Artificial intelligence-based spatial analysis of the local tumor microenvironment in relation to c-MET expression in non-small cell lung cancer

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INTRODUCTION

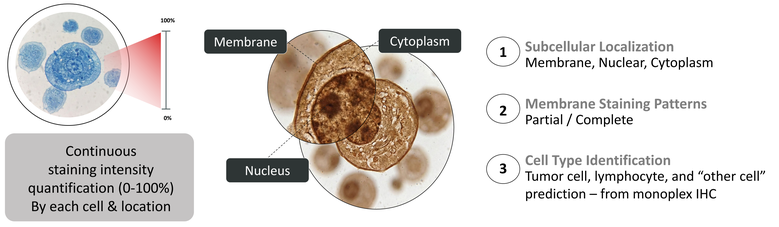
MET is a well-known oncogenic driver that confers various genomic aberrations. Recent approval of antibody-drug conjugates has expanded therapeutic options for c-MET expressing non-small cell lung cancer (NSCLC). However, the relationship between MET expression, tumor microenvironment (TME), and immunotherapy response remains unclear. This study explores the association between c-MET expression and spatial TME features in NSCLC to better understand its immunologic behavior.

METHODS

- **Study cohorts**: a total of 25,674 NSCLC samples across multiple cohorts
  - Genomic analysis: 24,110 samples from AACR GENIE and 924 samples from TCGA
  - IHC and TME analysis: 589 slides from Ajou University Medical Center (AUMC) and 51 slides from Agilent Technologies
- **AI-based Quantification: Lunit SCOPE IO** and **Lunit SCOPE uIHC** were used for quantitative assessment of TME and IHC-based c-MET expression (**Figure 1**).
- **IHC Analysis:** Lunit SCOPE uIHC quantified
  1) % Staining intensity (≥T1+ , ≥T2+ , ≥T3+) & **tumor cell proportion** (scale 0–100)
  2) Subcellular compartment intensity (membrane, cytoplasm, nucleus)
- **Membrane-Specific Expression:**

$$\frac{Membrane\ intensity}{(membrane\ +\ cytoplasm)\ intensity} \geq 0.5$$

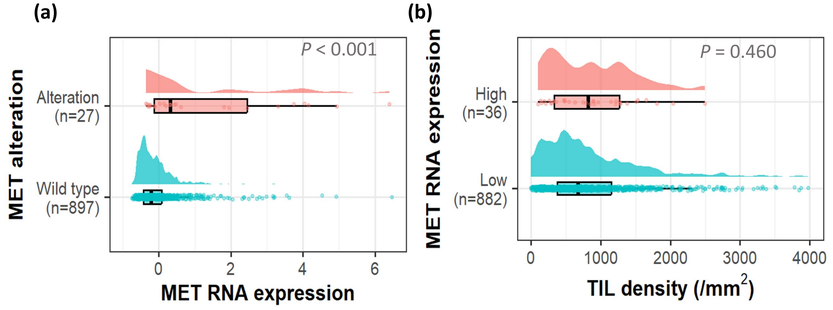
Figure 1. Overview of AI-powered Lunit universal IHC analysis. The AI model enables quantitative and spatial characterization of immunohistochemistry signals at single-cell resolution.



RESULTS

MET alterations occurred in 27 (2.9%) of TCGA and 909 (3.8%) of GENIE, including exon 14 skipping (n=388, 1.5%), amplification (n=380, 1.5%), and others (n=223, 0.9%). MET-altered tumors had higher MET RNA expression compared with wild-type tumors (median: 0.4 vs. -0.2, p<0.001) (**Figure 2a**). TME analysis of samples with high and low RNA expression showed no significant difference in tumor-infiltrating lymphocyte (TIL) density (/mm^2, median: 851 vs. 673, p=0.46) (**Figure 2b**).

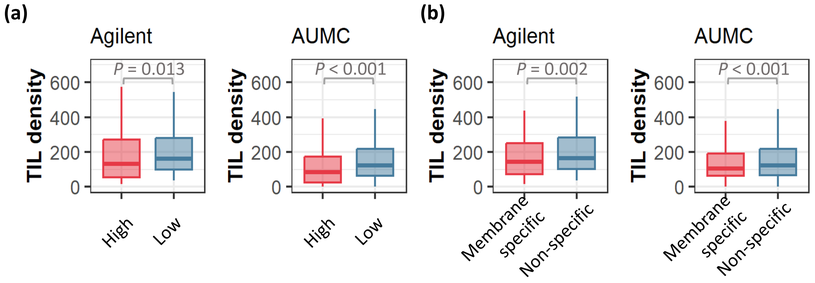
Figure 2. MET alterations, RNA expression, and TIL density in TCGA and GENIE cohorts. High MET expression was defined as Z-score ≥2; TIL density was compared by expression level.



In 640 pairs of H&E and IHC slides from Agilent and AUMC, c-MET positive (T3+, ≥50%) samples showed numerically lower TIL density at the slide level compared to c-MET negative samples; however, this difference was not statistically significant (Agilent: median 80.6 vs. 211.3, p=0.229; AUMC, 78.5 vs. 79.2, p=0.154).

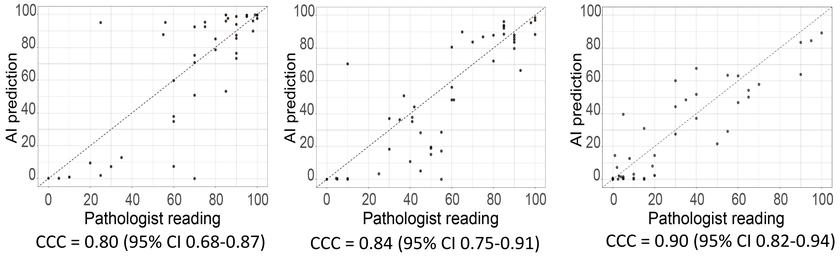
This trend became significant with cell and subcellular spatial analysis. The density of TIL was markedly reduced within 30μm of tumor cells exhibiting strong (3+) c-MET expression (median: 132.2 vs. 162, p=0.013; 85.5 vs.121.6, p<0.001 , respectively) (**Figure 3a**). Notably, a similar reduction in TIL density was also observed around tumor cells with membrane-specific c-MET expression (median: 144.9 vs.165.8, p=0.002; 106.6 vs. 122.3, p<0.001, respectively) (**Figure 3b**).

Figure 3. TIL density by c-MET expression patterns.
(a) TIL density according to c-MET IHC intensity (High vs. Low). (b) TIL density according to membrane-specific c-MET expression (membrane-specific vs. non-specific).



From the Agilent dataset, concordance between AI model–predicted and pathologist-assessed tumor cell proportions was evaluated. Alignment was observed across % staining intensity at ≥T1+ (**Figure 4a**), ≥ T2+ (**Figure 4b**), and ≥ T3+ (**Figure 4c**) scoring algorithms, with concordance correlation coefficients (CCC) ranging from 0.80 to 0.90.

Figure 4. Concordance between AI-predicted and pathologist-assessed tumor cell category proportions. (a–c) Scatter plots comparing AI and pathologist estimates of tumor cell proportions classified as % staining intensity at ≥T1+, ≥ T2+, and ≥ T3+, respectively.



CCC = 0.80 (95% CI 0.68-0.87)
CCC = 0.84 (95% CI 0.75-0.91)
CCC = 0.90 (95% CI 0.82-0.94)

CONCLUSION

- High or membrane-specific c-MET expression is associated with reduced immune cell infiltration, suggesting immune exclusion
- AI-derived tumor cell proportions demonstrates alignment with pathologist assessments in the subset of Agilent-provided samples.
- Findings support a spatial rationale for combination strategies with immunotherapy

D0145819