Background

- Tumor infiltrated lymphocytes (TILs), namely CD8+ TILs play a major role in antitumor immunity and tumor cell eradication.
- High-density infiltration of CD8+ cells in the tumor, in contrast to CD8+ cell excluded regions, is associated with improved prognosis and response to immunotherapy in multiple cancer types.
- However, since various TILs are indistinguishable using H&E, CD8+ evaluations require additional tissue slides for IHC staining and are not performed routinely in clinical practice.
- Here, we developed DL models and derived human interpretable spatial features to predict CD8+ cell density and immune phenotypes from standard H&E slides.

Methods and materials

- 138 pairs of sequential H&E and CD8 slides from 103 patients with metastatic NSCLC were procured.
- Two board-certified pathologists classified IHC slides into immune phenotypes: inflamed, desert, and excluded, based on CD8 density (Tables 1, 2).
- DL models were trained to classify tumor cells, lymphocytes, fibroblasts and tumor versus stromal areas on H&E, as well as positivity of CD8 per cell by IHC.
- 354 spatial features were calculated from the H&E slides and CD8+ density in the whole tumor region was calculated from IHC slides.
- Our biological hypotheses are based on prior knowledge from scientific literature regarding immune and spatial determinants for ICI response or immune phenotype. For example, high level of infiltration of TILs or CD8+ is associated with immune phenotypes, immune excluded regions, is associated with improved prognosis and response to immunotherapy in multiple cancer types.
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1. CD8 prediction

DL models accurately classify various cell types and classifies regions into tumor vs stroma on H&E images. Various areas including tumor core, tumor invasive margin, adjacent tumor microenvironment, outer tumor microenvironment were derived for spatial feature calculation.

2. Immune phenotype prediction

The H&E features most predictive of immune phenotype were proximity between lymphocytes and tumor cells or granulocytes, as well as lymphocyte:fibroblast density ratio. A multinomial logistic regression model was trained to predict immune phenotypes from the H&E images.

3. Phenotype visualization examples

Here, we developed DL models and derived human interpretable spatial features to predict CD8+ cell density and immune phenotypes from standard H&E slides.

Conclusions

- Spatial analysis of immune and tumor cells from standard H&E slides using DL identified human interpretable features that accurately predicted CD8+ cell density and identified immune phenotypes.
- Our framework is easily generalizable and can be extended to predict other IHC stains or gene signatures.
- By only requiring H&E images, these biomarkers important for checkpoint inhibitor therapy can be measured in clinical practice without the requirement of IHC staining.

References

- Li et al. EClinicalMedicine 2021; 41, 101134.
- El Baari et al. npj Breast Cancer 2021; 7, 150