cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

C-Reactive Protein, a Promising Approach for Acetaminophen Hepatotoxicity

Drug-induced liver injury is a major cause of acute liver failure (ALF) and one of the most challenging liver disorders with respect to its prediction, diagnosis, and management. Acetaminophen (APAP) is one of the most widely used pain relievers worldwide. Although relatively safe, APAP is a dose-dependent hepatotoxin and APAP overdose is a major cause of ALF, far exceeding other causes of ALF in industrialized countries. APAP hepatotoxicity in humans can be modelled in rodents after administration of an acute or cumulative overdose. However, despite intensive efforts, the mechanisms involved in APAP hepatotoxicity are not fully understood, which has hampered the availability of effective therapy for APAP hepatotoxicity.[1,2] *N*-acetylcysteine (NAC) is the standard treatment for APAP hepatotoxicity and other causes of ALF.[3] However, the effectiveness of NAC in APAP hepatotoxicity is limited to early administration, indicating the need to identify new strategies for adequate management of ALF caused by APAP hepatotoxicity.

C-reactive protein (CRP) is an acute phase protein produced predominantly by the liver in response to inflammation, whose levels increase rapidly following liver injury. CRP not only binds to phosphorylcholine after its exposure on membrane of injured hepatocytes, but it also regulates complement activation through recruitment of C1q and factor H, which results in the modulation of immune cell response via FcγRs.[4] Complement is an important component of innate immunity and mediates the assembly of membrane attack complex, which can cause direct cell injury and the generation of anaphylatoxins that further recruit and activate immune cells.[5] APAP-induced hepatotoxicity is initiated by early injury to hepatocytes, which can progress to ALF by an amplification wave of liver damage driven by the activation of immune cells. Prior studies reported a role for complement activation in APAP-induced liver injury, as its depletion by cobra venom factor or C3 deletion protected against APAP hepatotoxicity.[6]

The link between CRP and complement activation in APAP hepatotoxicity has remained elusive so far. In a recent study, Li et al[7] report the protective effect of CRP in APAP hepatotoxicity by preventing the overactivation of complement. In an elegant series of studies using mice and rats in which CRP was deleted, they provide evidence for the protective role of CRP against APAP-induced liver damage. Although CRP inactivation in mice or rats by CRISPR/Cas9 markedly sensitized to APAP-induced liver damage, this outcome could be rescued by genetic knockin, and by adeno-associated virus-mediated hepatic expression of CRP or direct administration of human CRP to the inactivation models. These findings therefore highlight that the protective effect of CRP against APAP hepatotoxicity is species independent. Although, as mentioned, CRP can modulate immune cell responses via its cellular receptor FcγR2B to inhibit the early phase injury to hepatocytes induced by APAP, Li et al[7] excluded this mode of action in the protective effects of CRP against APAP hepatotoxicity. Indeed, key players involved in this initial phase of APAP-mediated hepatocellular injury, such as GSH depletion or JNK activation,[8,9] were unaffected by CRP rescue, an outcome that could be explained by the lack of expression of FcγR on hepatocytes and validated with the knockout of FcγR2B, an inhibitory FcγR that mediates the anti-inflammatory activities of CRP in mice, because FcγR2B knockout mice exhibited marginal protection against APAP hepatotoxicity. Additional studies in mouse hepatocytes, human hepatic cell line Hep3B, and bone marrow–derived macrophages excluded a direct effect of CRP in the modulation of cytokine production, whereas the possibility that CRP may have exerted its protective effect by promoting liver regeneration was unlikely because CRP inactivation in mice did not impair the proliferation of hepatocytes, leading investigators to examine whether CRP targeted the late phase of APAP-induced ALF via complement overactivation. This possibility was suggested after the initial confirmation that mouse, rat, and human CRP could all interact with C1q and factor H to activate the initiation phase of the classic pathway of complement, indicating that the protective effect of CRP against APAP hepatotoxicity depended on complement-regulatory activities. Selective inhibitors against cellular receptors for anaphylatoxins indicated that C3aR but not C5aR antagonist protected against APAP-induced liver injury, lending support for a key role for C3a, but not C5a or membrane attack complex in amplifying the late-phase injury of APAP hepatotoxicity.[7] Interestingly, further studies using CXCR1/2 and CCR2/CCR5 inhibitors identified neutrophils as the cell type that responded to C3a activation, pointing to a potential role for a C3a-neutrophil axis in APAP hepatotoxicity. Unfortunately, this intriguing aspect was not further pursued and will require extensive additional work given the controversial role of neutrophils in APAP hepatotoxicity, and their emerging contribution to host defense and injury resolution following APAP overdose.[10]

In light of these findings, the therapeutic potential of human CRP against APAP hepatotoxicity was examined and compared with the effect of NAC. Importantly, unlike NAC that was only protective when administered early (2 hours) post APAP administration, human CRP treatment reduced APAP hepatotoxicity even when given 6 hours after APAP

dosage. Moreover, coadministration of NAC improved the therapeutic efficacy of CRP at 2 hours, but showed no improvement at 6 hours post APAP administration. Thus, the findings of Li et al[7] further confirm the role of complement overactivation in APAP hepatotoxicity and identify CRP as a promising approach for APAP hepatotoxicity with significant therapeutic advantage compared with NAC treatment, which needs to be further validated in future clinical trials.

CARMEN GARCIA-RUIZ, PhD
JOSE C. FERNANDEZ-CHECA, MD
Department of Cell Death and Proliferation
Institute of Biomedical Research of Barcelona, CSIC
Barcelona, Spain
Liver Unit, Hospital Clinic I Provincial de Barcelona
Instituto de Investigaciones Biomédicas August Pi i Sunyer
Barcelona, Spain
Center for the Study of Liver and Gastrointestinal Diseases
Carlos III National Institute of Health
Madrid, Spain
Center for ALPD, Keck School of Medicine
University of Southern California, Los Angeles
Los Angeles, California

References

1. Andrade RJ, Chalasani N, Björnsson ES, Suzuki A, Kullak-Ublick GA, Watkins PB, Devarbhavi H, Merz M, Lucena MI, Kaplowitz N, Aithal GP. Drug-induced liver injury. Nat Rev Dis Prim 2019;5:58.
2. Fernandez-Checa JC, Bagnaninchi P, Ye H, Sancho-Bru P, Falcon-Perez JM, Royo F, Garcia-Ruiz C, Konu O, Miranda J, Lunov O, Dejneka A, Elfick A, McDonald A, Sullivan GJ, Aithal GP, Lucena MI, Andrade RJ, Fromenty B, Kranendonk M, Cubero FJ, Nelson LJ. Advanced preclinical models for evaluation of drug-induced liver injury-consensus statement by the European Drug-induced liver injury Network (PRO-EURO-DILI-NET). J Hepatol 2021;75:935–959.
3. Shresta DB, Budhathoki P, Sedhai YR, Adhikari A, Poudel A, Aryaf B, Banyia R. N-Acetyl cysteine versus standard of care for non-acetaminophen induced acute liver injury: a systematic review and meta-analysis. Ann Hepatol 2021;24C:100340.
4. Bottazzi B, Doni A, Garlanda C, Mantovani A. An integrated view of humoral innate immunity: pentraxins as a paradigm. Annu Rev Immunol 2010;28:157–183.
5. Thorgersen EB, Barratt-Due A, Haugaa H, Harboe M, Pischke SE, Nilsson PH, Mollnes TE. The role of complement in liver injury, regeneration and transplantation. Hepatology 2019;70:725–736.
6. Singhal R, Ganey PE, Roth RA. Complement activation in acetaminophen-induced liver injury in mice. J Pharmacol Exp Ther 2012;341:377–385.
7. Li H-Y, Tang Z-M, Wang Z, Lv J-M, Liu X-L, Liang Y-L, Cheng B, Gao N, Ji S-R, Wu Y. C-reactive protein protects against acetaminophen-induced liver injury by preventing complement overactivation. Cell Mol Gastroenterol Hepatol 2022;13:289–307.
8. Torres S, Baulies A, Insausti-Urkia N, Alarcón-Vila C, Fucho R, Solsona-Vilarrasa E, Núñez S, Robles D, Ribas V, Wakefield L, Grompe M, Lucena MI, Andrade RJ, Win S, Aung TA, Kaplowitz N, García-Ruiz C, Fernández-Checa JC. Endoplasmic reticulum stress-induced upregulation of STARD1 promotes acetaminophen-induced acute liver failure. Gastroenterology 2019;157:552–568.
9. Win S, Than TA, Min RW, Aghajan M, Kaplowitz N. c-Jun N-terminal kinase mediates mouse liver injury through a novel Sab (SH3BP5)-dependent pathway leading to inactivation of intramitochondrial Src. Hepatology 2016;63:1987–2003.
10. Williams D, Bajt ML, Shape MR, McGill MR, Farhood A, Jaescke H. Neutrophil activation during acetaminophen hepatotoxicity and repair in mice and humans. Toxicol Appl Pharmacol 2014;275:122–133.

Correspondence
Address correspondence to: Jose C. Fernandez-Checa, MD, Institute of Biomedical Research of Barcelona, CSIC, 08036 Barcelona, Spain. e-mail: checa229@yahoo.com.

Conflicts of interest
The authors disclose no conflicts.

Funding
Supported by grants PID2019-111669RB-100 and PID2020-115055RB-I00 from Plan Nacional de I+D funded by the Agencia Estatal de Investigación and the Fondo Europeo de Desarrollo Regional; the CIBEREHD; and AGAUR of the Generalitat de Catalunya SGR-2017-1112, the Red Nacional 2018-102799-T de Enfermedades Metabólicas y Cáncer, Project 201916/31 from Fundació Marato TV3, and European Cooperation in Science & Technology (COST) ACTION CA17112 Prospective European Drug-Induced Liver Injury Network, www.cost.eu.

Most current article

2352-345X
https://doi.org/10.1016/j.jcmgh.2021.10.004