A tumor-intrinsic signature involving immunosuppression via MIF-CD74 signaling is associated with overall survival in ICT-treated lung adenocarcinoma

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INTRODUCTION

- Immune checkpoint therapies (ICT) have changed cancer care, yielding robust and durable responses in a subset of patients.
- Identifying patients who are likely to respond to ICT remains an ongoing challenge. In addition, only a portion of patients with clinical biomarkers respond to therapy.
- Signatures of RNA expression have been developed to predict response, the majority of which focus on T-cell and cytotoxicity markers, yet have been unable to substantially improve outcome predictions.
- Here, we present a RNA signature that instead describes tumor-intrinsic immune resistance and a potential mechanism of immunosuppression via tumor signaling on macrophages, derived from single-cell RNA-sequencing (scRNA-seq).

METHODS

scRNAseq Profiling

- Single-cell sequencing was performed on 15 lung adenocarcinoma disassociated (LUAD) tumor samples using the 10x Genomics Chromium platform
- FACS-separated CD45+ and CD45- fractions of each tumor sample were profiled independently and processed with the Cell Ranger pipeline and scanpy, resulting in 183,873 cells for downstream analysis

Dimensionality Reduction with Variational Autoencoder (VAE)

- The VAE model was trained on each sample for 250 iterations, yielding 20 signatures from each tumor sample
- The relationship of each signature with real-world overall survival (rwOS) was assessed in 1,983 bulk RNA-sequenced LUAD patients treated with an FDA approved ICT was assessed via a Cox proportional hazards model with risk set adjustment, using TMB and line of therapy as covariates.
- The NATMI python package was used to identify putative active ligand-receptor interactions between tumor cells and the immune environment.

SUMMARY

- Machine learning in scRNA-seq LUAD tumor samples identified a signature of immune resistance associated with shorter overall survival (HR = 4.2 [2.8-6.3]) in an independent cohort of 1,983 real-world LUAD patients.
- From the signature, we identify *MIF-CD74* as a key immunosuppressive ligand-receptor interaction between tumor cells and macrophages in the tumor microenvironment.

RESULTS

Identified a gene expression signature enriched in neoplastic cells from a highly infiltrated LUAD tumor

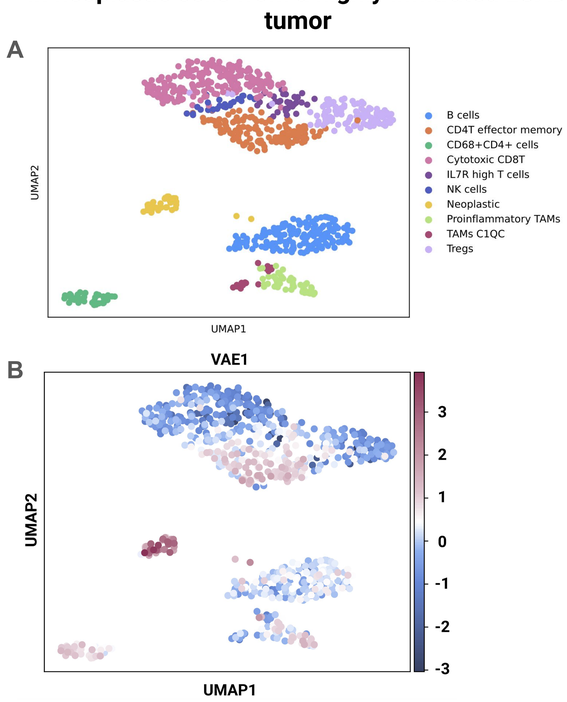

Figure 1. A UMAP of cell types derived from single-cell RNA-sequencing of a LUAD tumor (CD45- fraction). Even after sorting, there is a high proportion of immune infiltrate and few tumor cells. In this sample, many of sequenced cells were removed by CellRanger QC as likely dead or dying, suggesting there may have been an effective immune response and the remaining neoplastic population managed to avoid immune cytotoxicity. **B** UMAP of the signature weights in each cell. The signature created by unsupervised learning using a VAE and is significantly higher weighted in the neoplastic cells than any other cell group, suggesting it likely is capturing expression patterns particular to that group.

Tumor MIF signaling on infiltrating immune cells is a defining feature of the resistant tumor cells

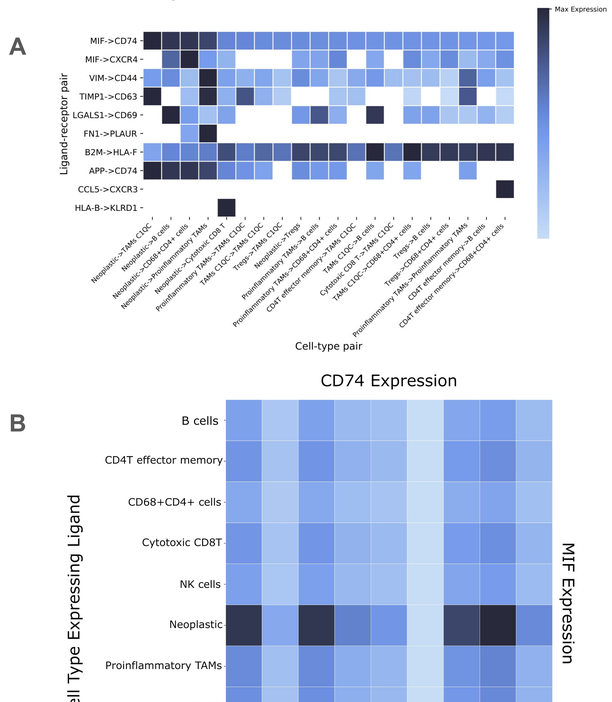

Figure 2. A Top ligand receptor pairs identified in the single cell sample described in Figure 1, using NATMI. **B** Intensity of predicted ligand receptor interactions between cell types between *MIF* and *CD74*.*MIF* expression is highest in neoplastic cells and *CD74* expression is highest in B cells and macrophages.

Projected MIF-CD74 single-cell Signature Associates with Decreased OS across real world LUAD cohort

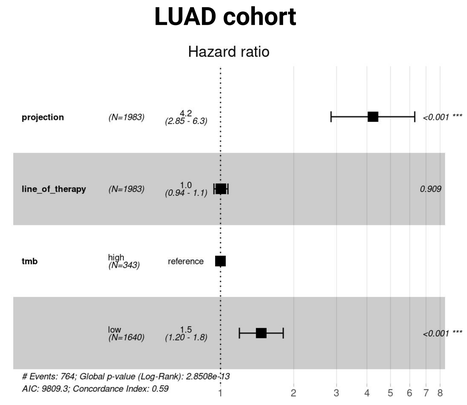

Figure 3. Across 1,983 lung adenocarcinoma patients a Cox proportional hazards model finds the signature derived from the single cell sample is strongly associated with reduced rwOS, accounting for line of therapy and TMB.

MIF Expression is associated with decreased rwOS in a rw LUAD ICT-treated cohort

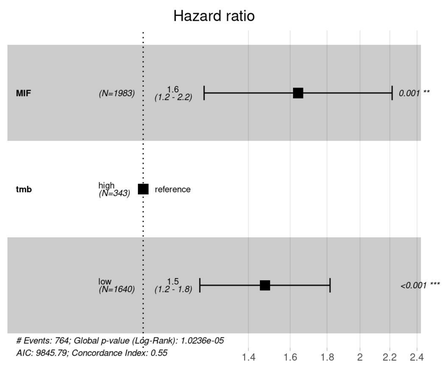

Figure 4. Forest plot of a multivariable Cox PH model with MIF and TMB as covariates.

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