Hepatic CD36 expression and traslocation to the plasma membrane are increased under hypoxic conditions

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BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is considered the hepatic component of the metabolic syndrome and is characterized by the progression from a benign steatosis to more severe liver injuries directly associated with lipotoxicity, such as nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma. It is well known that the intracellular lipid accumulation featuring steatosis results from an imbalance between the pathways involved in hepatic lipid homeostasis, including those that regulate hepatic free fatty acid (FFA) uptake. Recent evidence indicates that NAFLD severity is affected by obstructive sleep apnoea syndrome, a recurrent upper-airway obstruction during sleep, characterized by periods of intermittent hypoxia (IH). Indeed, dysregulation of the normal oxygen gradient in the liver that promotes the stabilization of the hypoxia-inducible factors (HIFs) can induce liver steatosis and inflammation.

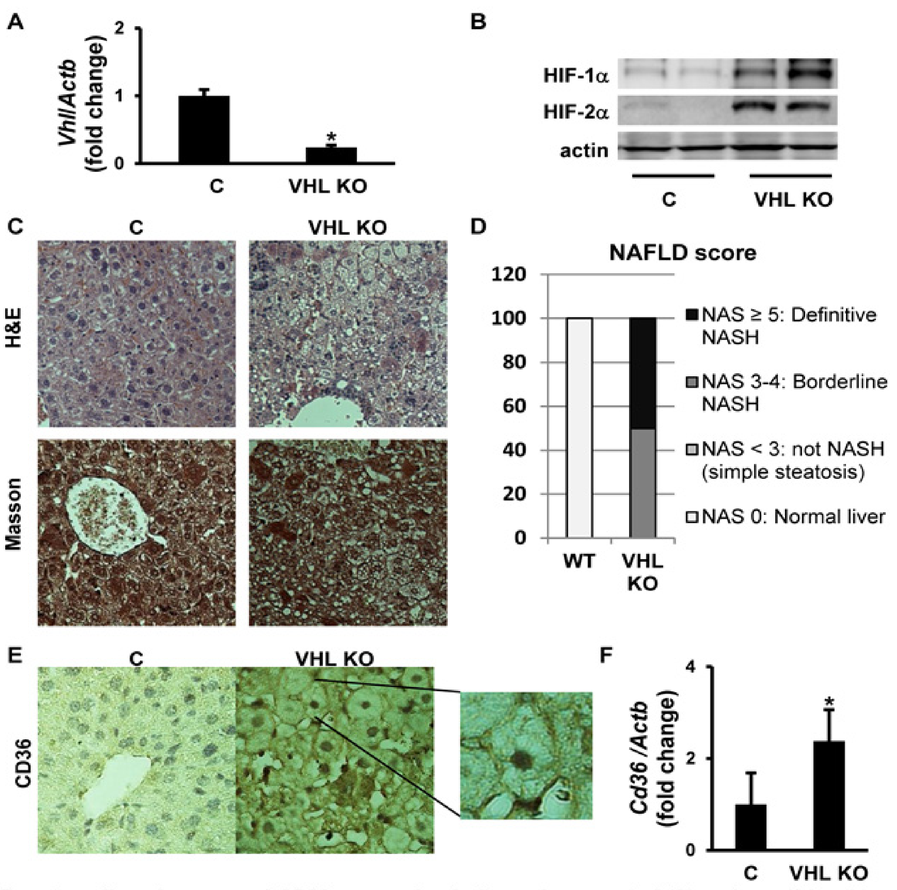
OBJECTIVE: The aim of this study was to investigate the effect of hypoxia on hepatic fatty acid uptake, focusing on the modulation of the Fatty Acid Translocase CD36 in both murine and cellular experimental models under hypoxic conditions.

METHODS: NAFLD score and hepatic CD36 expression were analyzed in livers from Von Hippel-Lindau knockout (VHL KO) mice, which display an overexpression of HIFs, and in livers from mice submitted to an IH protocol. In addition, accumulation of intracellular lipids and both total and membrane content of CD36 were determined in Huh7 cells submitted to a hypoxic environment.

CONCLUSION: Taken together these data indicate an important role of CD36 in hypoxia-induced lipid accumulation in the liver, and suggest that hypoxia may play a key pathogenic role in the development of hepatic steatosis and in the progression of NAFLD.

RESULTS: VHL KO MICE

Livers from VHL KO mice exhibited borderline or definitive NASH due to the presence of steatosis, inflammation and hepatocyte ballooning, and CD36 levels and its translocation to the plasma membrane of the hepatocytes were increased compared to control mice (C).

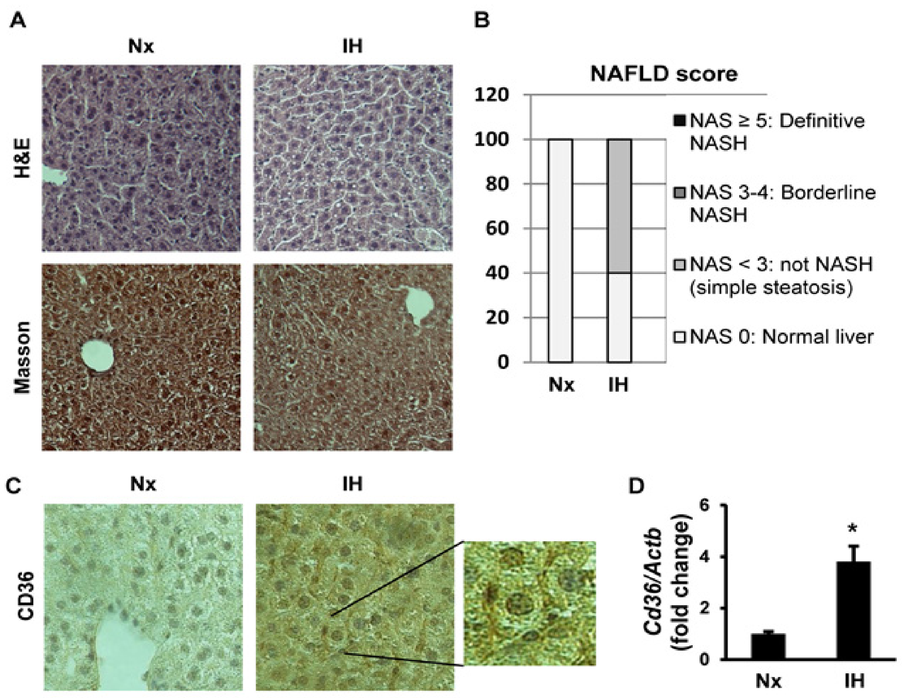


Analysis of HIF system, liver damage and CD36 expression in livers from control (C) and conditional tamoxifen-inducible Vhl knockout (VHL KO) mice. (A) *Vhl* mRNA levels determined by real-time PCR. (B) Representative blots with the indicated antibodies are shown. (C) Representative images (20x) from Hematoxylin & Eosin and Masson`s trichrome staining. (D) NAFLD score blindly assessed (%). (E) Representative images (40x) from CD36 staining. (F) Cd36 mRNA levels determined by real-time PCR.

Data are expressed as fold change relative to C mice (1) and presented as mean ± SEM. *P<0.05, VHL KO vs. control. (n=6-8 animals per condition).

RESULTS: INTERMITTENT HYPOXIA MICE

Hepatic features of simple steatosis were observed in livers from mice submitted to intermittent hypoxia, and CD36 levels and its translocation to the plasma membrane of the hepatocytes were higher compared to mice maintained in normoxia.

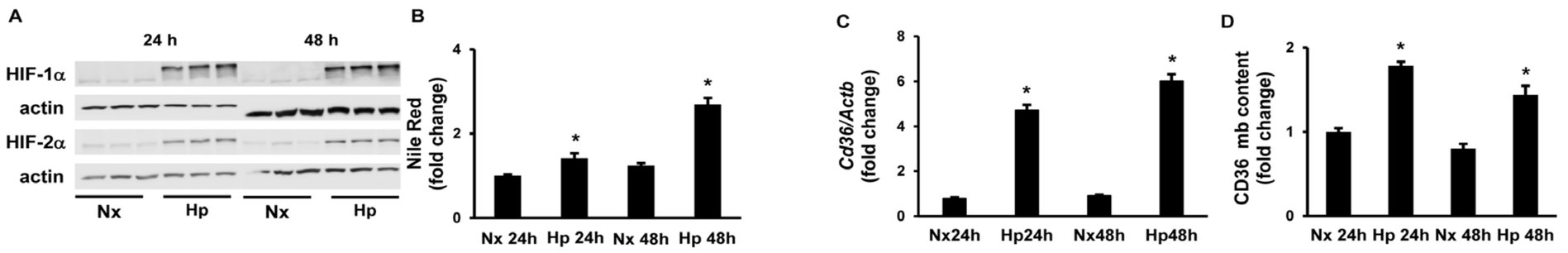


Analysis of liver damage and CD36 expression in livers from mice maintained in normoxic conditions (Nx) or submitted to intermittent hypoxia (IH) (A) Representative images (20x) from Hematoxylin & Eosin and Masson`s trichrome staining. (B) NAFLD score blindly assessed (%). (C) Representative images (40x) from CD36 staining. (D) Cd36 mRNA levels determined by real-time PCR.

Data are expressed as fold change relative to Nx mice (1) and presented as mean ± SEM. *P<0.05, IH vs. Nx. (n=10 animals per condition).

RESULTS: *IN VITRO* MODEL

Hypoxia itself enhanced lipid accumulation monitored by Nile Red staining in Huh7 cells. An increase of both total content and translocation to the plasma membrane of CD36 was detected in these cells under hypoxic conditions (1%O_2 for 24 and 48 hours).



Characterization of Huh7 cells maintained under normoxic (Nx, 21% O2) or hypoxic conditions (Hp, 1% O2) in a hypoxia chamber for 24h or 48h. (A) Representative blots with the indicated antibodies are shown. (B) Analysis of intracellular lipid content by Nile Red staining measured by flow cytometry. (C) *Cd36* mRNA levels determined by real-time PCR. (D) CD36 membrane content measured by flow cytometry.

Data are expressed as fold change relative to Nx condition (1) and presented as mean ± SEM. *P<0.05, Hp vs. Nx. (n=4 independent experiments performed in triplicate)

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Enfermedad hepática por depósito de grasa

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