

INTRODUCTION

Neoadjuvant chemoimmunotherapy (NCIT) has become a promising therapeutic strategy for LUAD. However, a significant proportion of patients fail to achieve a major pathologic response (MPR) due to primary or acquired resistance. Cancer-associated fibroblasts (CAFs), a central component of the tumour microenvironment, are increasingly recognized as a pivotal orchestrator of tumorigenesis, metastasis, and chemoresistance. This study aims to investigate the role of CAFs in neoadjuvant chemoimmunotherapy-resistant LUAD.

METHODS

- Single-cell sequencing analysis was used to map the intratumoral CAF landscape of 195,632 cells from an NCIT cohort of 60 samples (21 MPR vs. 39 non-MPR), revealing that iCAFs can impede the efficacy of NCIT.
- Following IP and LC-MS/MS screening to elucidate the downstream mechanisms within iCAFs, we investigated the metabolic crosstalk by tracking acetate transfer and utilized acetylation mass spectrometry to identify crucial acetylated targets.
- Confocal microscopy and western blot were applied to evaluate the autophagic phenotype in tumour cells.
- Several mice models were constructed to verify the above results in vivo.

RESULTS

Figure 1 AKR1C3^{high} iCAFs specifically enriched in the TME of non-MPR patients

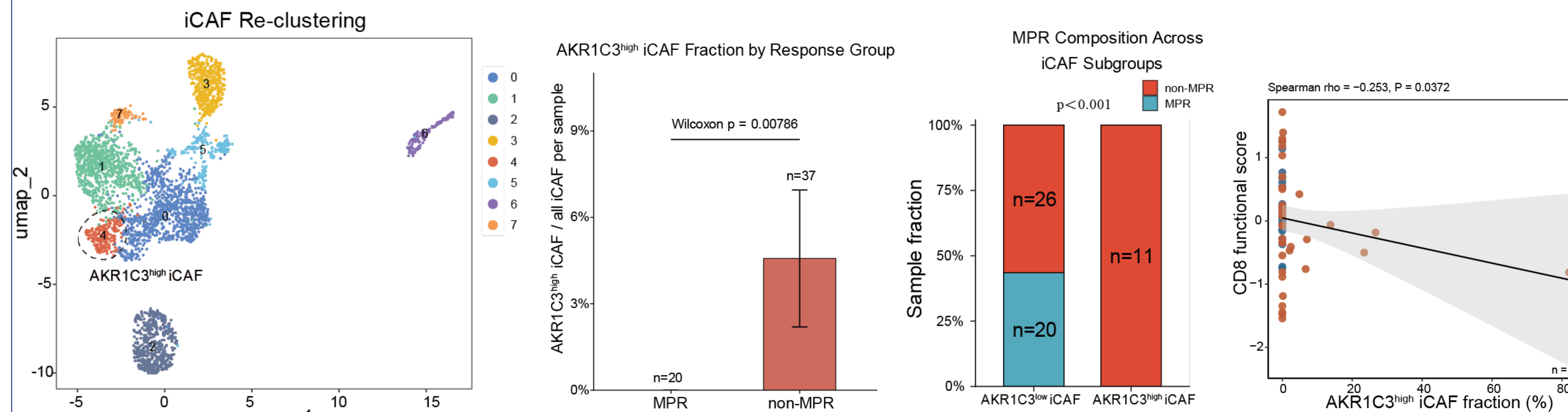


Figure 2 AKR1C3 upregulated ACLY through OTUB1-mediated deubiquitination in iCAFs

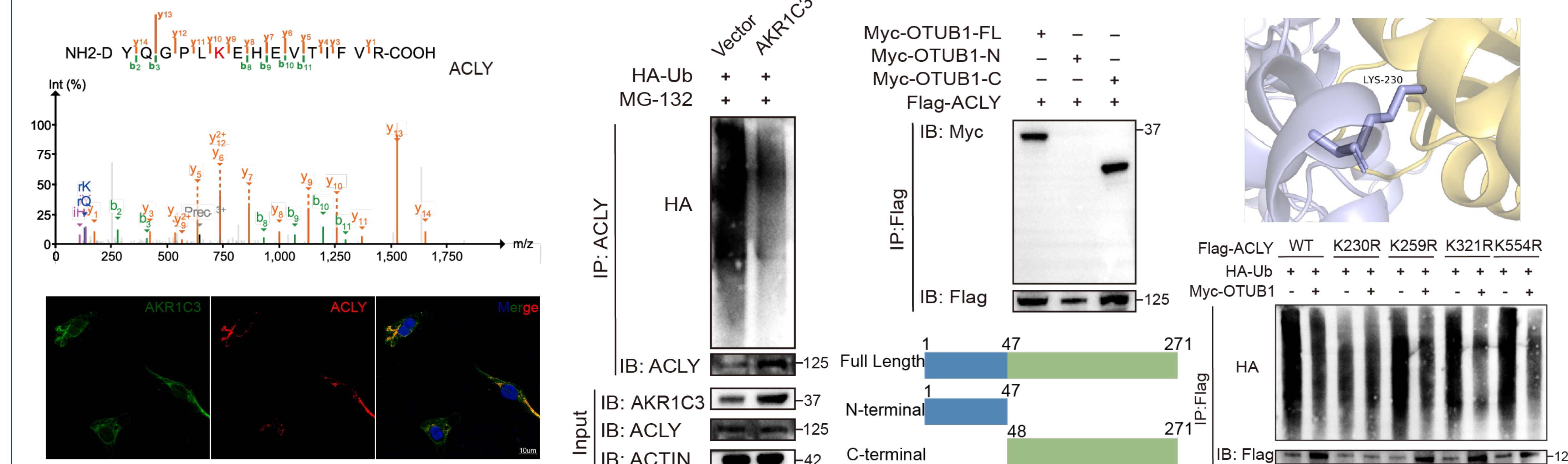


Figure 3 Acetate-derived acetyl-CoA promotes PACER acetylation to induce tumoral autophagy

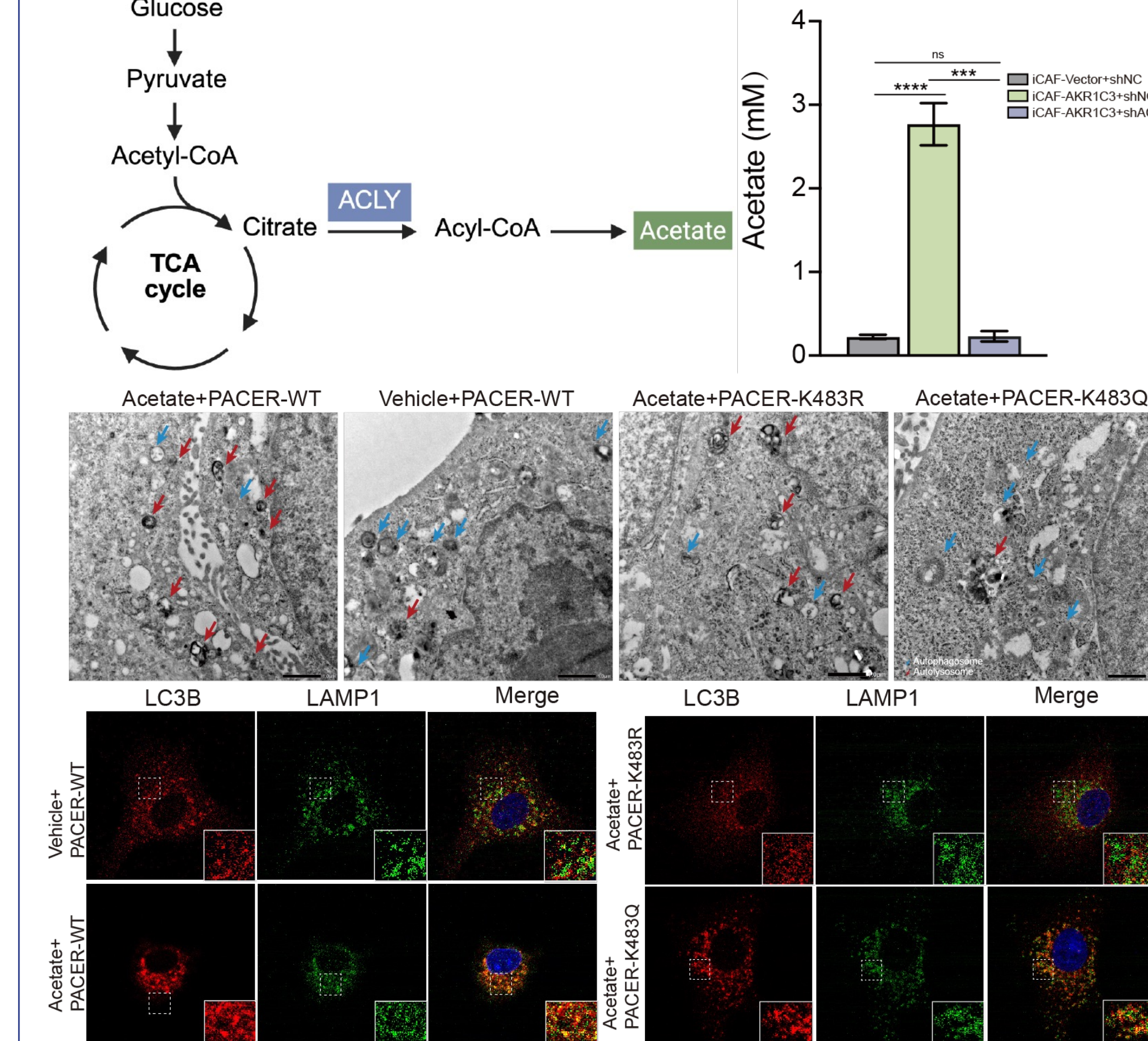
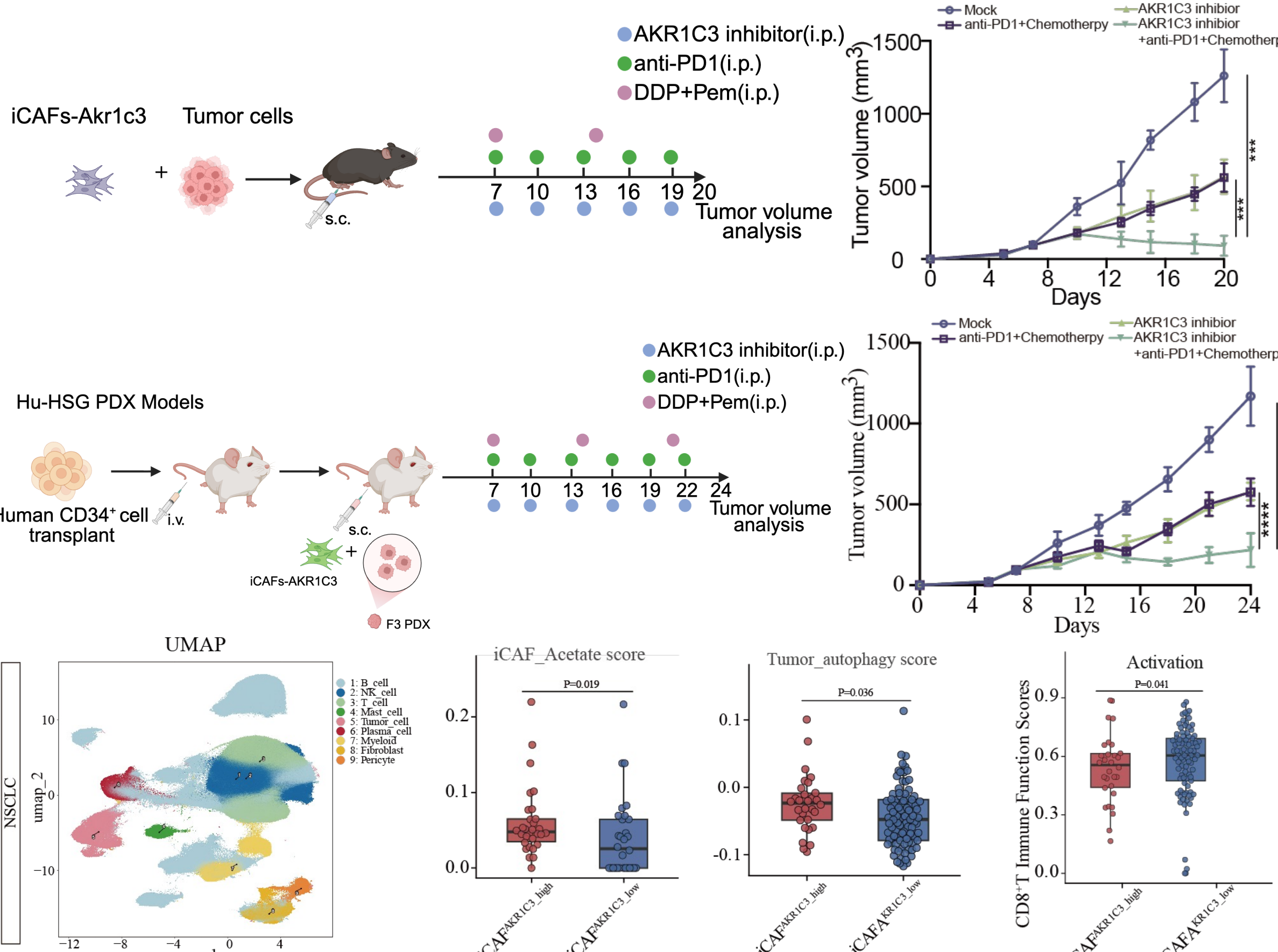


Figure 4 Targeting iCAFs with AKR1C3 inhibitor enhances chemoimmunotherapy efficacy



DISCUSSION AND CONCLUSION

We reported that iCAFs are associated with NCIT non-MPR in LUAD patients. Mechanistically, AKR1C3 is highly expressed in iCAFs of non-MPR patients and interacts with the deubiquitinase OTUB1 to stabilize ACLY. ACLY, functioning as a key enzyme in acetate metabolism, thereby dramatically enhancing the synthesis and secretion of acetate into the TME. Exogenous acetate secreted by iCAFs is uptake by tumours, where it serves to directly facilitate the post-translational acetylation of PACER. We further identify PACER acetylation enhancing cytoprotective autophagic flux to protect tumour cells from NCIT-induced apoptosis.

In summary, we reveal the role of AKR1C3^{high}iCAFs in compromising NCIT efficacy and propose applications for AKR1C3 inhibitors to improve the anti-tumour efficacy of NCIT in LUAD.

ACKNOWLEDGEMENTS

This study was supported by National Science Foundation of China (82472724, 82372709) & National Science and Technology Major Project (2023ZD0501904) & Yishan Research Project of Jiangsu Cancer Hospital (YSZD202408) & Jiangsu Province Capability Improvement Project through Science, Technology and Education, Jiangsu Provincial Medical Innovation Center (CXZX202224-01)