Intratumor microbiome confer chemoradiation resistance through NSUN2 lactylation mediated ferroptosis resistance

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Abstract

Chemoresistance remains a significant obstacle in breast cancer therapy, while the role of intratumoral microbiota in this process has yet to be fully elucidated. Here, we identify Lactobacillus iners (*L. iners*) as a critical microbial factor contributing to resistance against standard anthracycline–taxane–based neoadjuvant chemotherapy. Through integrated multi-omics analyses of longitudinal patient cohorts and 4T1 murine models, we demonstrate that *L. iners* promotes chemoresistance by reprogramming tumor GSH metabolism and inhibiting ferroptosis. Mechanistically, *L. iners*-derived L-lactate induces lysine lactylation of the RNA methyltransferase NSUN2, thereby enhancing m^5C modification and post-transcriptional stabilization of glutathione synthetase (GSS) mRNA. This subsequently upregulates GSS, augments GSH biosynthesis, and reinforces redox homeostasis, ultimately protecting tumor cells from ferroptotic cell death. Clinically, high intratumoral abundance of *L. iners* correlates with diminished treatment response and shorter recurrence-free survival. Notably, selective depletion of *L. iners* using a tumor-targeted antibiotic nanoplatform restores chemosensitivity, suppresses NSUN2 lactylation, and reactivates ferroptosis without disrupting systemic microbiota homeostasis. Collectively, these findings uncover a microbiota–NSUN2 lactylation–GSS regulatory axis underlying chemotherapy resistance and provide a translational strategy for microbial-targeted therapy in breast cancer.

Graphical Abstract

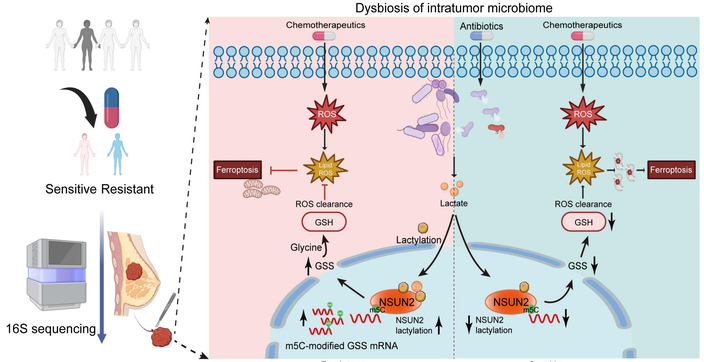


Figure 1

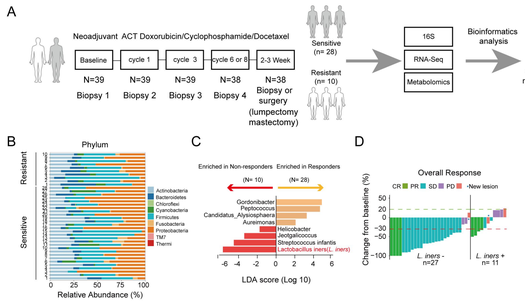


Figure 2

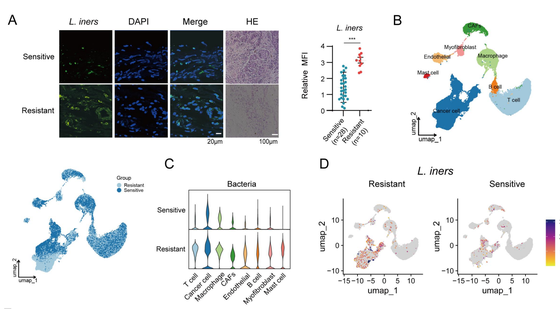


Figure 3

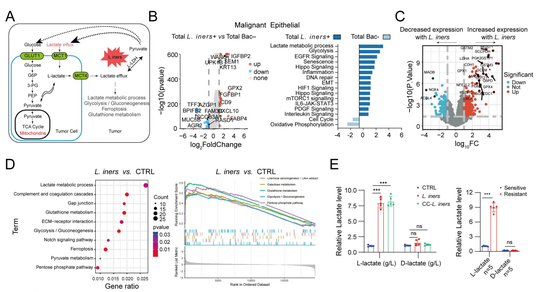


Figure 4

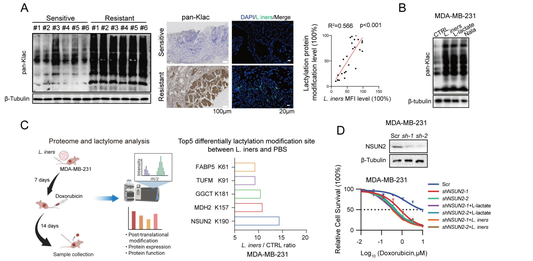


Figure 5

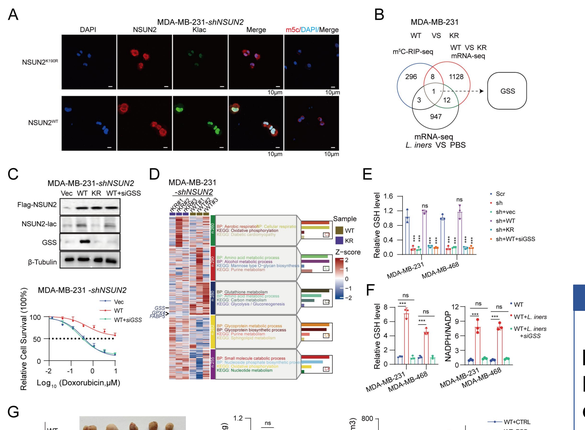


Figure 6

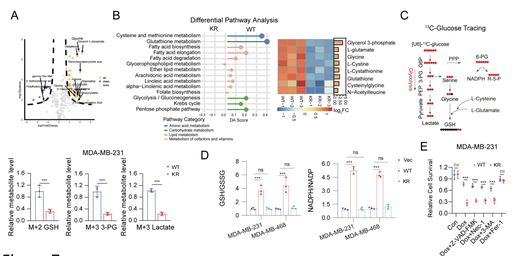
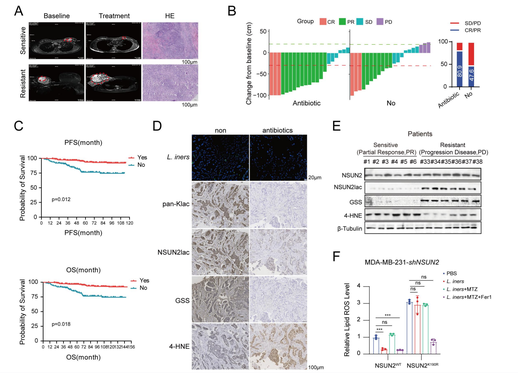


Figure 7



Discussion

In summary, we uncover a novel "*L. iners*→NSUN2 lactylation→ GSH metabolism → ferroptosis evasion" axis in breast cancer, integrating microbial metabolism with epitranscriptomic regulation to drive chemoresistance. Critically, our study demonstrates that tumor-targeted biomimetic nanoparticles can selectively remove intratumoral bacteria, disrupt ferroptosis resistance, and restore chemotherapy sensitivity, offering a promising translational approach to overcome refractory breast cancer.

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