

Hdfx: A Potential New Treatment and Prophylactic against Nonalcoholic Steatohepatitis (NASH) and Subsequent Hepatocellular Carcinomas: Is Hypomagnesemia a Complication of the Disease?

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Editorial

Nonalcoholic steatohepatitis (NASH) occurs, frequently, when the liver accumulates fat which is accompanied by inflammation, fibrosis, cellular damage, and finally cirrhosis [1]. NASH is often thought to be the hepatic manifestation of a growing epidemic of the metabolic syndrome which is associated with obesity, non-insulin-dependent diabetes and hypertriglyceridemia [2]. It has been estimated that approximately 20% of the populations living in the Western world have NASH [3]. Often the disease progresses to hepatocellular carcinoma [1-3]. Although a number of investigations have been undertaken into the molecular mechanisms of NASH, its treatment and prevention, knowledge regarding the disease initiation, progressive mechanisms, and treatment remain speculative [2-4]. Most of the people who develop hepatocellular carcinoma live without any symptoms until the late, severe stages of the disease which often takes 10-20 years to develop. The increased prevalence appears to be related to rising obesity in the Western world [2-4]. Insights into the mechanism (s) and potential treatment (s), until recently, have been hampered by the lack of good animal models [2-4].

A few years ago, our group discovered a new immune host defense factor (i.e., HDFx) which we reported to be a conserved protein molecule (35-40 KDa) and found in at least mice, rats, guinea-pigs, rabbits, and sub-human primates [5]. HDFx was found to possess a range of unique immunological protective qualities against a variety of pathophysiological insults, e.g. hemorrhage, traumatic shock, intestinal ischemic shock, combined injuries, and a host of lethal gram-negative and gram-positive bacterial microorganisms [5,6]. HDFx was also found to protect injured animals from losses in Kupffer cells, natural killer (NK) cells, and "pit cells" as well as many of their functional attributes in the liver ([5,6] unpublished findings). In addition, several of our experiments suggested that NASH animals given HDFx, over several weeks, demonstrated a dramatic restoration of Kupffer cell elements and "pit cells" [7], thus leading us to believe that HDFx has certain "regenerative attributes" that we had demonstrated earlier in rodent models of diverse injuries [8]. We have recently suggested that HDFx might be a valuable molecule for the treatment and prevention of hemorrhagic fevers and "superbugs" [9]. A series of preliminary experiments in our labs, using two different forms of liver cancer in rodents, suggested that HDFx could dramatically attenuate the growth of the tumors and their lethal effects ([5] unpublished findings).

In view of our interesting results with use of HDFx [5,6-9], we decided to investigate whether this newly-discovered immune factor

might yield protective effects against NASH [7]. As indicated above, NASH has been associated with obesity, non-insulin dependent, type-2 diabetes mellitus, and hypertriglyceridemia. We and other investigators have reported that all three of these syndromes are characterized by magnesium deficiency (MgD), particularly reduced blood and cellular levels of the free, ionized form of Mg (i.e., Mg^{2+}) [10-15]. We, therefore, suspected that a possible, underlying causative factor in the progression of NASH might be a MgD. Preliminary studies were, therefore, initiated to determine whether a MgD is a factor in NASH [16].

So far, our preliminary studies utilizing mouse models of NASH indicate a number of important findings: 1) Early treatment with HDFx ameliorates the inflammatory and fibrotic reactions normally seen in the animal models [7]; 2) Early treatment with HDFx reduced the expressions of several proteins which are predominant in NASH, i.e., platelet-derived growth factor, collagens I, II and III, the liver enzymes (e.g., alanine transaminase, aspartate transaminase, alkaline phosphatase), tumor necrosis factor, transforming growth factor beta, and insulin [7]; 3) HDFx treatment of NASH animals ameliorated the losses in macrophage-Kupffer cell and NK cell functional activities in the liver [7]; 4) HDFx also seemed to prevent NASH-induced losses in "pit cells" [unpublished findings]; 5) NASH-induced production of pro-inflammatory cytokines (i.e., IL-1 α , IL-6; TNF- α) and chemokines (eg., RANTES) were dramatically reduced by pretreatment with HDFx [7,16]; and 6) Although considerable blood and tissue hypomagnesemia were noted in the untreated, control mice, pretreatment with HDFx ameliorated the degrees of MgD [16].

Conclusion

Using animal models of NASH, we were able to reproduce many of the manifestations found in human patients [7,16]. More importantly, we so far have found a potential new treatment for NASH in human patients, and possibly a way to reduce the frequency of the disease and its often terminal event, namely hepatocellular carcinomas in the Western world. And, lastly, it would appear from our preliminary studies that MgD may be an unrecognized factor in the development and progression of NASH.

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