Evaluation of induced chronic liver disease in mice with protein S and Gas6 deficiency

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1 Abstract

Chronic liver disease (CLD) refers to a progressive destruction and regeneration of liver parenchyma leading to fibrosis and cirrhosis. In those patients, the coagulation system changes and tendencies to either hemorrhage or thrombosis occur. The aim of this research was the induction and evaluation of cirrhosis in mice by using two different models: The thioacetamide / TAA and the carbon tetrachloride / Phenobarbital (CCl4 / PB) model. Another aim of this study was to observe, if protein S (PS, natural anticoagulant) or growth factor-specific gene 6 (Gas6, natural procoagulant) deficiencies have any influence on cirrhosis by using Pros1−/− and Gas6−/− genotyped mice with induced cirrhosis. To reach these aims, observations on histopathological evaluations, blood cell count, hepatic profile and experimental monitoring were done. Results showed that CCl4 / PB treated mice developed a more severe cirrhosis compared to the other treatment when looking over all measurements. Furthermore, both genotypic PS deficiency in mice seems to have a progressive effect on cirrhosis development while the lack of Gas showed oppositely a protective role in cirrhosis development. Further experiments are ongoing in order to increase the significance of the results.

2 Introduction

Cirrhosis represents the final stage of fibrosis and is characterized by disrupted liver architecture. With chronic injury, continuous proliferation and activation of hepatic stellate cells (HSC) induce the progressive substitution of liver parenchyma with scar tissue, leading to portal hypertension, ascites, varices and liver failure. 

3 Aims and leading questions

The first aim of this study is to compare the CCl4 / PB model with the TAA induced cirrhosis model in mice.

- Are both CCl4 / PB and TAA inducing a CLD in mice?
- Are there changes in hemostasis after CCl4 / PB or TAA treatment?

The second aim is the investigation of the effects of PS and Gas6 deficiency in cirrhotic mice.

- Do PS and Gas6 deficiency affect fibrosis development and progression?
- Do PS and Gas6 deficiency have an influence on hemostasis in CLD mice?

4 Material and methods

5 Results

6 Discussion

- Are both CCl4 / PB and TAA inducing a CLD in mice?
- Both toxins developed fibrosis. However, CCl4 combined with PB was a stronger toxin than TAA alone. This data are explainable, considering the enhancement of PB.

- Are there changes in hemostasis after treatment?

- Increase of FVIII reflects stage of fibrosis, elevated in CCl4/PB, as expected. Tendencies in increased TAT level showed a possible coagulation activation. Moreover, TM resistance was observed, suggesting an acquired protein C (PC) deficiency in CLD mice.

- Do PS and Gas6 deficiency affect CLD progression?

- While Gas6 deficiency was known to have a protective role on fibrosis progression, PS deficiency progressed CLD. Mice with both deficiencies had a similar stage of fibrosis as wild type mice did, meaning that the prothrombotic and anticoagulant characteristics were re-balanced.

- Do PS and Gas6 deficiency have an influence on hemostasis in CLD?

- While PT seemed prolonged in wild and PS deficient mice, Gas6 deficiency had a normalizing effect on it. Furthermore, APC resistance was detected in TAA treated PS deficient mice due to the reduced PB levels in plasma. AP was not able to fully express its anticoagulant effects. In addition, PS deficient mice had a resistance similar to wild mice, suggesting an additional acquired PC deficiency, which is a risk factor for thrombosis.

Outlook

References of the literature

References of the figures

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Outlook

Further experiments are still on going to normalize the groups and collect data.