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## Taurine inhibits oxidative damage and prevents fibrosis in carbon tetrachloride-induced hepatic fibrosis

Hepatic fibrosis stems from a complex and dynamic process, which, depending on the cause of the liver damage, involves different cellular and molecular mediators. Activated hepatic stellate cells (HSC) are the main cellular effectors of hepatic fibrosis, although portal fibroblasts and myofibroblasts also participate in the deposition of extracellular matrix. HSC activation is mediated by a complex interplay of growth factors and cytokines, which elicit intracellular signaling. Transforming growth factor-$\beta$1 (TGF-$\beta$1), released by inflammatory cells, is a well-documented profibrogenic cytokine capable of activating HSC. In addition, oxidative stress, which occurs in clinical and experimental models of chronic liver disease, modulates tissue and cell events necessary for the progression of liver fibrosis. In nonalcoholic fatty liver disease, for example, oxidative stress acts as a 'second hit', which induces inflammation (steatohepatitis) and fibrosis in the steatotic liver.

**Miyazaki *et al***[1] used carbon tetrachloride ($CCl_4$) poisoning as a model for oxidative stress to test the effect of an antioxidant taurine on hepatic fibrogenesis. Taurine was administered orally to rats with $CCL_4$-induced liver damage. Histological assessment of the livers showed less damage and fibrosis, and significantly fewer activated, $\alpha$-smooth muscle actin ($\alpha$-SMA) reactive HSC in rats fed with taurine compared to untreated animals. The protective effect was observed predominantly in acinar zone 3, the main site of $CCl_4$-induced damage and the site of taurine synthesis from cysteine. In addition, $\alpha$-SMA protein expression and TGF-$\beta$1 mRNA were reduced in the livers of treated animals, thus supporting the antifibrotic action of taurine. The concentrations of lipid hydroperoxide and 8-hydroxy-2′-deoxyguanosine were also lower in the serum and liver of treated rats. These data suggest that the antifibrotic effect of taurine may be mediated by the protection it affords against oxidative stress-induced liver damage. In this study, the authors also demonstrated that, unlike the expression of MAP-kinase and Akt which remained unchanged, lipid hydroperoxide and hydroxyproline concentrations, and TGF-$\beta$1 mRNA levels in isolated HSC were significantly reduced. Both *in vivo* and *in vitro* analyses suggest that HSC are the cellular targets of the antioxidant effect of taurine.

In this issue of Lab Invest, **Comporti *et al***[2] used the same $CCL_4$ intoxication model to produce further evidence linking oxidative stress to liver fibrosis. The study showed that serum $F_2$-isoprostanes, the most proximal products of lipid peroxidation, increased, together with the hepatic collagen content. $F_2$-isoprostanes also increased collagen synthesis in cultured HSC and TGF-$\beta$1 production in U937 liver macrophage cells.

Taken together, these two studies confirm the important role of oxidative stress in liver damage and liver fibrosis. Elucidating mechanisms underlying hepatic fibrosis is the key to the development of antifibrotic strategies.

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### References

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## Regulatory effect of proteasome on ectodomain shedding of TACE substrates

Human TNF-$\alpha$ is synthesized as a transmembrane protein and is secreted after cleavage by the metalloprotease TNF-$\alpha$ converting enzyme (TACE). Binding of TNF-$\alpha$ to its transmembrane receptors (TNFRs) mediates proinflammatory, apoptosis and cell survival responses. While the primary component of the protein degradation pathway in the cell is the proteasome the regulatory effect of proteasomes on the ectodomain shedding of TACE substrates is unknown. Among the key proteins modulated by the proteasome are those involved in the control of inflammatory processes, cell cycle and apoptosis regulation. The use of proteasome inhibitors as an anti-inflammatory strategy is mainly based on the ability of these molecules to inhibit the activation of NF-$\kappa$B.

In a recently published article, **Peiretti *et al***[1] studied whether the TNF-$\alpha$–TNFRs axis can be regulated by the shedding of its transmembrane components in a proteasome-dependent manner. They found that proteasome inhibition increases the ectodomain shedding of TNF-$\alpha$ and TNFRs by TACE, an effect involving the transient activation of MAP kinase, which then triggered the redistribution of TACE substrates from their Golgi-associated pool towards the plasma membrane and stimulated

TACE-substrate ectodomain shedding. This finding provides evidence that proteasome inhibitors increase TACE-dependent TNFR shedding, which justifies the use of these molecules in inflammatory diseases. Furthermore, the proapoptotic effect of TNF-α was dramatically increased by the combination of proteasome and TACE inhibitors, which might be of interest for antitumor therapy.

In this issue, **Alvarez-Iglesias *et al***[2] developed an assay, based on fluorescence resonance energy transfer (FRET) technology, that enabled accurate and reproducible determination of continuous real-time TACE activity on the surface of intact viable cells. This assay offers a valuable tool for *in vivo* analysis of TACE activity, potentially leading to new insights into the roles of TACE and TNF-α in inflammatory diseases, and facilitates the development of assays to measure activities of other sheddases.

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## References

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