Use of LIF and LIFR Expression to Characterize Survival and Tumor Microenvironment Composition in Lung Adenocarcinoma

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Abstract 8553

Background:

- Leukemia inhibitory factor (LIF) and its receptor LIFR are part of the interleukin-6 (IL-6) family with oncogenic potential via key downstream pathways including JAK/STAT3, MAPK/ERK, PI3K/AKT, and Hippo/YAP
- Elevated LIF expression in tumors, including NSCLC, has been associated with aggressive tumor biology, therapy resistance, and adverse outcomes. The contrast has been seen with LIFR expression
- The clinical significance of LIF and LIFR expression in lung adenocarcinoma (LUAD), particularly in *EGFR*-mutant disease, remains undefined
- We analyzed the LUAD outcomes, immune composition and transcriptional signaling states based on LIF and LIFR expression, including *EGFR*-mutant LUAD

Methods:

- 10,041 LUAD tumors were profiled at Caris Life Sciences (DNA: 592-gene panel/WES; RNA: whole transcriptome).
- Tumors were stratified by LIF and LIFR RNA expression quartiles (Q1 = lowest quartile; Q4 = highest quartile).
- QuantiSEQ was used to profile the tumor immune microenvironment (immune cell composition); MAPK activation, T-cell–inflamed, and IFN-γ signaling scores derived from transcriptomic data.
- Overall survival (OS) was estimated from insurance claims data using Cox proportional hazards models to calculate hazard ratios and log-rank tests to determine p-values.
- Statistical significance for the TME and signatures were calculated via chi-square and Mann–Whitney U tests.

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LIF and LIFR expression characterize biologically and clinically distinct prognostic subgroups in LUAD, with superior outcomes observed in low LIF and high LIFR expressors. Differences in immune cell composition suggest qualitative variation in immune activation between LIF- and LIFR-driven tumors. These patterns are further supported by enrichment of *EGFR* mutations within favorable-prognosis groups and by additional survival stratification in EGFR-mutant LUAD treated with osimertinib, where low LIF expression identifies improved outcomes. Collectively, these findings support LIF and LIFR as prognostic and biologically informative biomarkers and identify the LIF–LIFR axis as a key stratifier of immune state and survival heterogeneity in LUAD, with potential relevance for therapeutic targeting and patient selection.

Figure 1

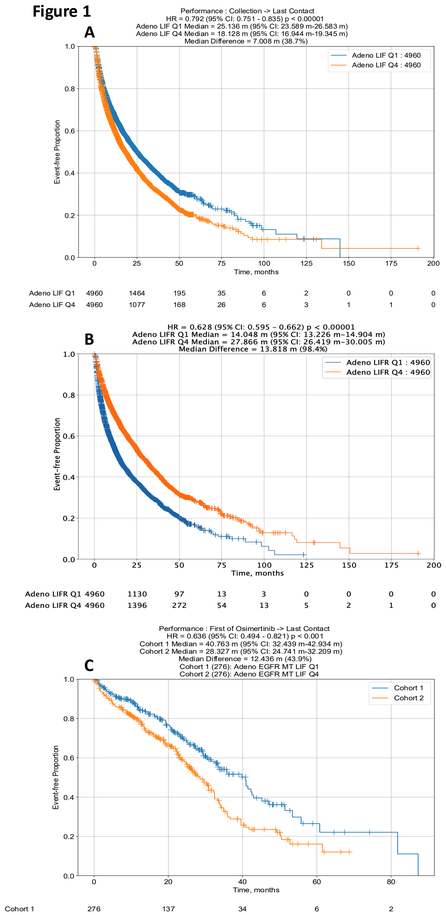

Figure 1. Kaplan–Meier OS by LIF/LIFR quartiles in LUAD. A) Low LIF Q1 was associated with longer OS vs Q4 (25.1 vs 18.1 months; HR 0.79, p < 0.001). B) High LIFR Q4 was associated with longer OS vs Q1 (27.9 vs 14.0 months; HR 1.59, p < 0.001). C) In *EGFR*-mutant tumors treated with osimertinib, low LIF Q1 was associated with improved OS (40.8 vs 28.3 months).

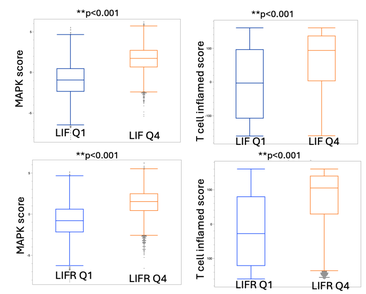

Figure 2
MAPK and T cell inflamed score for LIF/LIFR Q1 vs Q4

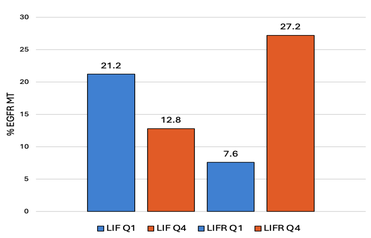

Figure 3
EGFR mt prevalence in LIF/LIFR quartiles.

Results:

- Low LIF expression (Q1) was associated with longer OS compared to LIF Q4 (25.1 vs 18.1 months; HR 0.79, 95% CI: 0.75–0.84; p < 0.001)
- High LIFR expression (Q4) was associated with longer OS compared to LIFR Q1 (27.9 vs 14.0 months; HR 0.63, 95% CI: 0.59–0.67; p < 0.001).
- In *EGFR*-mutant LUAD treated with osimertinib, survival differences associated were accentuated, with significantly longer OS in LIF Q1 versus Q4 tumors (40.8 vs 28.3 months; HR 0.792, 95% CI: 0.751–0.835; p < 0.00001).
- The TME composition demonstrated distinct signatures based on LIF and LIFR expression. LIF Q4 tumors demonstrated reduced CD8+ T cells and higher Tregs compared to Q1. LIFR Q4 were enriched for dendritic cells, NK cells, and M2 macrophages compared to LIFR Q1.

Figure 4

Tumor Microenvironment Cell Fraction Distribution by LIF and LIFR Quartiles in LUAD

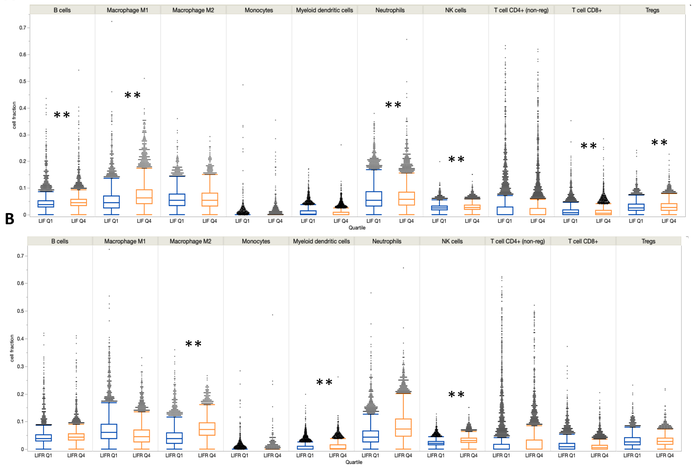

Figure 4 A) The distribution of the TME cell fractions for LIF Q1 vs Q4. LIF-high (Q4) tumors showed reduced CD8⁺ T cells and higher fractions of NK cells, M1 macrophages, neutrophils, Tregs and B cells compared with LIF-low (Q1) tumors. B) The distribution of the TME cell fractions for LIFR Q1 vs Q4. Tumors with high LIFR expression (Q4) display higher fractions of dendritic cells, NK cells and M2 macrophages compared with those in the lowest quartile (Q1). **Legend:** **: p < 0.001