Molecular & Cellular Toxicology (2025) 21:387–397
https://doi.org/10.1007/s13273-025-00521-6

ORIGINAL ARTICLE

Overview of the hazardous impacts of metabolism-disrupting chemicals on the progression of fatty liver diseases

Garam An[1] · Jisoo Song[1] · Wei Ying[2] · Whasun Lim[1]

Accepted: 13 February 2025 / Published online: 27 February 2025

Abstract

Background Given the global increase in obesity, metabolic dysfunction-associated steatotic liver disease (MASLD) is a major health concern. Because the liver is the primary organ for xenobiotic metabolism, the impact of environmental stressors on liver homeostasis and MASLD has garnered significant interest over the past few decades. The concept of metabolism-disrupting chemicals (MDCs) has been introduced to underscore the importance of environmental factors in metabolic homeostasis. Recent epidemiological and biological studies suggest a causal link between exposure to MDCs and prevalence and progression of MASLD.

Objective This review aims to introduce the emerging concept of MDCs and their representative toxic mechanisms. In particular, this review focuses on broadening the understanding of their impacts on MASLD or metabolic dysfunction-associated steatohepatitis (MASH) progression.

Result Recent research has highlighted the environmental contaminants, such as heavy metals, microplastics, and pesticides, have the potential to influence hepatic metabolism and aggravate MASLD/MASH progression. These MDCs not only directly affect lipid metabolism in hepatocytes but also affect other cell types, such as immune cells and stellate cells, as well as the gut-liver axis.

Conclusion Collectively, these findings contribute to establishing a well-defined adverse outcome pathway and identify novel therapeutic options for liver diseases associated with pollutants.

Keywords Metabolism-disrupting chemicals · Metabolic dysfunction-associated steatotic liver diseases · Metabolic-associated steatohepatitis · Hepatocytes

Introduction

Lifetime exposure to environmental pollutants is inevitable in the context of global pollution; however, their precise contribution to adverse health outcomes remains elusive. Although the genotoxicity and carcinogenicity of pollutants were primary concerns decades ago, there is a steady accumulation of evidence showing that these pollutants are linked to the rising prevalence of metabolic diseases, including obesity, type 2 diabetes, fatty liver disease, and hyperlipidemia (Heindel et al. 2015a, 2017).

The hypothesis that environmental pollutants disrupt lipid metabolism, thereby exacerbating obesity, was initially proposed by Grun and Blumberg in 2007 (Grün and Blumberg 2007). In 2015, metabolism-disrupting chemicals (MDCs) were proposed as a new subclass of endocrine-disrupting chemicals (EDCs) to highlight the importance of environmental factors in the global increase in metabolic diseases. MDCs are environmental chemicals that can affect the risk of metabolic disorders throughout an individual's lifespan (Heindel et al. 2015a, b).

Given the pivotal role of the liver in xenobiotic metabolism, this review focused on the role of MDCs in metabolic

Garam An and Jisoo Song contributed equally to the study.

✉ Wei Ying
weying@health.ucsd.edu

✉ Whasun Lim
wlim@skku.edu

[1] Department of Biological Sciences, Institute of Basic Science, College of Science, Sungkyunkwan University, Suwon 16419, Republic of Korea

[2] Division of Endocrinology and Metabolism, Department of Medicine, University of California, San Diego, La Jolla, CA 92093, USA

dysfunction-associated steatotic liver disease (MASLD). Recent research will be discussed to expand our understanding of the connection between MASLD progression and exposure to representative MDCs such as heavy metals, microplastics, and pesticides. Additionally, this review addresses the adverse effects of MDCs on various cell types within the liver and gut-liver interactions.

Overview of MASLD development

Because the liver is one of the crucial organs responsible for metabolism, especially lipids, the pathogenesis and progression of MASLD are highly influenced by other metabolic factors, such as insulin resistance, hyperlipidemia, and obesity. This correlation with liver disease prevalence in the obese population has been validated using many clinical databases (Quek et al. 2023). MASLD, formerly termed nonalcoholic fatty liver disease (NAFLD), represents a broad spectrum of liver disorders initiated by the overaccumulation of lipids in hepatocytes (Li et al. 2024). This initial phase of MASLD, defined as lipid accumulation (steatosis) in > 5% of hepatocytes, is considered reversible without severe inflammation or fibrosis (Chalasani et al. 2018). As simple steatosis advances to include significant liver injuries, such as fibrosis, it is classified as metabolic dysfunction-associated steatohepatitis (MASH). These liver disorders lead to irreversible and fatal liver conditions, including cirrhosis and hepatocellular carcinoma (HCC) (Suresh et al. 2020) (Fig. 1).

MASLD is a growing health concern worldwide. According to a meta-analysis published in 2016, the global prevalence of MASLD was approximately 25%, and the overall mortality was estimated at 15.44 and 25.56 per 1000 person-years for the MASLD and MASH cohorts, respectively (Younossi et al. 2016). While overnutrition and lifestyle changes are thought to be key contributors to the growing prevalence of MASLD, environmental toxicants, such as heavy metals, microplastics, and pesticides, have recently gained recognition as significant factors (Fig. 2). Such toxicants may directly affect various cell types within the liver or act indirectly by influencing the gut-liver axis or endocrine systems.

Link between MDCs and MASLD/MASH progression

Heavy metals

The increasing environmental presence of heavy metals driven by industrial activities has recently made widespread exposure inevitable. The deleterious influence of heavy metals on human health is well recognized, with frequent suggestions of their link to liver diseases. For instance, a study with a 23-year American cohort demonstrated that exposure to cadmium (Cd) during early adulthood (ages 20–32 years) is significantly associated with MASLD prevalence in middle age (Li et al. 2022a, b, c, d). Another study utilizing epidemiological data from the USA (2003–2018) also identified positive correlations between the urinary levels of heavy metals, including arsenic (As), cobalt (Co), and Cd, and MASLD risk (Xie et al. 2023).

The implications of Cd in liver disease have been highlighted, as the liver and kidney account for approximately 50% of the body load for Cd (Bernard 2004). With

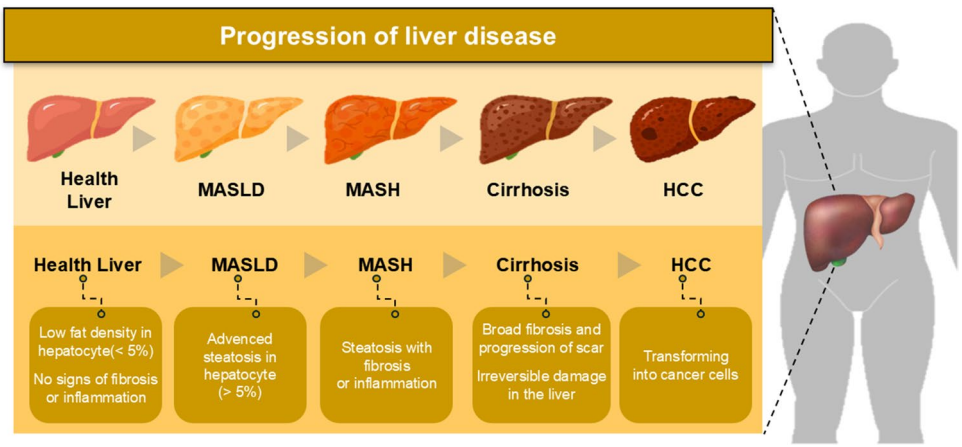

Fig. 1 The progression of metabolic dysfunction-associated steatotic liver diseases (MASLD) to hepatocellular carcinoma (HCC). MASLD is characterized by excessive lipid accumulation in over 5% of hepatocytes and can evolve into metabolic dysfunction-associated steatohepatitis (MASH), which has inflammation or fibrosis. Persistent inflammatory and fibrotic conditions can further develop into cirrhosis and hepatocellular carcinoma (HCC), both of which pose life-threatening risks

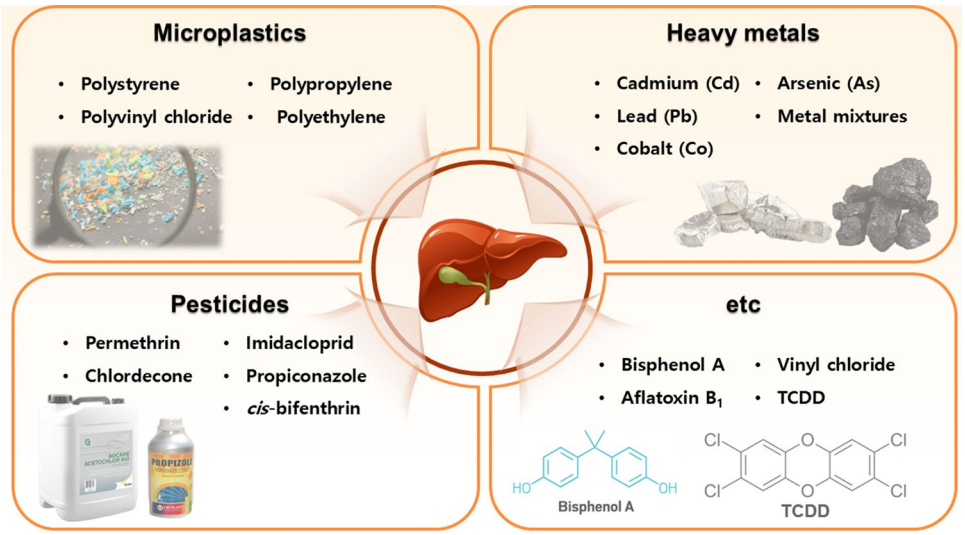

Fig. 2 Representative metabolic-disrupting chemicals (MDCs) linked to liver dysfunction or MASLD/MASH progression through epidemiological or biological evidence

epidemiological evidence demonstrating the impact of Cd on MASLD, numerous studies have aimed to uncover the biological mechanisms driving the development of MASLD/MASH. When mice were exposed to Cd in drinking water (10 mg/L of $CdCl_2$) from the onset of a high-fat diet for six or twelve weeks, hepatic lipid deposition and inflammation were exacerbated. This lipogenic effect was mediated through the peroxisome proliferator-activated receptor (PPAR) pathways related to fatty acid metabolism (Zhu et al. 2022). Cd also induces hepatic inflammation by modulating macrophage polarization. Specifically, saturated fatty acids and Cd synergistically enhance pro-inflammatory M1 polarization, causing hepatic steatohepatitis in vivo (Zhu et al. 2023).

Lead (Pb) also induces hepatic damage because the liver is the main organ for Pb accumulation when it is inhaled or ingested (González Rendón et al. 2018; Mudipalli 2007). Pb-induced hepatotoxicity was demonstrated by increased serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which are representative markers of hepatic damage (González Rendón et al. 2018). The exact hepatotoxic mechanisms of Pb remain debatable, and several mechanisms have been suggested. In HepG2 cells, Pb impairs autophagic flux via the SIRT1/mTOR pathway, which causes abnormal hepatic lipid accumulation (Zhao et al. 2022). Pb can directly affect hepatocytes but is also thought to be involved in the gut-liver axis. Mice chronically exposed to 0.1 mg/L Pb (15 weeks) showed an alteration in gut microbiota and subsequent hepatic triglyceride accumulation (Xia et al. 2018). Dysbiosis has also been observed in Pb-exposed common carp, leading to the synthesis of microbially-derived lipopolysaccharide (LPS), which subsequently induces hepatocyte ferroptosis (Miao et al. 2023).

Microplastics

The production and use of plastics in daily life have been increasing, leading to greater environmental leakage of microplastics (Thompson et al. 2024; Wang et al. 2024a, b, c). These microplastics are found in various locations and are considered new pollutants that cause environmental contamination and ecosystem problems (Du et al. 2021; Enyoh et al. 2019). Recent studies suggest that microplastics may affect body accumulation and liver disease. A study conducted in Germany and across Europe analyzed tissue samples from healthy individuals and cirrhosis patients for microplastics. The findings suggest a potential link between the accumulation of microplastics in the liver and the development of liver disease. (Horvatits et al. 2022). Moreover, in a cohort study of obese individuals with or without MASH, those with persistent MASLD at 12 months after bariatric surgery had higher levels of microplastic fragments, which affected the portal vein, macrophages, and T cells (Schwenger et al. 2024).

Polypropylene and polystyrene are the most commonly detected microplastics, even in tap water, and considerable research has been conducted on their effects on the liver (Liu et al. 2022; Tong et al. 2020; Wang et al. 2024a, b, c). First, polypropylene mainly interferes with lipid biosynthesis and homeostasis in the liver, affecting lipid droplet formation, which can lead to energy storage issues and metabolic dysfunction (Liu et al. 2023). Furthermore, regulating the $NADH/NAD^+$ ratio induces oxidative stress in the liver, decreases the cellular energy supply, and causes mitochondrial dysfunction and triglyceride accumulation, ultimately leading to metabolic disorders (Cheng et al. 2024). Furthermore, polystyrene, when exposed through oral intake, primarily accumulates in the kidneys, intestines,

and liver, inducing changes in metabolic profiles, such as energy metabolism, lipid metabolism, and oxidative stress in the liver (Hasegawa et al. 2024). It regulates the pathways related to oxidative stress and inflammation, ultimately causing liver damage, which is linked to the development of MASLD (Sheng et al. 2024; Zhou et al. 2023; Zou et al. 2023). A previous study demonstrated that administering polystyrene to mice caused physiological disturbances, including lipid accumulation, increased liver weight, and elevated glucose, ALT, and AST levels. It also increases the levels of oxidative stress biomarkers (SOD and HNE-AM) and inflammatory cytokines in the liver, suggesting potential metabolic dysfunction and liver toxicity that resemble MASH symptoms (Lee et al. 2024). In another study, when mice were treated with 4.3 g per week, based on the maximum weekly intake in humans (5 g), polystyrene accumulated in the blood vessels, liver, and kidneys. This exposure results in histological liver damage and elevated AST levels. Furthermore, polystyrene induces glucose intolerance and insulin resistance, exacerbated under high-fat diet conditions (Huang et al. 2022). Additionally, polyvinyl chloride (PVC), produced using vinyl chloride, a known carcinogen, has been reported to primarily target the liver, leading to liver damage and exacerbation of immune responses (Zarus et al. 2023). Chronic exposure to PVC causes disruptions in lipid metabolism and increased AST and ALT levels, leading to hepatocyte death, toxicity, and functional impairment (Chen et al. 2022). Furthermore, polyethylene, one of the most frequently detected microplastics in bottled water and food, has been identified as a potential health risk due to its low biodegradability and high thermal stability (Maurya et al. 2024). Exposure to polyethylene induces gene expression changes related to fatty acid metabolism, promotes oxidative stress, and increases *Pdgfa* expression and collagen accumulation, contributing to liver fibrosis (Djouina et al. 2023). Moreover, polyethylene has been confirmed to induce inflammation, disrupt gut microbiota homeostasis, and activate the TLR/NF-κB/NLRP3 pathway, leading to liver damage (Xu et al. 2024).

Pesticides

Human exposure to pesticides directly or indirectly affects workers via residues in their environment and food. According to a meta-analysis, the risk of MASLD was positively associated with the urinary levels of mixed pesticide groups, which comprised six metabolites from pyrethroids, organophosphates, and herbicides (Li et al. 2022a, b, c, d).

Despite evidence of the hazardous effects of pesticides on human health, restrictions on their use remain controversial owing to economic benefits and uncertainties regarding their toxicity. For instance, paraquat, which is extensively used for weed control, has been banned in many countries since 2011, yet an estimated 10 million pounds were applied in 2017, according to the US Geological Survey (Gerald McGwin and Griffin 2022; US Geological Survey 2017). However, its effect on human diseases, including fatty liver disease, has been extensively reported (Ma et al. 2024). Therefore, understanding the biological mechanisms underlying their toxicity is crucial for preventing and treating pesticide-induced diseases.

One of the classes of pesticides, pyrethroids, has been considered to have lower mammalian toxicity than other pesticides, such as organophosphates and organochlorine (Hodoșan et al. 2023). However, one of the pyrethroids, permethrin, showed the greatest effect on triglyceride accumulation in HepG2 cells compared to other pesticide groups. These effects are mediated by the regulation of acetyl-CoA carboxylase (ACC) phosphorylation, which is the rate-limiting enzyme during lipogenesis (Yang et al. 2019). A recent study also showed that oxidative stress and disruption of lipid metabolism through PPAR and GLUT signaling were induced in the livers of zebrafish larvae (Khan et al. 2024). The potential effect of another pyrethroid, *cis*-bifenthrin, on MASLD has also been suggested. In *Xenopus laevis*, exposure to environmentally relevant levels of *cis*-bifenthrin led to elevated AST, ALT, and hepatic lipid levels, with suggested mechanisms involving molecular interactions with PPAR isoforms to promote lipogenesis (Li et al. 2022b). Liver damage by *cis*-bifenthrin can be linked to microbiota dysbiosis, leading to altered deoxycholic acid levels and disruption of bile acid circulation (Li et al. 2022a). Several findings have highlighted the potential link between pyrethroids and hepatic lipogenesis. However, there is still a lack of epidemiological data establishing a direct correlation with the prevalence of MASLD.

In addition to hepatic steatosis, pesticides promote fibrosis, potentially progressing to MASH. For example, chlordecone, an organochlorine pesticide, has been reported to trigger fibrosis in liver organoids comprising hepatocytes, macrophages, and stellate cell lines (Léger et al. 2024). Additionally, several pesticides, namely imidacloprid, propiconazole, and deltamethrin, have been identified as pro-fibrogenic on the liver through TGF-β1/Smad pathway (Han et al. 2020; Kwon et al. 2021; Lv et al. 2020). However, research on the influence of pesticides on fibrotic or non-parenchymal cells, in addition to hepatocytes, remains limited, highlighting the need for further studies.

Toxic effects of MDCs on different liver cell population

While hepatocytes constitute the majority of liver, non-parenchymal cells (NPCs) also significantly contribute to its function. MDCs can exert toxicity by directly affecting

hepatocyte lipogenesis or by indirectly disrupt liver homeostasis through their effects on NPCs, including immune and stellate cells (Fig. 3).

Hepatocytes

Hepatocytes are the parenchymal cells of the liver, constituting most of their mass, and are known to perform various cellular functions essential for maintaining liver homeostasis, as well as playing a critical role in the development of liver inflammation and fibrosis (Gong et al. 2023). Hepatic steatosis occurs due to an imbalance in the uptake and production of fatty acids and fatty acid oxidation within hepatocytes, stimulating triglyceride synthesis and accumulating neutral lipids in the cell. When free fatty acids (FFAs) are abnormally processed, triglycerides trigger resident and infiltrating macrophages via the toll-like receptor 4 (TLR4) signaling pathway, initiating an inflammatory cascade that contributes to MASLD (Foulds et al. 2017; Wree et al. 2013).

Recent studies have shown that hepatocytes, under the influence of MDCs, may induce MASLD and other diseases through mechanisms such as oxidative stress, insulin resistance, and increased de novo lipogenesis (Li et al. 2015; Marmugi et al. 2012; Moon et al. 2015). For instance, when bisphenol A, an MDC compound, was applied to HepG2 cells, it increased the mitochondrial membrane potential and reactive oxygen species (ROS) production within the cells, thereby inducing mitochondrial dysfunction, lipid accumulation, lipid peroxidation and the release of cytokines, leading to a state of steatosis (Huc et al. 2012). Additionally, when propiconazole was applied to HepG2 and HepaRG cells, it increased the liver weight, activated ALT. It targeted the pregnane X receptor (PXR) gene, which elevated fat absorption, leading to the accumulation of neutral lipids in the cells. Furthermore, administration of high doses of propiconazole induces liver inflammation and fibrosis, confirming that propiconazole induces hepatic steatosis within the liver and is associated with liver diseases (Attema et al. 2024). In addition, treatment of hepatocytes with MDCs such as perfluoroalkyl substances (PFAS), DEHP, and tributyltin chloride (TBT) has been shown to regulate cholesterol biosynthesis pathways, activate the PPARα and SREBP-1c signaling pathways, and bind to PPARγ/RXRα, leading to lipid accumulation, lipid production, and the induction of oxidative stress (Louisse et al. 2020; Stossi et al. 2019; Zhang et al. 2017). These studies demonstrate that MDCs primarily induce lipid accumulation and mitochondrial dysfunction in hepatocytes by promoting de novo lipogenesis.

Immune cells

In addition to being a pivotal organ for controlling metabolism and detoxification, the liver contains various immune cells that significantly influence hepatic homeostasis, both directly and indirectly. According to recent transcriptomic studies, the reshaping of immune cell populations has been observed in the livers of MASH mice and cirrhotic humans (Ramachandran et al. 2019; Remmerie et al. 2020). Although more research is required to fully elucidate the exact mechanisms by which an altered immune repertoire contributes to MASLD/MASH progression, considerable evidence supports a connection between immune cells and hepatic injury (Huby and Gautier 2022). Therefore, elucidating the effect of environmental pollution on the hepatic immune system may provide novel insights into its role in MASLD/MASH progression.

Among the various environmental pollutants, the role of microplastics in disrupting the homeostasis of the hepatic immune system has been a particularly active area

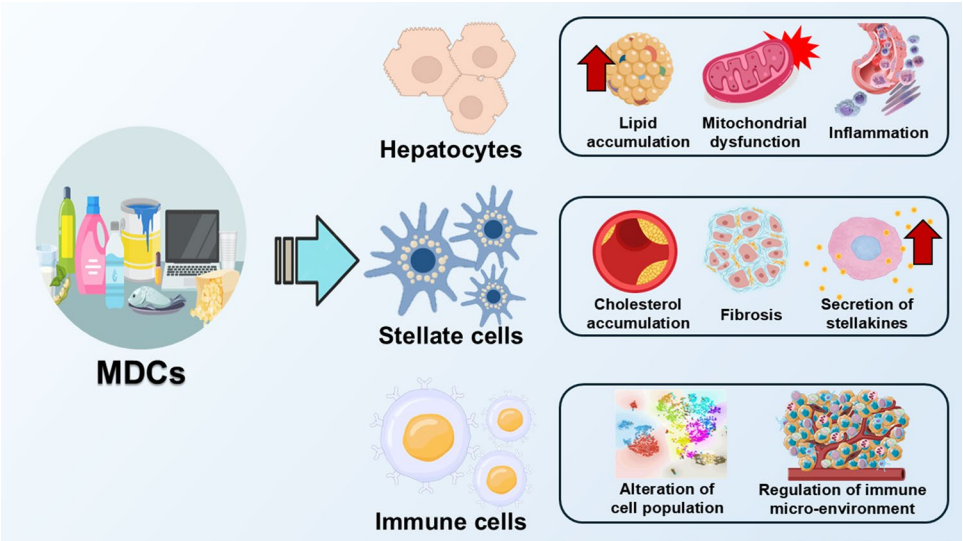

Fig. 3 Influence of metabolic-disrupting chemicals (MDCs) on distinct cell populations in the liver

of research. In research published in 2021, oral ingestion of 0.5 μm polystyrene-microplastics (0.5 mg/100 μL for 28 days) caused hepatic injury in mice, along with changes in immune cell composition, including a decrease in $CD4^+$ T cells, and an increase in NK cells and pro-inflammatory M1 macrophage (Zhao et al. 2021). Although this study did not explicitly link microplastics to MASLD, it offers foundational knowledge regarding the involvement of immune processes in the hepatotoxic effects of microplastics. Recent studies have expanded our understanding of the role of microplastics in metabolic diseases from an immunological perspective. Administration of microplastics (1 μm of polystyrene for 18 weeks) exacerbated MASLD features such as steatosis, ballooning, and inflammation in mice fed with a high-fat diet (HFD). In that study, single-cell transcriptome analysis revealed that HFD feeding combined with microplastics decreased $Vsig4^+$ and increased $S100a6^+$ macrophages (Liu et al. 2024). $Vsig4^+$ hepatic macrophages are responsible for opsonizing pathogens, and a reduction in this population has been observed during hepatic injury (Duan et al. 2021; Zheng et al. 2015). Additionally, elevated S100A6 levels in Kupffer cells aggravate inflammation and increase the infiltration of monocytes/macrophages (Tong et al. 2023). These findings suggest that MP exposure may exacerbate MASLD progression by modulating the immune microenvironment.

In addition to altering immune cell populations, environmental pollutants can affect disease progression by modulating molecular pathways within these cells. As a representative mycotoxin, aflatoxin B_1 drives crosstalk between the aryl hydrocarbon receptor (AhR) and TLR4 in hepatic macrophages, thereby reducing the phosphorylation of $STAT3^{Ser727}$, which functions as a ROS blocker and contributes to the onset of steatohepatitis (Zhang et al. 2024). MicroRNAs (miRNAs) are another example of ant-mediated immune regulation. In BALB/c mice, intradermal exposure to trichloroethylene, an industrial environmental pollutant, shifts Kupffer cells to a proinflammatory phenotype through miR-205-5p modulation. This miRNA mainly targeted retinoic acid receptor-related orphan receptor-α (RORα), resulting in M1 polarization (Wang et al. 2024a, b, c). These recent findings highlight the need for further investigation into the role of immune cells in MASLD/MASH progression could provide key insights into understanding pollutant-induced hepatotoxicity.

Stellate cells

Hepatic stellate cells (HSCs), located in the space of Disse, are mesenchymal cells that form a small population within the liver and play a critical role in response to liver injury (Kamm and McCommis 2022). The transition of HSCs from a quiescent to an activated state upon liver injury, caused by oxidative stress and inflammatory signals, primarily leads to fibrosis (Tsuchida and Friedman 2017; Zisser et al. 2021). The activation of HSCs involves their differentiation from vitamin A-storing cells into contractile, inflammatory, and myofibroblast-like cells, which enhance the production of extracellular matrix (ECM) (Friedman 2008; Puche et al. 2013). Additionally, HSCs communicate with surrounding endothelial and immune cells by secreting stellakines, further enhanced during MASH and liver injury. Dysregulation of stellakine secretion by HSCs has been suggested as a potential factor in the pathogenesis of MASH (Xiong et al. 2019).

Recent studies have reported that MDCs influence HSC activation and contribute to liver damage. The effects of MDC treatment include vitamin A depletion, cholesterol accumulation, and fibrosis progression. For instance, when Di(2-ethylhexyl) phthalate (DEHP) was applied to the hepatic stellate cell line LX-2, it promoted inflammation, apoptosis, and fibrosis within the cells, along with an increased expression of genes associated with inflammation and fibrosis, such as α-SMA, COL-I, COL-III, TGF-β, and Smad2 (Zhao et al. 2019). Long-term exposure to low doses of DEHP increases cholesterol synthesis in HSCs, causing an imbalance between HSCs proliferation and apoptosis (Lee et al. 2020). Furthermore, when hepatic stellate cells and animal models were co-exposed to cadmium and microplastics, an increase in the expression of α-SMA, TGF-β, collagen I, and collagen IV was observed in the animal models. To investigate the activation mechanism of HSCs, they were treated with AML12 medium and co-treated with cadmium and microplastics. These results confirm that the cells were activated through the interaction between ATP released via the hemichannels and the P2X7 receptor (Sun et al. 2023). In summary, previous studies have suggested that metabolism-disrupting chemicals exert direct and indirect effects on HSCs, activating these cells and contributing to liver disease.

Effects of MDCs on liver dysfunction via disruption of gut-liver axis

The implications of the intestine on MASLD/MASH progression have been reported. Altered gut microbial populations lead to changes in intestinal permeability and increased circulating endotoxins and bacterial metabolites that can reach the liver and activate inflammatory responses (Fukui 2015). Indeed, the severity of steatosis positively correlates with increased gut permeability in MASLD patients (Miele et al. 2009). Based on these findings, various studies have explored whether the hazardous impact of MDCs on the liver are mediated through gut-liver axis, with reports suggesting that MDCs can indeed affect MASLD via this

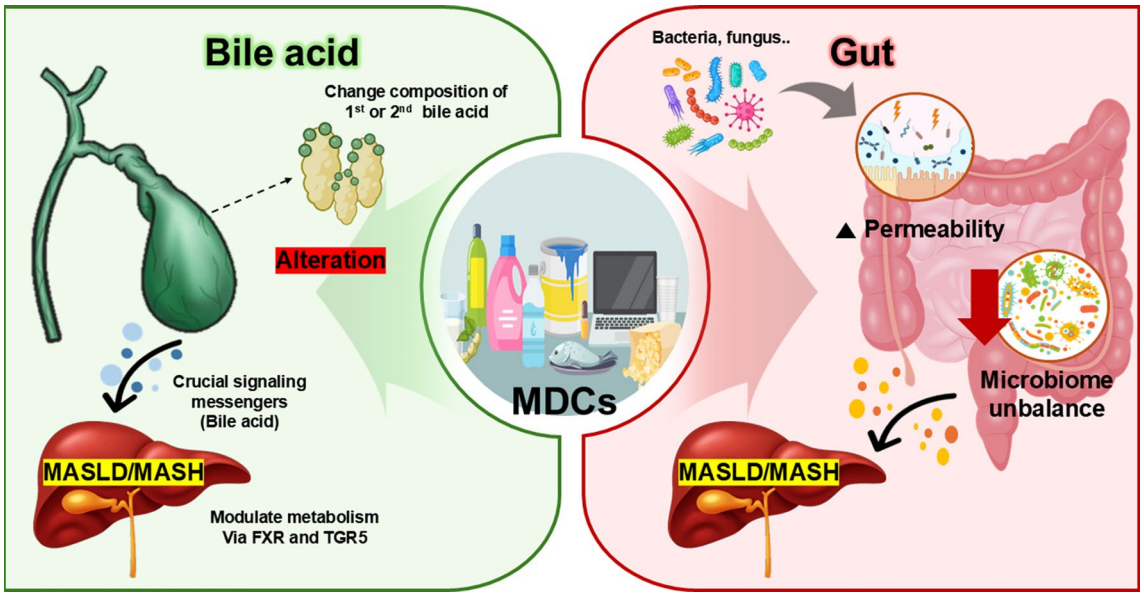

Fig. 4 Impacts of metabolic-disrupting chemicals (MDCs) on liver dysfunction by disrupting intestine-liver interactions. MDC exposure can lead to dysbiosis or altered gut permeability, resulting in increased levels of circulating bacterial metabolites. MDCs also interfere with bile acid homeostasis, disrupting their vital functions as key messengers in gut-liver communication

pathway (Fig. 4). A recent study, as an example, confirmed a correlation between the altered gut microbiota composition and the serum concentrations of various environmental toxicants, with a particular focus on synthetic industrial compounds, in male and female Danes (Sen et al. 2024).

Dysbiosis is associated with liver disease. For instance, an increase in Proteobacteria and a decline in Firmicutes have been observed as liver disease progresses to advanced fibrosis in humans (Loomba et al. 2017). Similarly, reduced microbial diversity and the presence of *Coprococcus* and *Ruminococcus gnavus* were associated with steatosis in a large-scale analysis of 1355 adults (Alferink et al. 2021). Thus, environmental compounds that alter the gut microbiota are considered potential risk factors for MASLD/MASH development. For instance, Pb hepatotoxicity is accompanied by gut mucosal ablation, a decline in the biodiversity of gut microbes, and an altered bacterial composition (*Ruminococcus* and *Streptococcus*) (Duan et al. 2024). Feeding with environmentally relevant levels of bisphenol A (50 µg/kg/day) elevated Proteobacterium and decreased the abundance of Akkermansia, resulting in steatosis and hepatic inflammation in mice (Feng et al. 2020). Akkermansia has been reported to have a protective function in the intestinal mucosal layer and gut barrier (Ottman et al. 2017), impair intestinal permeability, and further increase serum LPS levels, which are considered to be the cause of bisphenol A-mediated hepatotoxicity (Feng et al. 2020).

Within the enterohepatic circulation, bile acids serve as crucial signaling messengers that modulate metabolism in various tissues, primarily through the regulation of the farnesoid X receptor (FXR) and Takeda G-protein receptor 5 (TGR5) (Perino and Schoonjans 2022). Owing to their impact on metabolic regulation, bile acids are attractive etiological candidates for MASLD (Chávez-Talavera et al. 2019). For instance, recent research has identified that reduced 3-succinylated cholic acid causes MASLD development, as it contributes to reshaping microbiota populations to alleviate MASLD/MASH progression (Nie et al. 2024). Based on recent insights into the role of bile acids, the impact of environmental factors on bile acids has become a concern. Hepatic damage induced by polystyrene microplastics (5 mg/kg for 30 days) was accompanied by an altered balance between primary and secondary bile acids in mouse feces (Wen et al. 2024). Maternal exposure to procymidone affected glucolipid metabolism in the F1 generation in the mouse model. In the offspring, serum levels of bile acids change with different microbiota populations, suggesting that the gut microbiota and bile acids play important roles in transgenerational toxicity (Wang et al. 2023).

Conclusion and perspectives

Recent findings suggest that the global surge in MASLD/MASH cases may be influenced by a lack of exercise, overnutrition, and exposure to environmental pollutants. Growing evidence shows that exposure to heavy metals, microplastics, and pesticides, classified as MDCs, can perturb the metabolic homeostasis of hepatocytes, non-parenchymal cells such as immune and stellate cells, and the gut-liver

axis. However, further in vivo and in vitro studies are necessary to elucidate the direct connection between biological causes and negative health outcomes based on epidemiological evidence that reflects realistic human exposure to specific pollutants. Such research could contribute to establishing a well-defined adverse outcome pathway (AOP) and identify novel therapeutic options for liver diseases associated with pollutants.

Author contributions GA: validation, investigation, data curation, visualization, and writing—original draft; JS: investigation, data curation, and writing—original draft; WY: conceptualization, validation, writing—review and editing, supervision, project administration; WL: conceptualization, methodology, validation, writing—review and editing, supervision, and project administration.

Funding Open Access funding enabled and organized by SungKyunKwan University. This research was supported by the National Research Foundation (NRF) grant funded by the Korean government (MSIT) (Grant number: RS-2024-00411768 and RS-2024-00453204). This work was also funded by U.S. NIH grants (R21HD107516, R00DK115998, and R01DK125560 to W.Y.). This work was supported by the Sungkyunkwan President Fellowship Program (2024).

Data availability All datasets presented in this study can be obtained by contacting the corresponding author.

Declarations

Conflict of interest Garam An declares that she has no conflict of interest. Jisoo Song declares that she has no conflict of interest. Wei Ying declares that he has no conflict of interest. Whasun Lim declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

Alferink LJM, Radjabzadeh D, Erler NS, Vojinovic D, Medina-Gomez C, Uitterlinden AG, de Knegt RJ, Amin N, Ikram MA, Janssen HLA, Kiefte-de Jong JC, Metselaar HJ, van Duijn CM, Kraaij R, Darwish Murad S (2021) Microbiomics, metabolomics, predicted metagenomics, and hepatic steatosis in a population-based study of 1,355 adults. Hepatology 73:968–982. https://doi.org/10.1002/hep.31417

Attema B, Kummu O, Krutáková M, Pavek P, Hakkola J, Hooiveld GJEJ, Kersten S (2024) The fungicide propiconazole induces hepatic steatosis and activates PXR in a mouse model of diet-induced obesity. Arch Toxicol. https://doi.org/10.1007/s00204-024-03942-9

Bernard A (2004) Renal dysfunction induced by cadmium: biomarkers of critical effects. Biometals 17:519–523. https://doi.org/10.1023/B:BIOM.0000045731.75602.b9

Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ (2018) The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 67:328. https://doi.org/10.1002/hep.29367

Chávez-Talavera O, Haas J, Grzych G, Tailleux A, Staels B (2019) Bile acid alterations in nonalcoholic fatty liver disease, obesity, insulin resistance and type 2 diabetes: what do the human studies tell? Curr Opin Lipidol 30:244. https://doi.org/10.1097/MOL.0000000000000597

Cheng W, Chen H, Zhou Y, You Y, Lei D, Li Y, Feng Y, Wang Y (2024) Aged fragmented-polypropylene microplastics induced ageing statues-dependent bioenergetic imbalance and reductive stress: *in vivo* and liver organoids-based *in vitro* study. Environ Int 191:108949. https://doi.org/10.1016/j.envint.2024.108949

Chen X, Zhuang J, Chen Q, Xu L, Xia Y, Qiao D (2022) Chronic exposure to polyvinyl chloride microplastics induces liver injury and gut microbiota dysbiosis based on the integration of liver transcriptome profiles and full-length 16S rRNA sequencing data. Sci Total Environ 839:155984. https://doi.org/10.1016/j.scitotenv.2022.155984

Djouina M, Waxin C, Dubuquoy L, Launay D, Vignal C, Malapel MB (2023) Oral exposure to polyethylene microplastics induces inflammatory and metabolic changes and promotes fibrosis in mouse liver. Ecotoxicol Environ Saf 264:115417. https://doi.org/10.1016/j.ecoenv.2023.115417

Du J, Zhou Q, Li H, Xu S, Wang C, Fu L, Tang J (2021) Environmental distribution, transport and ecotoxicity of microplastics: a review. J Appl Toxicol 41:52–64. https://doi.org/10.1002/jat.4034

Duan Y, Chu H, Brandl K, Jiang L, Zeng S, Meshgin N, Papachristoforou E, Argemi J, Mendes BG, Wang Y, Su H, Sun W, Llorente C, Hendrikx T, Liu X, Hosseini M, Kisseleva T, Brenner DA, Bataller R, Ramachandran P, Karin M, Fu W, Schnabl B (2021) CRIg on liver macrophages clears pathobionts and protects against alcoholic liver disease. Nat Commun 12:7172. https://doi.org/10.1038/s41467-021-27385-3

Duan Y, Yang Y, Zhang Z, Nan Y, Xiao M (2024) The toxic effect of lead exposure on the physiological homeostasis of grouper: Insight from gut-liver axis. Mar Pollut Bull 207:116926. https://doi.org/10.1016/j.marpolbul.2024.116926

Enyoh CE, Verla AW, Verla EN, Ibe FC, Amaobi CE (2019) Airborne microplastics: a review study on method for analysis, occurrence, movement and risks. Environ Monit Assess 191:668. https://doi.org/10.1007/s10661-019-7842-0

Feng D, Zhang H, Jiang X, Zou J, Li Q, Mai H, Su D, Ling W, Feng X (2020) Bisphenol A exposure induces gut microbiota dysbiosis and consequent activation of gut-liver axis leading to hepatic steatosis in CD-1 mice. Environ Pollut 265:114880. https://doi.org/10.1016/j.envpol.2020.114880

Foulds CE, Treviño LS, York B, Walker CL (2017) Endocrine-disrupting chemicals and fatty liver disease. Nat Rev Endocrinol 13:445–457. https://doi.org/10.1038/nrendo.2017.42

Friedman SL (2008) Hepatic stellate cells: protean, multifunctional, and enigmatic cells of the liver. Physiol Rev 88:125–172. https://doi.org/10.1152/physrev.00013.2007

Fukui H (2015) Gut-liver axis in liver cirrhosis: How to manage leaky gut and endotoxemia. World J Hepatol 7:425. https://doi.org/10.4254/wjh.v7.i3.425

Gerald McGwin J, Griffin RL (2022) An ecological study regarding the association between paraquat exposure and end stage renal disease. Environ Health 21:127. https://doi.org/10.1186/s12940-022-00946-9

Gong J, Tu W, Liu J, Tian D (2023) Hepatocytes: a key role in liver inflammation. Front Immunol. https://doi.org/10.3389/fimmu.2022.1083780

González Rendón ES, Cano GG, Alcaraz-Zubeldia M, Garibay-Huarte T, Fortoul TI (2018) Lead inhalation and hepatic damage: morphological and functional evaluation in mice. Toxicol Ind Health 34:128–138. https://doi.org/10.1177/0748233717750981

Grün F, Blumberg B (2007) Perturbed nuclear receptor signaling by environmental obesogens as emerging factors in the obesity crisis. Rev Endocr Metab Disord 8:161–171. https://doi.org/10.1007/s11154-007-9049-x

Han B, Lv Z, Zhang X, Lv Y, Li S, Wu P, Yang Q, Li J, Qu B, Zhang Z (2020) Deltamethrin induces liver fibrosis in quails via activation of the TGF-β1/Smad signaling pathway. Environ Pollut 259:113870. https://doi.org/10.1016/j.envpol.2019.113870

Hasegawa Y, Okamura T, Ono Y, Ichikawa T, Saijo Y, Nakanishi N, Sasano R, Hamaguchi M, Takano H, Fukui M (2024) Oral exposure to high concentrations of polystyrene microplastics alters the intestinal environment and metabolic outcomes in mice. Front Immunol. https://doi.org/10.3389/fimmu.2024.1407936

Heindel JJ, Balbus J, Birnbaum L, Brune-Drisse MN, Grandjean P, Gray K, Landrigan PJ, Sly PD, Suk W, Slechta DC, Thompson C, Hanson M (2015a) Developmental origins of health and disease: integrating environmental influences. Endocrinology 156:3416–3421. https://doi.org/10.1210/en.2015-1394

Heindel JJ, vom Saal FS, Blumberg B, Bovolin P, Calamandrei G, Ceresini G, Cohn BA, Fabbri E, Gioiosa L, Kassotis C, Legler J, La Merrill M, Rizzir L, Machtinger R, Mantovani A, Mendez MA, Montanini L, Molteni L, Nagel SC, Parmigiani S, Panzica G, Paterlini S, Pomatto V, Ruzzin J, Sartor G, Schug TT, Street ME, Suvorov A, Volpi R, Zoeller RT, Palanza P (2015b) Parma consensus statement on metabolic disruptors. Environ Health 14:54. https://doi.org/10.1186/s12940-015-0042-7

Heindel JJ, Blumberg B, Cave M, Machtinger R, Mantovani A, Mendez MA, Nadal A, Palanza P, Panzica G, Sargis R, Vandenberg LN, vom Saal F (2017) Metabolism disrupting chemicals and metabolic disorders. Reprod Toxicol Dev Orig Dis 68:3–33. https://doi.org/10.1016/j.reprotox.2016.10.001

Hodoșan C, Gîrd CE, Ghica MV, Dinu-Pîrvu C-E, Nistor L, Bărbuică IS, Marin Ș-C, Mihalache A, Popa L (2023) Pyrethrins and pyrethroids: a comprehensive review of natural occurring compounds and their synthetic derivatives. Plants 12:4022. https://doi.org/10.3390/plants12234022

Horvatits T, Tamminga M, Liu B, Sebode M, Carambia A, Fischer L, Püschel K, Huber S, Fischer EK (2022) Microplastics detected in cirrhotic liver tissue. EBioMedicine. https://doi.org/10.1016/j.ebiom.2022.104147

Huang D, Zhang Y, Long J, Yang X, Bao L, Yang Z, Wu B, Si R, Zhao W, Peng C, Wang A, Yan D (2022) Polystyrene microplastic exposure induces insulin resistance in mice via dysbacteriosis and pro-inflammation. Sci Total Environ 838:155937. https://doi.org/10.1016/j.scitotenv.2022.155937

Huby T, Gautier EL (2022) Immune cell-mediated features of non-alcoholic steatohepatitis. Nat Rev Immunol 22:429–443. https://doi.org/10.1038/s41577-021-00639-3

Huc L, Lemarié A, Guéraud F, Héliès-Toussaint C (2012) Low concentrations of bisphenol A induce lipid accumulation mediated by the production of reactive oxygen species in the mitochondria of HepG2 cells. Toxicol in Vitro 26:709–717. https://doi.org/10.1016/j.tiv.2012.03.017

Kamm DR, McCommis KS (2022) Hepatic stellate cells in physiology and pathology. J Physiol 600:1825–1837. https://doi.org/10.1113/JP281061

Khan A, Khan B, Hussain S, Wang Y, Mai W, Hou Y (2024) Permethrin exposure impacts zebrafish lipid metabolism via the KRAS-PPAR-GLUT signaling pathway, which is mediated by oxidative stress. Aquat Toxicol 273:107021. https://doi.org/10.1016/j.aquatox.2024.107021

Kwon HC, Sohn H, Kim DH, Shin DM, Jeong CH, Chang YH, Yune JH, Kim YJ, Kim D-W, Kim SH, Han SG (2021) In vitro and in vivo study on the toxic effects of propiconazole fungicide in the pathogenesis of liver fibrosis. J Agric Food Chem 69:7399–7408. https://doi.org/10.1021/acs.jafc.1c01086

Lee C-Y, Suk F-M, Twu Y-C, Liao Y-J (2020) Long-term exposure to low-dose di-(2-ethylhexyl) phthalate impairs cholesterol metabolism in hepatic stellate cells and exacerbates liver fibrosis. Int J Environ Res Public Health 17:3802. https://doi.org/10.3390/ijerph17113802

Lee S-H, Lin T-A, Yan Y-H, Chien C-C, Cheng T-J (2024) Hepatic and metabolic outcomes induced by sub-chronic exposure to polystyrene microplastics in mice. Arch Toxicol 98:3811–3823. https://doi.org/10.1007/s00204-024-03847-7

Léger T, Alilat S, Ferron P-J, Dec L, Bouceba T, Lanceleur R, Huet S, Devriendt-Renault Y, Parinet J, Clément B, Fessard V, Le Hégarat L (2024) Chlordecone-induced hepatotoxicity and fibrosis are mediated by the proteasomal degradation of septins. J Hazard Mater 476:135177. https://doi.org/10.1016/j.jhazmat.2024.135177

Li S, Tan H-Y, Wang N, Zhang Z-J, Lao L, Wong C-W, Feng Y (2015) The role of oxidative stress and antioxidants in liver diseases. Int J Mol Sci 16:26087–26124. https://doi.org/10.3390/ijms161125942

Li M, Liu T, Yang T, Zhu J, Zhou Y, Wang M, Wang Q (2022a) Gut microbiota dysbiosis involves in host non-alcoholic fatty liver disease upon pyrethroid pesticide exposure. Environ Sci Ecotechnol 11:100185. https://doi.org/10.1016/j.ese.2022.100185

Li M, Lv M, Liu T, Du G, Wang Q (2022b) Lipid metabolic disorder induced by pyrethroids in nonalcoholic fatty liver disease of *Xenopus laevis*. Environ Sci Technol 56:8463–8474. https://doi.org/10.1021/acs.est.2c00516

Li W, Xiao H, Wu H, Pan C, Deng K, Xu X, Zhang Y (2022c) Analysis of environmental chemical mixtures and nonalcoholic fatty liver disease: NHANES 1999–2014. Environ Pollut 311:119915. https://doi.org/10.1016/j.envpol.2022.119915

Li Y, Chen C, Lu L, Guo W, VanWagner LB, Shikany JM, Zhang S, Kahe K (2022d) Cadmium exposure in young adulthood is associated with risk of nonalcoholic fatty liver disease in midlife. Dig Dis Sci 67:689–696. https://doi.org/10.1007/s10620-021-06869-8

Li Y, Yang P, Ye J, Xu Q, Wu J, Wang Y (2024) Updated mechanisms of MASLD pathogenesis. Lipids Health Dis 23:117. https://doi.org/10.1186/s12944-024-02108-x

Liu J, Zhang L, Xu F, Meng S, Li H, Song Y (2022) Polystyrene microplastics postpone APAP-induced liver injury through impeding macrophage polarization. Toxics 10:792. https://doi.org/10.3390/toxics10120792

Liu M, Mu J, Wang M, Hu C, Ji J, Wen C, Zhang D (2023) Impacts of polypropylene microplastics on lipid profiles of mouse liver uncovered by lipidomics analysis and Raman spectroscopy. J Hazard Mater 458:131918. https://doi.org/10.1016/j.jhazmat.2023.131918

Liu W, Li M, Guo H, Wei S, Xu W, Yan Y, Shi Y, Xu Z, Chang K, Wei G, Zhao S (2024) Single-cell transcriptome analysis of liver immune microenvironment changes induced by microplastics in mice with non-alcoholic fatty liver. Sci Total Environ 912:168308. https://doi.org/10.1016/j.scitotenv.2023.168308

Loomba R, Seguritan V, Li W, Long T, Klitgord N, Bhatt A, Dulai PS, Caussy C, Bettencourt R, Highlander SK, Jones MB, Sirlin CB, Schnabl B, Brinkac L, Schork N, Chen C-H, Brenner DA, Biggs W, Yooseph S, Venter JC, Nelson KE (2017) Gut microbiome-based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. Cell Metab 25:1054-1062.e5. https://doi.org/10.1016/j.cmet.2017.04.001

Louisse J, Rijkers D, Stoopen G, Janssen A, Staats M, Hoogenboom R, Kersten S, Peijnenburg A (2020) Perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), and perfluorononanoic acid (PFNA) increase triglyceride levels and decrease cholesterogenic gene expression in human HepaRG liver cells. Arch Toxicol 94:3137–3155. https://doi.org/10.1007/s00204-020-02808-0

Lv Y, Bing Q, Lv Z, Xue J, Li S, Han B, Yang Q, Wang X, Zhang Z (2020) Imidacloprid-induced liver fibrosis in quails via activation of the TGF-β1/Smad pathway. Sci Total Environ 705:135915. https://doi.org/10.1016/j.scitotenv.2019.135915

Ma P, Gao H, Shen N, Zhang L, Zhang Y, Zheng K, Xu B, Qin J, He J, Xu T, Li Y, Wu J, Yuan Y, Xue B (2024) Association of urinary chlorpyrifos, paraquat, and cyproconazole levels with the severity of fatty liver based on MRI. BMC Public Health 24:807. https://doi.org/10.1186/s12889-024-18129-1

Marmugi A, Ducheix S, Lasserre F, Polizzi A, Paris A, Priymenko N, Bertrand-Michel J, Pineau T, Guillou H, Martin PGP, Mselli-Lakhal L (2012) Low doses of bisphenol a induce gene expression related to lipid synthesis and trigger triglyceride accumulation in adult mouse liver. Hepatology 55:395. https://doi.org/10.1002/hep.24685

Maurya AC, Bhattacharya A, Vij V, Khare SK (2024) Deciphering the seasonal dynamics of microplastic morphotypes and associated co-contaminants along the northwest coast of India. Chemosphere 354:141690. https://doi.org/10.1016/j.chemosphere.2024.141690

Miao Z, Miao Z, Teng X, Xu S (2023) Melatonin alleviates lead-induced fatty liver in the common carps (*Cyprinus carpio*) via gut-liver axis. Environ Pollut 317:120730. https://doi.org/10.1016/j.envpol.2022.120730

Miele L, Valenza V, La Torre G, Montalto M, Cammarota G, Ricci R, Mascianà R, Forgione A, Gabrieli ML, Perotti G, Vecchio FM, Rapaccini G, Gasbarrini G, Day CP, Grieco A (2009) Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. Hepatology 49:1877–1887. https://doi.org/10.1002/hep.22848

Moon MK, Jeong I-K, Oh TJ, Ahn HY, Kim HH, Park YJ, Jang HC, Park KS (2015) Long-term oral exposure to bisphenol a induces glucose intolerance and insulin resistance. J Endricol. https://doi.org/10.1530/JOE-14-0714

Mudipalli A (2007) Lead hepatotoxicity & potential health effects. Indian J Med Res 126:518

Nie Q, Luo X, Wang K, Ding Y, Jia S, Zhao Q, Li M, Zhang J, Zhuo Y, Lin J, Guo C, Zhang Z, Liu H, Zeng G, You J, Sun L, Lu H, Ma M, Jia Y, Zheng M-H, Pang Y, Qiao J, Jiang C (2024) Gut symbionts alleviate MASH through a secondary bile acid biosynthetic pathway. Cell 187:2717-2734.e33. https://doi.org/10.1016/j.cell.2024.03.034

Ottman N, Geerlings SY, Aalvink S, de Vos WM, Belzer C (2017) Action and function of *Akkermansia muciniphila* in microbiome ecology, health and disease. Best Pract Res Clin Gastroenterol Gut Microb Health Dis 31:637–642. https://doi.org/10.1016/j.bpg.2017.10.001

Perino A, Schoonjans K (2022) Metabolic messengers: bile acids. Nat Metab 4:416–423. https://doi.org/10.1038/s42255-022-00559-z

Puche JE, Saiman Y, Friedman SL (2013) Hepatic stellate cells and liver fibrosis. Comprehensive physiology. Wiley, Oxford, pp 1473–1492. https://doi.org/10.1002/cphy.c120035

Quek J, Chan KE, Wong ZY, Tan C, Tan B, Lim WH, Tan DJH, Tang ASP, Tay P, Xiao J, Yong JN, Zeng RW, Chew NWS, Nah B, Kulkarni A, Siddiqui MS, Dan YY, Wong VW-S, Sanyal AJ, Noureddin M, Muthiah M, Ng CH (2023) Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 8:20–30. https://doi.org/10.1016/S2468-1253(22)00317-X

Ramachandran P, Dobie R, Wilson-Kanamori JR, Dora EF, Henderson BEP, Luu NT, Portman JR, Matchett KP, Brice M, Marwick JA, Taylor RS, Efremova M, Vento-Tormo R, Carragher NO, Kendall TJ, Fallowfield JA, Harrison EM, Mole DJ, Wigmore SJ, Newsome PN, Weston CJ, Iredale JP, Tacke F, Pollard JW, Ponting CP, Marioni JC, Teichmann SA, Henderson NC (2019) Resolving the fibrotic niche of human liver cirrhosis at single-cell level. Nature 575:512–518. https://doi.org/10.1038/s41586-019-1631-3

Remmerie A, Martens L, Thoné T, Castoldi A, Seurinck R, Pavie B, Roels J, Vanneste B, Prijck SD, Vanhockerhout M, Latib MBA, Devisscher L, Hoorens A, Bonnardel J, Vandamme N, Kremer A, Borghgraef P, Vlierberghe HV, Lippens S, Pearce E, Saeys Y, Scott CL (2020) Osteopontin expression identifies a subset of recruited macrophages distinct from kupffer cells in the fatty liver. Immunity 53:641-657.e14. https://doi.org/10.1016/j.immuni.2020.08.004

Schwenger KJP, Ghorbani Y, Bharatselvam S, Chen L, Chomiak KM, Tyler AC, Eddingsaas NC, Fischer SE, Jackson TD, Okrainec A, Allard JP (2024) Links between fecal microplastics and parameters related to metabolic dysfunction-associated steatotic liver disease (MASLD) in humans: an exploratory study. Sci Total Environ 953:176153. https://doi.org/10.1016/j.scitotenv.2024.176153

Sen P, Fan Y, Schlezinger JJ, Ehrlich SD, Webster TF, Hyötyläinen T, Federsen O, Orešič M (2024) Exposure to environmental toxicants is associated with gut microbiome dysbiosis, insulin resistance and obesity. Environ Int 186:108569. https://doi.org/10.1016/j.envint.2024.108569

Sheng S, Han N, Wei Y, Wang J, Han W, Xing B, Xing M, Zhang W (2024) Liver injury induced by exposure to polystyrene microplastics alone or in combination with cadmium in mice is mediated by oxidative stress and apoptosis. Biol Trace Elem Res 202:2170–2183. https://doi.org/10.1007/s12011-023-03835-5

Stossi F, Dandekar RD, Johnson H, Lavere P, Foulds CE, Mancini MG, Mancini MA (2019) Tributyltin chloride (TBT) induces RXRA down-regulation and lipid accumulation in human liver cells. PLoS ONE 14:e0224405. https://doi.org/10.1371/journal.pone.0224405

Sun J, Qu H, Ali W, Chen Y, Wang T, Ma Y, Yuan Y, Gu J, Bian J, Liu Z, Zou H (2023) Co-exposure to cadmium and microplastics promotes liver fibrosis through the hemichannels -ATP-P2X7 pathway. Chemosphere 344:140372. https://doi.org/10.1016/j.chemosphere.2023.140372

Suresh D, Srinivas AN, Kumar DP (2020) Etiology of hepatocellular carcinoma: special focus on fatty liver disease. Front Oncol. https://doi.org/10.3389/fonc.2020.601710

Thompson RC, Courtene-Jones W, Boucher J, Pahl S, Raubenheimer K, Koelmans AA (2024) Twenty years of microplastic pollution research—what have we learned? Science 386:eadl2746. https://doi.org/10.1126/science.adl2746

Tong H, Jiang Q, Hu X, Zhong X (2020) Occurrence and identification of microplastics in tap water from China. Chemosphere 252:126493. https://doi.org/10.1016/j.chemosphere.2020.126493

Tong H, Wang L, Zhang K, Shi J, Wu Y, Bao Y, Wang C (2023) S100A6 activates kupffer cells via the p-P38 and p-JNK pathways to induce inflammation, mononuclear/macrophage infiltration

sterile liver injury in mice. Inflammation 46:534–554. https://doi.org/10.1007/s10753-022-01750-w
Tsuchida T, Friedman SL (2017) Mechanisms of hepatic stellate cell activation. Nat Rev Gastroenterol Hepatol 14:397–411. https://doi.org/10.1038/nrgastro.2017.38
US Geological Survey, 2017. Estimated Agricultural Use for Paraquat [WWW Document]. URL https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2017&map=PARAQUAT&hilo=L&disp=Paraquat. Accessed 18 Nov 2024.
Wang X, Weng Y, Geng S, Wang C, Jin C, Shi L, Jin Y (2023) Maternal procymidone exposure has lasting effects on murine gut-liver axis and glucolipid metabolism in offspring. Food Chem Toxicol 174:113657. https://doi.org/10.1016/j.fct.2023.113657
Wang H, Wang F, Li Y, Zhou P, Cai S, Wu Q, Ding T, Wu C, Zhu Q (2024a) Exosomal miR-205-5p contributes to the immune liver injury induced by trichloroethylene: pivotal role of RORα mediating M1 Kupffer cell polarization. Ecotoxicol Environ Saf 285:117050. https://doi.org/10.1016/j.ecoenv.2024.117050
Wang X, Deng K, Zhang P, Chen Q, Magnuson JT, Qiu W, Zhou Y (2024b) Microplastic-mediated new mechanism of liver damage: from the perspective of the gut-liver axis. Sci Total Environ 919:170962. https://doi.org/10.1016/j.scitotenv.2024.170962
Wang Y, Fu Z, Guan D, Zhao J, Zhang Q, Liu Q, Xie J, Sun Y, Guo L (2024c) Occurrence characteristics and ecotoxic effects of microplastics in environmental media: a mini review. Appl Biochem Biotechnol 196:5484–5507. https://doi.org/10.1007/s12010-023-04832-z
Wen J, Sun H, Yang B, Song E, Song Y, Jiang G (2024) Environmentally relevant concentrations of microplastic exposure cause cholestasis and bile acid metabolism dysregulation through a gut-liver loop in mice. Environ Sci Technol. https://doi.org/10.1021/acs.est.3c07108
Wree A, Broderick L, Canbay A, Hoffman HM, Feldstein AE (2013) From NAFLD to NASH to cirrhosis—new insights into disease mechanisms. Nat Rev Gastroenterol Hepatol 10:627–636. https://doi.org/10.1038/nrgastro.2013.149
Xia J, Jin C, Pan Z, Sun L, Fu Z, Jin Y (2018) Chronic exposure to low concentrations of lead induces metabolic disorder and dysbiosis of the gut microbiota in mice. Sci Total Environ 631–632:439–448. https://doi.org/10.1016/j.scitotenv.2018.03.053
Xie Z, Aimuzi R, Si M, Qu Y, Jiang Y (2023) Associations of metal mixtures with metabolic-associated fatty liver disease and non-alcoholic fatty liver disease: NHANES 2003–2018. Front Public Health. https://doi.org/10.3389/fpubh.2023.1133194
Xiong X, Kuang H, Ansari S, Liu T, Gong J, Wang S, Zhao X-Y, Ji Y, Li C, Guo L, Zhou L, Chen Z, Leon-Mimila P, Chung MT, Kurabayashi K, Opp J, Campos-Pérez F, Villamil-Ramírez H, Canizales-Quinteros S, Lyons R, Lumeng CN, Zhou B, Qi L, Huertas-Vazquez A, Lusis AJ, Xu XZS, Li S, Yu Y, Li JZ, Lin JD (2019) Landscape of intercellular crosstalk in healthy and NASH liver revealed by single-cell secretome gene analysis. Mol Cell 75:644-660.e5. https://doi.org/10.1016/j.molcel.2019.07.028
Xu R, Cao JW, Lv HL, Geng Y, Guo MY (2024) Polyethylene microplastics induced gut microbiota dysbiosis leading to liver injury via the TLR2/NF-κB/NLRP3 pathway in mice. Sci Total Environ 917:170518. https://doi.org/10.1016/j.scitotenv.2024.170518
Yang JS, Qi W, Farias-Pereira R, Choi S, Clark JM, Kim D, Park Y (2019) Permethrin and ivermectin modulate lipid metabolism in steatosis-induced HepG2 hepatocyte. Food Chem Toxicol 125:595–604. https://doi.org/10.1016/j.fct.2019.02.005
Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M (2016) Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 64:73. https://doi.org/10.1002/hep.28431
Zarus GM, Muianga C, Brenner S, Stallings K, Casillas G, Pohl H, Mumtaz MM, Gehle K (2023) Worker studies suggest unique liver carcinogenicity potential of polyvinyl chloride microplastics. Am J Ind Med. 66(12):1033–1047. https://doi.org/10.1002/ajim.23540
Zhang W, Shen X-Y, Zhang W-W, Chen H, Xu W-P, Wei W (2017) The effects of di 2-ethyl hexyl phthalate (DEHP) on cellular lipid accumulation in HepG2 cells and its potential mechanisms in the molecular level. Toxicol Mech Methods 27:245–252. https://doi.org/10.1080/15376516.2016.1273427
Zhang J, Liu H, Shen Y, Cheng D, Tang H, Zhang Q, Li C, Liu M, Yao W, Ran R, Hou Q, Zhao X, Wang J-S, Sun X, Zhang T, Zhou J (2024) Macrophage AHR-TLR4 cross-talk drives p-STAT3 (Ser727)-mediated mitochondrial oxidative stress and upregulates IDO/ICAM-1 in the steatohepatitis induced by aflatoxin B1. Sci Total Environ 923:171377. https://doi.org/10.1016/j.scitotenv.2024.171377
Zhao Z, Ji K, Shen X, Zhang W, Wang R, Xu W, Wei W (2019) Di(2-ethylhexyl) phthalate promotes hepatic fibrosis by regulation of oxidative stress and inflammation responses in rats. Environ Toxicol Pharmacol 68:109–119. https://doi.org/10.1016/j.etap.2019.03.008
Zhao L, Shi W, Hu F, Song X, Cheng Z, Zhou J (2021) Prolonged oral ingestion of microplastics induced inflammation in the liver tissues of C57BL/6J mice through polarization of macrophages and increased infiltration of natural killer cells. Ecotoxicol Environ Saf 227:112882. https://doi.org/10.1016/j.ecoenv.2021.112882
Zhao Y, Mao A, Zhang R, Guan S, Lu J (2022) SIRT1/mTOR pathway-mediated autophagy dysregulation promotes Pb-induced hepatic lipid accumulation in HepG2 cells. Environ Toxicol 37:549–563. https://doi.org/10.1002/tox.23420
Zheng F, Devoogdt N, Sparkes A, Morias Y, Abels C, Stijlemans B, Lahoutte T, Muyldermans S, De Baetselier P, Schoonooghe S, Beschin A, Raes G (2015) Monitoring liver macrophages using nanobodies targeting Vsig4: concanavalin A induced acute hepatitis as paradigm. Immunobiology 220:200–209. https://doi.org/10.1016/j.imbio.2014.09.018
Zhou W, Shi W, Du X, Han Y, Tang Y, Ri S, Ju K, Kim T, Huang L, Zhang W, Yu Y, Tian D, Yu Y, Chen L, Wu Z, Liu G (2023) Assessment of nonalcoholic fatty liver disease symptoms and gut-liver axis status in zebrafish after exposure to polystyrene microplastics and oxytetracycline, alone and in combination. Environ Health Perspect 131:047006. https://doi.org/10.1289/EHP11600
Zhu Y, Zhao Y, Chai X-X, Zhou J, Shi M-J, Zhao Y, Tian Y, Wang X-M, Ying T-X, Feng Q, Sheng J, Luo C (2022) Chronic exposure to low-dose cadmium facilitated nonalcoholic steatohepatitis in mice by suppressing fatty acid desaturation. Ecotoxicol Environ Saf 233:113306. https://doi.org/10.1016/j.ecoenv.2022.113306
Zhu Y, Chai X-X, Zhao Y, Feng Q, Dong R, Shi M-J, Zhou J, Zhao Y, Peng J, Tian Y, Chen G, Luo C, Sheng J (2023) Saturated fatty acids synergizes cadmium to induce macrophages M1 polarization and hepatic inflammation. Ecotoxicol Environ Saf 259:115040. https://doi.org/10.1016/j.ecoenv.2023.115040
Zisser A, Ipsen DH, Tveden-Nyborg P (2021) Hepatic stellate cell activation and inactivation in NASH-fibrosis—roles as putative treatment targets? Biomedicines 9:365. https://doi.org/10.3390/biomedicines9040365
Zou H, Qu H, Bian Y, Sun J, Wang T, Ma Y, Yuan Y, Gu J, Bian J, Liu Z (2023) Polystyrene microplastics induce oxidative stress in mouse hepatocytes in relation to their size. Int J Mol Sci 24:7382. https://doi.org/10.3390/ijms24087382