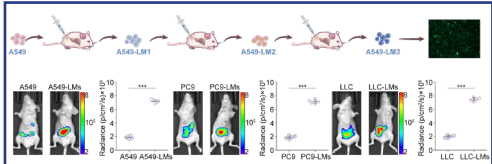


INTRODUCTION

(1) Liver metastasis is an aggressive manifestation of lung adenocarcinoma (LUAD) and is associated with poor survival. The hypoxic and metabolically distinct hepatic microenvironment promotes oxidative stress and cellular senescence, creating a barrier to tumour colonization. However, the mechanisms by which liver-colonizing LUAD cells adapt to this environment remain poorly understood. Lactate-driven histone lactylation links metabolic reprogramming to transcriptional regulation, but its role in hepatic adaptation is unclear.

(2) Here, we investigated whether MOF-mediated H4K12 lactylation enables LUAD cells to resist hypoxia-induced senescence through ATF4-BNIP3-dependent protective mitophagy. We further examined its regulation by aHSC-derived TGF- β -STAT3 signalling and its potential as a target for enhancing anti-angiogenic therapy.

METHODS



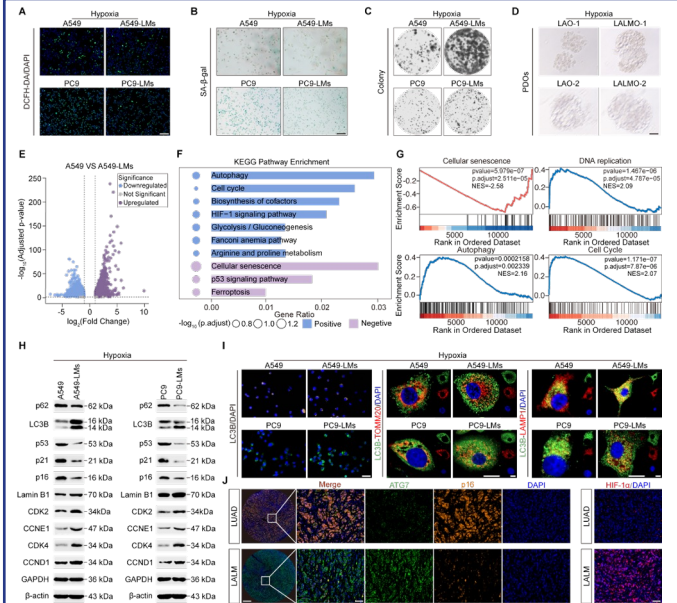
Spleen injection liver metastasis model: Luciferase-labelled, puromycin-resistant A549, PC9, and LLC cells were injected intrasplenically into nude mice. Tumour cells recovered from hepatic lesions were dissociated, selected with puromycin, expanded in vitro and re injected for successive rounds of in vivo selection. This process generated the liver-selected A549-LM, PC9-LM, and LLC-LM sublines with enhanced hepatic colonization capacity.

RESULTS

Liver metastatic cells initiate protective mitophagy to resist cellular senescence induced by the hepatic hypoxic barrier

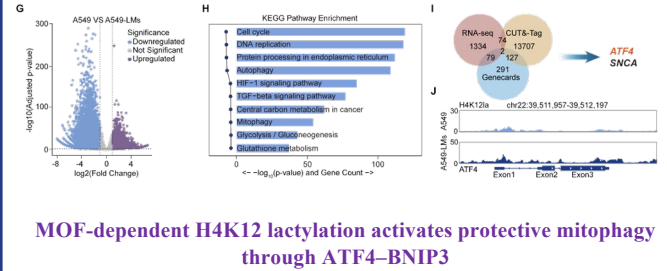
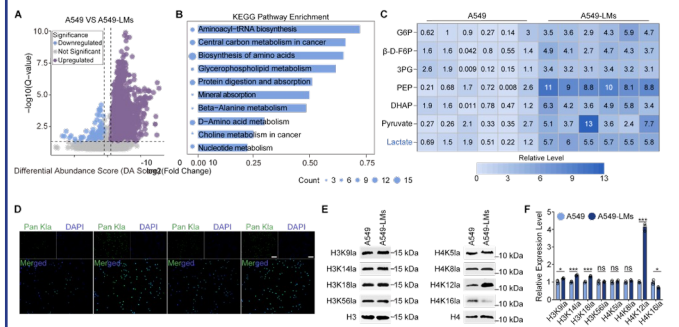
Section 1: Compared with parental LUAD cells, liver-selected sublines exhibited enhanced mitophagic flux, reduced ROS accumulation and senescence, and sustained proliferation under hypoxia. Autophagy inhibition increased senescence and suppressed hepatic tumour growth, supporting protective mitophagy as an adaptive mechanism during liver colonization.

RESULTS



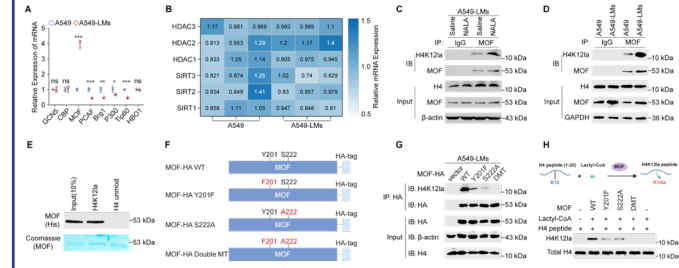
Lactate-Driven H4K12Lactylation Activates ATF4-BNIP3-Dependent Mitophagy

Section 2: Liver-selected LUAD cells exhibited enhanced glycolysis and lactate production, resulting in increased H4K12 lactylation. H4K12Lactylation at the ATF4 promoter increased ATF4 expression and BNIP3-dependent mitophagy, thereby limiting ROS accumulation and cellular senescence and sustaining adaptive proliferation under hypoxia.



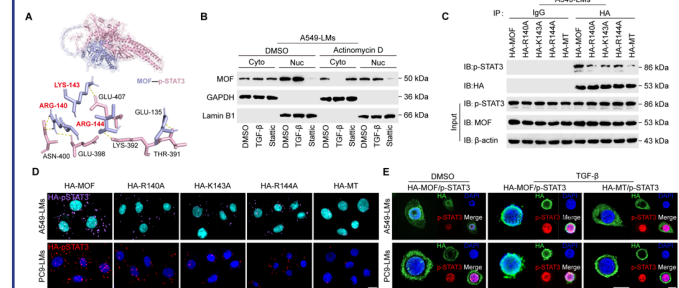
MOF-dependent H4K12 lactylation activates protective mitophagy through ATF4-BNIP3

Section 3: MOF-mediated H4K12 lactylation activated the ATF4-BNIP3 mitophagy programme, limiting ROS accumulation and senescence while promoting hepatic colonization. Mutation of MOF Y201 or S222 impaired H4K12Lactylation and its downstream effects, with the double mutant producing the strongest inhibition.



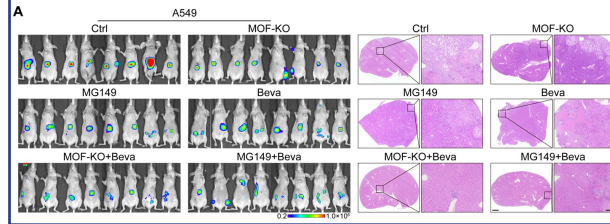
aHSC-derived TGF- β promotes STAT3-dependent MOF expression and nuclear localization

Section 4: Activated hepatic stellate cells secreted TGF- β , activating JAK2-STAT3 signalling in liver-selected LUAD cells. p-STAT3 increased MOF transcription through promoter binding and independently promoted its nuclear localization through interaction with the MOF NLS. Disrupting this stromal signalling axis suppressed hepatic tumour growth.



MOF targeting enhances the response to anti-angiogenic therapy

Section 5: Bevacizumab increased hypoxia-associated stress and activated protective mitophagy in residual tumour cells. Genetic or pharmacological MOF inhibition further increased ROS and senescence while suppressing proliferation. Combining MOF targeting with bevacizumab reduced hepatic tumour burden and prolonged survival, with similar effects observed across LUAD, colorectal and pancreatic cancer models.



DISCUSSION AND CONCLUSION

Our findings reveal a metabolic-epigenetic adaptation that enables liver-colonizing LUAD cells to withstand hypoxic stress. MOF-mediated H4K12 lactylation activates ATF4-BNIP3-dependent protective mitophagy, while aHSC-derived TGF- β -STAT3 signalling increases MOF expression and nuclear availability. Disrupting this axis promotes ROS accumulation and senescence, suppresses hepatic tumour outgrowth and improves the response to bevacizumab. The MOF-H4K12Lactylation pathway therefore represents a potential therapeutic vulnerability, warranting the development of more selective inhibitors and validation in physiologically representative models.

REFERENCES & ACKNOWLEDGEMENTS

References

Sun Z, Zhou M, Song N, et al. SKA3-mediated hypoxia tolerance and metabolic reprogramming promote liver metastasis in lung adenocarcinoma. Cell Death Dis. 2026;17:65. doi:10.1038/s41419-025-08270-z.

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Artificial Intelligence Use Disclosure

Generative AI was used solely to assist with language editing and text condensation. All scientific content, data interpretation and conclusions were independently reviewed and approved by the authors.