Tox is in the air: Air pollution as a major component of the liver exposome

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The liver exposome.

The exposome integrates all types of exposures over the lifetime and is the complement of the genome in influencing well-being and health(1). Exposures are diverse and cover chemical, physical, biological and psycho-social stressors. There are also multiple exposure pathways, such as dietary, airborne, cutaneous routes. Because of its physiological functions in endogenous and xenobiotic metabolism, the liver is exposed to a variety of stressors including dietary imbalance, alcohol consumption, microbiome metabolites, food contaminants in addition to different infectious agents. While much of the studies on toxicants have focused on liver cancer as a health outcome, more recent studies have broadened the spectrum of these outcomes to include liver steatosis, fibrosis and inflammation. Metabolic Associated Fatty Liver Disease (MAFLD), the liver manifestation of the metabolic syndrome, is characterized by fat accumulation and inflammation in the liver which ultimately can trigger excess fibrosis deposition and progression to liver cancer (2,3). The liver in MAFLD patients appears to be the target of a systemic low grade inflammation that affects other body tissues and organs, including adipose tissue, pancreatic β-cells and the cardiovascular system, a condition that is initiated by metabolic stress and may lead to multi organ

co-morbidities (4). As the clinical burden of MAFLD has increased steadily since the 1980s, currently affecting a quarter of the global population and a majority of patients with adult onset diabetes (5), this condition has become one of the globe's largest public health burdens. For these reasons, more efforts should be devoted to prevention measures.

Airborne toxicants.

In addition to the relatively direct exposure to dietary contaminants, the liver is also exposed to contaminants having a different entry point, i.e. airborne contaminants. Inhalation of these contaminants through the lungs and their uptake in the bloodstream leads to a widespread exposure of a variety of organs. Since the liver is the primary detoxication organ, it is particularly sensitive to these contaminants either through the signaling pathway that they trigger or through their metabolism. Alternatively, these contaminants could lead to a systemic inflammation and induce oxidative stress leading to an indirect injury of the liver. In all cases, liver pathophysiology should now take into account this expanding liver exposome which is not restricted to exposures originating from the diet, but also includes other types of exposures and in particular airborne contaminants. The outcomes of the large scale epidemiologic study by Guo and coworkers goes in this direction, as it shows an association between ambient air pollution and MAFLD (7). Indeed, Guo and coworkers (7) examined the associations between long-term ambient pollution exposure and MAFLD prevalence in more than 90,000 adult individuals which were prospectively enrolled into the China Multi-Ethnic Cohort (CMEC) between 2018 and 2019. Residence-specific levels of air pollutants, including PM with aerodynamic diameters of ≤1 μm (PM1), ≤2.5 μm (PM2.5), and ≤10 μm (PM10), and nitrogen dioxide (NO2), were estimated by validated spatiotemporal models. Increased exposure levels to all four air pollutants were found to be significantly, though not linearly, associated with increased risk of MAFLD. Further, males, alcohol drinkers, smokers, individuals with obesity and consumers of a high-fat diet, all representing the populations at high risk of MAFLD progression, turned out to be more vulnerable to adverse effects of ambient pollution than other individuals.

All organs including liver "breathe" air toxicants.

Air pollution (AP) is the most critical component of global pollution and is likely to be responsible for millions of deaths per year world-wide. Respiratory and cardiovascular diseases were considered to be the primary health outcomes related to exposure to AP. More recent experimental and epidemiological studies showed that other health outcomes were to be considered such as neurological effects, reproductive health, obesity and metabolic diseases and now liver diseases. The main conclusion from all these recent studies is that air pollution is not only involved in local outcomes but is rather a determinant of systemic disorders. Liver biology provides some clues to better understand liver effects of AP. Indeed, air pollutants consist not only in PM and NO_2 but also include a large variety of chemicals such PolyAromatic Hydrocarbons (PAH) and metals. Experimental studies have shown that exposure to PM could induce a NASH-like phenotype in mice (9,10). Furthermore, several PAHs as well as dioxins activate the Arylhydrocarbon Receptor (AhR). The combination of AhR activation and high fat diet leads to a phenotype in mice combining fat accumulation, fibrosis and inflammation, a NASH-like phenotype (11). These effects might be mediated by the induction by AhR of genes involved in metabolic and inflammatory pathways as well as in epithelial mesenchymal transition (12). Altogether, these studies indicate that MAFLD related to AP could be mediated by a variety of AP components leading to both inflammatory systemic effects and liver-targeted toxicity elicited by specific pollutants.

New paths for prevention.

Whereas physical activity together with a healthy diet stand as a primary pillar in the fight against metabolic syndrome associated morbidities, including MAFLD, the findings that ambient pollution could exacerbate MAFLD risk might offer new clues to refining the counseling of these patients, for instance by restricting exposure of risk populations to open air settings at high level of pollution. It also constitutes an additional incentive for decision makers to speed up the efforts to conform with the WHO guidelines and limits on air pollution, as many cities in Europe and world-wide are still well above those limits (13).

References

1. Wild CP. Complementing the genome with an « exposome »: the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. août 2005;14(8):1847-50.
2. Cotter TG, Rinella M. Nonalcoholic Fatty Liver Disease 2020: The State of the Disease. Gastroenterology. mai 2020;158(7):1851-64.
3. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol. juill 2020;73(1):202-9.
4. Stefan N, Häring H-U, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. Lancet Diabetes Endocrinol. avr 2019;7(4):313-24.
5. Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM. Changes in the Global Burden of Chronic Liver Diseases From 2012 to 2017: The Growing Impact of NAFLD. Hepatol Baltim Md. nov 2020;72(5):1605-16.
6. Cheung AC, Walker DI, Juran BD, Miller GW, Lazaridis KN. Studying the Exposome to Understand the Environmental Determinants of Complex Liver Diseases. Hepatol Baltim Md. janv 2020;71(1):352-62.
7. Guo B, Guo Y, Nima Q. Exposure to air pollution is associated with an increased risk of metabolic dysfunction-associated fatty liver disease. J Hepatol.
8. Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu NN, et al. The Lancet Commission on pollution and health. Lancet Lond Engl. 3 févr 2018;391(10119):462-512.
9. Zheng Z, Xu X, Zhang X, Wang A, Zhang C, Hüttemann M, et al. Exposure to ambient particulate matter induces a NASH-like phenotype and impairs hepatic glucose metabolism in an animal model. J Hepatol. janv 2013;58(1):148-54.
10. Zheng Z, Zhang X, Wang J, Dandekar A, Kim H, Qiu Y, et al. Exposure to fine airborne particulate matters induces hepatic fibrosis in murine models. J Hepatol. déc 2015;63(6):1397-404.
11. Duval C, Teixeira-Clerc F, Leblanc AF, Touch S, Emond C, Guerre-Millo M, et al. Chronic Exposure to Low Doses of Dioxin Promotes Liver Fibrosis Development in the C57BL/6J Diet-Induced Obesity Mouse Model. Environ Health Perspect. 2017;125(3):428-36.
12. Larigot L, Benoit L, Koual M, Tomkiewicz C, Barouki R, Coumoul X. Aryl Hydrocarbon Receptor and Its Diverse Ligands and Functions: An Exposome Receptor. Annu Rev Pharmacol Toxicol. 9 sept 2021;
13. Burki T. WHO introduces ambitious new air quality guidelines. Lancet Lond Engl. 25 sept 2021;398(10306):1117.