Identification of PRMT5 as a therapeutic target in cholangiocarcinoma

Info

PUBLISHED DATE
2024-09-11

JOURNAL
Gut

LINK
https://doi.org/10.1136/gutjnl-2024-332998

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Abstract

Background: Cholangiocarcinoma (CCA) is a very difficult-to-treat cancer. Chemotherapies are little effective and response to immune checkpoint inhibitors is limited. Therefore, new therapeutic strategies need to be identified.

Objective: We characterised the enzyme protein arginine-methyltransferase 5 (PRMT5) as a novel therapeutic target in CCA.

Design: We evaluated the expression of PRMT5, its functional partner MEP50 and methylthioadenosine phosphorylase (MTAP)—an enzyme that modulates the sensitivity of PRMT5 to pharmacological inhibitors—in human CCA tissues. PRMT5-targeting drugs, currently tested in clinical trials for other malignancies, were assessed in human CCA cell lines and organoids, as well as in two immunocompetent CCA mouse models. Transcriptomic, proteomic and functional analyses were performed to explore the underlying antitumoural mechanisms.

Results: PRMT5 and MEP50 proteins were correlatively overexpressed in most CCA tissues. MTAP was absent in 25% of intrahepatic CCA. PRMT5-targeting drugs markedly inhibited CCA cell proliferation, synergising with cisplatin and gemcitabine and hindered the growth of cholangiocarcinoma organoids. PRMT5 inhibition blunted the expression of oncogenic genes involved in chromatin remodelling and DNA repair, consistently inducing the formation of RNA loops and promoting DNA damage. Treatment with

PRMT5-targeting drugs significantly restrained the growth of experimental CCA without adverse effects and concomitantly induced the recruitment of CD4 and CD8 T cells to shrinking tumourous lesions.

Conclusion: PRMT5 and MEP50 are frequently upregulated in human CCA, and PRMT5-targeting drugs have significant antitumoural efficacy in clinically relevant CCA models. Our findings support the evaluation of PRMT5 inhibitors in clinical trials, including their combination with cytotoxic and immune therapies.