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Ghrelin and fibrogenesis: Relief for a hungry liver

Fabio Marra*

Dipartimento di Medicina Interna, University of Florence, Viale Morgagni 85, I-50134 Firenze, Italy

COMMENTARY ON:

Ghrelin attenuates hepatocellular injury and liver fibrogenesis in rodents and influences fibrosis progression in humans. Moreno M, Chaves JF, Sancho-Bru P, Ramalho F, Ramalho LN, Mansego ML, Ivorra C, Dominguez M, Conde L, Millán C, Marí M, Colmenero J, Lozano JJ, Jares P, Vidal J, Forns X, Arroyo V, Caballería J, Ginès P, Bataller R. Hepatology 2010;51(3): 974–985.

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For many years, liver cell biologists have concentrated almost exclusively on hepatocytes. It is only in the last two decades that the identification of the cellular and molecular mechanisms of fibrogenesis has directed the attention of several investigators to the role played by hepatic myofibroblasts and by the complex networks involving parenchymal and non-parenchymal cells [1]. Even more recently, many groups investigating hepatic fibrogenesis have started to look outside the liver, in order to understand if signals derived from other systems may affect the hepatic 'wound healing' response that leads to tissue fibrosis. Adipose tissue is a clear example of how changes in extrahepatic sites may influence the fibrogenic process, as highlighted by clinical studies that have indicated the detrimental role played by fat accumulation on the development and progression of chronic liver diseases [2]. As a molecular counterpart, leptin and adiponectin, which are increased and decreased in obese patients, respectively, play opposite roles in the modulation of the fibrogenic process [3]. At a different level, the bone marrow has been shown to provide the liver with fibrogenic cells, or to limit the development of fibrosis with the contribution of different cell types [4].

Ghrelin, the focus of the paper by Moreno *et al.* [5], expands the list of extrahepatic factors, which modulate the fibrogenic process. Ghrelin is mainly produced by enteroendocrine cells of the gastric mucosa and secreted in the circulation, to exert hormonal action on different tissues [6]. Originally identified for its role in the release of growth hormone and as a potent stimulant of appetite, ghrelin is also implicated in development, gastrointestinal motility, sleep, memory, depression, and cancer [6]. Its actions are mediated, at least in part, by the growth hormone secretagogue receptor 1a (GHS-R1a), which belongs to the seven-transmembrane domain superfamily. Nonetheless, there are actions of ghrelin that are mediated by a yet unrecognized receptor.

Moreno *et al.* [5] have used a panel of experimental approaches in rodents and humans to provide evidence that ghrelin has antifibrotic effects in the liver (Fig. 1). In rats subjected to ligation of the common bile duct, a well-established model of fibrosis, both recombinant ghrelin and a specific agonist of GHS-R1a resulted in a significant reduction of fibrotic tissue accumulation. This was associated with modulation of hepatic gene expression in agreement with the observed antifibrotic effects. Complementary data were obtained in mice defective in the ghrelin gene, where the absence of endogenous ghrelin resulted in more marked fibrosis upon chronic carbon tetrachloride administration. The cellular and molecular mechanisms of the anti-fibrogenic action of ghrelin were also investigated in detail. An important feature of animals treated with ghrelin was the lower degree of hepatocellular injury, highlighted by dedicated experiments using an acute toxic model of liver injury. The ability of ghrelin to counteract tissue damage is in line with the protective roles reported in other tissues [7,8]. In the liver, ghrelin affected several components of tissue injury, namely inflammation, apoptosis, and generation of oxidative stress-related molecules (Fig. 1). These actions, which by themselves may justify a reduced fibrogenic stimulus, were associated with direct effects on many, but not all, the profibrogenic features of activated stellate cells, thus providing another level of modulation of the tissue repair process. Interestingly, while activation of the GHS-R1a was sufficient to reproduce the effects of ghrelin, it is possible that other, yet unknown, membrane receptors contributed to the observed effects.

This study is a brilliant example of translational research, where the role of a putative factor and its mechanisms of action were studied in cultured cells, animal models, and finally in humans. In fact, circulating levels of ghrelin were lower in patients with advanced fibrosis and a polymorphism of the ghrelin gene segregated individuals with faster fibrosis progression during chronic HCV infection. Thus, these data provide strong pre-clinical evidence for a possible interventional study evaluating the role of ghrelin as an antifibrotic agent. The good news is that this peptide is already being investigated in clinical trials for several disorders in humans (clinicaltrials.gov, accessed November 10, 2010), and its safety profile could be less of a concern compared to other 'experimental' anti-fibrogenic

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* Tel.: +39 0 554271087; fax: +39 0 55417123.
E-mail address: f.marra@dmi.unifi.it

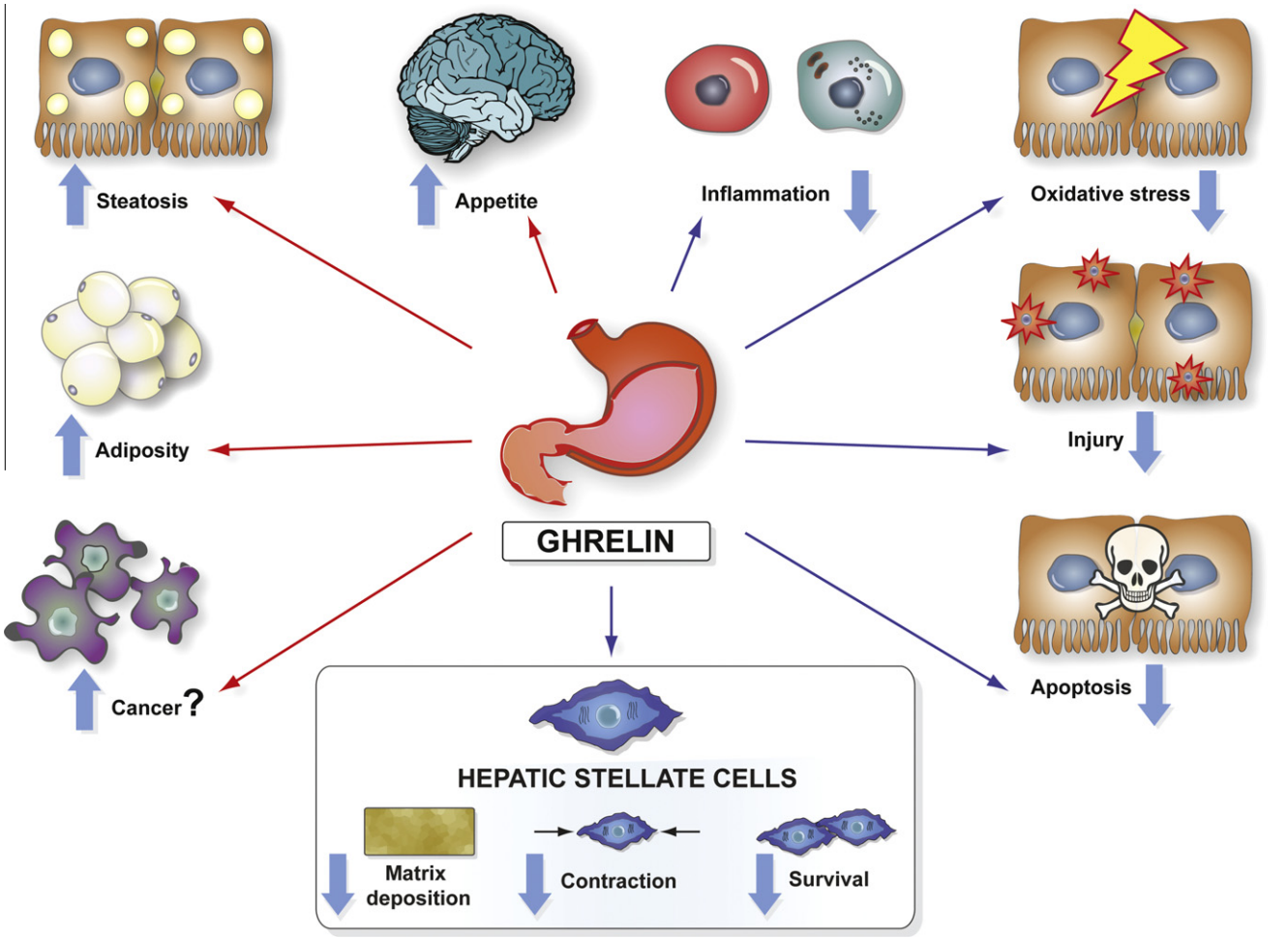

Fig. 1. Regulatory mechanisms of the hepatic response to injury by ghrelin. Ghrelin is secreted by the stomach and acts at distant sites in a hormonal fashion, but it may also be produced locally. The work by Moreno *et al.* [5] (blue arrows) shows that ghrelin exerts several hepatoprotective actions limiting hepatic damage and the resulting profibrogenic stimuli. In addition ghrelin may interfere with the pathophysiology of liver tissue through actions, demonstrated by other groups (red arrows), directly on liver cells or on other tissues.

therapies. Interestingly, treatment with ghrelin has also been suggested for patients with end-stage liver disease, where anorexia and malnutrition are common.

The effects of ghrelin on fibrosis are another piece of the puzzle that puts together metabolic regulation and the wound healing response. In recent years, leptin, a potent regulator of food intake and lipid partitioning, has emerged as an important stimulus to hepatic fibrogenesis, with actions on hepatic stellate cells and other non-parenchymal cells [9,10]. The actions of leptin on the hypothalamus are contrary to those of ghrelin, resulting in the stimulation of neuronal circuits that reduce appetite, and the observed anti-fibrogenic effects of ghrelin identify an additional condition in which these two hormones have opposing effects. Adiponectin and leptin, which also have opposite actions in terms of fibrogenesis [3], are mutually regulated in hepatic stellate cells [11], and it will be interesting to investigate whether ghrelin or leptin affect their reciprocal expression or that of their receptors. Along these lines, leptin prevents ectopic fat deposition through central and peripheral mechanisms, these latter including activation of hepatic AMP-activated protein kinase (AMPK) [3]. In contrast, ghrelin has been found to favor hepatic steatosis and to inhibit hepatic AMPK activation [12]. AMPK activation by a given ligand is cell-specific, and AMPK has been recently identified as an anti-fibrogenic pathway in HSC [13]. Thus, the possibility that at least some of the effects of ghrelin are mediated through activation of this pathway deserves future investigation.

Soluble factors targeting the liver from distant sites act as circulating hormones. Nonetheless, components of a wide number of these systems are also expressed within the liver, suggesting that at least some of their actions may be mediated by local ligand generation. Moreno et al. [5] found that the ghrelin gene is expressed in normal and fibrotic human livers, and that both hepatocytes and HSC contribute to its expression. Nonetheless, other cells within the liver may express ghrelin, and additional work is required to better elucidate the cellular sources of this factor in the normal and inflamed tissue. Hepatic expression of ghrelin is reminiscent of data previously reported for other 'systemic' factors, such as the renin-angiotensin system, and several adipokines, including leptin and adiponectin [11,14]. Interest-

ingly, intrahepatic expression of ghrelin was found to directly correlate with expression of profibrogenic genes, and patients with a haplotype of the promoter that is transcriptionally more active had more severe fibrosis. Although these findings sound surprising based on the anti-fibrogenic effects of ghrelin in animal models, they raise the hypothesis that the liver may be resistant to the effects of ghrelin, despite its increase in local expression. Resistance to leptin has been shown in obese patients and its mechanisms partially unraveled [15], and additional data on ghrelin are awaited.

The data provided by Moreno *et al.* [5] advocate the administration of recombinant ghrelin or stimulation of its signaling as a possible treatment strategy for liver fibrosis. However, antagonism of ghrelin's action has been suggested for the therapy of other conditions, such as obesity and fatty liver. In fact, ghrelin-deficient mice were less susceptible to obesity, and in conditions of excess adiposity, reduction of ghrelin-mediated signal may reduce hyperphagia and lead to weight loss [16,17]. As obesity and steatosis are well-known risk factors for the progression of chronic liver diseases, the possibility that chronic ghrelin administration could favor these conditions must be taken into account. Conversely, antagonism of ghrelin's action, proposed for the treatment of obesity, may favor the progression of fibrosis in a population with a high prevalence of nonalcoholic liver disease and in general more susceptible to accelerated fibrogenesis [18]. Another point that will deserve further clarification is related to the observed mitogenic effect of ghrelin on cultured cancer cells, including hepatocellular carcinoma cells [19]. As a treatment of fibrosis is expected to encompass a long period of time, and fibrogenic liver diseases are preneoplastic conditions, the possibility that ghrelin promotes the appearance or progression of hepatocellular carcinoma is a critical issue. In spite of these caveats, it is from well-conducted and methodologically sound work like the one performed by Moreno *et al.* that new approaches for the treatment of fibrosis are likely to be developed.

A post-translational modification of ghrelin results in acylation of serine-3 with an eight-carbon fatty acid, octanoate. While des-acyl ghrelin, the peptide devoid of the acyl moiety, has been long considered a non-functional form of ghrelin, recent data indicate that it actually participates in the regulation of food intake, gastrointestinal physiology, and metabolism, with actions that are in general opposite to those elicited by ghrelin [6]. This may have relevance also for hepatic fibrosis, considering that des-acyl ghrelin represent the most abundant form secreted in the circulation. Ghrelin *O*-acyltransferase (GOAT) is the enzyme which catalyzes acylation of des-acyl ghrelin to provide ghrelin. Expression of GOAT is limited to tissues that secrete ghrelin, and the reaction is highly specific for this peptide [6]. Thus, future investigations should take into account the regulation of GOAT, and interference with its activity is currently being considered to modulate the ghrelin system. The complexity of the system is further demonstrated by the existence of two additional products of the ghrelin gene, des-Gln14-ghrelin, which is created by alternative splicing and binds GHS-R1a, and obestatin. The pathophysiological role of obestatin in the regulation of metabolism and other conditions is being actively investigated.

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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