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Hepassocin as a treatment for fulminant hepatic failure: will it translate from rats to human?

Vincenza Calvaruso

Acute liver failure (ALF) is defined as the abrupt loss of hepatic cellular function in a patient without pre-existing liver disease, with the subsequent development of coagulopathy, jaundice and encephalopathy. It remains one of the most challenging medical emergencies, due to the multiorgan nature of the disease, the rapid evolution of the clinical condition and the need for multidisciplinary supportive interventions in order to assess the necessity for liver transplantation (LT) correctly.[1]

Despite different causes of ALF, the mode of cell death typically follows one of two patterns: necrosis or apoptosis; apoptosis is manifest by nuclear and cytoplasmic shrinkage without disturbance of cell membrane integrity or liberation of intracellular content. Consequently, secondary inflammation is not a feature. Necrosis involves depletion of ATP with resultant cell swelling and lysis, leading to release of cellular content and secondary inflammation. However, there is increasing evidence that they are alternative outcomes of the same initiating factors and signalling pathways, a process known as necroapoptosis.[2] The main mechanism of liver cell death in ALF is the activation of cell membrane receptors. The cytokine, tumour necrosis factor α (TNFα), and the Fas ligand mediate hepatocellular death through interaction with structurally related cell membrane receptors. In addition to TNFα, other proinflammatory and anti-inflammatory cytokines may have a role in the pathogenesis of acute liver injury of various aetiologies, both experimentally and clinically. Although all the factors responsible for regeneration in the setting of such severe liver cell loss remain incompletely understood, it has been shown that increased circulating levels of TNFα and other cytokines such as interleukin-6 (IL-6) are key initiators of liver regeneration. Other mechanisms involved in regeneration are the elevation of plasma levels of stimulatory hepatocyte growth factor (HGF) and inhibitory transforming growth factor β (TGFβ), presumably due to release from damaged extracellular matrix. Furthermore, increased activity of the fibrinolytic system, responsible for activation of both HGF and TGFβ, is also evident.[3] On the basis of these findings, therapeutic options to bridge patients to recovery or LT can be investigated and, in terms of potential clinical applications, functional studies using animal models are absolutely crucial, albeit not always translatable to the human setting.

In this issue of *Gut*, Li *et al* (***see page 817***) demonstrate in a rat model of fulminant hepatic failure (FHF) that administration of recombinant human hepassocin (HPS) after D-galactose and carbon tetrachloide (CCl_4) treatment protected against the liver injury, reduced apoptosis and enhanced proliferation.[4]

HPS, also named hepatocyte-derived fibrinogen-related protein-1 (HFREP-1), belongs to a fibrinogen family and has been found to be present in plasma and to associate non-covalently with the fibrin matrix of a plasma clot.[5]

HPS was first isolated in a rat model using differential cDNA expression cloning of a cDNA[6]; the authors have found that mRNA expression of this factor is upregulated in the rat liver after partial hepatectomy, suggesting its potential role as a potent mitogenic growth factor in the process of liver regeneration.[6]

Moreover, the same group cloned the human counterpart of rat HPS to determine if HPS is also implicated in liver regeneration in humans, and they concluded that during liver regeneration the expression of HPS mRNA was strongly upregulated.[7]

After the confirmation that recombinant human HPS is a specific mitogenic factor on human hepatocytes in vitro, Li *et al*[4] assessed the effect of human HPS on growth of hepatocytes in vivo. The administration of HPS to rats with partial hepatectomy (PHx) or liver injury induced by D-galactose and CCl_4 indicated that recombinant human HPS exerted an important role in promoting cell proliferation in hepatocytes in vivo. It significantly inhibited the development of FHF in both models by preventing the high mortality rate and improving liver histology in the HPS treatment group that showed significantly less hepatic necrosis.

The authors also investigated the role of HPS on apoptotic mechanisms and the results revealed that HPS is able to inhibit the upregulation of proapoptotic factors (Bax, cleaved caspase 9) induced by toxin, while increasing the expression level of antiapoptotic factors (Bcl-2, Bcl-xL). Furthermore, lack of expression of HPS by RNA interference resulted in hepatocyte growth inhibition, suggesting that human HPS may be one of the endogenous physiological regulators of hepatocyte proliferation. This focuses on the potential role of HPS in the management of patients with acute hepatitis with ALF.

In this setting, the assessment of HPS expression might correlate with the prognosis and the likelihood of recovery or continuing hepatic failure, and consequently the rate of survival or LT. HPS expression could be different according to the aetiology of liver damage and/or other patient demographic and clinical features.

Genetic mutations of the HPS gene may be discovered and could be causal in relation to the absence of protection against liver injury and to impaired liver regeneration. This can be useful in the setting of drug-induced liver injury, mostly in patients who would need long-term treatment with potentially hepatotoxic drugs.

Moreover, the therapeutic role of HPS should be investigated. Li *et al*[4] focused on the protective role of HPS that results in a reduction of liver necrosis, lower levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and decreased lethality. There could be several clinical applications of this finding and although ALF is likely to be the setting for this growth factor, HPS expression assessment and/or HPS administration may extend, in the future, to the treatment of exacerbations of chronic liver diseases. This is supported by the interesting finding that human HPS did not promote DNA synthesis in established cell lines such as HepG2 (human hepatocarcinoma) or HeLa, PC12 and NIH/3T3 cells

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(non-liver derived cells). It is assumed that HPS only acts on normal hepatocytes, possibly because its receptor is only present in normal hepatocytes.[4 7]

Furthermore, in line with these results, HFREP-1 has been found to be specifically expressed in normal human liver tissue, but reduced or undetectable in most hepatocellular carcinoma (HCC) specimens at both the RNA and protein level, suggesting that it might possess growth suppression activity in this context.[8] How can we interpret these findings? Can we suppose that tissue and/or serum HPS expression may be significantly different in patients with chronic liver disease according to their rate of development of HCC? Should we promote further investigation on the potential growth suppression activity of HPS on HCC to evaluate its potential role in HCC systemic treatment?

We should not forget that this study, like all studies performed on animal models, suffers from the limitations related to the transferability of the results to the human setting. In fact, no direct data have shown the upregulation of HPS in humans.

Moreover, the disadvantage of surgical models such as the hepatectomised animal is that these models lack the milieu of inflammatory mediators produced by damaged and/or necrotic hepatic cells. This limits the pathophysiological study of certain systemic features of ALF. Another limitation of the therapeutic applications of HPS could be the potential procoagulant effects that need to be investigated accurately in order to evaluate the risk of thrombotic events.

What is truly exciting about this study is the strong correlation between HPS expression and improvement of hepatic regenerative activity and the reduction of hepatocyte apoptosis in toxin-induced liver disease.

Future research on the assessment and the administration of HPS will lead to a new therapeutic strategy for the management and treatment of liver disease.

Competing interests None.

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Role of microRNA in IBS with increased gut permeability

María Vicario, Cristina Martínez, Javier Santos

Paradoxically, irritable bowel syndrome (IBS), a leading reason for medical consultation, is presently lacking sensitive and specific biological markers, and hence its diagnosis still relies on clinical symptom-based criteria. Luckily, and in close liaison with the progressive advent of innovative and ultrasensitive technologies and their rapid incorporation into research protocols, our mechanistic understanding of the origin of IBS may be undergoing a giant leap forward. One such remarkable advance could be the identification of a pathophysiological substrate common to the intestine of some patients with IBS—that is, a combined process of low-grade mucosal inflammation and immune activation, and disruption of the epithelial barrier.[1–4] Physical and functional disintegrity of the intestinal barrier, reflected by distorted expression patterns of key selective transporters and structural proteins, and enhanced permeability, also characterises a number of inflammatory conditions including coeliac disease, inflammatory bowel disease, food allergy or type 1 diabetes, suggesting a role in disease pathogenesis.[5] As for IBS, this may also be clinically relevant because the grade of barrier dysfunction has been related to the onset and severity of abdominal pain and visceral hypersensitivity.[6] Interestingly, the above observations, although not unique to patients with diarrhoea-predominant IBS (d-IBS), tend to predominate in this IBS subtype.

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MicroRNAs (miRNAs) are 18–25 nucleotide long RNAs serving as master endogenous fine-tuners of gene expression commonly operating via partial binding complementarity to target mRNAs. Indeed, the stability and functional expression of at least 30% of all protein-coding human genes are governed by miRNAs, acting primarily but not exclusively at the post-transcriptional level.[7] In humans, the low grade repression induced by miRNAs, rarely exceeding twofold,[8] mainly affects protein translation and infrequently causes degradation or cleavage of the cognate mRNA. In mammals, miRNAs comprise 2–3% of genes, found spread throughout the genome, with the exception of the Y chromosome, with ~700 different sequences so far identified in humans (miRBase 14.0). While current computational estimations predict dozens to thousands of targets for each single miRNA, their dominant pattern of expression is tissue or cell type specific.[9]

Only a small fraction of miRNAs have been functionally characterised in detail. However, as witnessed by growing and compelling documentation, these molecules harbour a vast competence to impact on every cellular process, from survival and renewal to apoptosis, and, by