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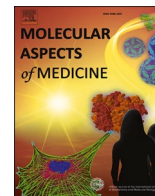
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Editorial

Molecular aspects of exposome and metabolic diseases



The original definition of ‘exposome’ was coined by Prof Christopher Paul Wild almost two decades ago (Wild, 2005). Exposome refers to the external and internal environmental factors that determine human health status complementing the effects mediated by the genetic background (Wild, 2005, 2012). The external exposome includes air pollution, chemicals in food and water, and diet, and the internal exposome has age, genetic and metabolic profile. Connections between the function of different organs and the regulation of remote organs depend on the type and efficiency of signalling mechanisms governing the cell-cell, organ-organ and system-system communication. Thus, an appropriate immediate microenvironment is required for cell function and survival, securing a healthy individual.

A condition compatible with cell survival and organ/system function include the exposome from the external environment, i.e. the *ecto*-exposome, and the exposome from the immediate nearby extracellular environment, i.e. the *endo*-exposome. It is reported that persistent organic pollutants (POPs), also known as ‘endocrine-disrupting chemicals’, interfere with the endocrine system and are present in the environment with a life-long exposure in specific populations. Also, various heavy metals are present in the drinking water in concentrations at the border or definitively higher than recommended maximum concentrations before causing human diseases, including cancer and other metabolic disorders. An example of heavy metals contamination of water is Arsenic, where arsenic trioxide is one of the most active molecules found as environmental contaminants. Unfortunately, regions of the world where their population are known to have been exposed to elevated levels of Arsenic directly in their daily water requirement, such as the Antofagasta region in the north of Chile (Ramírez et al., 2018), are associated with high prevalence and incidence of different types of cancers. However, how these environmental toxins affect cell function is not fully understood.

The exposure to exposome also starts during in utero life. Pregnancy is a physiological phenomenon where the mother and the growing fetus are exposed to various molecules reaching elevated plasma and tissue concentrations compared with what is found in a non-pregnant woman. These molecules include hormones and other proteins released by the placenta. Their role is to modulate the physiological adaptations of the mother and the placenta to generate an appropriate environment and equilibrated metabolic state, securing the normal development and growth of the fetus. Pregnancy is a natural and physiological window of opportunity for the transgenerational programming leading to a healthy individual. However, when toxins (v.g. metabolites, pharmacological agents, contaminants) cross the physical and metabolic barrier of the placenta from the maternal to the fetal circulation, the development and growth of the fetus may be altered, as seen in intrauterine growth

restriction (IUGR), some cases of preeclampsia, and gestational diabetes mellitus (GDM). It is now accepted that exposure to toxins in uterus may result in the programming of diseases leading to an increased risk of developing young and adulthood diseases.

In the selected collection of contributions to this special issue presented by experts in the field of the exposome and associated molecular mechanisms involved in metabolic disorders, the review by Nadja Kupper & Berthold Huppertz (Kupper and Huppertz, 2022) proposed the various related mechanisms involved in maintaining regular and efficient crosstalk between the mother and the placenta. The authors’ proposal is that the mother is permanently exposed to fetal material released from the placenta, an organ of fetal origin, referred to as the ‘placental exposome’, which includes more than hormones and growth factors. Specifically, the placental exposome of fetal origin is released into the maternal circulation in various forms, including soluble chemicals, transplacental pass of macromolecules, or via the release of a variety of extracellular vesicles (EVs). The EVs are of a wide range of sizes going from a few nanometers (exosomes and ectosomes) to micrometres (migrasomes, apoptotic bodies, large oncosomes) in diameter (Chiarello et al., 2018). EVs contain specific molecules, including proteins, lipids, DNA, and microRNAs, which play distinct roles in promoting balanced homeostasis and maintaining a healthy pregnancy. The content carried by placenta-derived EVs, i.e. cargo, may also be potentially adverse to the maternal vascular system resulting in pregnancy pathologies such as preeclampsia. Kupper & Huppertz summarised the reported different types of placenta-derived EVs in pregnancy, particularly emphasizing the interplay between these placental vesicles and the maternal system and how the EVs released from the placenta may target the lungs and kidneys of the mother. The authors emphasised the critical concept and need to implement new techniques for analysing the placental exposome in the form of EVs to understand the mechanisms behind the potential action of placenta-derived EVs in healthy pregnancies and the aetiology of several other diseases of pregnancy. The potential benefit of analysing the effect of placental EVs under a dynamic flow rather than static conditions as *in vitro* assays may help understand their likely dynamic effects on target cells.

The potential actions of EVs in pregnancy are complemented by information addressing the role of placenta-derived EVs in pathologies such as gestational diabetes mellitus (GDM), IUGR, and potential increased risk of placental hypoxia. These concepts are also mentioned in the contribution by Priyakshi Kalita-de Croft and colleagues (Kalita-de Croft et al., 2022), where the role of EVs released from the placenta into maternal circulation as external and internal signals in cancer is reviewed. Interestingly, the concept of *endo*-exposome is presented as ‘unique to an individual’ involving factors such as the age and the

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individual physiological conditions of each subject. It is also mentioned that the effect of the ecto-exposome may determine the endo-exposome characteristics ending in specific modulated actions by the EVs cargo that is required by the tissues. The latter include nucleic acids and proteins that can be transferred to the tissues changing the metabolic state of the cells. It is worth noting the findings showing that the cargo of syncytiotrophoblast-derived EVs (with a large proportion corresponding to exosomes and ectosomes) includes functional endothelial nitric oxide synthase (eNOS) (Motta-Mejia et al., 2017) —a protein that generates nitric oxide (NO) after metabolising the cationic amino acid L-arginine in the vasculature and other cell types—. Also, exosomes isolated from human umbilical vein endothelial cells (HUVECs) from women with GDM show a potential cargo that might either include molecules that increase the expression level or delay the protein degradation of eNOS or carry the actual eNOS protein to insert this protein in HUVECs from normal pregnancies (Saéz et al., 2018).

Interestingly eNOS contained in syncytiotrophoblast-derived exosomes/ectosomes from women with preeclampsia generated minor NO in vitro compared with EVs from normal pregnancies (Motta-Mejia et al., 2017). Also, incubation of HUVECs from normal pregnancies with HUVECs-derived exosomes from women with GDM, a pathology associated with higher eNOS activity (estimated by increased activator eNOS phosphorylation at Ser¹¹⁷⁷ and higher NO level) in this cell type, resulted in higher eNOS activity resembling the GDM effects on eNOS (Sáez et al., 2018). Furthermore, HUVECs-derived exosomes from women with normal pregnancies were beneficial in cells from GDM pregnancies since a reversion of the GDM-increased eNOS activity was found. Thus, exosomes/ectosomes generated at the human fetoplacental unit carry a cargo that will modulate the phenotype in target tissues and cells. These findings, along with several others available in the literature, support the concept of the influence of environmental factors from conception onwards and are part of the cellular microenvironment that may even be considered as early markers of tumours and perhaps insights into cancer progression.

Paola Valero and colleagues (Valero et al., 2022a) proposed that the prevalence and risk of developing GDM are higher in women exposed to heavy metals, including Arsenic, Lead, Mercury, and Copper, contained in the ecto-exposome. These metals may enhance or cause potential alterations in the microenvironment required for appropriate fetal development and growth, leading to a programmed newborn (female and male) to develop GDM in a future pregnancy. Worryingly, these components of an adverse ecto-exposome may accumulate in the placenta and stay for long periods affecting the health of the fetus, newborn, infant, child, and adult. Unfortunately, the prevalence of obesity (body mass index (BMI) ≥ 30 kg/m²) and overweight (BMI 25–29.9 kg/m²) in the last decades has been regularly increasing (World Health Organization (WHO), 2021).

Since the increase in overweight and obesity includes women in their child bearing age, it is expected that a large number of these women will get pregnant being to pre-pregnancy obesity (Garmendia et al., 2020). Thus, a different metabolic condition in this group of pregnant women is highly likely compared with women with pre-pregnancy normal weight (BMI 18.5–24.9 kg/m²) (Cornejo et al., 2021). Whether this group of women with pre-pregnancy obesity develop GDM, a condition referred to as ‘gestational diabetes’ (Cornejo et al., 2021), configures an even more complex state than obesity or GDM by itself is still under initial consideration. Indeed, preliminary studies suggest that HUVECs from women with gestational diabetes show increased eNOS activity and H⁺ efflux leading to an intracellular alkalization compared with cells from women with lean GDM (i.e. women with GDM and normal pre-pregnancy weight) (Fuentes et al., 2019). Therefore, the potentially harmful effects of the ecto-exposome and endo-exposome may have a differential impact on the fetoplacental vasculature function with future transgenerational consequences.

Interestingly, the review by Jamie Strain and colleagues (Strain et al., 2022) highlights the potential lack of a life-course (i.e. health

trajectory) approach to the environmental exposures influencing human health. These colleagues contributed with a systematic review investigating early life metabolic exposures and offspring weight and obesity outcomes. Early life exposures, including maternal obesity, diabetes mellitus and adverse nutrition, result in the programming of an elevated risk of high weight at birth and postnatally and excess adipose accumulation. The high newborn growth and obesity risk may result from epigenetic modifications associated with changes in the placental function, the gut microbiome and breast milk composition, and metabolic inflammation. It is proposed that these alterations will likely result in abnormal development of the central appetite system, adipose tissues and liver. Understanding early-life risks and the molecular and systemic mechanisms through which the ecto-exposome and endo-exposome modify health trajectories is critical for developing and applying early interventions to prevent offspring obesity later in life. The contribution by Jane K. Cleal and colleagues (Cleal et al., 2022) highlights the importance of looking at the evidence for placental responses to environmental signals and their involvement in programming offspring health. Epigenetics involves changes within the placenta induced by altered maternal metabolic and endocrine status, unhealthy nutrition, high stress and increased concentrations of toxins. Epigenetics mediate persistent effects on placental function, and whether these changes trespass to the new generations may also persist in the early life after birth making them more prone to developing chronic diseases such as hypertension and diabetes mellitus. The authors mentioned that adverse outcomes might not manifest for many decades after birth. Thus, performing population studies based on collecting and biobanking placental tissue samples for future research purposes is a need.

A central point in the type of studies that are needed for a better understanding of the effects of the exposome in humans is reconstituting signalling pathways from the exposure to harmful exposome to the adverse outcome, as highlighted in the review by Heqing Shen and colleagues (Shen et al., 2022). Exposome is the measure of all exposures of an individual in a lifetime, and how the exposures relate to disease and how to accurately measure their effect on human health is of crucial importance. The authors of this contribution have proposed a meet-in-metabolite analysis model to bridge the gap between environmental risk factors and adverse outcomes. Indeed, analysing the molecular traces in human biological samples is the most direct pathway. The latter is an approach including systemic measurement of exposures and their effects unveiling molecular aspects from the listed environmental pollutants by integrated high-throughput technologies. Metabolomics of small exogenous and endogenous molecular biomarkers (xenobiotics from contaminants and microbes, metabolic adducts and others), adductomics for DNA and protein, computational aided exposure identification including molecule annotation and non-targeting strategies, and detection and characterisation of biomarkers at large-scale data mining and statistical associations among exposures is crucial. After analysing all these aspects, the authors conclude that the metabolome encompasses all exposure burden information and exhibits more significant potential to generate data to enhance exposure assessment regarding exposomics than any other omics research. Perhaps, lifetime dimensional information can be obtained by repeatedly measuring life-staged blood and urine, biological samples that have convened all possible global postnatal information on the investigated population, including chemical exposure, biological response, and the potential linkage to a defined health outcome. The latter also applies to ‘prenatal’ exposure, where it is possible to have access to cord blood, placenta, and meconium.

Besides all the considerations mentioned above, the findings available in the literature regarding the damaging effects of the exposome relate to changes in the heart, pancreas, thyroid, and immune system. The review by Gonzalo Ferreira and colleagues (Ferreira et al., 2022) highlights that the +2 cationic state of Lead and Mercury makes these heavy metals active oxidizing agents interfering with processes that require specific divalent cations. Acute or chronic exposure to Lead and

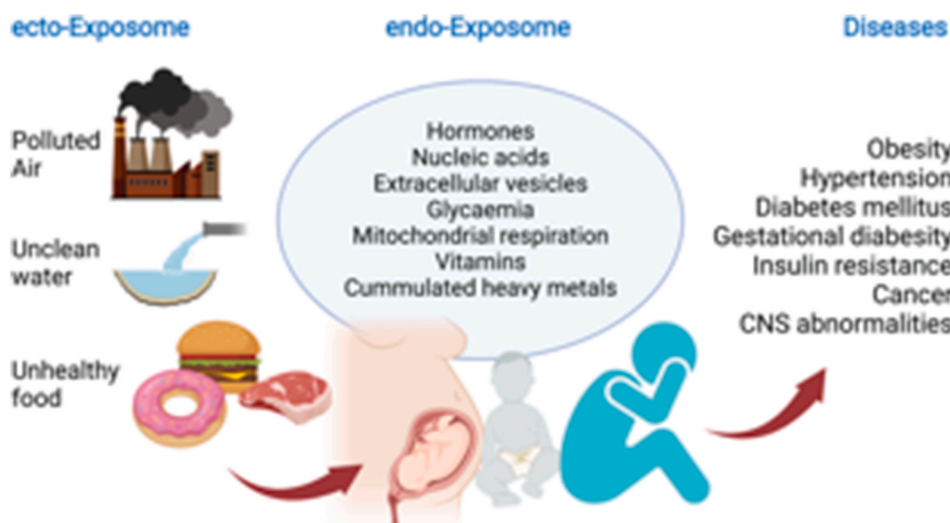


Fig. 1. Exposome effects from gestation to adult diseases. The contamination of air, water and food is a dangerous part of the ecto-exposome, resulting in alterations of the internal factors that form the endo-exposome required for maintaining a healthy state. The ecto-exposome alters the endo-exposome affecting several mechanisms leading to the loss of internal homeostasis. This phenomenon starts imprinting alterations, including epigenetic modifications from the early stages of pregnancy to the child and adolescence. The abnormal endo-exposome carried by the new generation results in the manifestation of different young and adult diseases, including abnormal development or function of the central nervous system (CNS) and the appearance of cancer and gestational diabetes.

Mercury leads to multisystemic damage affecting the cardiovascular system and the heart, either directly through their action on cardiomyocytes or indirectly through their effects on innervation, humoral responses or blood vessel alterations. The effects of these metals on the heart include alterations in the heart rate, contraction, excitability, and rhythm. Unfortunately, the mechanisms for the detrimental action of these metals are essentially unveiled. [David J. Hill \(2022\)](#) shows that the development and plasticity of the endocrine pancreas respond to both the intrauterine and postnatal exposome in best efforts to predict and respond to alterations in nutritional availability and metabolic requirements. Both under- and over-nutrition in utero can lead to a mismatch in pancreatic hormonal demands and hormone-secreting capacity postnatally. These alterations can be further exacerbated by metabolic stress postnatally, such as obesity, resulting in an increased risk of GDM, T2DM, and even T1DM. However, the plastic potential of pancreatic b cells appears to be set early in life in response to the exposome, but critical windows may exist during the lifespan where therapeutic interventions may reduce the risk of adult metabolic diseases. A key message derived from this contribution is that since β -cell mass has a limited capacity for cell turnover or regeneration in adult life, the most likely windows of therapeutic opportunity are during pregnancy and childhood.

The review by [Jelmer R. Prins and colleagues \(Prins et al., 2022\)](#) refers to the influence of the dietary exposome and pregnancy complications regarding reactive species as part of the ecto-exposome and endo-exposome. IUGR, preeclampsia, preterm birth, and GDM are associated with increased reactive oxygen species (ROS) and inflammation, as part of the described ‘Great Obstetrical Syndromes’—preterm labour and premature rupture of membranes, preeclampsia, spontaneous pregnancy loss, stillbirth, and abnormal fetal growth, with a placental component as part of their aetiology ([Brosens et al., 2011](#))—, which will cause stress of the cells explaining the disease pathophysiology. In this contribution, a description of dietary interventions aiming to reduce ROS to attenuate adverse pregnancy outcomes is given. It is proposed that nutritional interventions may be a promising therapeutic approach to minimise the risk of an abnormal pregnancy.

In the review by [Mark Lucock \(2022\)](#), the role of vitamin D and folic acid in life processes maintaining the integrity and function of the genome and epigenome is emphasised. The role of these micronutrients in phenotypic adaptation to exposome across the human life cycle (as a short perspective) and under a point of view of an evolutionary timescale (long-term perspective), including the ultraviolet (UV) as a factor determining activation of vitamin D as well as the nutrient availability such as dietary folate is proposed. The UV radiation exposure from

conception to around 90 days post-conception may result in the modulation of vitamin D biological actions by compromising the vitamin D receptor due to epigenetic modifications involving abundant methylation. The latter is proposed as a phenomenon that might correlate with photoperiods and vitamin D receptor polymorphisms. Cumulative UV irradiance could also associate with female adult height and osteoporosis. The author proposed we tuned with the exposome from the earliest lifecycle phase.

Another disrupted homeostasis associated with the exposome regards the levels of thyroid hormones, which regulate growth and development, energy homeostasis, thermogenesis, lipolysis and cholesterol metabolism, among others. The latter is reviewed by [Meri De Angelis & Karl-Werner Schramm \(De Angelis and Schramm, 2022\)](#). As mentioned, some POPs can interfere with the endocrine system and a sensitive period to these chemicals is the prenatal and postnatal time. The fetus depends on maternal thyroid hormones supply across the placenta for its development, and POPs interfere with this process. It is proposed that small changes in maternal thyroid hormone levels in the early stages of pregnancy can influence the fetus’s neurological and cardiovascular development and childhood body composition. This contribution’s authors focused on understanding the placenta and breastmilk and their link with pollutants, thyroid hormone dysregulation and adverse outcome. Another contribution in this series of reviews regards human behaviour and its incapacity in many cases to stop auto-exposure to tobacco smoking which constitutes an avoidable exposome causing alterations to human health. This topic is discussed in the contribution of [Diana M. Morales-Prieto and colleagues \(Morales-Prieto et al., 2022\)](#), emphasizing the association between tobacco smoking and IUGR and GDM. Tobacco smoke components modulate the immunoregulation in pregnancy. The latter avoidable practice is also involved in alterations of the trophoblast function and placental vasculature development and metabolism. This review’s summarised data shows that smoking in any trimester is unsafe for pregnancy and that smoking cessation is recommended for future mothers.

In conclusion, several factors part of the exposome might be negatively related to human health. Factors included in the ecto-exposome may alter the endo-exposome resulting in abnormal functioning of the cells and tissues ([Fig. 1](#)). How these environmental toxins affect cell function is not fully understood, especially in utero life. Since cell metabolism requires a broad series of elements to secure and provide energy for living, the long-term effects of the exposome on specific organelles are crucial. Cell-to-cell signalling mechanisms, such as EVs, extracellular levels of D-glucose, and others, are damaged or abnormal in the immediate environment to which tissues and cells are exposed.

Metabolic diseases, such as cancer, GDM, hypertension, and obesity, increase the vulnerability of human subjects to the damaging exposome. However, not only elevated or decreased level of specific metabolites as factors of the exposome is determinant, but changes in a defined period delineating a dynamic (v.g. glycaemia dynamics in patients with diabetes mellitus) (Valero et al., 2022b) and its consequences in the regulation of internal homeostasis (Sobrevia, 2022) are conditions that deserve to be considered. High-resolution metabolomics and omics integration tools enable studies to connect function to environmental exposures at a population level. It is now evident that the analysis of the early life exposome and how it programs metabolic diseases from a developmental origin of health and diseases (DOHaD) perspective is required to predict and optimize later metabolic health. This special issue covers omics passing through gene expression, epigenetics and metabolism to understand the effect of the exposome on human health.

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Declaration of competing interest

The authors confirm that there are no conflicts of interest.

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