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EDITORIAL

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Ironing out Steatohepatitis

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Article commented

Handa P, Maliken BD, Nelson JE, Hennessy KA, Vemulakonda LA, Morgan-Stevenson V, Dhillon BK, et al. **Differences in hepatic expression of iron, inflammation and stress-related genes in patients with nonalcoholic steatohepatitis.** *Ann Hepatol* 2017; 16: 77-85.

The increasing prevalence of obesity and the metabolic syndrome worldwide is well recognized, the tight association of non-alcoholic fatty liver disease (NAFLD) with these conditions increasingly so. NAFLD can progress to the more severe form of the disorder non-alcoholic steatohepatitis (NASH), which is characterized by worsening liver pathology. The prevalence of iron disorders, in particularly the genetic iron overload disorder hereditary hemochromatosis, is also high in the European population; up to 1:200 individuals carry the at-risk gene variant –the p.C282Y mutation in the *HFE* gene– which results in significant hepatic iron accumulation.[1] A number of studies have examined the association between increased iron levels, the prevalence of *HFE* mutations and NAFLD/NASH with conflicting results (reviewed recently in reference 2); increased iron has also been proposed as the "second hit" in NAFLD/NASH.[3]

In this issue of *Annals of Hepatology*, Handa, *et al.*[4] report on the analysis of hepatic gene expression in NAFLD and NASH patients. The authors have a longstanding interest in this field and have continued their work towards understanding the pathophysiology of NAFLD/NASH and the relationship of iron to liver disease. In an attempt to define the genes which may be involved in the progression of NAFLD to NASH they examined the expression of a large number genes involved in the regulation of iron metabolism, inflammation, and oxidative stress in patients with NAFLD and NASH, with or without liver iron accumulation, and correlated this with levels of a number cytokines in serum. Their analysis showed that expression of many genes involved in iron regulation were increased in patients with NASH compared to NAFL; these included *HAMP* (encoding the iron regulatory hormone hepcidin), *TMPRSS6* (encoding the negative regulator of hepcidin, transmembrane serine protease 6), *STAT3* (encoding the cytokine signalling factor, signal transducer and activator of transcription 3). Gene expression of proinflammatory cytokines IL-1β and TNF-α were also increased significantly in livers of NASH patients; while an increase in serum levels of IL-6 and IL-8 was noted. Gene expression of HIF1α (hypoxia inducible factor 1) was significantly reduced in livers of NASH compared to NAFL patients. NAFLD patients with liver iron accumulation also had increased gene expression of *HAMP* levels; however they had lower cytokine gene expression levels and reduced gene expression of *CREBH* (the liver-specific cAMP responsive- element binding protein). Based on this data the authors go on to suggest that hepcidin has a regulatory role in the progression from NAFL to NASH in patients. While other studies have previously noted the increase in *HAMP* in patients with NASH;[5] it is unclear why an increase in *TMPRSS6* levels is associated with an increase in *HAMP*, since *TMPRSS6*, at the protein/enzyme level, cleaves hemojuvelin and thus is a negative regulator of *HAMP*. Similarly while many studies have examined the response of hepcidin to inflammatory cues, a direct role for hepcidin, as suggested by the authors, in modulating the inflammatory response itself is unclear.

One of the strengths of the study by Handa, *et al.* is the use of liver biopsies and the significant number available for their analysis; they also examined gene expression of a range of genes involved in iron regulation, inflammation and stress response. Measurements of serum iron, ferritin, transferrin saturation, cytokine levels, markers of inflammation, liver function and cholesterol with a correlation

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of liver histology and injury provide significant data in this study. However, one of the major limitations of the study, as highlighted by the authors, was the absence of data on serum hepcidin levels, and more importantly *HFE* genotyping in the patients; the *HFE* genotype has been shown to affect both serum and hepatic iron and hepcidin levels. It is unclear if the interpretation of the data would be affected and if so how significantly.[6] A second aspect is the absence of protein data on some iron regulatory proteins which are post-translationally regulated; these include phosphorylated *STAT3* which is the mediator of IL-6 regulation of hepcidin and hemojuvelin (*HJV*, a positive regulator of hepcidin and a substrate for *TMPRSS6*). However, this may be due to the usual and expected paucity of protein material which is obtained from liver biopsies.

Previous studies have attempted to do examine the hepatic gene expression profiles in NAFLD and NASH; the majority of studies however have been performed in cell lines or in animal models of liver disease. In one recent study the authors concluded that expression of a number genes and variants in these genes may contribute to development of NAFLD.[7] In addition recent studies suggest that epigenetics, an inheritable but potentially reversible phenomena which affects expression of genes, may also play a role in this chronic liver disease (reviewed in reference 8).

In conclusion, the study by Handa, *et al.* has been important in re-examining the role of iron, inflammation and stress in the progression of NAFLD to NASH and the genes involved; it is however apparent that additional systematic and high-powered molecular studies are required to enable a more thorough understanding of this complex and chronic liver disease.

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