



P2.254: Incomplete Cryoablation Promotes Lung Adenocarcinoma Recurrence via CREB1-Mediated CCL20 Secretion and Macrophage-Driven T Cell Exhaustion

Yuenian Xing^{1,2}, Chuanyong Mu^{1,2}, Zeyi Liu^{1,2}, Jianan Huang^{1,2}

Zeyi Liu^{1,2}, Jianan Huang^{1,2}

Correspondence: Zeyi Liu^{1,2}

¹Institute of Respiratory Diseases, Soochow University, ²Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Soochow University



IASLC 2026 World
Conference on Lung Cancer
SEPTEMBER 12 - 15, 2026
SEOUL, REPUBLIC OF KOREA

INTRODUCTION

Incomplete cryoablation (ICA) causes local recurrence in lung adenocarcinoma (LUAD) due to unresolved immunosuppression. Although CCL20 is implicated in recruiting myeloid cells and M2 macrophage polarization, whether ICA induces a specific transcriptional program in residual tumor cells to secrete CCL20 is unknown. We hypothesized that ICA triggers CREB1 nuclear translocation in residual LUAD cells, upregulating secreted CCL20 to drive M2 polarization and CD8⁺ T cell exhaustion via the CCR6 axis.

METHODS

We established ICA models using sub-lethal freezing in vitro and partial cryoablation of LUAD xenografts in vivo. RNA-seq identified transcriptional changes in residual tumors. Transcription factor binding sites on the CCL20 promoter were predicted using UCSC Genome Browser and JASPAR, and validated via subcellular fractionation, ChIP-qPCR. The functional role of secreted CCL20 was assessed using neutralizing antibodies and shRNA-mediated knockdown in tumor cells, followed by co-culture with THP1 macrophages to evaluate M2 polarization (CD206/Arg1). Consequential CD8⁺ T cell exhaustion (PD-1/TIM-3) was examined in triple co-cultures. In vivo rescue experiments, including intratumoral recombinant CCL20 injection in knockdown models and CCR6 antagonist administration in wild-type ICA mice, were performed to confirm axis specificity.

DISCUSSION AND CONCLUSION

- Incomplete cryoablation induces CREB1-driven CCL20 secretion in residual LUAD, promoting M2 polarization, CD8⁺ T cell exhaustion, and recurrence. Targeting the CREB1-CCL20 axis may prevent post-cryoablation relapse.
- Our findings provide a rationale for refining complete cryoablation criteria in clinical guidelines and designing post-procedural combination therapies, with planned clinical trials to validate these translational opportunities.

REFERENCES & ACKNOWLEDGEMENTS

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- Acknowledgement
- We sincerely thank Professor Chuanyong Mu, Zeyi Liu and Jian'an Huang for their invaluable advice on the study design.

RESULTS

- RNA-seq revealed that CCL20 is upregulated by 4.2-fold in residual LUAD tissues following ICA ($p < 0.001$, Fig A-E), with in vitro cold stress inducing a 4.0-fold increase ($p < 0.001$, Fig F-G).
- Following iCA, CREB1 undergoes nuclear translocation and directly binds to the CCL20 promoter to activate its transcription (Fig H-L).
- Co-culture assays and in vivo experiments in mice demonstrated that knockdown or neutralization of CCL20, as well as blockade of its downstream receptor CCR6, effectively suppressed ICA-induced tumor recurrence, accompanied by diminished infiltration of both M2 macrophages and exhausted CD8⁺ T cells (Fig L-O).

