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BASAL LINE TUMOR OF ACT RESPONDERS EXHIBIT TUMOR-INNOCENT IMMUNOGENICITY AND GENOMIC INSTABILITY, T CELL EXHAUSTION AND ACTIVATED MACROPHAGES

- Single cell transcriptomic atlas of baseline tumors from melanoma patients subjected to TIL-ACT (A).
- Malignant cells of responders are characterized by higher interferon γ (IFN-γ) indicative of genomic instability (B) and are enriched in inflammation-related pathways (C).
- CD8 T cell subclustering revealed 10 different CD8 subtypes (D) among which precursor-coupled and exhausted CD8 T cells were found more abundant in the CD45+ compartment of responders (E).

MELANO MA RESPONSING TO TIL-ACT ARE CHARACTERIZED BY A RICH CELLULAR CROSS-TALK WHILE NON-RESPONDERS LACK CELL-TO-CELL COMMUNICATION

- Interactor analysis performed in single-cell data indicated that responders exhibit a very dense cellular crosstalk while non-responders almost completely lack cell-to-cell communication (A).
- Naturally occurring physical doublets between T-lymphoid cells or T:B cells were detected in single-cell data and were higher in the TME of responders (B).
- An in situ interaction between myeloid (CD11c) and CD8 T cells were significantly higher in responding baseline melanomas by measuring distance between cell types in immunofluorescence microscopy images (C-D).
- Single-cell RNAseq data profiling day-30 post ACT biopsies were used to study the evolution of the TME from baseline to day-30 post ACT (D).
- Cell type interactions analyses revealed a prominent connectivity and cellular interaction network between myeloid and CD8 T cells in its after ACT (E).

CONCLUSIONS AND PERSPECTIVES

- TIL and TME in site-derived biomarkers could improve patient selection and guide the next generation of ACT clinical trials.

REFERENCES


CELULAR CROSS-TALK IN TUMOR MICROENVIRONMENT PREDICTS RESPONSE TO ADAPTIVE THERAPY IN MELANOMA PATIENTS

KEY QUESTIONS

Adoptive T cell therapy (ACT) using ex vivo expanded tumor infiltrating lymphocytes (TILs) can mediate durable responses in metastatic melanoma. However, 1) long-term clinical efficacy remains unsatisfactory and 2) no tissue biomarker predicting TIL-ACT activity in patients exists to date.

We comprehensively interrogated the malignant compartment and tumor-microenvironment (TME) of single-cell and bulk RNA sequencing on longitudinal samples from 13 melanoma patients treated with TIL-ACT in our clinical study (NCT03475134).

The goal of this study was to unravel malignant, TIL and TME biomarkers that predict success to TIL-ACT.

RESULTS

- ATILAT CLINICAL TRIAL DESIGN AND RESULTS
- Thirteen patients received TIL-ACT (A).
- Two patients achieved an ongoing and long-lasting complete response (CR), 4 achieved partial response (PR), 1 showed stable disease (SD) and 6 patients exhibited progressive disease (PD) (B).
- Multiplex immunofluorescence (mf) imaging of screening biopsies revealed that tumors of responders contained significantly higher albeit variable densities of total intra-epithelial CD8+ and CD8+PD-1+ TILs compared to non-responders (C).
- Myeloid cell subclustering revealed 11 different myeloid subtypes (D).
- DGE analysis (E) and Gene enrichment analysis (F) of macrophages from B versus NR revealed that macrophages of responders overexpressed interferon, complement and antigen presentation-related genes and pathway.