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INTRODUCTION

Over 70% of acquired resistance to chemoimmunotherapy in NSCLC occurs exclusively in lymph nodes (LNs). The mechanisms behind LN-specific resistance remain unclear. To identify immune cell subsets and chemokine axes driving LN resistance and to develop targeted therapies.

METHODS

Human samples: 10 NSCLC patients (5 resistant, 5 sensitive) post-chemoimmunotherapy.

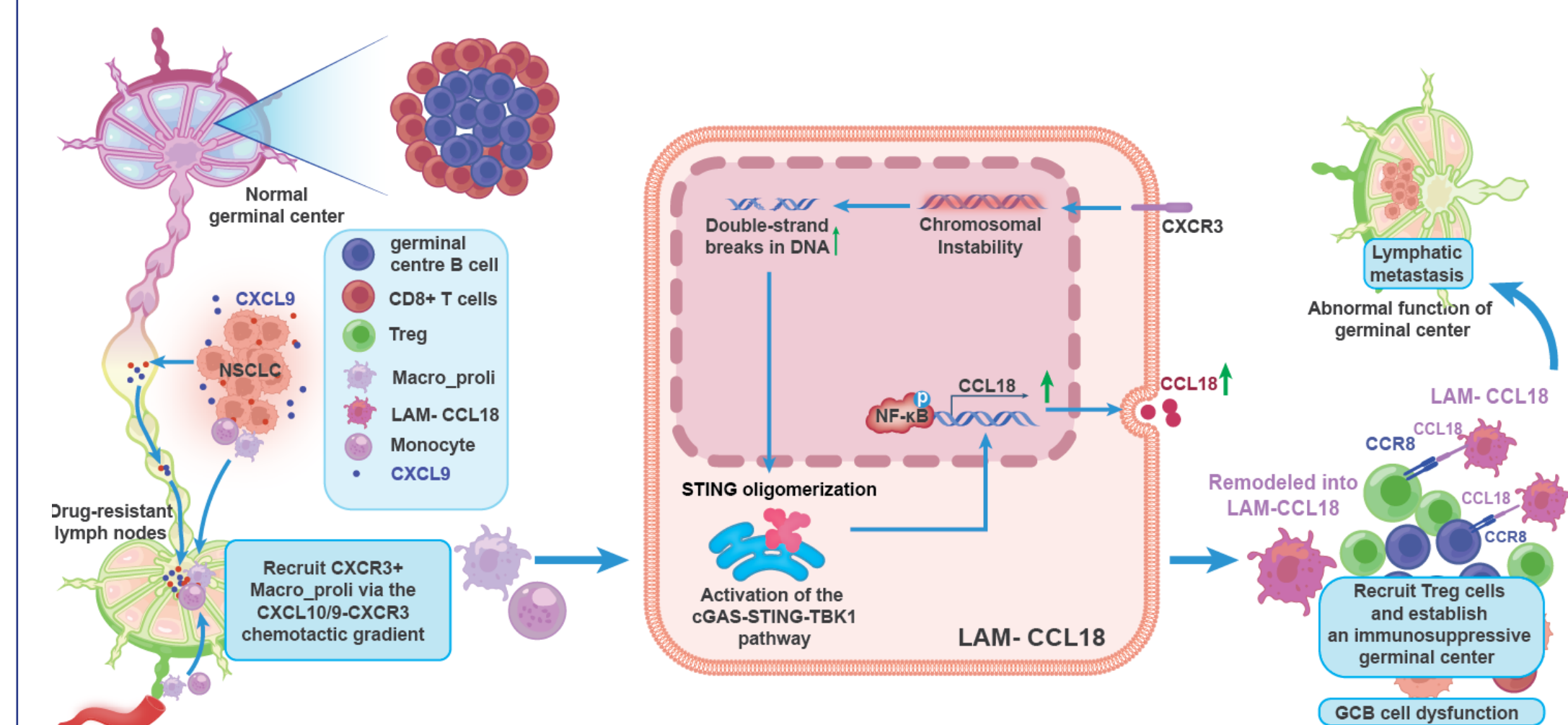
Single-cell RNA-seq + spatial transcriptomics on primary tumors and LNs.

OPCM mouse model (ICB-resistant) for in vivo validation.

Design

•LAM-CCL18⁺ macrophages and dysfunctional GCBs form an “immunological tolerant niche” within germinal centers of resistant lymph nodes

•CXCR3 signaling drives Maco_prolif-to-LAM-CCL18⁺ differentiation via CIN-STING-NF-κB-CCL18 activation and CCR8 engagement on GCBs



DISCUSSION AND CONCLUSION

Actionable Take Away Message

LAM-CCL18⁺ macrophages and dysfunctional GCBs form an “immunological tolerant niche” within germinal centers of resistant lymph nodes. CXCR3 signaling drives Maco_prolif-to-LAM-CCL18⁺ differentiation via CIN-STING-NF-κB-CCL18 activation and CCR8 engagement on GCBs.

Future Direction for Research

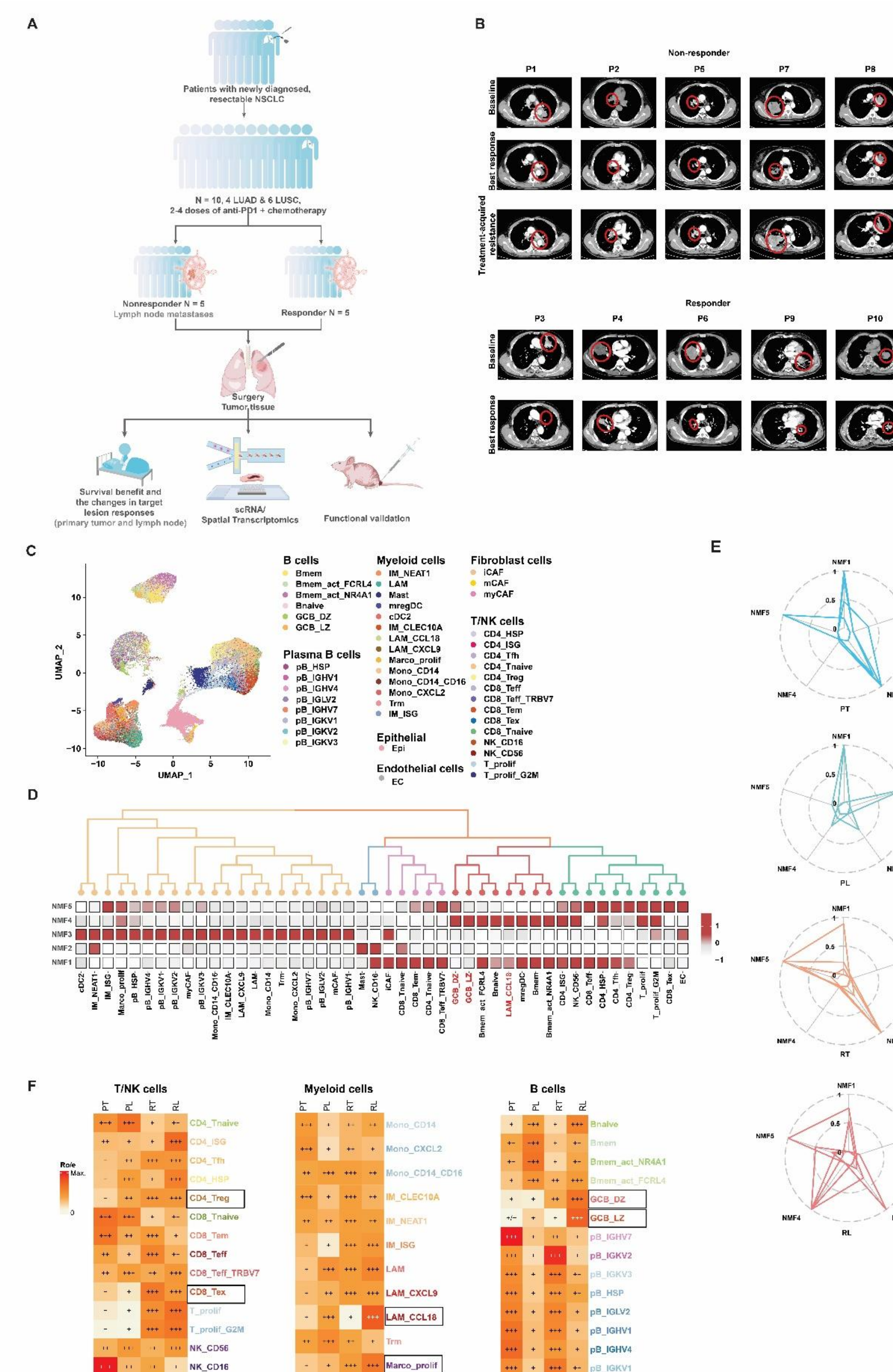
Therapeutic targeting of the CXCR3-CIN-STING-CCL18-CCR8 axis with CXCR3⁺TREM2⁺ CAR T cells reverses immune suppression and overcomes resistance.

ACKNOWLEDGEMENTS

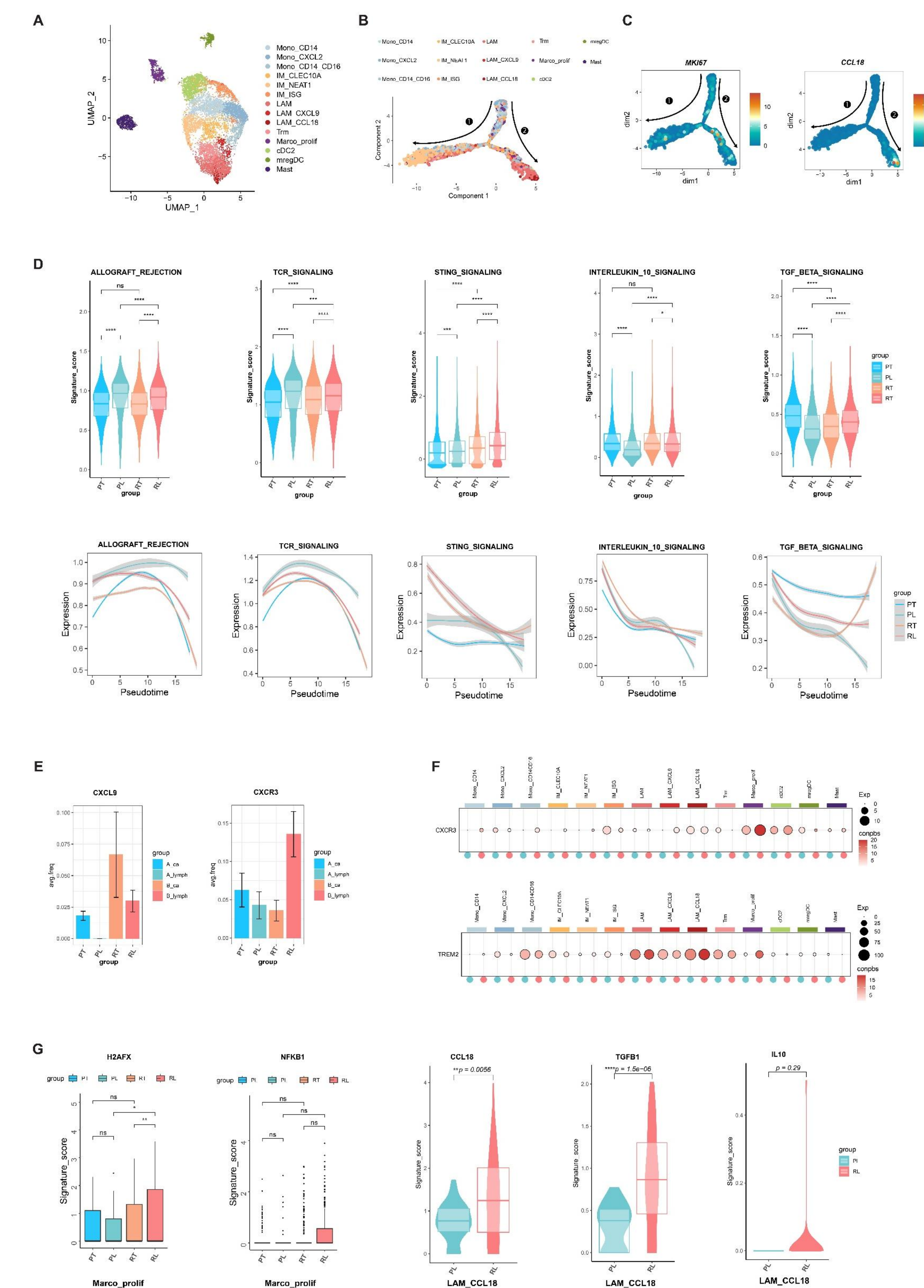
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RESULTS

1. A Unique Macrophage Subset (LAM-CCL18⁺) Accumulates in Resistant LNs



2. CXCR3⁺ Macrophage Precursors Differentiate into LAM-CCL18⁺ in Resistant LNs and CXCL9-CXCR3 Axis Mediates Migration to Resistant LNs



3. CXCR3 Signaling Induces Genomic Instability and CCL18-CCR8 interaction strength between LAM-CCL18⁺ macrophages and GCBs

