Metabolic and Inflammatory Outcomes of DPP9 Depletion in Liver

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Introduction

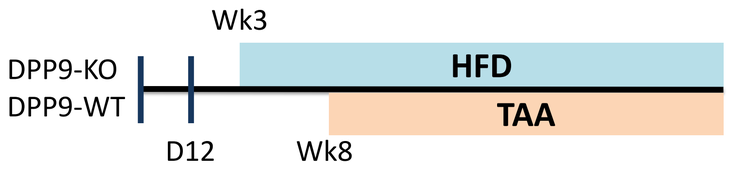
- Proteases perform irreversible, post-translational modifications that regulate many processes.
- The dipeptidyl peptidase 4 (DPP4) gene family is involved in cancer and contains four enzymes; DPP4, DPP8, DPP9 and fibroblast activation protein alpha.
- DPP9 is an emerging cancer associated multifunctional protease that is upregulated in liver tumours.
- DPP9 has roles in cancer via suppression of NLRP1 inflammasome activation and DNA double strand break repair.

Aim

To investigate DPP9 depletion from hepatocytes in a model of primary liver cancer.

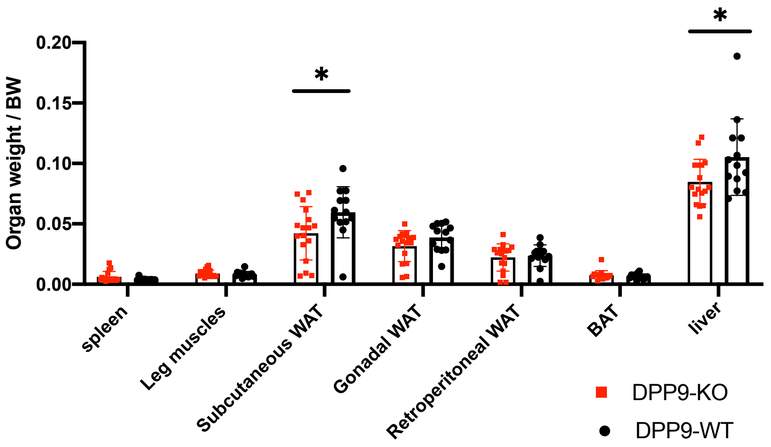
Methods

- Global DPP9 depletion leads to neonatal death, thus, Cre recombinase was used to deplete DPP9 in adult mice.
- Hepatocyte-specific (Albumin (Alb) promotor) DPP9 depleted male mice and control mice were treated with the carcinogen diethylnitrosamine (DEN), then the hepatotoxin thioacetamide (TAA) and an atherogenic High Fat Diet (HFD) until 28 weeks of age.
- Liver histopathology assessment included tumour burden, inflammation and steatosis.
- Inflammasome, immunological, autophagy and DNA repair pathways were investigated.

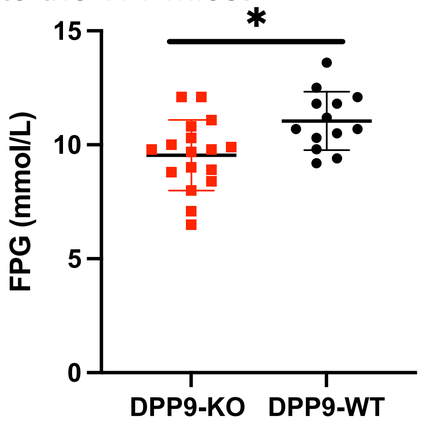


Results

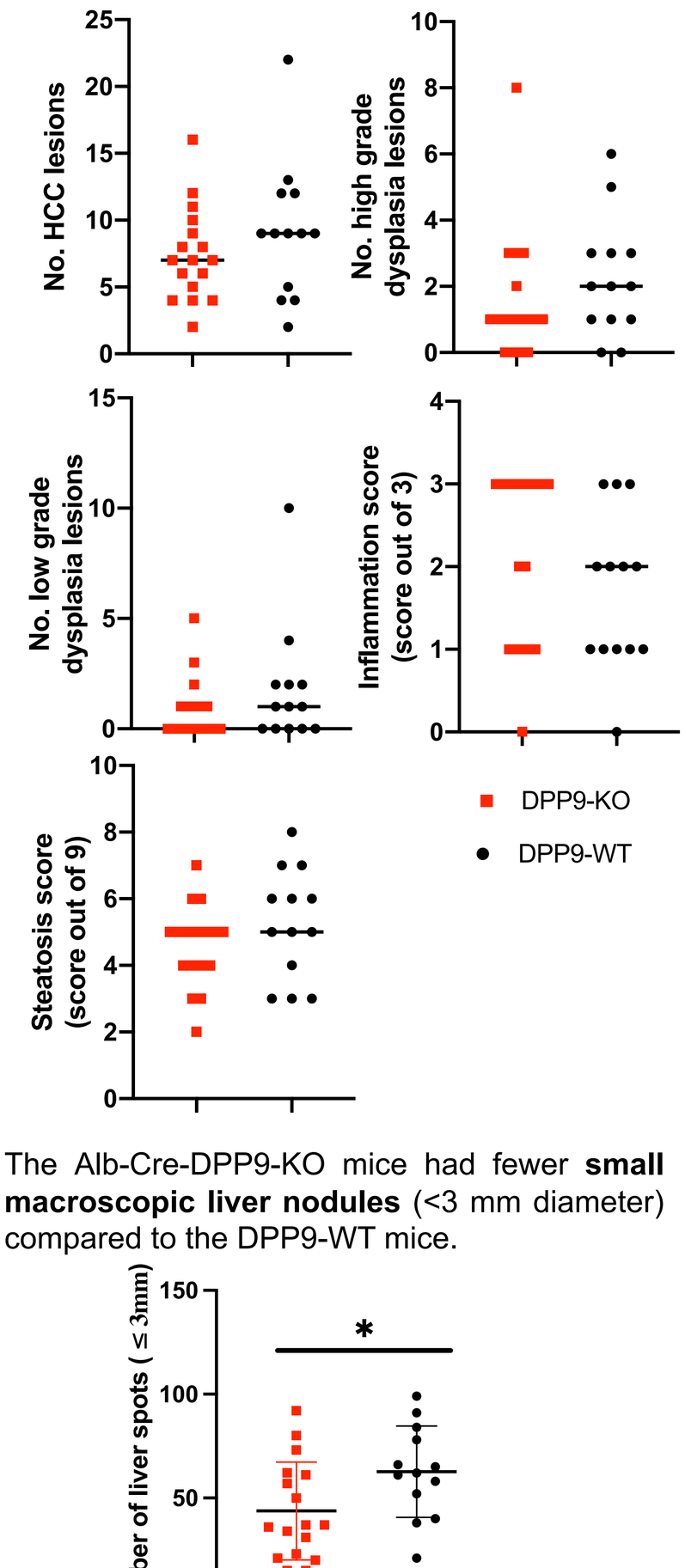
Liver mass and **subcutaneous adipose tissue mass in** Alb-Cre-DPP9-KO mice were significantly less than controls.



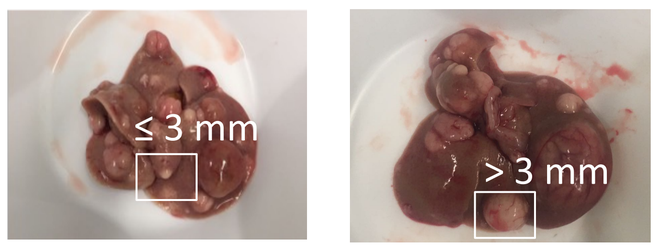
The **fasting plasma glucose (FPG)** was lower in the Alb-Cre-DPP9-KO mice compared to the WT mice.



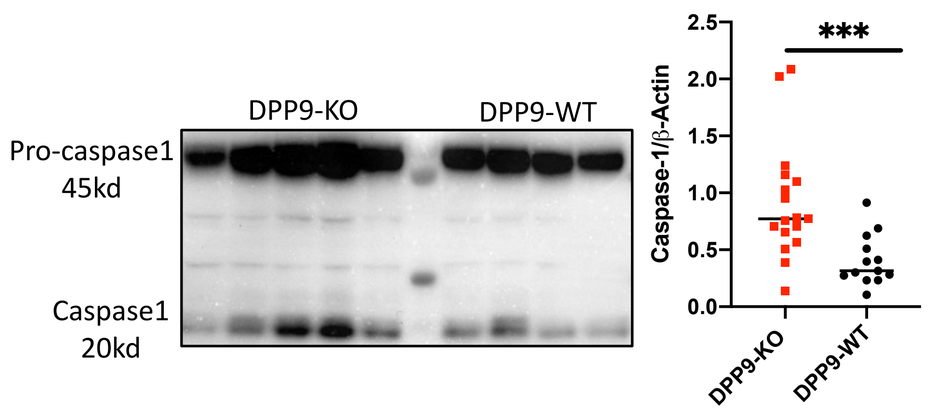
There were no differences between the two genotypes in **inflammation**, **steatosis**, total number of **macroscopic liver nodules**, or in the **total tumour burden** by volume.

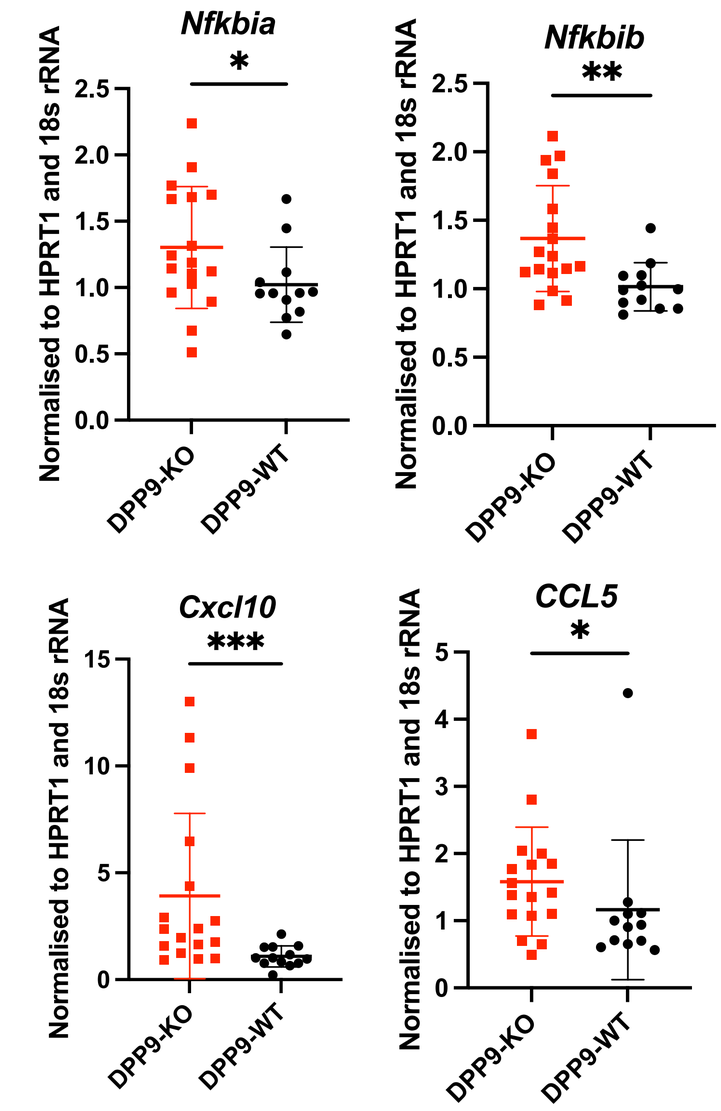


The Alb-Cre-DPP9-KO mice had fewer **small macroscopic liver nodules** (<3 mm diameter) compared to the DPP9-WT mice.

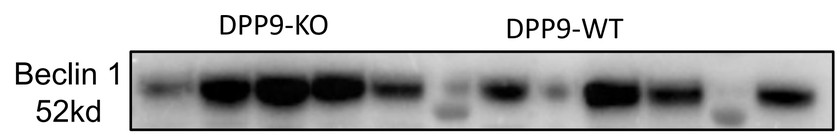


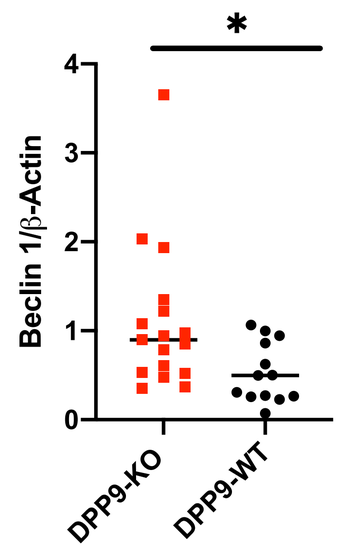
A function of DPP9 is suppression of NLRP1 inflammasome activation. Mice depleted of DPP9 had increased intrahepatic expression of active **caspase-1** protein and inflammation associated genes ***Nfkbia***, ***Nfkbib***, ***Cxcl10*** *and* ***Ccl5.***





The Alb-Cre-DPP9-KO mice showed increased protein levels of the **autophagy marker Beclin 1**. The data suggests that DPP9 depletion caused increased inflammation and autophagy.





Discussion

- NLRP1 has a role in preventing obesity, NAFLD and metabolic syndrome in mice via stimulating IL-18 production. DPP9 deficiency increased NLRP1 activation, possibly causing IL-18 release.
- Smaller liver mass was not associated with less steatosis, so a potential link with autophagy should be explored.

Conclusions

DPP9 depletion in hepatocytes influenced inflammation and metabolism, with little influence on liver cancer formation, in this model of liver cancer.