

LETTER

The insulin-like growth factor 2 (*IGF2*) mRNA-binding protein p62/IGF2BP2-2 as a promoter of NAFLD and HCC?

Non-alcoholic fatty liver disease (NAFLD) represents the most common hepatic manifestation of chronic liver diseases in developed countries. Since non-alcoholic steatohepatitis (NASH) is responsible for a large proportion of cryptogenic cirrhosis and cirrhosis represents the main risk factor for hepatocellular carcinoma (HCC), HCC is a severe complication of end-stage NAFLD.¹

Recent evidence published in this journal showed the therapeutic potential of an inhibition of the chemokine (C-C motif) ligand 2 (CCL2)/monocyte chemoattractant protein-1 (MCP-1) in NASH.² The study by Baeck *et al* elegantly demonstrated that the pharmacological administration of an RNA oligonucleotide against

MCP-1 ameliorates murine steatosis and inflammation. Since mice deficient of the MCP-1 receptor also showed attenuated fibrosis, MCP-1 was suggested as a critical link in the axis steatosis–inflammation–fibrosis.²

Here, we report that animals with a liver-specific overexpression of the insulin-like growth factor 2 (*IGF2*) mRNA-binding protein p62/IMP2-2/IGF2BP2-2 exhibit distinctly elevated *Ccl2* expression levels (figure 1A) when fed a methionine–choline-deficient (MCD) diet, which models all hepatic stages of NAFLD. Accordingly, in addition to elevated inflammatory gene expression, *p62* transgenics had higher fat deposition (figure 1B) and an earlier onset and more pronounced manifestation of fibrosis than their wild-type littermates on MCD diet (figure 1B). These data further support a critical role for MCP-1 in NASH and NASH-induced fibrosis as suggested previously.²

The autoantigen p62 was originally isolated from a patient with HCC and was found to be overexpressed in HCC patients and in premalignant cirrhotic

nodules.^{3–5} We previously reported that *p62* transgenic animals on regular chow develop a fatty liver.⁶ Our new findings suggest that the lipogenic action of p62 on the MCD diet is facilitated by the induction of the lipogenic transcription factor *Srebp1c* (figure 1C). Interestingly, sterol regulatory element binding protein (SREBP) has also been reported to play a critical role in HCC lipogenesis and correlates with a poor prognosis in HCC.¹

In order to elucidate the molecular mechanism of fibrogenesis in *p62* transgenic mice on the MCD diet, the expression levels of transforming growth factor β (*Tgfb*) and its downstream target gene connective tissue growth factor (*Ctgf*) were measured. Surprisingly, *Tgfb* levels were not elevated in animals fed the MCD diet (data not shown), whereas *Ctgf* expression was induced (figure 1D), suggesting a TGF- β -independent production of collagen. Liu *et al*⁷ demonstrated that the cytokine interleukin (IL)-13 induces *Ctgf* irrespective of TGF- β . Interestingly, serum IL-13 levels were increased in *p62* transgenic mice ($p=0.002$), suggesting a

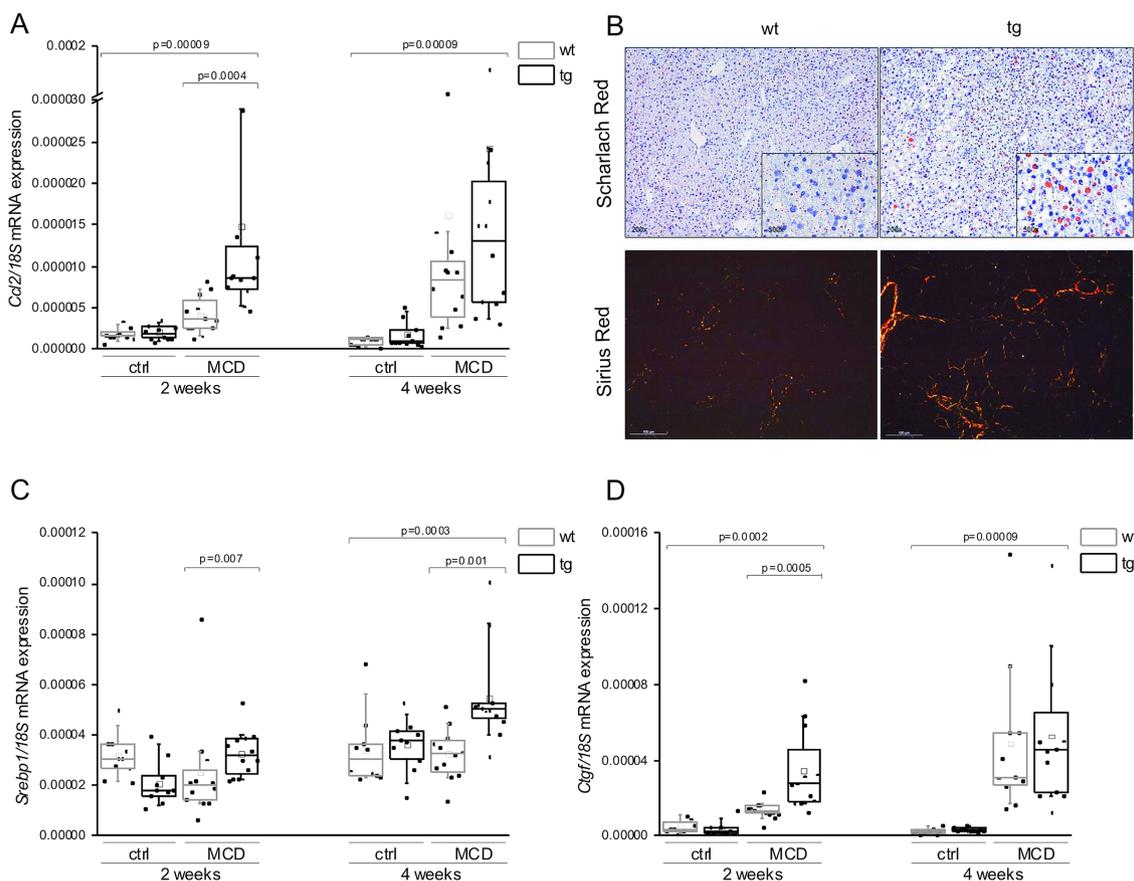


Figure 1 p62 amplifies steatosis, inflammation and fibrosis in murine methionine–choline-deficient (MCD)-induced non-alcoholic steatohepatitis. (A) Gene expression of *Ccl2/Mcp1* normalised to 18S of wild-type (wt) or *p62* transgenic (tg) livers on control (ctrl) or MCD diet. (B) Lipid accumulation after 2 weeks on MCD diet is visualised by Scharlach Red stain and hepatic collagen deposition after 4 weeks on MCD diet is visualised by polarisation microscopy after Sirius Red staining. (C) Relative hepatic mRNA expression of *Srebp1c* normalised to 18S. (D) Relative mRNA expression of *Ctgf* normalised to 18S. Data in A, C and D are represented as individual values and box plots with median (—) and mean (□) in a five-number summary ($n=9–12$).

p62-induced, IL-13-dependent *Ctgf* expression resulting in liver fibrosis. Similarly, in human NASH patients, serum IL-13 levels are increased and the inhibition of the IL-13 receptor in a rat model of NASH led to a reduction of fibrosis.⁸

These findings on p62 in the MCD mouse model strongly support a pathophysiological role of the tumour-associated autoantigen p62 in all stages of NAFLD, probably involving the induction of MCP-1. In fact, recent data also suggested a potential role for MCP-1 in HCC.⁹

We suggest that p62 might also drive the progression from NAFLD towards HCC. Interestingly, p62 induces or amplifies several of the most important mechanistic links between NAFLD and HCC as highlighted by Stickel and Hellerbrand.¹ These comprise, for example, a downregulation of the tumour suppressor phosphatase and tensin homolog¹⁶ or the activation of pro-oncogenic signalling pathways, such as extracellular-signal regulated kinase.¹⁻⁴ The induction of the lipogenic Srebp transcription factor as reported above might also be of special interest.¹

Having in mind that p62 expression correlates with poor outcome in HCC,⁴ our data suggest that p62 potentially represents a critical pathophysiological factor linking NAFLD to hepatocarcinogenesis.

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