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Deep-Learning–Based Prediction of c-MET Status From Digitized H&E-Stained Non-small Cell Lung Cancer Tissue Samples

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OBJECTIVE

To develop a machine learning (ML)-powered method that identifies c-MET overexpression status directly from hematoxylin and eosin (H&E)-stained non-small cell lung cancer (NSCLC) samples

CONCLUSIONS

The human-interpretable features (HIF) generated by the convolutional neural networks (CNN) models showed that the composition of the tumor microenvironment (TME) is significantly different in tissue, including lymphocyte density, when c-MET is overexpressed

Multivariate regression (MR) based on TME features and graph neural networks (GNN) models was able to identify patients with tumors that overexpressed c-MET; however, the performance of the GNN model was stronger

These results indicate there is potential to develop and validate an H&E-based screening tool for patient selection for c-MET–targeting therapies, thereby increasing efficiency and access

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INTRODUCTION

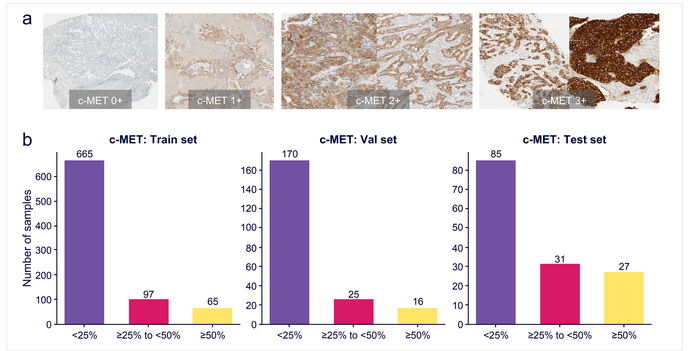
- Genetic drivers of NSCLC have been identified including perturbations that lead to overexpression of *c-MET*[1-3]
- c-MET, a receptor tyrosine kinase mesenchymal-epithelial transition factor, is an attractive therapeutic target because dysregulation of its expression leads to cellular proliferation, migration, invasion, angiogenesis, and epithelial-to-mesenchymal transformation[1]
- Telisotuzumab vedotin is an antibody-drug conjugate that targets c-MET to block activation of downstream pathways[2-4]
- Currently, pathologist evaluation of immunohisotchemical staining is used to determine c-MET expression in lung tissue and identify eligible patients
  - c-MET overexpression can be difficult and time-consuming to quantify by immunohistochemistry-based pathologist assessment[5,6]
- PathAI ML models have shown success in predicting various molecular and genetic markers from the H&E slide alone[7]; it was hypothesized that a similar approach could be applied to identify c-MET status on the basis of the H&E NSCLC tissue samples

METHODS

Data Sets

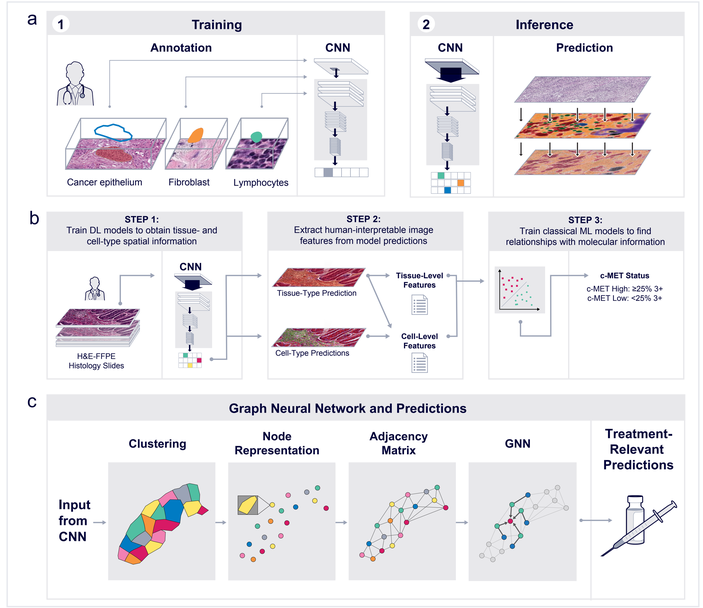
- These data sets of paired H&E- and SP44-stained NSCLC tissue samples were digitized to whole-slide images (WSI) using an Aperio AT2 scanner (Leica Biosystems, Deer Park, IL, USA)
- c-MET predictive models (MR and GNN) were developed using discovery representative subset of 1,181 H&E-stained NSCLC slides from a phase 2 clinical trial of telisotuzumab vedotin (NCT03539536) and commercial sources (80% for training and 10% for validation). Model predictions were assessed on a held-out test data set (10% of data set)
- For all slides, c-MET expression status (ground truth) was determined by a trained pathologist's scoring of c-MET–stained samples (SP44, Ventana Medical Systems, Inc., Tucson, AZ, USA) as follows:
  - c-MET positive if ≥25% c-MET–positive tumor cells at 3+ intensity
  - c-MET negative if <25% c-MET–positive tumor cells at 3+ intensity

Balanced Divide of Data Set on the Basis of c-MET Expression for Model Training and Validation



(a) Representative c-MET–stained slides. A pathologist determined the c-MET status of each slide on the basis of the intensity of IHC staining for the c-MET protein. Intensity of staining across both membrane and cytoplasm was used to determine and score the intensity and distribution of expression from 0 to 3+. (b) To train models to predict c-MET status, the data set was split into training, validation, and held-out test sets with similar distributions of all c-MET intensity scores.
IHC, immunohistochemical; val, validation.

Deep-Learning Models for TME Quantification and c-MET Status Prediction



(a) Pathologists' annotations were used to train a CNN model to predict different cell types and tissue regions within the TME. (b) When applied to WSI, predictions from CNN models were used to extract HIF that represent the quantity and spatial distribution of cell types and area proportion of tissue types. Statistical modeling was applied to predict the c-MET status on the basis of HIF distribution. (c) A stand-alone GNN model was trained to use CNN model overlays as well as slide-level c-MET status label, to predict the c-MET status of the sample.
CNN, convolutional neural networks; DL, deep-learning; FFPE, formalin fixed, paraffin embedded; H&E, hematoxylin and eosin; GNN, graph neural networks; HIF, human-interpretable features; ML, machine learning; TME, tumor microenvironment; WSI, whole-slide images.

- HIFs correlated with cMET expression were generated through deployment of a CNN model on 349 clinical trial samples and validated on 81 held-out commercial samples

Model Development

- Previously trained ML models based on CNN[8] were applied to WSI to identify and quantify features of the TME including cancer cells, plasma cells, fibroblasts, lymphocytes, macrophages, granulocytes, as well as regions of cancer epithelium, cancer stroma, and necrosis
- ML model-quantified characterizations of the TME were extracted to produce HIF that describe relationships between cells and tissues. c-MET status predictive potential of HIF was explored
- A GNN-based model that uses cell and tissue predictions from the CNN as input for graph assembly was also developed using 5-fold cross-validation

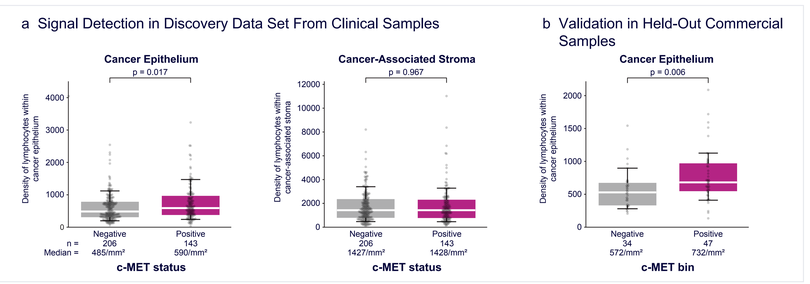
Statistical Analysis

- To determine if model-derived features could predict c-MET status, first, individual HIF were correlated with pathologist-predicted c-MET status using univariate logistic regression. The false-discovery rate was corrected with the Benjamini-Hochberg and Empirical Brown's methods
- HIF were also grouped using agglomerative clustering with Pearson-R^2 and multivariate logistic regression with Elastic Net regularization was used to assess their predictive potential for c-MET

RESULTS

- Identified HIF were validated with the held-out test set sourced from commercial samples. c-MET overexpression was significantly associated with a cluster of related HIF that describe elevated immune cell densities in multivariate analysis
  - Specifically, c-MET–positive samples had a significantly higher density of lymphocytes in the cancer epithelium than c-MET–negative samples (p = 0.017) while no association was observed in the cancer stroma (p = 0.967)

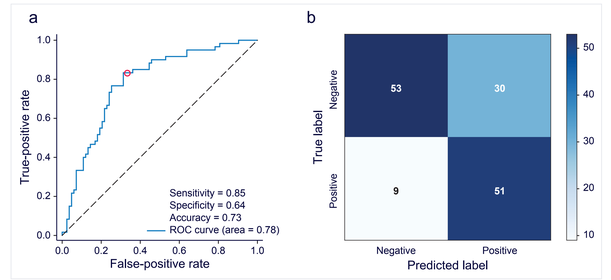
Density of Lymphocytes in Cancer Epithelium Is Significantly Associated With c-MET Positivity



The HIF correlated with c-MET expression were generated by CNN models trained on a subset of these data (349 clinical trial slides, plus 81 commercial samples) split into training (80%), validation (10%), and test (10%) sets similar to model development.
HIF, human-interpretable features.

- A multivariate logistic regression model was then used to assess predictive power of the c-MET–associated HIF
  - The resulting area under the receiver operating characteristic curve (AUROC) of 0.58 (accuracy: 0.58) showed that these HIF were only moderately predictive (data not shown); however, the GNN model was strongly predictive of c-MET when applied to the test data set

GNN Model Was Strongly Predictive of c-Met Status, Indicating a Potential Use in Identifying c-MET Overexpression



(a) AUROC of 0.78 indicated exceptional performance of the model to predict c-MET status. A model with 0.85 sensitivity and specificity of 0.64 was used as the optimal model (red circle) for the patient-triaging use case. Its performance is highlighted in the confusion matrix. (b) Confusion matrix characterizing GNN model's performance on the held-out test set (c-MET positive: n = 60; c-MET negative: n = 83). This result shows that the majority of cases (104 of 143 cases) were classified the same as the ground truth. The model by design was picked to minimize false negatives, at the expense of higher false-positive rates.
AUROC, area under the receiver operating curve; GNN, graph neural network.