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Review article

Air pollution and the fetal origin of disease: A systematic review of the molecular signatures of air pollution exposure in human placenta

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ABSTRACT

Background: Fetal development is a crucial window of susceptibility in which exposure-related alterations can be induced on the molecular level, leading to potential changes in metabolism and development. The placenta serves as a gatekeeper between mother and fetus, and is in contact with environmental stressors throughout pregnancy. This makes the placenta as a temporary organ an informative non-invasive matrix suitable to investigate omics-related aberrations in association with *in utero* exposures such as ambient air pollution.
Objectives: To summarize and discuss the current evidence and define the gaps of knowledge concerning human placental -omics markers in association with prenatal exposure to ambient air pollution.
Methods: Two investigators independently searched the PubMed, ScienceDirect, and Scopus databases to identify all studies published until January 2017 with an emphasis on epidemiological research on prenatal exposure to ambient air pollution and the effect on placental -omics signatures.
Results: From the initial 386 articles, 25 were retained following an *a priori* set inclusion and exclusion criteria. We identified eleven studies on the genome, two on the transcriptome, five on the epigenome, five on the proteome category, one study with both genomic and proteomic topics, and one study with both genomic and transcriptomic topics. Six studies discussed the triple relationship between exposure to air pollution during pregnancy, the associated placental -omics marker(s), and the potential effect on disease development later in life. So far, no metabolomic or exposomic data discussing associations between the placenta and prenatal exposure to air pollution have been published.
Conclusions: Integration of placental biomarkers in an environmental epidemiological context enables researchers to address fundamental questions essential in unraveling the fetal origin of disease and helps to better define the pregnancy exposome of air pollution.

1. Introduction

Both genetic and environmental factors contribute to a multitude of complex diseases, while the precise environmental causes and early pathophysiological mechanisms of these diseases remain poorly understood (Ellis et al., 2014). The development of diseases can find its origin in every stage of human life. However, the distinct time windows, i.e. pregnancy, infancy, adolescence, adulthood, and old age are characterized by differences in age-specific susceptibilities (Cohen Hubal et al., 2008). During the last decade, a major public health concern has focused on the pregnancy period during which the exposure to harmful substances should be avoided to give the newborn the chance to start life as healthy as possible (Sun et al., 2016).

Over the entire intrauterine period, the placenta plays a crucial role for growth, development, and survival of the fetus (Burton et al., 2016). After the syncytiotrophoblast cells of the blastocyst have invaded the

Abbreviations: 3-NTp, 3-nitrotyrosine; 8-oxodG, (8-oxo-2′-deoxyguanosine); AHH, aryl hydrocarbon hydroxylase; BC, black carbon; BDNF, brain-derived neurotrophic factor; CI, confidence interval; CYP1A1, cytochrome P450 1A1; ECOD, 7-ethoxycoumarin O-deethylase; GST, glutathione S-transferase; GSTM1, glutathione S-transferase M1; LEP, leptin; miRNA, MicroRNA; MT, metallothionein; mtDNA, mitochondrial DNA; NAT2, N-acetyl transferase 2; NO_2, nitrogen dioxide; PAH, polycylic aromatic hydrocarbon; PECO, population, exposure, comparator, and outcome elements; PM, particulate matter; $PM_{2.5}$, particulate matter with a diameter smaller than 2.5 μm; PM_{10}, particulate matter with a diameter smaller than 10 μm; SO_2, sulfur dioxide; SYN1, synapsin 1

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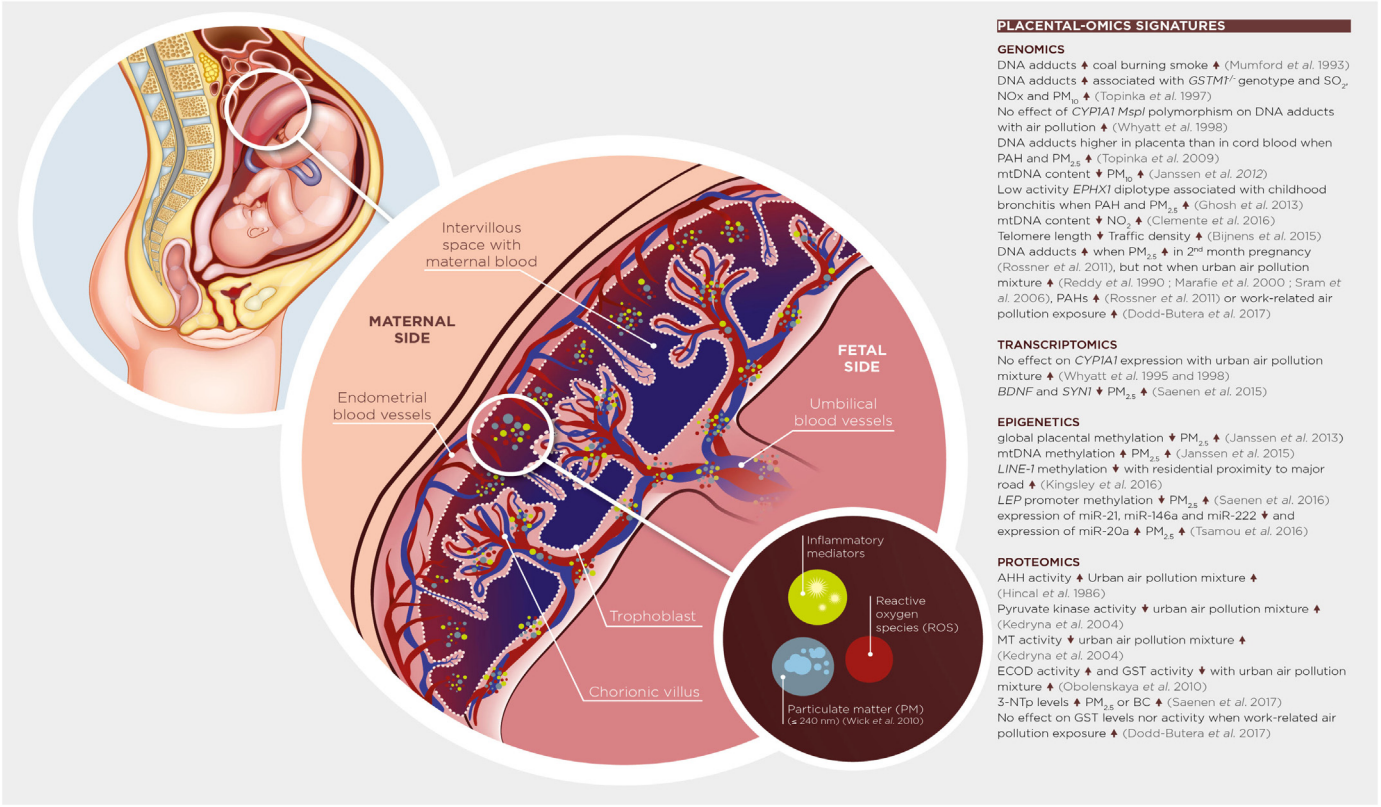

Fig. 1. Placental migration of direct (particulate matter) and indirect (reactive oxygen species and inflammatory mediators) potential effectors of exposure to air pollution during pregnancy. The column on the right summarizes the -omics characteristics (genomics, transcriptomics, epigenetics, and proteomics) as described in this systematic review in association with exposure to *in utero* ambient air pollution.

uterine wall, the placenta starts to grow with the formation of chorionic villi, which constitute the fetal side of this temporary organ (Fig. 1). One of the first functions of placental cells is to suppress the maternal immune system in such a way that the developing embryo is not rejected (Nugent and Bale, 2015). In later stages of pregnancy, the placenta develops a wide spectrum of functions to ensure proper fetal growth. It is endowed with an important transport function mediating the transfer of oxygen, nutritional components, growth factors, and hormones from mother to child, while carbon dioxide and other waste substances are transferred in the opposite direction (Levkovitz et al., 2013). This may occur by means of simple diffusion, (energy driven) transporter proteins, and endo- or exocytosis within complex matrices of different cell types, such as trophoblasts, amniotic cells, endothelium lining of the placental blood vessels, decidual cells, Hofbauer cells, and mesenchymal cells (Burton et al., 2016).

In this way, the placenta comes in contact with, contains and interacts with the substances to which both mother and fetus are exposed to during the timespan of the entire pregnancy. In addition, the placenta itself is an important endocrine organ regulating the production of hormones such as progesterone, human chorionic gonadotrophin (hCG), and human placental lactogen (hPL), to ensure the continuation of pregnancy and to acquire the appropriate maternal responses to optimize the development of the fetus (Burton et al., 2016; Nugent and Bale, 2015). Furthermore, within the feto-placental unit, a great number of signals are sent from the placenta to the fetus – and *vice versa* – to regulate developmental processes (Dötsch et al., 2010). Such signals can also elicit the appropriate reactions to various environmental exposures. Together, all these properties make the placenta an essential organ for the regulation of fetal development. Indeed, placental dysfunction has been linked to for example the occurrence of preeclampsia and adverse birth outcomes such as intrauterine growth restriction (Cha and Kim, 2010).

Intrauterine exposure to pollutants can lead to altered metabolic functions that may be detrimental for fetal development. For example, the embryonic brain has a great plasticity and its development depends on, and can be influenced by, various environmental factors (Buss et al., 2013). The etiology of diseases in adulthood may have a fetal origin and may be attributed to the effects of adverse environmental exposures *in utero*. This causality concept is known as the Barker hypothesis or the Developmental Origins of Health and Disease (DOHaD). Professor David Barker was the first to recognize this potential link when he became concerned about the association between malnutrition during pregnancy and the development of coronary heart disease in adult life (Barker, 1995). Since then, many implications of this hypothesis have been reported (Deng et al., 2016, 2017; Lu et al., 2017). Adverse environmental exposures during pregnancy already identified in this context are active and passive cigarette smoke (Mund et al., 2013), and exposure to ambient air pollution [including nitrogen dioxide (NO_2) (Ballester et al., 2010), polycyclic aromatic hydrocarbons (PAH) (Jedrychowski et al., 2015), and particulate matter (PM) (Rappazzo et al., 2014)]. Particles with a diameter smaller than 500 nm are known to pass the placental barrier during the gestational period, while particles with a diameter smaller than 240 nm are even able to reach the fetal bloodstream (Wick et al., 2010) (Fig. 1), possibly affecting the newborn's metabolism before birth.

Various reviews have already described the associations between prenatal ambient air pollution exposure and birth outcomes such as prematurity and birth weight (Lamichhane et al., 2015; Shah and Balkhair, 2011). However, none of these reviews described the placenta as an intermediate matrix having the potential to express distinct biological (-omics) signatures associated with prenatal exposure to ambient air pollution. Hence, the goal of this systematic review is to provide a structured overview and an evaluation of the current knowledge on the potential of placental tissue as a non-invasive