DNMT mRNA stability and YB-1 cooperatively regulate ABCB1 to drive cisplatin chemoresistance in cholangiocarcinoma

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Abstract

Background and Aims:

Intrahepatic cholangiocarcinoma (iCCA) is a tumor type with a high lethality due to late diagnosis and profound resistance to conventional chemotherapy. To date the molecular mechanisms underlying multidrug resistance remain poorly defined. Here, we integrate single-cell transcriptomics, clinicopathological analysis, and functional genomics to elucidate the molecular basis of cisplatin resistance in iCCA.

Approach and Results:

Single-cell RNA sequencing of iCCA and adjacent liver tissues revealed pronounced expression of Y-box–binding protein 1 (YB-1) in aneuploid malignant cholangiocarcinoma cells, with YB-1 expression progressively increasing during malignant evolution and strongly associated with chemoresistance. Clinically, elevated YB-1 expression-particularly its nuclear localization-robustly predicts poor overall survival and chemotherapy failure in patients with iCCA. Mechanistically, we demonstrate that cisplatin induces phosphorylation-dependent nuclear translocation of YB-1, enabling direct transcriptional activation of the drug efflux transporter ABCB1. Importantly, this process requires ABCB1 promoter demethylation, which is driven by cisplatin-induced, m^6A-dependent destabilization of DNMT1 and DNMT3B mRNAs. This destabilization occurs through disruption of the YB-1-IGF2BP1/3-DNMT mRNA stabilizing complex and subsequent recruitment of DNMT transcripts to YTHDF2-mediated processing bodies for degradation.

Conclusions:

Our findings uncover a previously unrecognized YB-1-m^6A-DNMT regulatory axis that drives chemotherapeutic resistance in iCCA, highlighting YB-1 as both a prognostic biomarker and a promising therapeutic target.