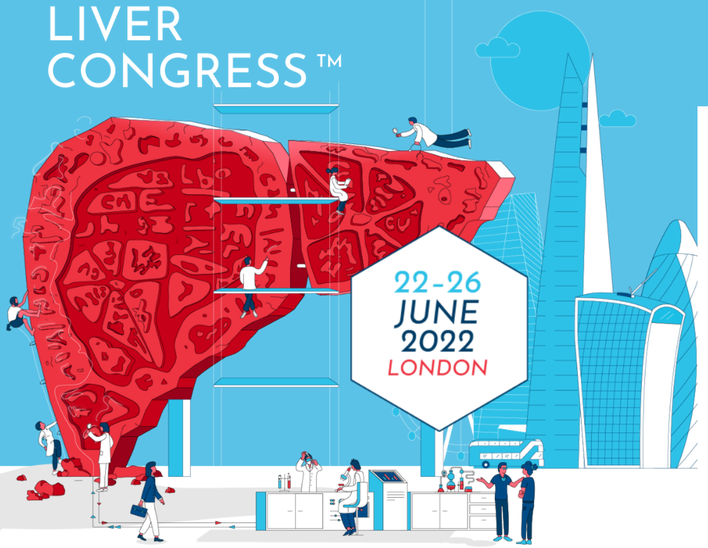

mTORC1 plays an important role in PiZ induced liver injury

The role of the mechanistic target of rapamycin (mTOR) in Alpha-1 Antitrypsin Deficiency

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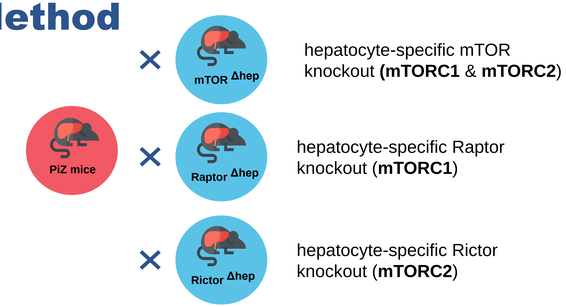
1 Introduction

- Alpha-1 Antitrypsin deficiency (AATD) is a hereditary disease with lung and liver manifestation
- Alpha1-antitrypsin (AAT) mutations lead to the retention of the otherwise secreted hepatocellular protein in the endoplasmic reticulum (ER)
- Liver disease arising due to the proteotoxic stress is the second leading cause of mortality in AATD

2 Aim

- Since liver disease in AATD is induced by chronic proteotoxic stress, proteostatic homeostasis is of particular relevance
- The mTOR pathway is an important regulator of protein synthesis and degradation and can be targeted by several FDA-approved drugs
- In order to better understand the underlying mechanisms of the disease, the role of the mechanistic target of rapamycin (mTOR) in the AATD mouse model (PiZ mouse) was investigated

3 Method



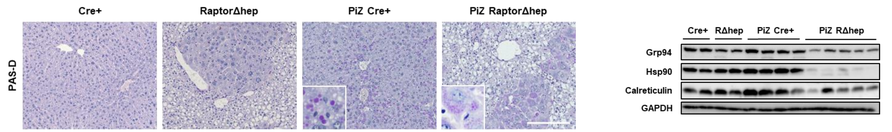
hepatocyte-specific mTOR knockout (**mTORC1** & **mTORC2**)

hepatocyte-specific Raptor knockout (**mTORC1**)

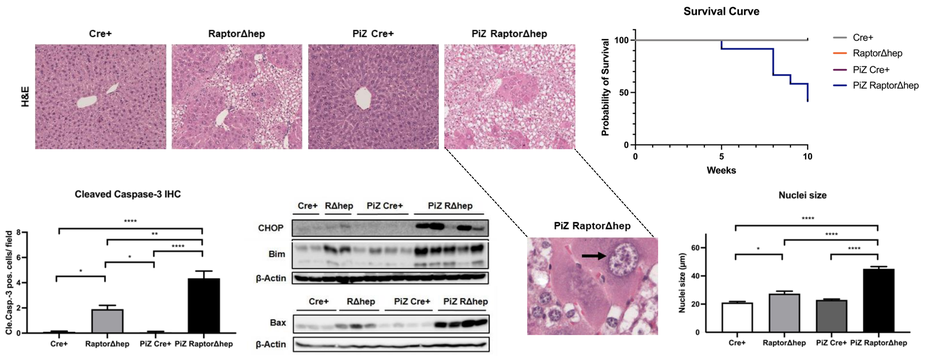
hepatocyte-specific Rictor knockout (**mTORC2**)

4 Results

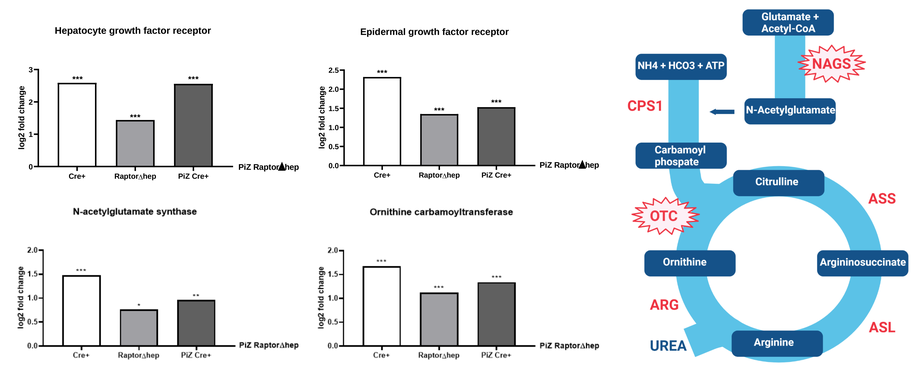
Reduced Z-AAT inclusion size, protein levels but decreased chaperone levels in PiZ mTORΔhep and PiZ RaptorΔhep but not PiZ RictorΔhep mice



Decreased survival, activation of pro-apoptotic signaling and liver regeneration defects after mTOR and Raptor knockout (mTORC1) in PiZ mice



Proteomics of liver tissue reveals a decrease in cMet and EGFR and a reduction of important urea cycle proteins



5 Conclusions

- mTOR dysregulation leads to cell death under proteotoxic stress conditions
- ablation of mTOR and Raptor but not Rictor leads to liver injury in the PiZ mouse model
- mTORC1 disruption in PiZ mice leads to shutdown of many programs vital to hepatocytes, including protein folding machinery (chaperones), cMet and EGFR signaling, urea cycle and liver regeneration

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