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**Targeting MMP9 in CTNNB1 mutant hepatocellular carcinoma**

Cai N, Cheng K, Ma Y, et al. [Targeting MMP9 in CTNNB1 mutant hepatocellular carcinoma restores CD8+ T cell-mediated antitumour immunity and improves anti-PD-1 efficacy.](https://gut.bmj.com/content/73/6/985) Gut 2024;73: 985-999. doi: 10.1136/gutjnl-2023-331342.

Compared to other types of tumours, hepatocellular carcinoma (HCC) has lower response (15%) to immunotherapy. A third of HCCs have mutations in CTNNB1 (Catenin beta-1). Gain of function (GOF) mutations in CTNNB1 are known to reduce T cell and dendritic cell recruitment through the Wnt/beta-catenin pathway, and thus reduce the efficacy of immunotherapy.

To further investigate this, the Cai et al., developed HCC mouse models with CTNNB1-GOF mutations. Flow cytometry showed reduced recruitment of dendritic cells, CD4 and CD8 T cells to the tumour. RNA and gene analysis identified MMP9 (matrix metalloproteinase-9) as the key up-regulated gene, whose expression was associated with shorter survival. This observation was consistent across different available gene datasets from real-life HCC patients.

Knockdown of MMP9 in HCC mouse models significantly reduced tumour burden, with restoration of a suppressive immune microenvironment. In MM9-knockdown mice, treatment with an antibody that neutralised CD8 (but not CD4) T cells led to increased tumour burden. This suggests MMP9 acts specifically by inhibiting CD8 T cells (with subsequent analysis confirming it is the CXCR3+ (C-X-C Motif Chemokine Receptor 3) subset that is affected).

Treatment with anti-PD-1 (Programmed cell death protein 1) had higher efficacy in MMP9 knockout HCC models compared to MMP9 wild-type models. Anti-PD-1 was also more effective when combined with a monoclonal antibody against MMP9. Thus, Cai et al., have identified a valuable new drug target to improve the efficacy of immunotherapy in the management of HCC. Further studies are required before translation to clinical trials.