman correlation was performed, and p-values were adjusted using Bonferroni correction. Pairwise associations between HOCs and HIFs were confirmed using linear regression analysis. To identify associations between HIFs and continuous smoking signature and TMB, univariate linear regression was performed. The associations between the dichotomized smoking signature and tumor mutation burden (TMB) with overall survival (OS) were characterized using univariate Cox proportional hazards analysis.

RESULTS

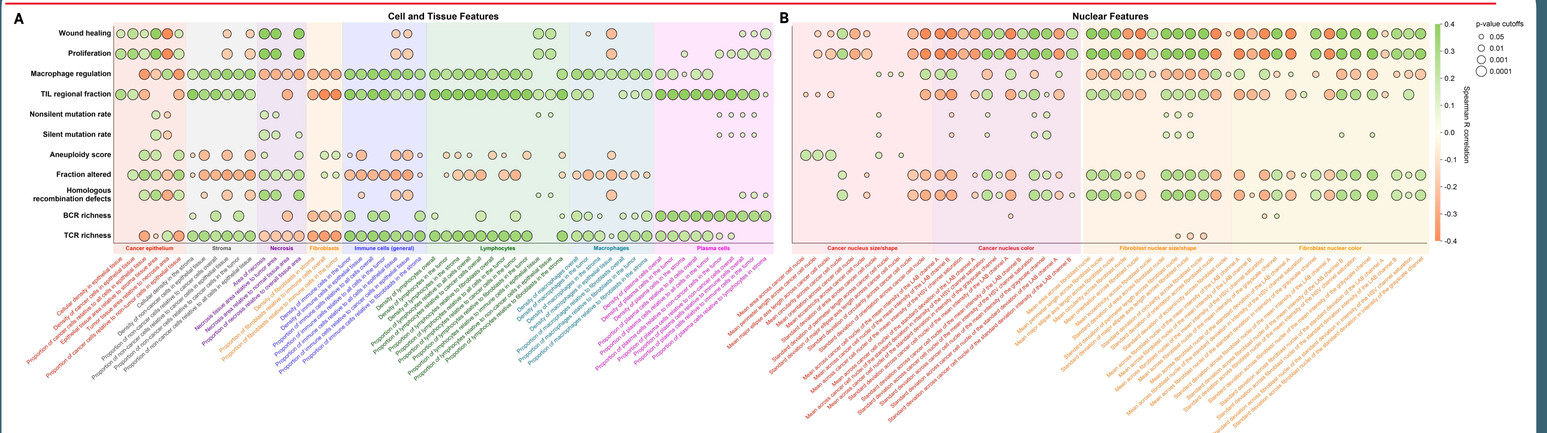

Figure 4. Associations between HOC-related gene expression signatures and tissue- and nuclei-based features in NSCLC. Significant associations (corrected p<0.05) were observed between sequencing-derived signatures of HOC (y-axis) and A) TME HIFs derived from cells and tissues and B) features derived from cancer cell and fibroblast nuclei. Homologous recombination defects were associated with increased necrosis (Spearman r=0.29), and aneuploidy score was associated with larger cancer cell nuclei (Spearman r=0.21). Expression signatures of wound healing and proliferation were associated with increased tumor necrosis (Spearman r=0.45) and fibroblast nuclear morphology (size and shape, Spearman r>0.6).

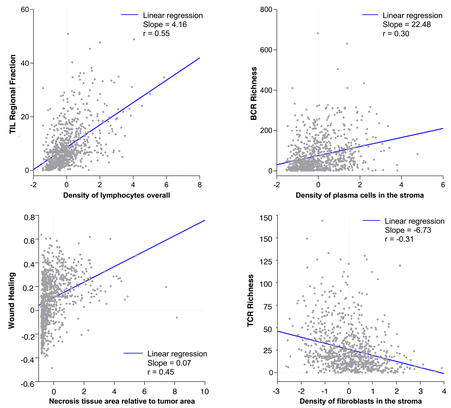

Figure 5. Pairwise associations between HOC-associated gene signatures and TME HIFs.

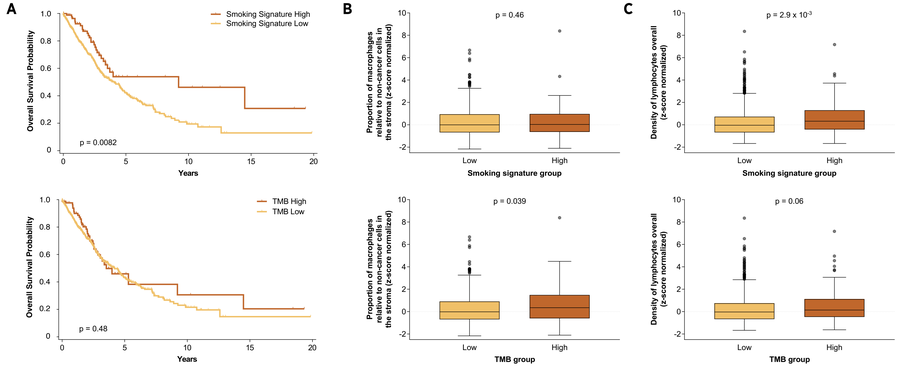

Figure 6. Clinically relevant distinctions between smoking signature and tumor mutation burden (TMB) in NSCLC. A) Dichotomized SNV smoking signature was associated with OS (HR=0.59, p=8.2x10^{-3}), but dichotomized TMB was not (HR=0.88, p=0.48). B) TMB was associated with increased presence of macrophages in the stroma, (p=0.039). C) SNV smoking signature was associated with increased overall lymphocyte density (p=2.9x10^{-3}).

CONCLUSIONS

Integrating tumor morphology features with multi-omic NGS data has revealed significant associations in NSCLC. Associations were observed between tissue-based and nuclei-based features and pathways associated with HOC. Furthermore, associations were observed between clinically-relevant metrics such as smoking signature and TMB and tissue features in NSCLC. Further application of this approach will continue to reveal clinically-relevant associations in NSCLC.

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REFERENCES

1) Hanahan D. and R.A. Weinberg. *Cell*. 2000; 100(1):57-70.
2) Hanahan D. and R.A. Weinberg. *Cell*. 2011; 144(5):646-74.
3) Hanahan D. *Cancer Discov*. 2022; 12(1):31-46.
4) Diao J.A. *et al.* Nat Comms. 2021; 12:1613.
5) Abel J. *et al. Cancer Res*. 2022; 82(12_Supplement):464.
6) Thorsson V. *et al. Immunity*. 2018; 48:812-30.
7) Rosenthal R. *et al. Genome Biol.* 2016; 17:31.

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