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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Netrin-1: Needed Help for Throughput in the ER in Patients With Liver Disease

Production of mature, properly folded proteins is a critical function of the endoplasmic reticulum. Under periods of stress, unfolded proteins accumulate, potentially compromising cell function and viability. To deal with this problem, stress sensors in the endoplasmic reticulum, including double-stranded, RNA-activated protein kinase-like endoplasmic reticulum kinase, activating transcription factor 6α and β, and inositol-requiring kinase 1α, are activated, leading to far-reaching alterations in transcription that ultimately enhance the protein folding and processing capacity of the cell. This process is termed the *unfolded protein response* (UPR).

This fundamental quality-control mechanism is ubiquitous, and defects in this process have been implicated in the pathogenesis of diseases as diverse as atherosclerosis, breast cancer, leukemia, neurodegenerative disorders, and inflammatory bowel disease. In particular, this pathway has been implicated in both fibrosis and neoplasia involving the liver. For this reason, the UPR is associated with the vast majority of clinically relevant liver disease.

In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Lahlali et al[1] examined the role of netrin in the UPR. Through a series of detailed studies, they identify a previously unrecognized yet critical role for netrin-1 in preventing UPR-induced hepatocyte death.

The investigators used HepaRG cells, which increasingly have been recognized as an in vitro system that recapitulates a variety of important hepatocellular functions. By using these cells, the investigators showed that the 5' untranslated region (UTR) of the netrin-1 RNA is able to drive translation of an internal cistron that, in turn, can be displaced by an RNA transcript containing the HCV internal ribosome entry site (IRES). These data indicate that the netrin-1 5'UTR contains an IRES. Further analyses showed that the netrin 5' UTR folds into a complex double pseudoknot, and the investigators concluded that this IRES folding is required for translation.

Functional analyses then were performed using netrin-1–targeted small interfering RNA. These analyses showed that reduced netrin-1 expression was associated with dramatic increases in caspase-3 activity, apoptosis, and hepatocellular death. To assess the potential therapeutic utility of altering netrin-1 levels to ameliorate stress-associated injury, the investigators overexpressed netrin-1 in HepaRG cells and showed significant protection from dithiothreitol-induced caspase-3 activation and apoptosis. The investigators then performed further analyses showing the importance of UNC5A and UNC5C netrin-receptor signaling via the death-associated protein kinase 1/protein phosphatase 2A complex in UPR-induced apoptosis.

Taken together, these findings identify a possible therapeutic target in what may be a final common pathway that leads to hepatocellular damage in diverse liver diseases. The careful, mechanistically oriented studies reported identify specific strategies that could be used to enhance netrin-1 expression and thereby limit hepatic injury and both delay progression and reduce the severity of liver disease.

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Reference

1. Lahlali T, Plissonnier M-L, Romero-Lopez C, et al. Netrin-1 protects hepatocytes against cell death through sustained translation upon the unfolded protein response. Cell Mol Gastroenterol Hepatol 2016;2:281–301.

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Conflicts of interest
The author discloses no conflicts.

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2352-345X
http://dx.doi.org/10.1016/j.jcmgh.2016.02.006