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Hepatology highlights

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Sutter, *et al.* Development of steatohepatitis in Ob/Ob mice is dependent on Toll-like receptor 4

Sutter, *et al.* Studies in animals models and human subjects have suggested that leptin signaling may play a causal role in the development of steatohepatitis perpetuating the inflammatory state. However, clinical observations have been conflicting, since serum leptin was linked neither to necroinflammatory grade and the fibrosis stage. Sutter, *et al.* explored the long-term effects of liver steatosis in in aleptinemic mice (OB), one of the oldest models for obesity/NAFLD. The authors also evaluated the role of TLR4 (as a measurement of intestinal permeability) on the development of the hepatic injury. TLR4 KO mice was extensively used in studies with high fat diet and/or high fructose diet where TLR deletion protected from body weight gain and glucose intolerance.[1,2] The experiments were performed in adult mice (20 weeks) both in OB mice, TRL4 KO and in double knockout animals TLR4 KO OB. OB animals presented not only a significant macrosteatosis but also signs of initial steatohepatitis with an increase neutrophil accumulation and production of proinflammatory mediators. The body weight gain of TLR4 KO OB mice was comparable with the OB counterparts, although hepatocellular injury was significantly reduced with fewer necroinflammatory foci, no neutrophils infiltration, ballooned hepatocytes and lower expression of inflammatory mediators.

This study suggests that leptin is not necessary for the development of inflammation in the steatotic liver, instead this could be a consequence of hyperphagia and subsequent steatosis. Moreover, authors showed that the extent of hepatic steatosis was comparable between TLR4 KO OB and OB animals, suggesting that TLR4 has not a direct effect on this phenomenon. This work showed in a simple elegant manner that the TLR4 does not affect the development of obesity but significantly contributes to the progression towards steatohepatitis through modulation of the inflammation. The data agree with another study recently published in humans where it was reported that TLR4 expression is up-regulated in a large cohort of NASH patients, when compared to those with NAFLD.[3]

Gutiérrez-Vidal R, *et al.* SFRP5 hepatic expression is associated with non-alcoholic liver disease in morbidly obese women

Gutiérrez-Vidal R, *et al.* SFRP5 was identified as a novel adipocytokine that has a reduced expression in the adipose tissue in obese rodents,[4] and has been proposed to exert a potential protective effect. However, this role in NAFLD human subjects has not been confirmed yet. In this study, Gutiérrez-Vidal, *et al.* explored the expression of SFRP5 in serum, hepatic and adipose tissue and correlated it with the presence of NAFLD in morbidly obese women. The study comprised 54 morbidly obese women (age 21-60 years-old) undergoing bariatric surgery; other causes of hepatic injury (HCV, HBV, alcohol, drugs) were excluded. Among the 54 patients, 9 had no signs of hepatic steatosis, 13 had steatosis, 10 with non-defining NASH, and 22 had NASH. The serum levels of SFRP5 showed a trend of reduction with the progression of NAFLD, even if the results did not reached the significance relevance due to the limited number

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of cases in each group. Interestingly the reduction of SFRP5 showed a significant positive correlation with serum adiponectin and a negative correlation with serum leptin levels and Leptin/Adiponectin ratio (LAR). The hepatic expression of SFRP5 showed a significant negative correlation with the Hepatic Triglyceride content (TGC) and the liver injury markers (ALT and GGT) and was negatively correlated with the progression of NASH. Of notice the observation that hepatic protein levels allowed to discriminate only NASH subjects from controls ($p < 0.001$) but did not differ in different stages of fibrosis. The hepatic SFRP5 protein content together with T2DM, HOMA-IR, serum ALT, leptin and adiponectin levels were predictive factors independently associated with NAFLD activity score. Besides of the limits of this study (low number of cases, only female population), this report shows the association of a reduced SFRP5 hepatic expression with the hepatic triglycerides accumulation and with the severity of NAFLD in humans. Whether this may be useful in the diagnosis and treatment of NASH remains to be defined.

Ramos-Lopez, *et al*. Association of a novel *TAS2R38* haplotype with alcohol intake among Mexican-Mestizo population

Ramos-Lopez, *et al*. The human population displays high variation in taste perception, and this difference is supported by scientific evidences since the bitter taste perception is mediated by the taste 2 receptors (TAS2R). A well-characterized example is the variable perception of bitter compounds such as 6-n-propylthiouracil (PROP) and phenylthiocarbamide (PTC), which can be accounted for at the molecular level by polymorphic variants in the specific type 2 taste receptor (*TAS2R38*). Three single polymorphisms (A49P, V262A and I296V) within the *TAS2R38* gene have been described, and it was recently demonstrated that alcohol bitterness depends upon the expression of these three *TAS2R38* SNPs. In this study, Ramos-Lopez, et al. determined the prevalence of the *TAS2R38* among Mexican mestizo population, and analyzed its association with alcohol intake. A total of 375 unrelated mestizo individuals (182 females and 193 males) were included in the analysis, and were classified as drinkers (DRS, who consume more than 2 drinks per occasion) and non-drinkers (NDRS, who consumed equal or less than two drinks per occasion) according to the recommendations of alcohol intake to prevent liver damage. Smokers and subject with sinus problems or prescribed medication that might affect the taste perception were excluded. In contrast with the global prevalence, the authors found that among Mexican mestizo population the AVV and PAI haplotypes were the most predominant (66 and 36.5%, respectively). Among the most frequent haplotype, 36% were AVV homozygotes, 45.1% heterozygotes and 12.8% PAI homozygotes. Interestingly the frequency of AVV homozygotes was significantly higher in DRS than NDRS ($p < 0.05$) and this genotype was associated with a higher alcohol intake when compared with heterozygotes and PAI homozygotes (OR = 1.79, CI 1.13-2.84, $p < 0.05$ and OR = 2.23, CI 1.11-4.48 $p < 0.05$, respectively). These findings are consistent with other reports evaluating the *TAS2R38* haplotypes and alcohol intake, where a decreased receptor function was associated with the AVV haplotype leading to an increase in taste perception thresholds and ultimately to a higher alcohol consumption. The prevalence of this haplotype among Mexican mestizo population might explain the high alcohol consumption observed in this country. The study might have an impact in the possible association between the haplotypes and the alcohol dependency from one side and the correlation between the alcohol liver damage and the different haplotypes from the other. This will allow defining if alcoholic liver damage is primarily a matter of individual taste or a metabolic predisposition.

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