Letter to the Editor: High Mobility Group Box Protein 1 Release Is an Identified Driver of Inflammation in the Pathogenesis of Biliary Atresia

TO THE EDITOR:

With great interest, we read the study by Mohanty et al.[1] demonstrating that rotavirus-infected cholangiocytes actively release high mobility group box protein 1 (HMGB1), contributing to the pathogenesis of biliary atresia (BA). Activation of HMGB1 secretion involves viral induction of reactive oxygen species and is mediated by the p38/STAT1 (signal transducer and activator of transcription 1) axis. Moreover, the level of serum HMGB1 at the time of Kasai portoenterostomy could help identify BA patients who are potentially responsive to anti-inflammatory administration. After reading the publication carefully, we would like to add a few comments.

Inflammation is a prominent pathogenic factor in BA, but its underlying mechanisms remain unclear. A recent large-scale immune profiling has indicated that immune dysfunction contributes to liver failure in infants with BA.[2] Hyperactivation of inflammatory

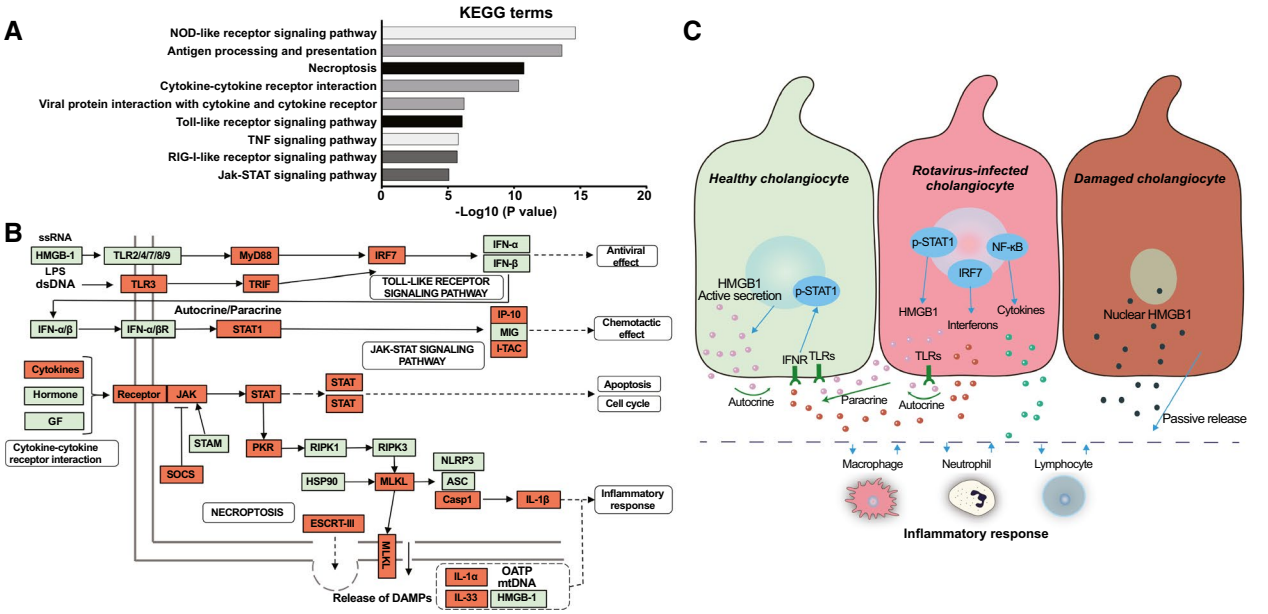

FIG. 1. The role of HMGB1 in pathogenic inflammation of rotavirus-related biliary atresia. (A) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of differentially expressed genes in rotavirus infected and uninfected ICOs. (B) Toll-like receptor (ID: hsa04620), JAK-STAT (ID: hsa04630), and Necroptosis (ID: hsa04217) signaling pathway from KEGG indicating upregulation (red) in ICOs upon rotavirus infection. (C) Graphic model of the autocrine and paracrine actions by HMGB1 during pathogenic inflammation induced by rotavirus infection of cholangiocytes. Abbreviations: ASC, apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain; Casp1, caspase 1; dsDNA, double-stranded DNA; ESCRT, endosomal sorting complexes required for transport; GF, epidermal growth factor; HSP90, heat shock protein 90; IFN-α/βR, interferon-alpha/beta receptor; IFNR, interferon receptor; IP-10, IFN-γ-inducible protein 10; IRF7, interferon regulatory factor 7; i-TAC, IFN-inducible T-cell α chemoattractant; LPS, lipopolysaccharide; MIG, monokine induced by IFN-gamma; MLKL, mixed lineage kinase domain-like; mtDNA, mitochondrial DNA; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor kappa B; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; NOD, nucleotide-binding oligomerization domain; OATP, organic anion-transporting peptide; PKR, protein kinase R; p-STAT1, phosphorylated STAT1; RIPK, receptor-interacting serine/threonine-protein kinase; SOCS, suppressor of cytokine signaling; STAM, signal transduction adaptor molecule; ssRNA, single-stranded RNA; TLRs, Toll-like receptors; TRIF, TIR-domain-containing adapter-inducing interferon-β.

cells is classically implicated, but whether and how cholangiocytes are involved in the pathogenic inflammation of BA is largely unknown. The intriguing findings by Mohanty et al. shed light in this respect. They have demonstrated that rotavirus-infected cholangiocytes evoke immune activation involving release and signaling by HMGB1. Our group recently demonstrated that human cholangiocyte organoids (ICOs) are susceptible to rotavirus infection and mirror BA development,[3] which could be reverted by antiviral therapies. Interestingly, our transcriptomic analysis unravels a robust activation of inflammatory pathways in ICOs upon rotavirus infection, such as cytokine receptor, Toll-like receptor, and Janus kinase (JAK)/STAT signaling (Fig. 1A,B). Combined with the results of Mohanty et al., we speculate that the p38/STAT1 axis might also be activated upon rotavirus infection by proinflammatory factors in autocrine and paracrine manners (Fig. 1C). Thus, either direct neutralization of HMGB1 or antiviral therapy represents potential interventions targeting inflammation in BA.

The outcome and therapeutic responsiveness of BA patients heavily depend on the phenotypic variations of BA and the progression stages at the time of diagnosis. Currently, systematic evaluation of disease severity is still lacking, which hampers clinical interventions with the best chances to benefit BA patients. Immunosuppression agents, such as corticosteroids, have been applied to confine inflammation during the Kasai procedure, but showed contradictory results.[1] Mohanty et al.[1] identified serum HMGB1 as a noninvasive biomarker, possibly reflecting "the right window" for anti-inflammatory therapy. This insight may also help to stratify BA patients together with histological scoring approaches and molecular signatures, such as inflammatory, virus, fibrotic, and cell-death–related markers, to improve the therapeutic effect.

Taken together, this study provides insight into the pathogenic role of HMGB1 in the development of BA and brings up a direction for the precise treatment of BA patients. Further validation studies on experimental models and in clinical trials should be implemented.

Author Contributions: S.S. drafted the manuscript. S.C., M.M.A.V., and Q.P. reviewed the manuscript critically. L.J.W.L. critically reviewed, revised, and approved the manuscript.

Shaojun Shi, M.D.[1]
Sunrui Chen, Ph.D.[2]
Monique M.A. Verstegen, Ph.D.[1]
Qiuwei Pan, Ph.D.[2]
Luc J.W. van der Laan, Ph.D.[1]
[1]**Department of Surgery**
Erasmus MC-University Medical Center
Rotterdam, The Netherlands
[2]**Department of Gastroenterology and Hepatology**
Erasmus MC-University Medical Center
Rotterdam, The Netherlands

REFERENCES

1) Mohanty SK, Donnelly B, Temple H, Ortiz-Perez A, Mowery S, Lobeck I, et al. HMGB1 release by cholangiocytes governs biliary atresia pathogenesis and correlates with increases in afflicted infants. Hepatology 2021;74:864-878.
2) **Wang J**, **Xu Y**, **Chen Z**, **Liang J**, **Lin Z**, **Liang H**, et al. Liver immune profiling reveals pathogenesis and therapeutics for biliary atresia. Cell 2020;183:1867-1883.e26.
3) Chen S, Li P, Wang Y, Yin Y, de Ruiter PE, Verstegen MMA, et al. Rotavirus infection and cytopathogenesis in human biliary organoids potentially recapitulate biliary atresia development. mBio 2020;11:e01968-20.

Author names in bold designate shared co-first authorship.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.32026

Potential conflict of interest: Nothing to report.