ID: 82

AhR deficiency improves the cytokine network in the "priming phase" of the regeneration

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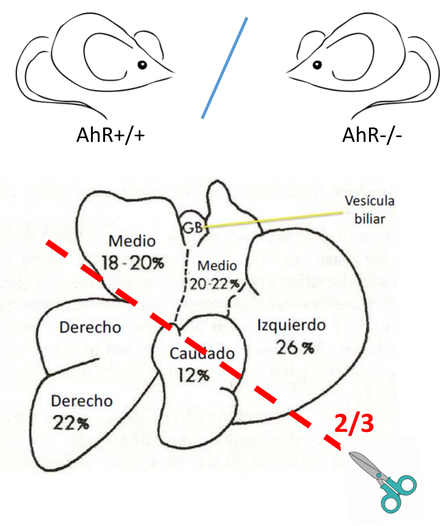
INTRODUCTION: Injuries and pathological processes can damage the liver. However, this organ has an efficient regenerative capacity to recover its size, architecture and function. The 2/3 partial hepatectomy (PHx) model in rodents allow the understanding of the complex and organized network of signaling pathways in the liver regeneration. After PHx, the hepatocytes come out of their quiescent state and begin to enter in cell cycle. The initiation of this proliferation occurs thanks to the activation of the immune system. The Aryl hydrocarbon receptor (AhR) participates in primordial signaling pathways in liver function and development. Thus, AhR-Knockout mice have a severe impact in this organ presenting an altered development, reduced size and intrahepatic portosystemic shunt. The importance of AhR in the regulation of the immune system is beginning to emerge, recent studies have shown the limitation in the inmunite responses to inflammatory stimull dependent on AhR activation.

METHODS:

HPx 2/3: C57BL/6J (*AhR+/+* VS *AhR-/-*)



RESULTS:

1. Lack of AhR increases recovery of liver tissue after PHx

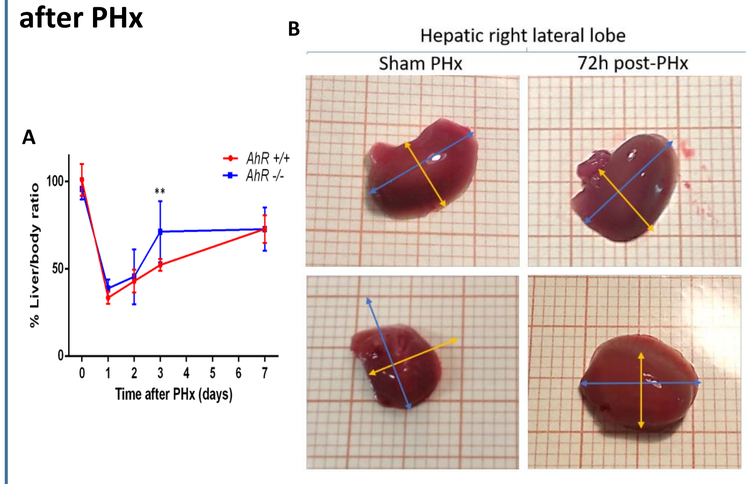


Figure 1. (A) Representative hepatic right lateral lobe morphology of wildtype and Knockout mice, sham surgeried (control) and 72 h after PHx. (B) Liver to body weight ratios at the indicated time after PHx,

2. AhR is induced and activated in the liver of wildtype mice after PHx

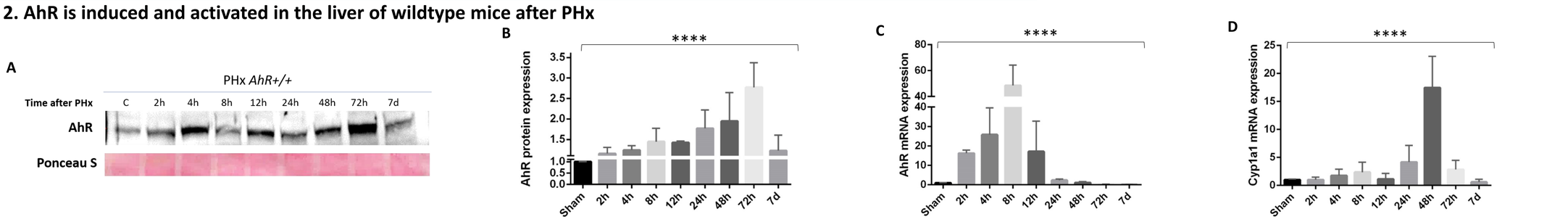


Figure 2.. (A-B) Protein expression of AhR analysed in liver extracts of wildtype mice at the indicated points after PHx by immunoblotting. Ponceau Staining was used to normalize protein levels. (A) Representative gels and (B) densitometric analysis. (C) mRNA expression of *AhR* and (D) its transcriptional target, *Cyp1a1*, using RT-qPCR. *Gapdh* was used to normalize target gene expression (ΔCt) and 2−ΔΔCt to calculate changes in mRNA levels with respect to sham surgery wildtype.

3. AhR-Knockout livers presented higher levels of inflammation after PHx

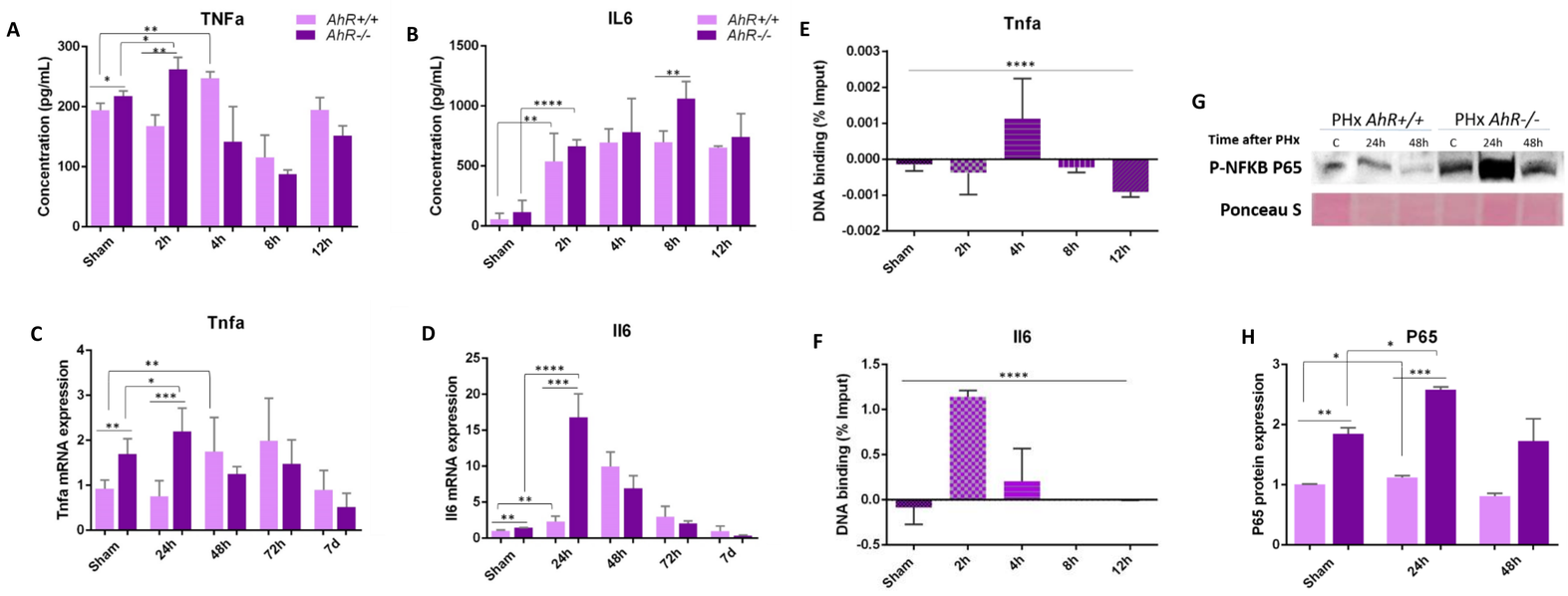


Figure 3. (A) TNFα and (B) IL6 levels were measured using serum samples. mRNA expression of *Tnfα,* (C) and *Il6* (D) using RT-qPCR. *Gapdh* was used to normalize target gene expression (ΔCt) and 2−ΔΔCt to calculate changes in mRNA levels with respect to sham surgery wild type (control). Chromatin immunoprecipitation (ChIP) for AhR binding to XRE binding sites located in the promoter of *Tnfα* (E) and *Il6* (F). qPCR was used to quantify changes in DNA binding and the results were normalized to the corresponding inputs. (G)Protein expression of NFκβ-pP65 (Ser536) was analysed in liver extracts of mice at the indicated points after PHx by immunoblotting. (H) Densitometric analysis of C. Ponceau Staining was used to normalize protein levels.

4. AhR absence increases downstream signaling of this cytokines, which improves induction of several genes related to cell proliferation.

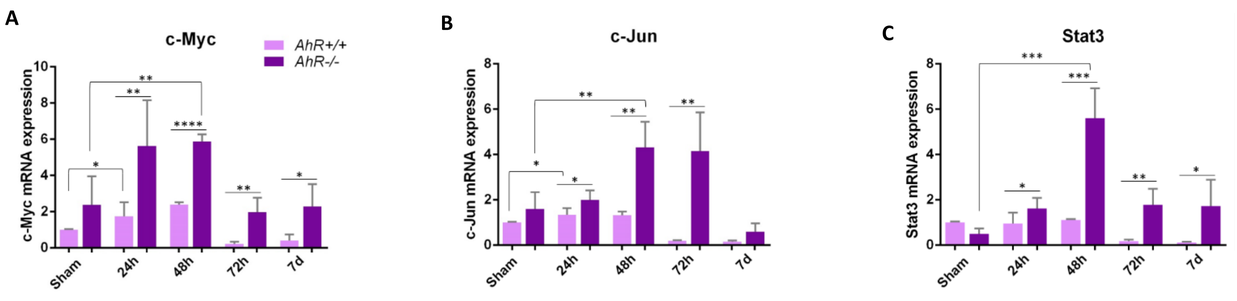


Figure 4. mRNA expression of *c-Myc (A)*, *c-Jun (B)*, and *Stat3 (C)* using RT-qPCR. *Gapdh* was used to normalize target gene expression (ΔCt) and 2−ΔΔCt to calculate changes in mRNA levels with respect to sham surgery wild type (control).

CONCLUSION: AhR delays liver regeneration and its expression increases at the beginning of the process and returns to basal levels once this process has advanced These results are interesting since the endogenous activation of the receptor shows its importance in physiological processes independent of its detoxifying function. However, AhR depletion improved regeneration and produced higher levels of inflammation after PHx. Thus, its pharmacological inhibition could stimulate the recovery of the functionality and structure of the liver after damage by toxins or pathological processes such as hepatocarcinoma, and even accelerate liver regeneration in recipients following liver transplantation.