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EDITORIAL

Novel insights into autophagy in gastrointestinal pathologies, mechanisms in metabolic dysfunction-associated fatty liver disease and acute liver failure

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Abstract

In this editorial, we comment on three articles published in a recent issue of *World Journal of Gastroenterology*. There is a pressing need for new research on autophagy's role in gastrointestinal (GI) disorders, and also novel insights into some liver conditions, such as metabolic dysfunction-associated fatty liver disease (MAFLD) and acute liver failure (ALF). Despite advancements, understanding autophagy's intricate mechanisms and implications in these diseases remains incomplete. Moreover, MAFLD's pathogenesis, encompassing hepatic steatosis and metabolic dysregulation, require further elucidation. Similarly, the mechanisms underlying ALF, a severe hepatic dysfunction, are poorly understood. Innovative studies exploring the interplay between autophagy and GI disorders, as well as defined mechanisms of MAFLD and ALF, are crucial for identifying therapeutic targets and enhancing diagnostic and treatment strategies to mitigate the global burden of these diseases.

Key Words: Gastrointestinal diseases; Autophagy; Metabolic dysfunction-associated fatty liver disease; High-normal alanine aminotransferase level; Silent information regulator sirtuin 1; Acute liver failure

Core Tip: Exploration of autophagy's role in gastrointestinal (GI) disorders, as well as metabolic dysfunction-associated fatty liver disease (MAFLD) and acute liver failure (ALF), is imperative for advancing diagnostic and treatment strategies in gastroenterological diseases. Despite advancements, understanding autophagy's intricate mechanisms in these conditions remains incomplete. Further research into MAFLD's diagnostic markers and treatment modalities, considering its hepatic steatosis and metabolic dysregulation, is crucial. Elucidating diagnostic and therapeutic approaches for ALF, a severe hepatic dysfunction, is essential. Investigating autophagy's implications in diagnosing and treating GI disorders, MAFLD, and ALF is pivotal for improving patient outcomes.

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INTRODUCTION

In recent years, there is a growing body of evidence for the critical role of autophagy in gastrointestinal (GI) health and disease. Autophagy, a fundamental process in the cells, involved in the breakdown and recycling of impaired or malfunctioning cellular elements, has emerged as a critical player in maintaining GI homeostasis and responding to various pathological conditions. However, despite significant advancements in our understanding of autophagy, numerous questions remain unanswered regarding its intricate mechanisms and implications in GI disorders[1].

One area of particular interest is elucidating the molecular mechanisms underlying metabolic dysfunction-associated fatty liver disease (MAFLD), previously referred to as nonalcoholic fatty liver disease (NAFLD). As a multifaceted disorder encompassing both hepatic steatosis and metabolic dysregulation, MAFLD represents a significant public health concern worldwide. Despite its prevalence and impact on global health, the precise mechanisms driving the progression from simple steatosis to more severe liver pathology, such as nonalcoholic steatohepatitis (NASH) and acute liver failure (ALF), remain incompletely understood[2].

Furthermore, the pathogenesis of ALF, a life-threatening condition characterized by sudden and severe hepatic dysfunction, is poorly understood, posing significant challenges in its management and treatment. While autophagy has been implicated in ALF pathophysiology, its precise role and potential therapeutic implications require further investigation[3].

Thus, there is an urgent need for innovative research and studies aimed at unraveling the intricate interplay between autophagy, MAFLD, and ALF. By elucidating the underlying mechanisms and signaling pathways involved in these complex GI disorders, novel therapeutic targets may be identified, paving the way for developing more effective diagnostic and treatment strategies to improve patient outcomes and alleviate the global burden of GI-related diseases.

This is why we focus on three particular papers published in the recent issue of the *World Journal of Gastroenterology* in this editorial.

AUTOPHAGY IN GASTROINTESTINAL DISEASES

The minireview by Chang *et al*[4], published in the *World Journal of Gastroenterology*, examined descriptively and in detail the role of autophagy in GI diseases. Even though the studies in the field of apoptosis, *i.e.*, programmed cell death, are excessively numerous, there is still a lack of those concerning autophagy processes. Therefore, this article sheds light on the future of science and could be an excellent basis for further research in basis science and clinical practice. We choose to include this minireview in our editorial because it is presented and distinguished by its relevance.

It is well-known that autophagy has been discovered to serve a supportive function in non-life-threatening GI conditions such as intestinal ischemia-reperfusion (I/R) injury, inflammatory bowel disease (IBD), and motility GI disorders[1].

However, autophagy encourages the membrane localization of the occludin protein, a key component of tight junctions (TJ) responsible for enhancing the TJ barrier. This mechanism potentially safeguards against the loss of barrier function induced by inflammation[5].

Additionally, dysfunction in autophagy has the potential to disrupt intestinal barrier and initiate an intestinal inflammation culminating in chronic condition. Genome-wide association studies identified certain mutations in autophagy-related genes linked to IBD, including *ATG16L1*, *ULK1*, *NOD2*, *LRRK2*, and *IRGM*[6,7].

The minireview also highlights that the mechanisms of autophagy are discovered not only in intestinal I/R injury but also in GI motility disorders and GI cancers (*i.e.*, gastric colorectal). Furthermore, Chang *et al*[4] discussed the role of autophagy in the onset and progression of GI cancer and drug resistance. Numerous studies have revealed that various natural compounds can induce autophagy, exerting anti-cancer effects. However, one of the major drawbacks of Chang *et al*'s[4] paper is that they focused relatively insufficiently on the autophagy and GI drugs. In fact, they mentioned mainly some herbs while did not include relevant papers on the mutual relationship of autophagy and GI drugs.

It is worth mentioning that several studies solidified the connection between autophagy and the normal functions of GI cells. Furthermore, morphological studies have yielded data on pro-survival function of autophagy in benign GI diseases. However, in pathological states, the role of autophagy may vary, potentially influenced by the degree of the process or other factors. Consequently, further research on the autophagy involvement in GI tumors is imperative to unravel these questions and hypothesis.

EXCESS HIGH-NORMAL ALT LEVELS AND NEW-ONSET MAFLD

This retrospective cohort study by Chen *et al*[8], published in the recent issue of the *World Journal of Gastroenterology*, is exceptionally well presented and valuable because, although it deals with one of the most common degenerations in the world, its relationship to excess high-normal ALT (ehALT) levels is understudied. The authors also described MAFLD in detail, including a morphological perspective.

This article is fascinating, and the idea in such a detailed study is extremely promising and practical for clinicians. The cohort included 3553 patients presented at four consecutive health examinations for four years. Of practical significance is that 83.13% of MAFLD patients exhibited normal ALT levels. However, the MAFLD incidence demonstrated a consistent linear increase in the cumulative elevated ALT (ehALT) group.

Since MAFLD is characterized by the presence of both NAFLD and metabolic dysfunction and encompasses conditions such as overweight or obesity, type 2 diabetes, or other metabolic disorders, the diagnosis relies on liver biopsy, imaging examinations, or blood tests for biomarkers indicating fatty liver[9,10].

In line with this, a recent study has suggested that normal ALT levels serve as a significant biomarker for predicting NAFLD. Moreover, it has been found that NASH or advanced fibrosis can be diagnosed in a considerable proportion of NAFLD patients, ranging from 37.5% to 59%, who have normal ALT levels. The authors' previous research has also indicated a correlation between a typical ALT trajectory and the risk of developing new-onset MAFLD, as observed in the cohort study. Based on these findings, the authors suggested that a specific ALT level, particularly a long-term high-normal ALT level, may be related with an increased hazard ratio for new-onset MAFLD development[11-14].

This study by Chen *et al*[8] utilized a population-based cohort to investigate the cumulative impact of elevated ALT levels and the risk of new-onset MAFLD. A key strength of this study lies in its assessment of optimal reference range for ALT and the utilization of various methods to determine the cumulative values of elevated ALT levels and weight cumulative impact.

On the contrary to prior research that predominantly focused on single ALT measurements or ALT trajectories, this study took a novel approach by reflecting the long-term quantitative cumulative impact of ALT employing a lifespan methodology. By doing so, the study aimed to understand better the association between elevated ALT levels and the risk of developing MAFLD. However, there are some limitations to this study, *i.e.*, the follow-up of the patients was relatively short, and the proportion of participants with consistently elevated ALT levels was low. Still, they are not fatal and can inform future research. Additionally, future randomized controlled trials are warranted to explore the efficacy of various lifestyle interventions, such as weight loss through dietary modifications and physical exercise, in improving long-term ALT levels among individuals with high-normal levels. Understanding the potential of these interventions in preventing MAFLD could provide valuable insights into disease prevention strategies. Based on all the study's strengths and weaknesses, we consider the paper to be reliable and the data are of utmost significance.

NOVEL INSIGHTS INTO MECHANISMS OF ACUTE LIVER FAILURE

The other paper of significance in the current issue of the *World Journal of Gastroenterology*, acknowledged by us, is the original paper by Zhou *et al*[15].

This article is extremely well presented and valuable, even though the article included a small number of patients and healthy subjects. The subject of this article is one of the most common causes of high mortality among patients with liver disease. These authors further discussed two interrelated processes, ferroptosis and pyroptosis, considering them as silent information regulators of sirtuin 1 (SIRT1) in the process of mediated deacetylation affecting apoptosis, cellular senescence, metabolism, oxidative stress and inflammation. The aim of this study was clearly stated. Still, we believe that further studies on a larger number of patients are needed to acquire practical applicability.

The authors explored the role of ferroptosis and pyroptosis in mouse ALF model (utilizing lipopolysaccharide/D-galactosamine-induced ALF). Their findings revealed that activation of the SIRT1 mitigated ALF by modulating the p53/glutathione peroxidase 4 (GPX4)/gasdermin D pathway, which facilitated the crosstalk between ferroptosis and pyroptosis. By elucidating the upstream regulatory mechanisms, our study established a connection between ferroptosis and pyroptosis in ALF. These results hold promise for identifying potential therapeutic targets for ALF.

Chen *et al*[16] discovered that the levels of p53 remained unaffected despite the loss of ACSL4 and GPX4, and p53-induced ferroptosis occurred independently of GPX4. However, increased GPX4 activity decreased p53 transcription in contrast to the Western blot findings. The described discrepancy between mRNA and protein levels implies that other processes protein levels: post-transcriptional regulation, translational effectiveness, and post-translational modifications. It is speculated that lower translational efficiency may be balanced by heightened transcriptional activity[16]. Nonetheless, the mechanism behind p53 transcription and translation differences remains unclear.

SIRT1 has been widely recognized for its defending role in nutrient deprivation, DNA repair, aging, oxidative stress, and inflammation[17,18]. Research suggests that suppressed SIRT1 negatively impacts pyroptosis (GSDMD) and exacerbates acute pro-inflammatory responses in the liver[19]. This observation aligns with another research indicating that SIRT1 is downregulated in APAP-induced hepatotoxicity[20]. Resveratrol, a small-molecule SIRT1 activator, used as a therapeutic agent demonstrates a protection against mouse liver ischemia-reperfusion injury[21,22].

The study by Zhou *et al*[15] used mainly mouse and cell models but not clinical settings. Although their research demonstrated reduced expression of SIRT1 in human ALF liver tissue, the effectiveness of SIRT1 activators in treating acute liver injury and failure remains uncertain. We have to mention the major limitation to this study: The authors focused only on cellular and mouse models, but not clinical studies. Further investigations are warranted to assess the safety and efficacy of SIRT1 activators in clinical settings. Comprehensive studies are required to evaluate the potential benefits and risks associated with SIRT1 activation as a therapeutic approach for ALF, ultimately paving the way for informed clinical decisions and developing novel treatment strategies.

CONCLUSION

The three discussed studies serve as a wake-up call, bringing attention to the complex mechanisms of autophagy in GI disorders, revealing how this knowledge could be employed in clinical practice. While the first article highlights the mechanisms of autophagy in GI disorders, further research is required to translate these findings into clinical practice. Regarding the observational study by Chen *et al*[18], we agree that persistent ehALT levels increase the risk of new-onset MAFLD development in all patients, therefore the detection and active measurements to reduce ehALT levels may prevent MAFLD. As for ALF, similar to MAFLD, both conditions present the significant challenges in diagnosis and treatment, and clinical and fundamental studies are required. However, the original data on SIRT1 activation for attenuation of ferroptosis and pyroptosis induced by lipopolysaccharide/D-galactosamine by suppressing the p53/GPX4/GSDMD signaling in ALF, is a significant breakthrough in the current knowledge. Innovative research is crucial to unraveling their underlying mechanisms and identifying novel therapeutic targets. Such efforts will improve patient outcomes and reduce the global burden of GI-related diseases.

FOOTNOTES

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REFERENCES

1 **Thein W**, Po WW, Choi WS, Sohn UD. Autophagy and Digestive Disorders: Advances in Understanding and Therapeutic Approaches. *Biomol Ther (Seoul)* 2021; **29**: 353-364 [PMID: 34127572 DOI: 10.4062/biomolther.2021.086]

2 **Gofton C**, Upendran Y, Zheng MH, George J. MAFLD: How is it different from NAFLD? *Clin Mol Hepatol* 2023; **29**: S17-S31 [PMID: 36443926 DOI: 10.3350/cmh.2022.0367]

3 **Shingina A**, Mukhtar N, Wakim-Fleming J, Alqahtani S, Wong RJ, Limketkai BN, Larson AM, Grant L. Acute Liver Failure Guidelines. *Am J Gastroenterol* 2023; **118**: 1128-1153 [PMID: 37377263 DOI: 10.14309/ajg.0000000000002340]

4 **Chang YF**, Li JJ, Liu T, Wei CQ, Ma LW, Nikolenko VN, Chang WL. Morphological and biochemical characteristics associated with autophagy in gastrointestinal diseases. World J Gastroenterol 2024; 30: 1524-1532 [PMID: 38617452 DOI: 10.3748/wjg.v30.i11.1524]

5 **Saha K**, Subramenium Ganapathy A, Wang A, Michael Morris N, Suchanec E, Ding W, Yochum G, Koltun W, Nighot M, Ma T, Nighot P. Autophagy Reduces the Degradation and Promotes Membrane Localization of Occludin to Enhance the Intestinal Epithelial Tight Junction

Barrier against Paracellular Macromolecule Flux. *J Crohns Colitis* 2023; **17**: 433-449 [PMID: 36219473 DOI: 10.1093/ecco-jcc/jjac148]

6 **Liu JZ**, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, Ripke S, Lee JC, Jostins L, Shah T, Abedian S, Cheon JH, Cho J, Dayani NE, Franke L, Fuyuno Y, Hart A, Juyal RC, Juyal G, Kim WH, Morris AP, Poustchi H, Newman WG, Midha V, Orchard TR, Vahedi H, Sood A, Sung JY, Malekzadeh R, Westra HJ, Yamazaki K, Yang SK; International Multiple Sclerosis Genetics Consortium; International IBD Genetics Consortium, Barrett JC, Alizadeh BZ, Parkes M, Bk T, Daly MJ, Kubo M, Anderson CA, Weersma RK. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet* 2015; **47**: 979-986 [PMID: 26192919 DOI: 10.1038/ng.3359]

7 **Chauhan S**, Mandell MA, Deretic V. IRGM governs the core autophagy machinery to conduct antimicrobial defense. *Mol Cell* 2015; **58**: 507-521 [PMID: 25891078 DOI: 10.1016/j.molcel.2015.03.020]

8 **Chen JF**, Wu ZQ, Liu HS, Yan S, Wang YX, Xing M, Song XQ, Ding SY. Cumulative effects of excess high-normal alanine aminotransferase levels in relation to new-onset metabolic dysfunction-associated fatty liver disease in China. World J Gastroenterol 2024; 30: 1346-1357 [PMID: 38596503 DOI: 10.3748/wjg.v30.i10.1346]

9 **Lim GEH**, Tang A, Ng CH, Chin YH, Lim WH, Tan DJH, Yong JN, Xiao J, Lee CW, Chan M, Chew NW, Xuan Tan EX, Siddiqui MS, Huang D, Noureddin M, Sanyal AJ, Muthiah MD. An Observational Data Meta-analysis on the Differences in Prevalence and Risk Factors Between MAFLD vs NAFLD. *Clin Gastroenterol Hepatol* 2023; **21**: 619-629.e7 [PMID: 34871813 DOI: 10.1016/j.cgh.2021.11.038]

10 **Eslam M**, Sanyal AJ, George J; International Consensus Panel. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology* 2020; **158**: 1999-2014.e1 [PMID: 32044314 DOI: 10.1053/j.gastro.2019.11.312]

11 **Kang Y**, Park S, Kim S, Koh H. Normal serum alanine aminotransferase and non-alcoholic fatty liver disease among Korean adolescents: a cross-sectional study using data from KNHANES 2010-2015. *BMC Pediatr* 2018; **18**: 215 [PMID: 29976192 DOI: 10.1186/s12887-018-1202-z]

12 **Seko Y**, Sumida Y, Tanaka S, Mori K, Taketani H, Ishiba H, Hara T, Okajima A, Yamaguchi K, Moriguchi M, Mitsuyoshi H, Kanemasa K, Yasui K, Minami M, Imai S, Itoh Y. Serum alanine aminotransferase predicts the histological course of non-alcoholic steatohepatitis in Japanese patients. *Hepatol Res* 2015; **45**: E53-E61 [PMID: 25429984 DOI: 10.1111/hepr.12456]

13 **Wu Y**, Yang X, Morris HL, Gurka MJ, Shenkman EA, Cusi K, Bril F, Donahoo WT. Noninvasive Diagnosis of Nonalcoholic Steatohepatitis and Advanced Liver Fibrosis Using Machine Learning Methods: Comparative Study With Existing Quantitative Risk Scores. *JMIR Med Inform* 2022; **10**: e36997 [PMID: 35666557 DOI: 10.2196/36997]

14 **Chen JF**, Qin Q, Wu ZQ, Yan S, Song XQ, Ding SY. [A cohort study on the correlation between alanine aminotransferase trajectories and new-onset metabolic fatty liver disease]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2022; **43**: 234-240 [PMID: 35184490 DOI: 10.3760/cma.j.cn112338-20210809-00621]

15 **Zhou XN**, Zhang Q, Peng H, Qin YJ, Liu YH, Wang L, Cheng ML, Luo XH, Li H. Silent information regulator sirtuin 1 ameliorates acute liver failure via the p53/glutathione peroxidase 4/gasdermin D axis. World J Gastroenterol 2024; 30: 1588-1608 [PMID: 38617450 DOI: 10.3748/wjg.v30.i11.1588]

16 **Chen D**, Chu B, Yang X, Liu Z, Jin Y, Kon N, Rabadan R, Jiang X, Stockwell BR, Gu W. iPLA2β-mediated lipid detoxification controls p53-driven ferroptosis independent of GPX4. *Nat Commun* 2021; **12**: 3644 [PMID: 34131139 DOI: 10.1038/s41467-021-23902-6]

17 **Yang Y**, Liu Y, Wang Y, Chao Y, Zhang J, Jia Y, Tie J, Hu D. Regulation of SIRT1 and Its Roles in Inflammation. *Front Immunol* 2022; **13**: 831168 [PMID: 35359990 DOI: 10.3389/fimmu.2022.831168]

18 **Chen C**, Zhou M, Ge Y, Wang X. SIRT1 and aging related signaling pathways. *Mech Ageing Dev* 2020; **187**: 111215 [PMID: 32084459 DOI: 10.1016/j.mad.2020.111215]

19 **Kadono K**, Kageyama S, Nakamura K, Hirao H, Ito T, Kojima H, Dery KJ, Li X, Kupiec-Weglinski JW. Myeloid Ikaros-SIRT1 signaling axis regulates hepatic inflammation and pyroptosis in ischemia-stressed mouse and human liver. *J Hepatol* 2022; **76**: 896-909 [PMID: 34871625 DOI: 10.1016/j.jhep.2021.11.026]

20 **Wang C**, Liu T, Tong Y, Cui R, Qu K, Liu C, Zhang J. Ulinastatin protects against acetaminophen-induced liver injury by alleviating ferroptosis *via* the SIRT1/NRF2/HO-1 pathway. *Am J Transl Res* 2021; **13**: 6031-6042 [PMID: 34306342]

21 **Nakamura K**, Zhang M, Kageyama S, Ke B, Fujii T, Sosa RA, Reed EF, Datta N, Zarrinpar A, Busuttil RW, Araujo JA, Kupiec-Weglinski JW. Macrophage heme oxygenase-1-SIRT1-p53 axis regulates sterile inflammation in liver ischemia-reperfusion injury. *J Hepatol* 2017; **67**: 1232-1242 [PMID: 28842295 DOI: 10.1016/j.jhep.2017.08.010]

22 **Nakamura K**, Kageyama S, Ke B, Fujii T, Sosa RA, Reed EF, Datta N, Zarrinpar A, Busuttil RW, Kupiec-Weglinski JW. Sirtuin 1 attenuates inflammation and hepatocellular damage in liver transplant ischemia/Reperfusion: From mouse to human. *Liver Transpl* 2017; **23**: 1282-1293 [PMID: 28719070 DOI: 10.1002/lt.24821]

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