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The exposome and liver disease - how environmental factors affect liver health

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Summary

Since the initial development of the exposome concept, much effort has been devoted to the characterisation of the exposome through analytical, epidemiological, and toxicological/mechanistic studies. There is now an urgent need to link the exposome to human diseases and to include exposomics in the characterisation of environment-linked pathologies together with genomics and other omics. Liver diseases are particularly well suited for such studies since major functions of the liver include the detection, detoxification, and elimination of xenobiotics, as well as inflammatory responses. It is well known that several liver diseases are associated with i) addictive behaviours such as alcohol consumption, smoking, and to a certain extent dietary imbalance and obesity, ii) viral and parasitic infections, and iii) exposure to toxins and occupational chemicals. Recent studies indicate that environmental exposures are also significantly associated with liver diseases, and these include air pollution (particulate matter and volatile chemicals), contaminants such as polyaromatic hydrocarbons, bisphenol A and per-and poly-fluorinated substances, and physical stressors such as radiation. Furthermore, microbial metabolites and the “gut-liver” axis play a major role in liver diseases. Exposomics is poised to play a major role in the field of liver pathology. Methodological advances such as the

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exposomics-metabolomics framework, the determination of risk factors' genomic and epigenomic signatures, and cross-species biological pathway analysis should further delineate the impact of the exposome on the liver, opening the way for improved prevention, as well as the identification of new biomarkers of exposure and effects, and additional therapeutic targets.

Keywords

MAFLD; hepatocellular carcinoma; viral hepatitis; biliary disease; exposomics; metabolomics; mutational signature; toxicological pathways; microbiota; xenobiotic metabolism

Introduction to the exposome

Although, there have been substantial advances over the past few decades in our understanding of the contribution of genetics to human diseases, the role of exposures to different environmental stressors has remained elusive. In a seminal article in 2005, Chris Wild elaborated a new concept, the exposome, which he defined as the totality of exposures from conception to death.[1] The aim of the proposal was to integrate, in a single framework, different types of exposures including chemical, physical, biological, and psycho-social stressors, and to take into consideration the temporal dimension. Within this definition, the exposome can be viewed as the complement of the genome and can be used to improve our understanding of disease determinants. Since the initial definition, different contributions have been made to further develop the concept and to delineate the approaches that support its practical implementation. Much of the focus has been on developing analytical tools to characterise the exposome.[2,3] Also, a significant effort has been devoted to better link the exposome to health, in particular through the integration of chemical, biological and computational approaches.[4,5] Exposomics can be defined as the study of the exposome, which relies on the application of internal and external exposure assessment methods. Recently, exposomics has been further integrated with the other omics, leading to the concept of functional exposomics, which has been defined as the biological translation of the exposome and its multiple exposures and the characterisation of mechanisms of action, much as functional genomics refers to the functional expression of the genome.[6]

Initial studies of the exposome have been primarily methodological and global, recent work has been more disease-oriented,[7,8] *e.g.* targeting the exposome relevant for cancer,[9–11] lung disease[12] or liver disorders.[13] These developments have been supported by the integration of exposomics within omics approaches and subsequently the characterisation of the mechanistic links between various stressors and disease-relevant biological pathways.[4,5] These disease-oriented health studies enable a more realistic evaluation of the most relevant determinants and allow for gene-environment interaction studies. Importantly, these developments contribute to bringing the exposome concept to the clinic and should support an improved understanding of disease determinants and ultimately improved prevention.[14]

In the present review, we have analysed studies linking a variety of exposures to different liver diseases. Most of these studies did not use a non-targeted large-scale exposomics approach, yet they were included in order to enable a more comprehensive assessment of environmental determinants of liver diseases. We will first describe different

biological pathways relevant to liver diseases, then we will discuss the implication of exposome components in different liver diseases, including metabolic, infectious, cholestatic diseases and cancer, highlighting specific or shared mechanistic aspects as well as clinical implications. In the conclusion, we identify the most promising approaches and tools to further develop this rapidly growing field.

Biological pathways in the liver

There are several physiological functions of the liver that are known to be modulated by environmental factors. Endogenous metabolism is a major function of the liver, and several metabolic pathways are either specific or highly represented in this organ, *e.g.* gluconeogenesis and the urea cycle as well as lipid metabolism (as discussed below). Exposure studies coupled with metabolomics studies in human biological fluids have suggested specific dysregulation of liver functions. This is the case for urea cycle intermediates which, when dysregulated in body fluids after exposure to a mix of metals and phthalates, point to a possible liver injury and specifically mitochondrial dysfunction (a part of the urea cycle occurs in the mitochondria).[15] It is expected that, with the development of coupled exposomics and metabolomics studies, such associations will be more frequently observed.[16] Yet, since endogenous metabolism is dependent on the interaction between several organs, it is critical to integrate the data at the organism level.

Xenobiotic metabolism is another major liver function, although it is not unique to the liver. Hepatocytes express a large number of genes involved in this function such as cytochromes P450, phase 2 enzymes, transporters and xenobiotic receptors.[17,18] It has been known for a long time that many of these genes are highly inducible by xenobiotics, in line with their adaptive biological functions.[19,20] Yet, the impacts of combined environmental chemicals have been less well studied.[21] The regulation of xenobiotic metabolism is not restricted to exogenous chemicals, since endogenous effectors such as hormones, microbiome metabolites, and inflammatory mediators are also implicated. A critical point is that while xenobiotic metabolism displays adaptive functions, it is also the source of toxic intermediates and reactive oxygen species and thus is also potentially involved in pathogenic pathways.[19] Thus, there is a clear relationship between the regulation of xenobiotic metabolism and different liver pathologies. Another important point is that because of the anatomy of the vascular system, the liver is the first organ to be exposed to a large number of xenobiotics, microbiome metabolites and dietary compounds. It filters many of these substances, but by protecting the rest of the body, it is also a privileged target.

There are several biliary functions in the liver which are involved in food digestion, metabolic fluxes and regulation, as well as waste and xenobiotic elimination.[22] The biliary system is integrated in the gastro-intestinal system, *e.g.* through the secretion of biliary salts (whose production depends on the metabolism of cholesterol), and any dysfunction leads to food intake anomalies. Furthermore, the biliary system is involved in the elimination of degradation products of endogenous compounds, such as haemoglobin. It is also critical for the elimination of exogenous toxicants and is thus part of the detoxification machinery of the liver. Thus, any dysfunction of the biliary system leads to the accumulation of waste

and toxicants and therefore to both liver and systemic toxicity. These functions of the biliary system explain why it is so critical for the link between environmental exposures and health.

The immune functions of the liver are diverse.[23] First during the foetal period, the liver is a haematopoietic organ and thus contributes to the development of immune cells. Second, the liver includes Kupffer cells (liver-resident macrophages) which contribute to the organism's immune defence system. In addition, a large number of inflammatory proteins are synthesised by the liver and contribute considerably to the global inflammatory response. For all these reasons, the liver is both a target of the immune system and also a contributor to certain functions of this system, *e.g.* local and central inflammatory processes.

The liver is also a storage site for a variety of metabolites and signalling compounds. In addition to the classical homeostatic functions of glycogen and to its role in the synthesis and transport of lipids, the liver stores important mediators such as retinoic acid in stellate cells.[24]

All these liver functions explain why there is a close interaction between this organ and the exposome. The different activities described above explain why the liver is the site where reactive and possibly genotoxic metabolites, as well as biologically active non-genotoxic compounds, are generated. They also explain why infectious agents, as well as endogenous metabolites, are likely to interact with exogenous compounds in disease development. Depending on the mechanisms involved, these diseases could be cancer, fibrosis, inflammation, metabolic dysregulation, or biliary diseases. In this review, we will attempt to establish such links and to identify gaps in knowledge.

Metabolic diseases, integration of contaminants and microbiome effects

As stated above, the central role played by the liver in endogenous and xenobiotic metabolism is based on a dialogue with other key organs. A typical example of such an inter-organ collaboration is the "pancreas-liver" crosstalk which takes place through the secretion of glucagon and insulin, two strategic drivers of the hepatic metabolism of carbohydrates and lipids. While any interference in such a crosstalk is thought to contribute to the development of several chronic liver diseases, including non-alcoholic fatty liver disease (NAFLD), these processes are also modulated by the "gut-liver" axis including the gut microbiota that integrates exposome responses to both food contaminants and dietary composition.[25] This crosstalk and its metabolic consequences are further discussed in this chapter and are illustrated by specific examples.

The liver plays a central role in the maintenance of lipid homeostasis, and this is accomplished through several functional activities which span from membrane composition and subcellular organelle compartmentalisation, trafficking, energy storage and production, to signal transduction in the modulation of hormone activity and response to hazardous stimuli (Fig. 1).[26] Several receptors regulate lipid metabolism (transport, synthesis, lipolysis). Indeed, despite some controversial observations, it has been shown that activation of the Aryl hydrocarbon receptor (AhR), a bHLH/PAS family member, is linked to increased fat accumulation in the liver.[27,28] Moreover, several nuclear receptors regulate

lipid metabolism, leading to adverse outcomes in some cases. The pregnane X receptor (PXR, alias NR1I2) and constitutive androstane receptor (CAR, alias NR1I3) have been shown in some studies to have opposite effects on lipid metabolism; indeed, while CAR activation leads to lower triglyceride accumulation in the liver,[29] PXR triggers liver steatosis through an increase in lipid accumulation.[30] However, these conclusions still need to be supported by additional evidence. Furthermore, these effects may be ligand-dependent because of the functional plasticity of those receptors (AhR, PXR, CAR), the biological outcome of their activation being highly dependent on the nature of their ligands.[31,32] Central to the liver's signal transducing role in lipid metabolism is the farnesoid X receptor (FXR, alias NR1H4), another member of the nuclear metabolic receptor superfamily which, among many functions, regulates the synthesis and enterohepatic circulation of bile acids and directly modulates the expression of genes involved in lipid and glucose metabolism, thereby having clear implications for atherosclerotic risk and hepatic fat content.[33] The peroxisome proliferator-activated receptors (PPARs: especially PPAR-α, alias NR1C1), which are also nuclear receptors, play key functions in the regulation of lipid synthesis and degradation; their dysregulation has been linked to hepatic steatosis, non-alcoholic steatohepatitis (NASH) and/or liver cancer.[34] Whenever the storage capacity of liver cells is overburdened, the accumulation of lipid intermediates like diacylglycerol, ceramides and fatty acyl-CoAs may lead to cell dysfunction and necroinflammation (lipotoxicity). While the process leading to liver injury following hepatocellular accumulation of fat is complex and its turning point not fully unravelled, liver damage appears to be fuelled by the shift of fat storage from subcutaneous to visceral adipose tissue in most patients, with the expansion of visceral adipose tissue being a powerful predictor of metabolic dysfunction-associated fatty liver disease (MAFLD).[35]

Many factors influence the occurrence of NAFLD or more generally MAFLD[36], including diet, sedentary lifestyle, dysregulated circadian homeostasis, alcohol abuse and tobacco consumption. They impact pathophysiological processes such as metabolism, fibrosis, and inflammation. Alcohol, even at moderate consumption, is also known to accelerate the course of MAFLD, leading to an increased risk of patients developing cirrhosis, clinical decompensation and liver cancer.[37] Interestingly, environmental pollutants which include metals, persistent organic pollutants (POPs: dioxins, polychlorinated biphenyl, or per- and polyfluoroalkyl substances [PFASs]) and particulate matter (PM) also influence such mechanisms. During the last few years, there has been a major focus on PFASs, which represent a large class of POPs; several of these compounds are highly persistent and are stored in the liver. Exposure to several of these substances is associated with health outcomes including immunotoxicity, metabolic diseases, reproductive and developmental toxicity, and cancer.[38] A recent systematic review and meta-analysis of the literature concluded that there was evidence for liver toxicity in rodents and associations with markers of liver disease in human studies.[39] There is also evidence for an impact of these substances on carbohydrate, amino acid, biliary and lipid metabolism under certain conditions.[40,41] In a recent metabolomics study in humans and rodents, PFAS exposure was associated with alterations in a variety of metabolic pathways which appeared to be more severe in females.[42] PPAR-α is one of the best identified molecular targets of PFASs.[43]

Moreover, epidemiological studies have recently shown that long-term exposure to ambient pollution (a source of metals and PM) can trigger MAFLD in humans.[44] Vulnerability to the development of liver diseases can be increased in males, in obese individuals, and in consumers of a high-fat diet, alcohol, or tobacco.[44] Several air pollutants are incriminated, including PM but also NO_2 and polyaromatic hydrocarbons (PAHs). NO_2 can indeed react with antioxidant molecules (decreasing their levels) and lipids, leading to a lower defence against pro-oxidants. NO_2-associated oxidative stress can lead to bron-choconstriction in the lungs but also to remote effects on other organs such as the heart or the immune system, whose functions are significantly reduced. Regarding PAHs, epidemiological and experimental studies suggest that the activation of AhR leads to an inflammatory phenotype accompanied by an epithelial-mesenchymal transition which, in the case of exposure to a high-fat diet, translates into fibrosis. Such an effect is not observed with single exposures alone (high-fat diet or PAHs).[27,44,45] This highlights the importance of considering the exposome and integrating the effects of multiple stressors on the development of MAFLD.

The “gut-liver” axis is one of the most historically studied systems in physiology. The intestine absorbs a large quantity of nutrients after digestion, which are taken up by the liver, such as glucose stored in the form of glycogen during the postprandial period. An unbalanced diet, for example one rich in fats, modifies the intestinal mucus, which alters the intestinal barrier[46] and results in the penetration of bacterial metabolites into the portal circulation, leading to hepatic inflammation.[47] Moreover, certain dietary deficiencies such as choline can lead to NAFLD. Choline is converted to phosphatidylcholine (lecithin) and plays a role in the assembly and secretion of very low-density lipoproteins by the liver. This step prevents the formation of hepatic steatosis due to triglycerides.[48] Choline deficiency is associated with a decrease in very low-density lipoprotein production and release, and thus triglyceride accumulation in the liver; this can be easily observed in mouse models.[49] In addition, the intestinal microbiota transforms choline into trimethylamine, which decreases the bioavailability of choline and leads to the supply of trimethylamine to the liver, where it is transformed into trimethylamine N-oxide, a metabolite with potent steatogenic effects.[50] In addition to the effects of an unbalanced diet, the uptake of several drugs (such as metformin or digoxin) also impacts the activity and composition of the microbiome and can lead to metabolic disruption in the liver.[51,52] Finally, if the intestine supplies the liver with the products of digestion (but also certain deleterious metabolites in case of loss of intestinal permeability), the liver influences the functioning of the intestine by secreting bile acids which can further modify the composition of the gut microbiota.

Indeed, trillions of bacteria, fungi, viruses, archaea, and protozoa residing in the distal segments of the gastrointestinal tract form the gut microbiota. When stressed by various disease processes, the human intestinal microbiome undergoes dysbiosis, which accelerates liver fibrosis development through upregulation of inflammation.[53] Dysbiosis-related liver injury may be driven either by an excessive immune response, by gut barrier alterations, or by the production of metabolites that modulate signalling pathways following the interaction with receptors in host cells. Some of these metabolites can target the liver due to altered epithelial barrier permeability. For example, short-chain fatty acids, lipopolysaccharide (a pathogen-associated molecular pattern), bioactive lipids and bile acids, as well as many other metabolites, act as regulators of the host metabolism, gut barrier, and inflammation.[54]

Yet, owing to the lack of cogent investigations demonstrating causality between gut dysbiosis and liver disease, effective therapeutic interventions aimed at modulating the gut microbiome have lagged behind.

During the last few years, the links between exposure to environmental chemicals and dysbiosis of the gut microbiota have been extensively studied. Indeed, the composition and function of the gut microbiota, which is responsible for the production of diverse biologically active molecules, can be altered by a variety of dietary contaminants, ultimately leading to dysbiosis. For example, in several models (mouse, zebrafish and dog), bisphenol A (BPA), a widely used compound in the plastic industry and in food packaging, causes dysbiosis by increasing the populations of two bacterial phyla (Protobacteria and CKC4),[55,56] while decreasing *Bacteroides*, *Flexispiraphyla*, *Oscillospira* and *Ruminococcaceae*.[57,58] Such patterns of dysbiosis are reminiscent of those observed in animals fed a high-fat diet (*e.g.*, the imbalance of Protobacteria populations); this raises the possibility that the combined exposure to BPA and a high-fat diet may have additive or synergistic effects. Moreover, recent evidence indicates that exposure to BPA may have sequential effects, leading to dysbiosis and therefore to the accumulation of hepatic lipids and steatosis.[59,60] In fact, the attenuated diversity of the intestinal microbiota results in the accumulation of phyla that release endotoxins responsible for increased intestinal permeability. In turn, these events promote extensive inflammation of the liver characterised by the accumulation of IL-1β and IL-6, and tumour necrosis factor-α, leading to the onset of NAFLD.[61] All in all, these findings are reminiscent of previous experiments in mice which demonstrated impaired glucose tolerance caused by increased insulin resistance and peripheral tissue inflammation after BPA exposure.[62]

Along the same line, chemical contaminants such as phthalates (*e.g.*, diethylphthalate or mono(2-ethylhexyl)phta-late), parabens (*e.g.*, methylparaben), biocides (triclosan), pesticides (carbemazine, dichlorodiphenyldichloroethylene [DDE], beta-hexachlorohexane, or pentachlorophenol) have clearly been shown to cause dysbiosis.[63–69] Among these molecules, DDE and beta-hexachlorohexane are POPs. DDE causes a dysbiosis which strongly correlates with altered blood levels of phospholipids (phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine) and triacylglycerols.[69] There are more insights into the mechanisms of action of other POPs, notably the Seveso dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin [TCDD]). TCDD leads to dysbiosis related to the disruption of the enterohepatic cycle, characterised by a significant depletion of faecal bile acids, increased intestinal permeability and delayed transit (due to the depletion of bile acids).[70] TCDD also binds to AhR, thereby hijacking the detection of tryptophan metabolites (some of which are endogenous metabolites produced by the microbiota), contributing to altered gut permeability and, subsequently, to the onset of metabolic syndrome in mice.[70–72] Likewise, a disruption of the metabolome is also observed at the intestinal or blood levels with BPA and the insecticide chlorpyrifos: BPA increases plasma bicarbonate concentrations in association with disruptions of *Bacteroides* populations,[58] while chlorpyrifos alters concentrations of short-chain fatty acids (such as propionate), which are known to prevent NAFLD by reducing transcription of several enzymes involved in *de novo* lipogenesis.[73]

Liver infectious diseases with focus on multiple stressors and interaction with chemical stressors

With regards to the global exposome, the liver is an organ particularly exposed to numerous external biological factors such as viruses, parasites, or pathogenic bacteria. Viral hepatitis is caused by five different viruses (hepatitis A, B, C, D, and E virus)[74] and these viruses are responsible for hundreds of millions of acute and chronic liver diseases worldwide, especially in Asia and Africa. Parasites can also infect the liver and activate the immune response, resulting in symptoms of acute or chronic hepatitis.[74] Among the protozoans, *Trypanosoma cruzi*, *Leishmania* species, and the malaria-causing *Plasmodium* species can all cause liver inflammation.[74] Concerning worm-based parasites, the cestode *Echinococcus granulosus* infects the liver and forms characteristic hepatic hydatid cysts. Fasciola *hepatica* and Clonorchis *sinensis* live in the bile ducts and cause progressive hepatitis and fibrosis.[74] Bacterial infections of the liver commonly result in pyogenic liver abscesses, acute hepatitis or granulomatous liver disease mainly involving enteric bacteria such as *Escherichia coli* and *Klebsiella pneumoniae*, but many other bacteria can induce acute hepatitis.[74] The intrahepatic interactions between chemical substances and the biological factors presented above are numerous since the liver is an obligatory pathway for the detoxification of chemical compounds.

Alcohol is undoubtedly the most frequently involved exogenous compound that interacts with biological factors in the liver. Alcohol alone is an important risk factor for chronic liver diseases including fibrosis, but combined with other biological factors, it increases the risk of developing liver pathologies.[75,76] Thus, alcohol adversely affects individuals infected with HBV or HCV by promoting viral replication, increasing oxidative stress, and suppressing viral immune responses. The interaction of alcohol with viral hepatitis contributes to an increased risk of developing HBV- or HCV-induced liver fibrosis, end-stage cirrhosis, and even deadly liver cancer. For example, heavy alcohol intake (>80 ml ethanol per day, as defined by IARC, https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Alcohol-Drinking-1988) and concomitant chronic viral hepatitis (HBV or HCV) were associated with a multivariate odds ratio for hepatocellular carcinoma (HCC) of 53.9.[77]

The exposure to aflatoxin B1 which is a mycotoxin produced by particular fungi (such as *Aspergillus* species) proliferating on certain foodstuffs increases the risk of HCC associated with both HBV and HCV infections. The co-exposure to aflatoxin B1 and HBV is particularly observed in sub-Saharan Africa and South-East Asia.[78] Several studies suggest that exposures to the still commonly used organophosphorus and carbamate pesticides, are additive risk factors to current HCV and HBV infections among males in a rural setting.[79] In the south of Vietnam, a study shows that exposure for 10 years or more to organophosphorus pesticides was associated with an increased risk of HCC.[80]

Although tobacco smoking can cause lung cancer by itself, its association with chronic hepatitis B and C infections is a strong risk factor for liver cancer. A meta-analysis has recently shown that tobacco smoking and HBV infection interact additively in the

development of liver cancer.[81] Chemical compounds in tobacco smoke have cytotoxic potential that increases necroinflammation and liver fibrosis. Additionally, smoking increases the production of pro-inflammatory cytokines involved in liver cell damage.[82] In contrast, several studies report that there is no evidence of an association between marijuana (cannabis) smoking and HCV or HBV infection in leading to significant liver fibrosis progression or to HCC.[83]

Metals such as arsenic (As), lead (Pb), mercury (Hg), cobalt (Co), copper (Cu), palladium (Pd), iron (Fe) and manganese (Mn) can be very toxic and some are known to cause pathological changes within organs which ultimately lead to cancer.[84] Regarding the co-exposure to toxic metals and viral agents inducing hepatitis, it is known that HCV-related hepatitis is associated with altered regulation of metal metabolism; such a deregulation can cause inflammatory changes and oxidative stress, which leads to enhanced HCV replication and reduces the efficacy of antiviral therapy in patients with chronic hepatitis C.[85] In addition, copper accumulation in fibrotic livers may contribute to hepatic injury and increase the impacts of HCV infection.[85] In contrast, zinc levels in the serum of patients with HCV are associated with a decrease in the severity of disease. An American cross-sectional human health survey based on 70,000 individuals suggests that the toxic effects of lead and cadmium may be associated with an increased susceptibility to chronic HBV infections.[86]

Cholestatic liver disease

Primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC) are rare cholestatic diseases of the liver, which affect the large- and small-to medium-sized bile ducts, respectively.[87,88] Both diseases are characterised by an accumulation of bile acids that likely serves to promote an inflammatory and tissue remodelling cascade, which ultimately leads to hepatic dysfunction and often progresses to end-stage liver disease.[22] The overarching pathogeneses of either PSC and PBC are complex and likely involve both genetic and environmental elements that are currently poorly understood. Both diseases are associated with co-morbid autoimmunity and about 70% of patients with PSC have concurrent inflammatory bowel disease.[87] From an exposome standpoint, the high incidence of inflammatory bowel disease in these populations is likely of high importance.[89] The intestine serves as a barrier to many of the chemicals ingested through the diet. Disruption of that barrier due to inflammation or disrupted microbial homeostasis may increase absorption of and exposure to more exogenous chemicals. This emphasises the importance of assessing intestinal integrity and microbial composition in future studies.

In the past decade, several genome-wide association studies have improved our understanding of the mechanisms underlying PSC and PBC pathogenesis and development, *i.e.* emphasising the contribution of immunity in disease processes.[90] Although genome-wide association studies provide key direction into factors involved in the development of these rare cholestatic diseases, they do not fully account for their exact pathogeneses, nor are they able to identify features of disease progression. Currently, treatments for PBC are primarily focused on altering the bile acid pool and two such treatments, ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) have been shown to be beneficial, although many patients do not respond adequately.[91] No medical therapy exists for PSC. Therefore,

elucidating the pathophysiology of these diseases is essential to improve their management and treatment. To this end, recent attention has been focused on the combined study of exposomics-metabolomics in PSC, with the aim of identifying likely pathogenic environmental exposures along with the metabolic alterations that may contribute to these diseases (Fig. 2).

In a recent study, an exposomics-metabolomics framework was applied in 40 patients with PSC, 40 patients with PBC and corresponding controls using high-resolution mass spectrometry (HRMS) capable of detecting several tens of thousands of features in plasma samples.[16] This approach employs gas chromatography HRMS for detection of semi-volatile compounds and environmental chemicals and liquid chromatography HRMS to measure endogenous metabolites (there is overlap between the two platforms). The study carried out separate exposome-wide and metabolome-wide association studies of PSC and PBC (results for PSC can be seen inFig. 2). Subsequently, these analyses reported chemicals and pathways associated with each disease. These elements were then integrated after applying an exposome-metabolome correlation matrix to describe for the first time exposure-response networks in PSC and PBC.[16] The study revealed many environmental chemicals with known hepatotoxic properties and endogenous metabolic pathways potentially underlying liver malfunction. The authors reported 54 compounds associated with PSC while none were associated with PBC. Attempted annotation of the 54 PSC-associated compounds using data available in the NIST 2017 library identified only one high-confidence match, underscoring a major challenge to gaining biological insight using untargeted gas chromatography HRMS. This chemical was terbucarb, a carbamate pesticide, a class of insecticide widely used in household, agricultural, and industrial applications.[92] The study also identified two fungicides, fenpropimorph and spiroxamine, that were elevated in patients with PSC and PBC, respectively.[16] These chemicals inhibit cholesterol metabolism in mammalian cells, leading to accumulation of polar sterols.[93] Subsequently, pathway enrichment analysis found the bile acid biosynthesis pathway included the greatest number of disease-associated metabolites in both PSC and PBC, consistent with known mechanisms of cholestatic liver disease.[94] Finally, an integrative network analysis that evaluated the correlation between disease-associated chemicals identified in exposome-wide association studies and the enriched metabolic pathways from metabolome-wide association studies, showed that the largest cluster in PSC centred on aldicarb sulfone, a commercial-use carbamate pesticide that is classified as an extremely hazardous substance in the United States and is no longer being distributed. Of note, this cluster did involve 17 of 27 PSC-associated pathways[16]

This recent report supports a role for environmental chemicals in contributing to the pathogenesis of PSC and PBC and presents a novel move towards adapting exposomic methodologies for precision medicine approaches to the study of liver disease. It should be noted that this was a relatively small sample size. A larger follow-up study of plasma-based exposomics-metabolomics, which includes 1,600 patients with PSC, PBC and controls is currently underway and will likely fill some knowledge gaps and provide the framework for new therapies for these enigmatic cholestatic liver diseases.

Liver cancers

The predominant primary liver cancers are HCC and cholangiocarcinoma. Both cancers are usually diagnosed at an advanced stage, which may explain their poor prognoses despite some progress in treatment. In this section we will focus on HCC, which is the most frequent liver cancer. In the vast majority of cases, HCC develops on a background of cirrhosis after a long evolution of chronic liver disease, mainly caused by HBV or HCV infection, alcohol consumption or toxins like aflatoxins, aristolochic acid and cyanotoxins, as well as drugs and occupational chemicals.[95] Whatever the risk factors, cirrhotic high-grade dysplastic nodules are the most frequent pre-neoplastic lesion from which HCC develops. However, HCC can also develop on a non-cirrhotic liver, this is particularly frequent in the context of NASH or HBV infection. Exceptionally, HCC can also occur in a normal liver through the malignant transformation of a hepatocellular adenoma with specific risk factors: high oestrogen exposure, including oral contraception, androgen intake, genetic metabolic diseases (such as glycogenosis), or high alcohol consumption[96] Therefore, the known exposome associated with HCC is diverse and it has expanded considerably over the years.

The mechanisms leading to HCC following exposure to environmental stressors are mostly indirect and related to the inflammation generated by the evolution of chronic liver disease, during which inflammation and metabolic pressures favour the accumulation of epigenetic and genetic alterations in hepatocytes.[95,97,98] Toxin exposure can also directly induce genomic alterations in cancer driver genes in hepatocytes before the malignant transformation: DNA viruses (HBV and adeno-associated virus type 2) can activate oncogenes through viral insertional mutagenesis, while aflatoxin B1 exposure, tobacco smoking and alcohol consumption induce DNA damage during life – mutational signatures specific for each risk factor have been observed in HCC and in normal tissues.[97,99–101] Moreover, the individual genetic background can modulate the risk and the severity of either chronic liver disease or cancer.[102,103] Genetic polymorphisms in several genes (*PNPLA3*, *TM6SF2* and *HSD17B13*) that encode for proteins involved in lipid metabolism modulate the severity of NASH and alcohol-related chronic liver diseases. These gene polymorphisms also modulate the risk of HCC associated with either one of these risk factors.[102–105] Other genetic polymorphisms in *WNT3A/WNT9A* or in *TERT* modulate the risk of HCC without impacting on the chronic liver disease. Finally, alongside genetic polymorphisms, exposure to different risk factors can have additive or synergistic effects on liver cancer development. The most demonstrative example is the co-occurrence of aflatoxin B1 exposure, with HBV viral infection and the null-polymorphism in *GSTM1* (glutathione-S-transferase mu), coding for an enzyme that detoxifies aflatoxin B1. Interestingly, these three risk factors cooperate together to drastically increase the risk of HCC in Africa and in East Asia by more than 90-fold compared to individuals without any of these risk factors.[106,107]

During the last few years, several behavioural and environmental exposures have been shown to increase the risk of liver cancers in humans. Smoking was shown to increase the risk of HCC by more than 80%.[108] Interestingly the increased risk of HCC tended to decrease considerably in former smokers and was absent or negligible after 30 years of smoking cessation. The increased risk of HCC related to smoking is of a similar magnitude

as that of alcohol abuse. Also, both alcohol abuse and smoking increase the risk of biliary tract cancers.[109] In contrast, coffee consumption and aspirin intake were associated with a decreased risk of HCC.[110,111]

Evidence for environmental exposure and increased HCC has also increased considerably lately. Air pollution has been shown to be associated with a moderate increase in the risk of HCC (15% increase).[112] Associations were strongest with air pollution components NO_2, $PM_{2.5}$ (particulate matter with a radius smaller than 2.5 μm) and black carbon.[113] It should be noted that PM, including $PM_{2.5}$, carry (in their compositions or by adsorption) a variety of compounds that are carcinogenic, such as metals and PAHs. Exposure to other environmental stressors has also been associated with increased risk of HCC: metals including arsenic and cadmium, polychlorinated biphenyl, PAHs, pesticides, organic solvents, and PFASs.[79,114–117] In a recent case-control study involving 100 individuals, high blood levels of a major PFAS, perfluorooctane sulfonic acid, were associated with a 4.5-fold increase in the risk of HCC.[118] A metabolome-wide association study and pathway-enrichment analysis showed that disruption of key metabolic pathways by perfluorooctane sulfonic acid may contribute to such an outcome. While the weight of evidence linking these exposures to HCC may be different, the global conclusion is that the extent of the exposome linked to HCC risk is much larger than previously thought.

Interestingly, analysis of the DNA mutational profile of different HCCs has identified mutational signatures associated with specific risk factors, notably viruses, alcohol and toxins.[99] Therefore, the molecular profile of the genetic alterations accumulated in the liver and in HCC reflects exposome components that triggered the carcinogenic process during life (Fig. 3). Using such large-scale profiling could improve our knowledge of the environmental determinants of HCCs. The same could be true for epigenetic profiling, such as miRNA profiles or the DNA methylation landscape.[119] On the other end of the biological mechanisms, the identification of initial events such as the activation of nuclear receptors or the modulation of xenobiotic metabolising enzyme activities could also be relevant. However, concerning the nuclear receptors implicated in HCC, there are still a lot of discussions and uncertainties, mostly related to the relevance of animal studies to human pathogenesis.[120] These controversies particularly concerning the receptors PPAR-α and CAR (whose expression levels and ligand patterns significantly differ in humans and rodents) have considerably delayed our capacity to correctly predict the hepatic carcinogenicity of industrial substances. Yet a cross-species understanding of the biological pathways associated with exposure to stressors on one hand and cellular transformation on the other hand would be extremely useful for predicting the impacts of exposome components.

Fewer well-organised studies were devoted to the role of environmental exposures on cholangiocarcinoma. Anatomically, cholangiocarcinoma is categorised into three subtypes: perihilar or Klatskin’s tumour, intrahepatic, and extrahepatic. The pathogenesis of each type is likely distinct and better studies are needed to classify these tumours on a molecular basis. Unfortunately, the anatomic classification was not followed properly for a variety of reasons, and thus, past environmental studies should be interpreted with caution.[121] Such reported exposures include liver parasites, dioxin and dioxin-like compounds, nitrosamines, tobacco

smoking, asbestos, and alcohol consumption as well as several occupational hazards.[121] Interestingly psychosocial stress also appears to play a role.[122–124]

Other exposure-related liver diseases

Several liver diseases are fully or partially related to changes in exposures but are usually considered as independent entities. We believe they should be discussed in the context of the exposome and summaries of these conditions and their relation to the exposome are developed below.

Drug-induced liver injury (DILI)

Drug-induced liver injury (DILI) is an adverse reaction to drugs or other xenobiotics that occurs either as a predictable event following exposure to toxic doses of a compound (intrinsic DILI) or as an unpredictable event with drugs in common use (idiosyncratic DILI).[125] While most of the cases reported in the US and Europe are secondary to conventional medications, traditional/complimentary and dietary supplements are the main causative agents of DILI in Asia.[126] Liver harm develops when the offending agents, often lipophilic drugs, are converted to reactive metabolites that have the potential to covalently bind to proteins and cause cellular organelle stress. This process may lead to hepatocyte death, which is mediated either by the collapse of mitochondrial function and necrosis, or by activation of regulated cell-death pathways.[127] DILI can present as any recognised pattern of liver enzyme derangement in susceptible individuals in whom the disease process is framed by genetic and environmental risk modulators like advancing age, sex, alcohol intake and underlying liver disease. Accordingly, the diagnosis of DILI is almost invariably challenging, requiring a step-by-step approach with accurate analysis of the temporal sequence of events, exclusion of alternative causes and navigation through the RUCAM (Roussel Uclaf Causality Assessment Method) algorithm or its revised version RECAM (Revised Electronic version of RUCAM). In selected cases, HLA genotyping may improve causality assessment and differential diagnosis with autoimmune hepatitis.[128] The overwhelming importance of a prompt assessment of causality relies on the potentially severe outcome of DILI that spans from a trivial illness to acute liver failure and the need for liver transplantation.

Unbalanced homeostasis of iron

Unbalanced homeostasis of iron is a good illustration of genome-exposome interactions in liver diseases. Iron is essential for the production of heme and iron-sulphur components of proteins and enzymes involved in vital biological processes. Its dysregulation may result in either deficiency or overload syndromes. Iron overload has the propensity to damage cell components owing to the fact that iron accepts and releases electrons, *i.e.* has the ability to cause oxidative stress (like lipid peroxidation) leading to shrunken and electrondense mitochondria and cell death (ferroptosis). Key genes related to ferroptosis include *GPX4* (glutathione peroxidase-4), *ACSL4* (acyl-CoA synthetase long-chain family member-4), *CBR3* (carbonyl reductase [NADPH] 3), and PTGS2 (prostaglandin peroxidase synthase-2). Notably, ferroptosis is involved in different pathological conditions, including neurological and liver and kidney diseases and different cancers.[129] Central to iron homeostasis is the

liver peptide hepcidin, which regulates serum iron levels through degradation of ferroportin in iron-absorptive enterocytes and in macrophages. Dysregulation of this pathway can be observed in steatohepatitis (NASH), alcohol-related liver disease, DILI, viral hepatitis, and haemochromatosis.[130] In haemochromatosis, mutations in genes of the hepcidin-ferroportin axis lead to increased iron absorption, high transferrin saturation and increased toxicity from non-transferrin bound iron species, which favours the onset of cirrhosis, liver cancer and extrahepatic diseases like diabetes, osteoporosis, arthropathy and, in patients with early onset haemochromatosis, hypogonadotrophic hypogonadism, hypothyroidism and heart failure. The commonest form of haemochromatosis in Caucasians is due to homozygous HFE(C282Y) mutations, but the exact disease penetrance is dependent on age and sex.[131] Congenital iron overload disease also occurs in individuals with alpha and beta thalassemia, syndromic and non-syndromic congenital sideroblastic anaemia, congenital dyserythropoietic anaemia, hypotransferrinaemia and in diseases related to divalent metal transporter 1 mutations. Genetically driven regional accumulation of iron and ferritin may occur, causing harm to the brain and lenses, whereas acquired iron overload due to chronic blood transfusions, inflammation or anaemia may have multiple clinical consequences.[130]

Dysregulation of copper homeostasis and Wilson disease

Dysregulation of copper homeostasis and Wilson disease is another relevant example of genome-exposome interactions. Copper is an essential metal required for the function of many metalloproteins that serve numerous metabolic needs of liver cells, including building of nascent ceruloplasmin, which carries more than 95% of the total copper in plasma.[132] Copper compounds are also active plant protection products, and it is likely that certain populations are exposed to high levels of copper. As excess hepatic copper is excreted via the biliary pathway into faeces, cholestasis is responsible for both hepatic retention and increased circulating levels of copper. The prototype clinical syndrome caused by excessive retention of copper is Wilson disease, a familial, neurological lethal disease accompanied by cirrhosis, which results from inactivation of the gene encoding a metal-transporting P-type ATPase, ATP7B, found mainly in hepatocytes. When exceeding storage capacity, copper deposits in various organs, especially the brain, kidneys and cornea. The disease may present with a broad spectrum of liver disease that ranges from asymptomatic to cirrhosis and acute liver failure. In teenagers, liver disease usually precedes neurologic manifestations by years, while most adult patients with neurologic symptoms have some degree of liver disease at presentation. Notably, acute liver failure occurs mostly among women. In the US it accounts for up to 12% of all listings for acute liver failure and is almost invariably fatal if not treated with emergency transplantation. Severe liver injury may cause the sudden release of copper into the blood and cause acute intravascular haemolysis with anaemia, haemoglobinuria, jaundice and progression to renal failure.[133] Wilson disease should be differentiated from aceruloplasminemia, MDR3 (multidrug resistance protein 3) deficiency, and certain congenital disorders of glycosylation through genetic, laboratory and clinical investigations.

Conclusions and perspectives

The range of external factors that compose the liver exposome is extremely diverse and several of its components have been linked to liver diseases in clinical, epidemiological, and experimental studies (Fig. 4). Some important conclusions can be drawn from the analysis of the impact of various exposures on liver diseases:

- One exposure, several pathologies. The analysis of the contribution of the exposome to different liver diseases shows that several exposures are common to different liver pathologies, for example alcohol consumption, smoking, viral infections, and some chemical exposures. This is not surprising as these diseases are linked to each other, for example the progression from MAFLD or viral hepatitis to cirrhosis to HCC.
- Combination of different exposures. Another important observation is that often a combination of different exposures is involved in disease development or progression, for example the combination of viral agents and chemicals for the progression of viral disease and HCC, or chemicals, dietary imbalance and dysbiosis for the progression of metabolic diseases and the likely contribution of multiple chemicals such as drugs, environmental and occupational chemicals in the progression of liver diseases. Indeed, it is likely that most liver disease results from a combination of multiple factors necessitating an exposome-based approach.
- Systemic and liver-specific impacts. While some risk factors like smoking, air pollution or obesity display systemic effects at the organism level with liver pathology being one component of a larger disease, other factors such as hepatitis viruses, mycotoxins, certain drugs and chemicals, elicit a more specific liver disease. Obviously both types of stressors could have combined effects.

All these considerations highlight the relevance of the exposome concept for improving our understanding of liver disease pathogenesis, with the aim of guiding prevention, biomarker identification and ultimately treatment.

There are still many unknowns concerning the actual contribution of the exposome to liver pathologies. In this regard, there is huge interest in the development of technologies and approaches that would fill these gaps. As highlighted in different sections of this review, in our view, the most promising technologies and approaches are the following:

- A combined and integrated exposomics-metabolomics framework to better characterise liver diseases, identify both exogenous exposures and endogenous processes and establish putative links between these two profiles.[4]
- Further development of chemical mixture studies to assess the effect of large mixtures of chemicals and their interaction with other stressors.[134] While drug-drug interactions have been extensively studied, it is important to extend this research to other types of chemicals and at a much larger scale. Since the liver is the primary organ of xenobiotic metabolism, mixtures studies should encompass parent molecules and their metabolites.

- Development of genomic and epigenomic mutational signatures correlated with specific exposures. This would help to link the observed molecular description of liver samples (*e.g.*, HCC or hepatocellular adenoma) with likely risk factors and exposures. Such approaches could benefit from both clinical and toxicological studies.
- A systematic characterisation of the microbiome because of its significant influence on organ metabolomes and since dysbiosis has been associated with a variety of diseases including metabolic and biliary diseases.[135] Importantly, disruption of gut permeability is linked to exposure to several chemicals and dysbiosis. Finally, there are sex-specific differences in microbial composition, which could account for differences in disease susceptibility in addition to hormonal effects.[136]
- A strategy to better integrate *in vivo*/*in vitro* and human studies to improve prediction. Such a strategy could involve a systems biology approach and biological pathway identification in order to better translate experimental approaches into human-relevant knowledge.[5]

Obviously, all these approaches will benefit from comprehensive clinical studies of liver diseases in which an exposome approach has been integrated. While in many such studies, genomics and other omics technologies have been included, it is time to introduce and integrate exposomics with the other omics.[6] This will primarily concern chemical exposomics but, as mentioned earlier, a more extensive microbiological characterisation is also relevant (microbiome, viral and parasitic agents) as well as a more extensive characterisation of physical stressors. The social component of the exposome is also critical for liver diseases, particularly concerning the social determinants of diets, dysbiosis and addictive behaviours.

We should also be aware of the limitations of the exposome framework in epidemiological and clinical studies. Indeed, by increasing the number of biomarkers and of factors influencing liver diseases, very large cohorts or clinical studies are needed to meet statistical requirements. This may not be possible for certain diseases and in all cases may prove to be very costly. Thus, it is critical to assess the cost-effectiveness of each study design. Despite these limitations, exposome studies may prove to be a hypothesis-generating first step. Hypothesis-driven studies will still be needed to confirm and to provide more precision on the causal links between exposures and outcomes.

Liver studies have benefited from the combination of clinical and experimental approaches. This should now be further developed with the exposome concept in mind. Experimental 2-dimensional or 3-dimensional model systems have been used and can still be further developed to link clinical and experimental observations.[137] Improving assessment of toxicity using these new methodologies could support preventive measures and protect public health. Furthermore, the combination of clinical and experimental studies could support the development of new biomarkers and lead to the development of new therapies. The latter could consist of dietary or microbial interventions or the development of drugs targeting critical biological pathways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AhR	aryl hydrocarbon receptor
beta-HCH	beta-hexachlorohexane
BPA	bisphenol A
CAR	constitutive androstane receptor (NR1I3)
DDE	dichlorodiphenyldichloroethylene
DEP	diethylphthalate
DILI	drug-induced liver injury
HRMS	high-resolution mass spectrometry
MEHP	mono(2-ethylhexyl)phthalate
NAFLD	non-alcoholic fatty liver disease
MAFLD	metabolic dysfunction-associated fatty liver disease
PAHs	polycyclic aromatic hydrocarbons
PBC	primary biliary cholangitis
PFASs	per- and polyfluoroalkyl substances
PM	particulate matter
POP	persistent organic pollutant
PPAR	peroxisome proliferator-activated receptor
PSC	primary sclerosing cholangitis
PXR	pregnane X receptor (NR1I2)
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin

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Key points

- The liver plays an important role in xenobiotic metabolism and elimination and is therefore a target of the chemical exposome.
- Chemicals, infectious and physical agents are important determinants of different liver diseases.
- Both traditional targeted studies and non-targeted exposomics studies have revealed the links between exposure to chemicals and liver diseases.
- The combination of different stressors, *e.g.* chemical and viral agents, plays a role in liver disease pathogenesis.
- Liver diseases can be related to exposure to liver-specific stressors, *e.g.* viral hepatitis, or to stressors displaying more systemic effects, *e.g.* air pollution.
- There is increasing concern about the liver toxicity of certain chemicals such as endocrine disruptors, pesticides and per- and polyfluoroalkyl substances.
- New methodologies including high-resolution mass spectrometry, genomic, epigenomic and metagenomic signature detection and computational approaches will further develop research in this field.

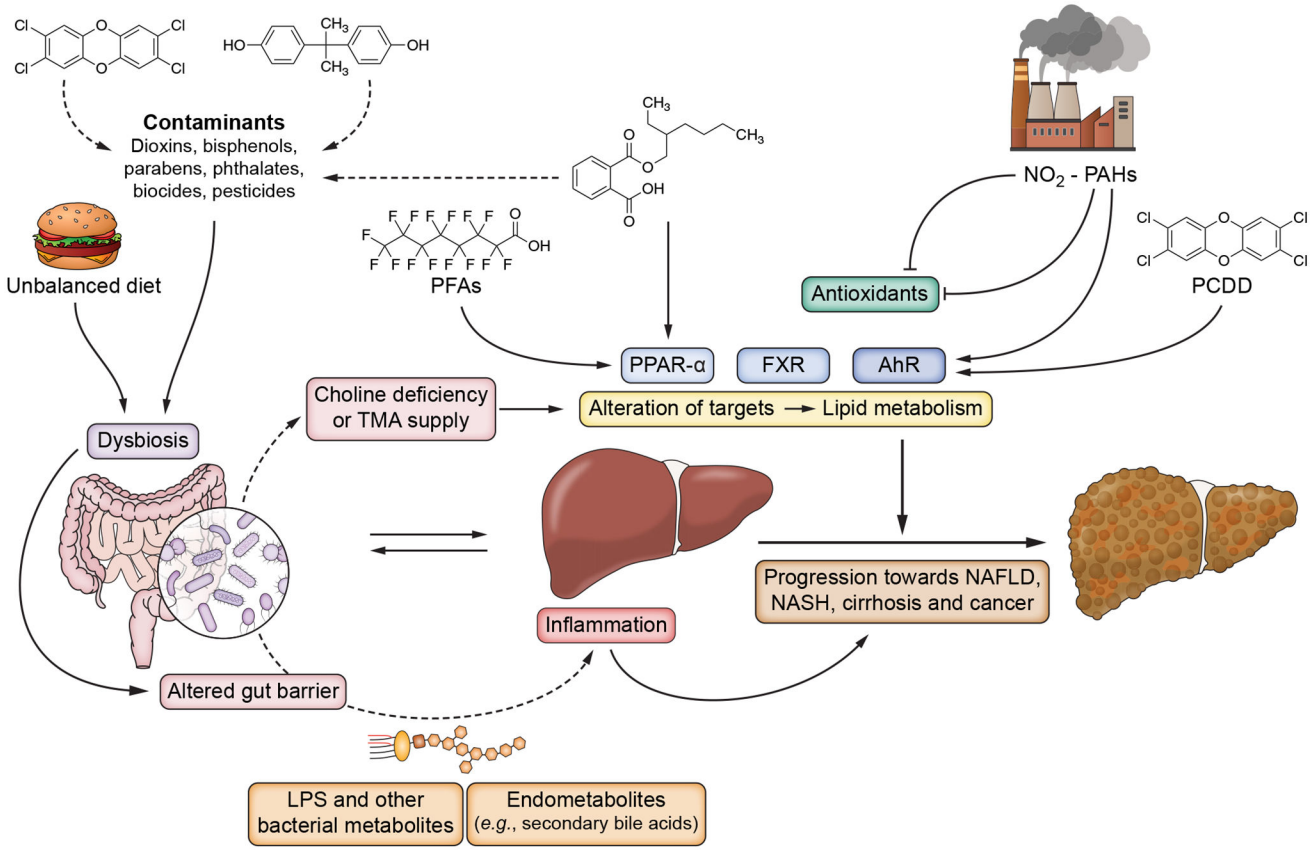

Fig. 1. Metabolic disruption and liver injury following exposure to contaminants and pollutants.

Exposure to food contaminants is associated with dysbiosis and gut barrier injury, ultimately leading to an alteration of the gut-liver axis and increased inflammation of the liver. Changes in microbial metabolites also impact metabolic pathways in the liver, such as lipid metabolism. A variety of contaminants and pollutants activate several receptors in the liver which also lead to significant metabolic disruption. The combination of these alterations increases the risks of developing liver diseases, such as NAFLD, NASH and ultimately cirrhosis and cancer. AhR, aryl hydrocarbon receptor; FXR, farnesoid X receptor; LPS, lipopolysaccharide; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PAHs, polyaromatic hydrocarbons; PCDD, polychlorinated dibenzodioxins; PFASs, per- and polyfluoroalkyl substances; PPAR, peroxisome proliferator-activated receptor; TMA, trimethylamine.

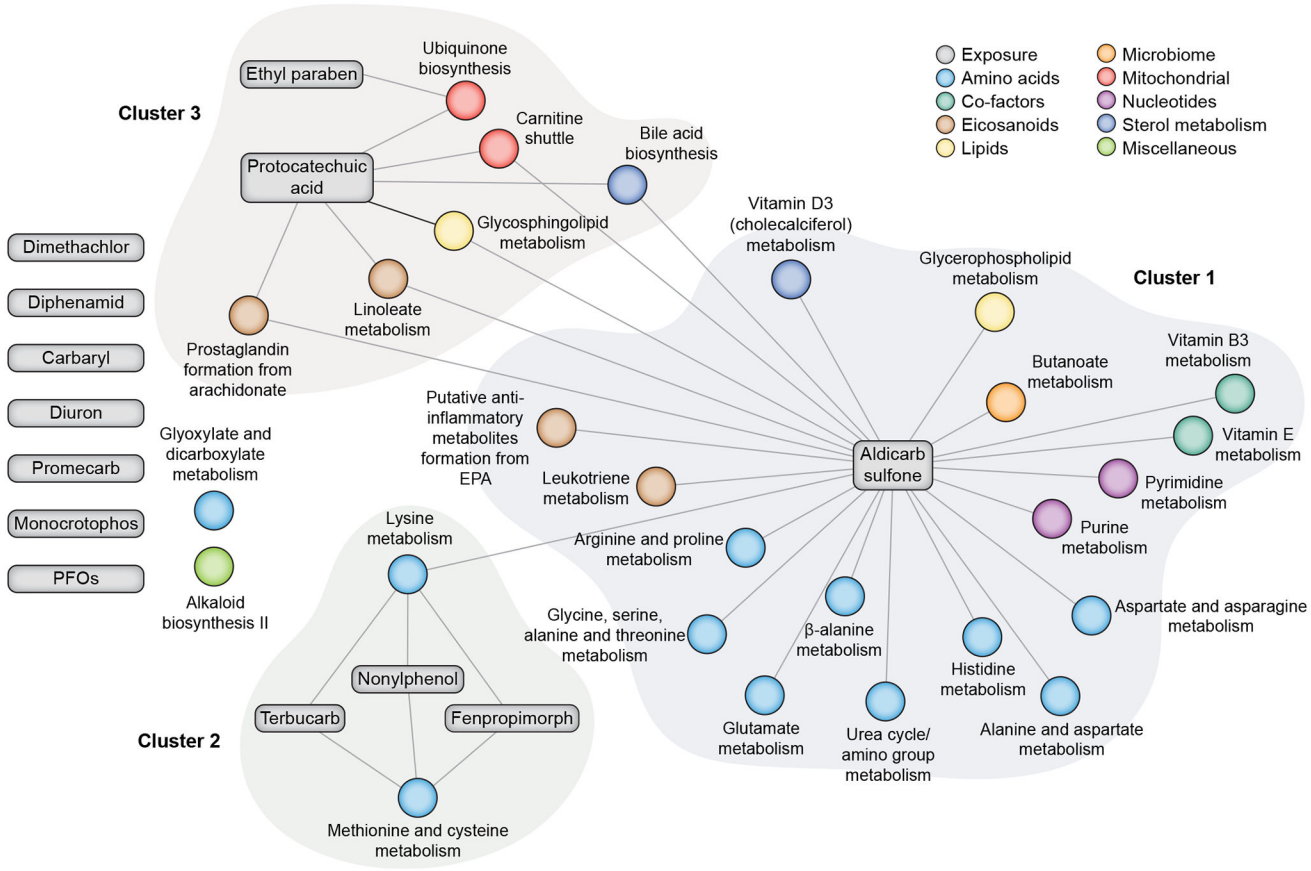

Fig. 2. Network interaction plot of exposures and metabolites in primary sclerosing cholangitis.

For each pathway, the first principal component was tested for association with each identified exposure biomarker; clusters (Cl1–3) were identified using multilevel community detection to identify communities of nodes that are tightly connected with each other, but sparsely connected with the rest of the network. Reproduced with permission from Hepatology Communications, 6: 965–979, 2022. PFOS, perfluorooctane sulfonic acid.

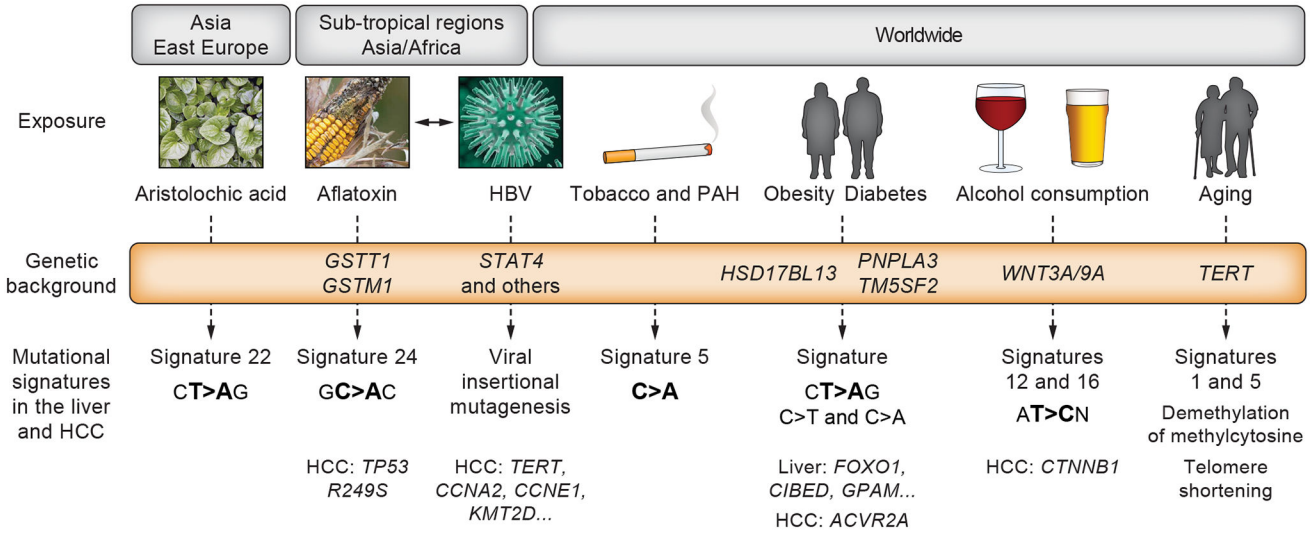

Fig. 3. Various mutational signatures identified in liver and HCC tissues and related to specific exposure during life.

The mutational signatures refer to the molecular profile of the genetic alterations accumulated in the liver and in HCC and reflect exposome components that triggered the carcinogenic process during life. Each exposure is believed to lead to a relatively specific set of mutations. Identifying such mutational profiles is helpful to determine which exposure is likely to have contributed to the development of the disease. The most frequent nucleotide changes are represented. For more details on the genes and pathways involved, please refer to Schulze *et al.*[99] HCC, hepatocellular carcinoma.

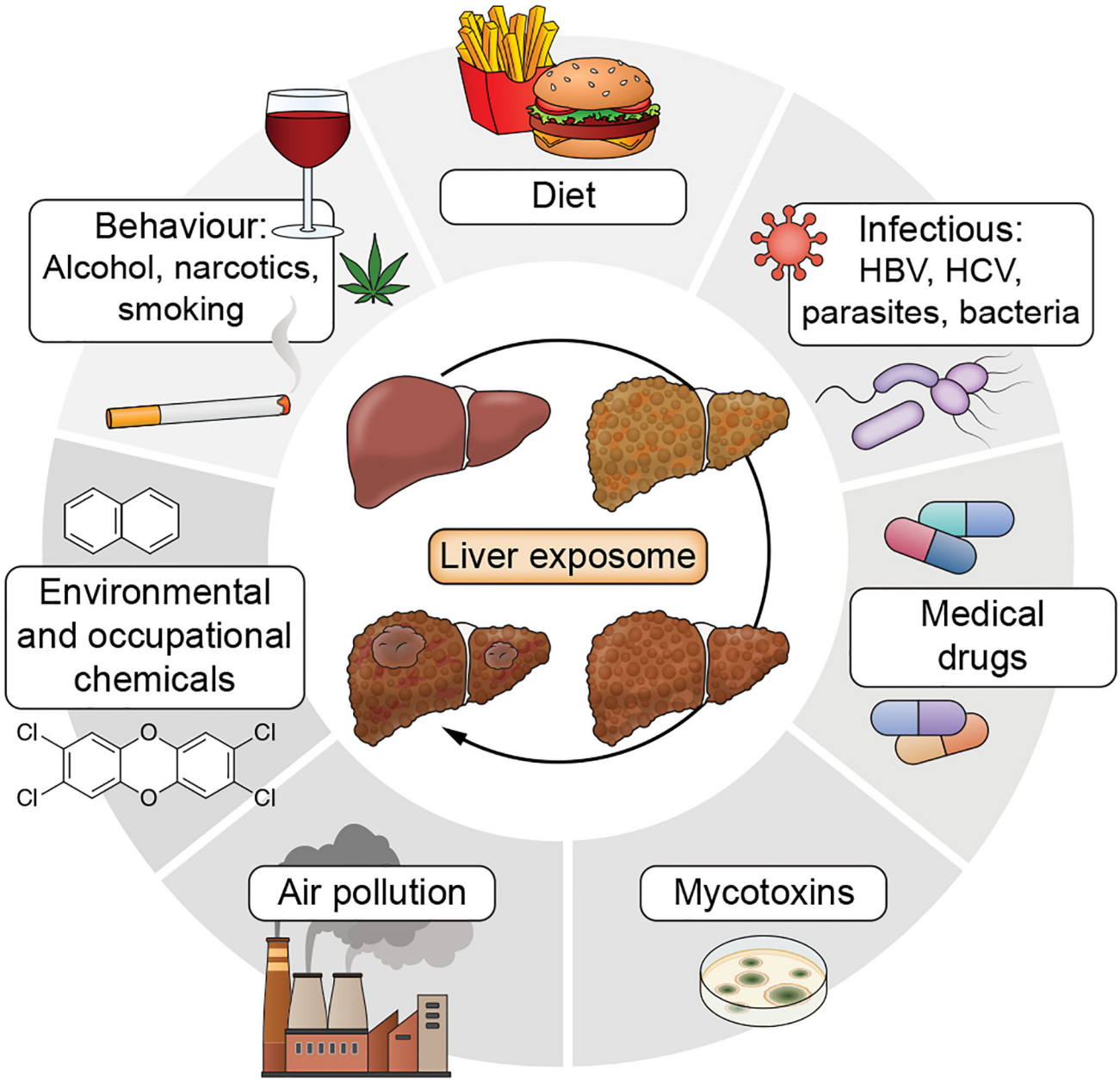

Fig. 4. The liver exposome and its impact on major liver diseases.

The central circle represents different liver diseases (steatosis, cirrhosis, hepatocellular carcinoma). It is not exhaustive and it illustrates the one pathway for the progression of these diseases. The outer circle illustrates the major contributors to the liver exposome. Note that there is no correlation between the location of the exposome component and the type of liver disease. Such correlations would be difficult to illustrate since many exposome components contribute to different stages of liver diseases.