Protection against acetaminophen-induced liver injury with MG53: muscle-liver axis and necroptosis

Hartmut Jaeschke, David S. Umbaugh

PII: S0168-8278(22)00134-9
DOI: https://doi.org/10.1016/j.jhep.2022.02.027
Reference: JHEPAT 8629

To appear in: Journal of Hepatology

Received Date: 27 February 2022
Accepted Date: 28 February 2022

Please cite this article as: Jaeschke H, Umbaugh DS, Protection against acetaminophen-induced liver injury with MG53: muscle-liver axis and necroptosis, Journal of Hepatology (2022), doi: https://doi.org/10.1016/j.jhep.2022.02.027.

© 2022 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.
Protection against acetaminophen-induced liver injury with MG53: muscle-liver axis and necroptosis

To the Editor:

We read with great interest a recent paper by Han et al. showing that the muscle protein Mitsugumin 53 (MG53 or Trim72), is highly effective in attenuating acetaminophen (APAP)-induced liver injury and mortality in a murine model. The authors provided evidence for the beneficial effect of MG53 through use of a MG53/- mouse and injection of human recombinant MG53. We want to focus on two fundamental problems with this study. First, the authors hypothesized that MG53 must come from the muscle. Our interrogation of single cell RNA-seq data sets confirmed that neither hepatocytes nor any non-parenchymal cells in the liver express MG53 mRNA in controls or after APAP (Fig. 1). However, according to the human protein atlas (https://www.proteinatlas.org/ENSG00000177238-TRIM72) MG53 is enriched in skeletal muscle cells. This raises the serious question how APAP metabolized in the liver signals to the muscle to release MG53 and how can it affect toxicity within 3 hours in the liver. The authors suggest that H$_2$O$_2$ from hepatocytes may be the signaling molecule that travels through the bloodstream to the muscle. However, this speculation is not supported by established mechanisms of APAP toxicity. It is well known that the major oxidant stress and peroxynitrite formation during APAP toxicity occurs inside mitochondria and that only a very limited amount of superoxide is released towards the cytosol where it functions to activate a mitogen-activated protein (MAP) kinase cascade. There is no evidence for enough cytosolic H$_2$O$_2$ that could escape hepatocellular glutathione peroxidase and get into the blood, where it would have to again escape erythrocyte glutathione peroxidase while being transported from the hepatic vein through the heart and lung and then eventually reaching muscle tissue, entering these cells and triggering a stress to release MG53. The released MG53 then travels again through the entire circulation to end up in the liver, specifically in centrilobular hepatocytes, to attenuate cell death. Given the strong temporal correlation between the occurrence of the mitochondrial oxidant stress and peroxynitrite formation and cell death, the proposed signaling mechanism between liver and muscle and back through H$_2$O$_2$ and MG53, respectively, is virtually impossible. The fact that MG53/- mice show enhanced ALT release from the earliest time point (3 hours), suggests the
possibility for off-target effects that are responsible for the aggravating effect in these knockout mice independent of MG53. Thus, the mechanisms of the detrimental effects in the knockout mice might be different from treatment with high doses of MG53, which has not been considered or investigated by the authors.

The second fundamental problem with this manuscript is the suggested mechanism of cell death, i.e., RIP3K- and MLKL-mediated necroptosis. Modes of APAP-induced cell death have been reviewed in detail and it is obvious that APAP causes liver injury through programmed necrosis but not necroptosis. The mechanism of cell death is critically dependent on Cyp2E1-mediated reactive metabolite formation, mitochondrial protein adduct formation, which initiates an oxidant stress that is amplified by the MAPK c-jun N-terminal kinase activation and mitochondrial translocation, leading to a peroxynitrite-dependent mitochondrial permeability transition pore opening. The severe mitochondrial dysfunction triggers the release of intermembrane proteins such as endonuclease G, which translocate to the nucleus and cause DNA fragmentation. The latter event is considered the point of no-return to cell death. Studies of the role of RIP1K and RIP3K in APAP hepatotoxicity have shown inconsistent results. However, reports indicating beneficial effects of RIP1K and RIP3K have shown reduced mitochondrial dysfunction and necrosis not necroptosis. In addition, MLKL-/- mice were not protected against APAP toxicity. Thus, reactive metabolite formation and mitochondrial protein adducts, mitochondrial oxidant stress, mitochondrial permeability transition pore opening, and nuclear DNA fragmentation are central events in the APAP-induced cell death in both the mouse model and in humans. Importantly, the current clinical standard of care antidote against APAP overdose, N-acetylcysteine, and fomepizole (4-methylpyrazole), a promising antidote in clinical development, both are targeting these key events in the pathophysiology. Because MLKL is not a relevant therapeutic target in APAP toxicity and it is highly unlikely to be a relevant target for other drug-induced liver injury models, it would be interesting to investigate how high doses of MG53 could interact with the established mechanisms of APAP-induced cell death and in the other models. MG53 is certainly a protein that can affect a multitude of intracellular signaling events and positively impact various pathophysiologies. However, it also has detrimental effects including negative regulation of myogenesis. Thus, a more detailed understanding of the mechanism of
protection in various liver disease etiologies but also potential adverse effects of MG53 treatment need to be achieved before this compound can be considered for a clinical application.

Financial support
Work in the authors’ laboratory was supported in part by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant R01 DK102142.

Conflict of interest
The authors declare no conflicts of interest that relate to this work.
Please refer to the accompanying ICMJE disclosure forms for further details.

Authors’ contributions
HJ: concept, drafting of manuscript. DSU: data acquisition, interpretation of data and critical review of manuscript. All authors read and approved the final manuscript.

References


Hartmut Jaeschke*

David S. Umbaugh

Department of Pharmacology, Toxicology & Therapeutics
University of Kansas Medical Center, School of Medicine
Kansas City USA

*Corresponding Author: 3901 Rainbow Blvd, MS 1018
Kansas City, KS 66160, USA
Tel. +1 913 588 7969
Email: hjaeschke@kumc.edu
Figure Legend:

**Fig. 1: Violin plots of Mg53/Trim72 and cell type specific gene expression.** Gene expression is shown for acetaminophen treated (n=14) or control mouse livers (n=8) from three independent single-cell RNA sequencing datasets grouped either by cell type or group (Datasets: GSE136679, dryad.t76hdr806, E-MTAB-8263).