

Commentary

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Histone H3K18 lactylation and cisplatin resistance in bladder cancer: insights from single-cell transcriptomic analysis

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Abstract

The study by Li et al., "Single-cell transcriptome analysis reveals the association between histone lactylation and cisplatin resistance in bladder cancer", investigated how histone lactylation contributes to cisplatin resistance in bladder cancer (BCa). Using high-resolution single-cell lineage tracing, the authors identified a distinct subpopulation of BCa cells with enhanced glycolytic metabolism that exhibited significant cisplatin resistance. Further analyses showed significant enrichment of histone H3 lysine 18 lactylation (H3K18la) at the promoter regions of the transcription factors YY1 and YBX1, which promoted their expression and facilitated the development of a drug-resistant phenotype. This study was the first to combine single-cell omics with lactylation modification mechanisms, providing new insights into strategies for overcoming cisplatin resistance in BCa. Nonetheless, potential limitations of the study should be carefully considered.

Keywords: Single-cell transcriptome technology, bladder cancer, histone lactylation, cisplatin resistance, transcription factors

THE APPLICATION OF SINGLE-CELL TRANSCRIPTOME TECHNOLOGY IN BCA RESEARCH

In their article^[1] published in *Drug Resistance Updates*, Li et al.^[1] used single-cell transcriptomic analysis to



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comprehensively characterize the relationship between post-translational modifications and cisplatin resistance in bladder cancer (BCa). In recent years, single-cell RNA sequencing (scRNA-seq) has emerged as a powerful tool for resolving tumor heterogeneity^[2]. In this study, the authors first identified tumor epithelial cell subpopulations linked to cisplatin resistance through bioinformatics analysis of BCa. They then further analyzed these subpopulations using the SCENIC and NetAct algorithms and identified a series of key transcription factors activated in the drug-resistant clusters, including YY1 and YBX1. By intersecting the genes regulated by YY1 and YBX1 with the marker genes of cisplatin-resistant epithelial subpopulations, they constructed a regulatory network encompassing DNA repair, apoptosis, and epithelial-mesenchymal transition (EMT). This analysis revealed that these transcription factors may drive cisplatin resistance in BCa by regulating multiple downstream drug resistance-related genes. Additionally, the authors inferred the differentiation trajectories of tumor cell subpopulations and analyzed the dynamic changes in key genes during tumor differentiation, providing a new perspective on the mechanisms of drug resistance.

HISTONE H3K18 LACTYLATION AND CISPLATIN RESISTANCE

Lactate, the final product of glycolysis, can form lactyl-CoA in the nucleus, thereby driving protein lactylation^[3]. Li *et al.*^[1] found that H3K18 lactylation (H3K18la) was significantly upregulated in resistant cells and demonstrated through ChIP-seq that H3K18la was enriched in the promoter regions of multiple genes. Notably, H3K18la was particularly enriched in the promoter regions of the transcription factors YY1 and YBX1, enhancing their transcriptional activation and expression, and ultimately driving the cisplatin-resistant phenotype. This discovery was the first to link histone lactylation with drug resistance in BCa, suggesting that lactate metabolism and epigenetic modifications jointly regulate the expression of drug-resistance-related genes. Both *in vitro* and *in vivo* studies by Li *et al.*^[1] further demonstrated that inhibiting glycolysis or disrupting lactylation markedly decreased H3K18la levels and restored tumor cell sensitivity to cisplatin, underscoring the functional significance of H3K18la in chemoresistance. Collectively, these findings suggest that H3K18la serves as a critical nexus between lactate metabolism and gene expression, thereby contributing to cisplatin resistance in BCa.

TRANSCRIPTION FACTORS YY1 AND YBX1 AS KEY REGULATORS OF CISPLATIN RESISTANCE

Li *et al.*^[1] identified YY1 and YBX1 as key transcriptional regulators of drug resistance. Both are multifunctional transcription factors implicated in drug resistance across various cancers^[4,5]. YY1 is a versatile protein that not only regulates gene transcription but also participates in protein modification. Its overexpression has been closely linked to chemotherapy tolerance in multiple tumor types^[6]. Consistent with this, Li *et al.*^[1] observed upregulated YY1 expression in resistant cells, which corresponded with H3K18la enrichment, suggesting that H3K18la may promote drug resistance by enhancing YY1 transcription.

YBX1, a member of the cold shock protein family, is recognized as a multifunctional driver of oncogenesis. Numerous studies have shown that YBX1 activates the transcription of genes related to proliferation, survival, and drug tolerance^[7,8]. In the study by Li *et al.*^[1], inhibition of glycolysis or disruption of histone lactylation not only diminished H3K18la levels but also impaired YBX1 activity, ultimately resensitizing BCa cells to cisplatin. These findings highlight YBX1 as a downstream effector that links metabolic reprogramming with epigenetic regulation, reinforcing its role in mediating drug resistance in BCa.

PROSPECTS FOR TRANSLATION AND RESEARCH LIMITATIONS

The study by Li *et al.*^[1] offers a novel strategy for overcoming cisplatin resistance in BCa through epigenetic-metabolic intervention. From a translational perspective, targeting lactate metabolism and

histone lactylation represents a promising therapeutic approach. For instance, combining glycolysis inhibitors with cisplatin may enhance chemotherapeutic efficacy, while H3K18la-specific inhibitors or modulators of lactylation-related enzymes could serve as potential drug candidates. In addition, the transcription factors YY1 and YBX1 themselves may be viable therapeutic targets in combination strategies. However, several limitations remain. First, the study relied primarily on publicly available single-cell transcriptomic datasets and in vitro cell line models, without extensive validation in large-scale clinical specimens. Second, although YY1 and YBX1 were identified as key transcription factors, their downstream regulatory networks remain largely unexplored, and the precise mechanisms underlying their activity require further elucidation. Finally, given the complexity of tumor metabolism and epigenetic regulation, targeting a single pathway may be insufficient to fully reverse drug resistance^[9,10]. Future studies should focus on assessing the clinical relevance of H3K18la in larger BCa patient cohorts and on developing more specific and safer lactylation-targeting agents to facilitate clinical translation.

CONCLUSION

The single-cell transcriptomic study by Li *et al.*^[1] innovatively revealed the key role of histone lactylation in cisplatin resistance in BCa and elucidated how lactate, a metabolic product, promotes drug resistance by regulating the expression of key transcription factors YY1 and YBX1. This discovery provides a new perspective on the mechanisms of tumor drug resistance and offers a theoretical basis for designing combined therapies that target metabolic-epigenetic pathways. Despite current limitations in experimental and clinical validation, this study provides important insights into BCa drug resistance and is expected to foster the development of more effective treatment regimens.

DECLARATIONS

Authors' contributions

Literature review (equal), writing - original draft: Yang Z

Literature review (equal), writing - review and editing: Chen S

Availability of data and materials

Not applicable.

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Conflicts of interest

Chen S is an Editorial Board member of *Journal of Translational Genetics and Genomics*. Chen S was not involved in any aspect of the editorial process for this manuscript, including reviewer selection, manuscript handling, or decision making. Yang Z declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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