[BIOINFO 2024]

Single-cell multi-omics analysis reveals factors in tumor microenvironment underlying poor immunotherapy responses in ALK-positive lung cancer

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Anaplastic lymphoma kinase (ALK) rearrangement is a major oncogenic driver in non-small cell lung cancer (NSCLC). While ALK tyrosine kinase inhibitors have shown promising therapeutic effects, overcoming resistance with immunotherapy becomes necessary when resistance develops. However, various clinical trials have revealed that their efficacies remain limited. To investigate the tumor microenvironment (TME) factors contributing to poor immune checkpoint blockade responses in ALK-positive patients, we performed single-cell RNA and ATAC sequencing on lung adenocarcinoma (LUAD) tumors with and without ALK rearrangements. Integrative analysis with additional public LUAD cohorts revealed distinct immune landscapes in ALK-positive tumors, marked by enriched innate immunity and depleted adaptive immunity. ALK-positive malignant cells exhibit higher stemness and aggressive phenotype. Tumor-associated macrophages (TAMs) in these tumors predominantly maintain

pro-tumoral M2-like states, reinforcing immune suppression. B cells show reduced immune reactivity and impaired tertiary lymphoid structure formation, while $CD8^+$ T cells display bystander-like signatures and reduced tumor reactivity. Single-cell chromatin accessibility profiles combined with regulatory network analysis suggest that differences in transcription factor activities, rather than chromatin accessibility, may underlie T cell dysfunction. These findings provide insights into the immunosuppressive TME of ALK-positive LUAD, potentially explaining the failure of recent immunotherapy trials and highlighting targets for improving efficacy.