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EDITORIAL

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Environmental pollutants cause placental dysfunctions to induce miscarriage

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Approximately 15%-25% pregnant women experience spontaneous miscarriage, and 1%-5% suffer from recurrent miscarriage (RM).[1] Miscarriage not only affects fertility but also seriously impacts families and society. Many factors might induce miscarriage, including chromosomal abnormalities, uterine deformation, hormonal abnormalities, infections, psychological trauma and stressful life events, and immune disorders. However, there are still 50% causes unidentified. Increasing epidemiologic evidences have indicated that exposure to environmental pollutants (such as heavy metals, endocrine disruptors, polycyclic aromatic hydrocarbons, et al.) is highly associated with unexplained miscarriage. However, the association, causation, and underlying mechanisms between these environmental toxicants and unexplained miscarriage are still largely unexplored. Therefore, it is great of significance for exploring whether and how these environmental toxicants might induce unexplained miscarriage. Meanwhile, placenta play essential roles in healthy pregnancy and its dysfunctions might always induce miscarriage. In recent years, this group have identified that many environmental toxicants, such as polycyclic aromatic hydrocarbons, nanoplastics, hypoxia, metals, and disinfection byproducts, could cause placental dysfunctions to induce miscarriage (Figure 1).

POLYCYCLIC AROMATIC HYDROCARBONS

Polycyclic aromatic hydrocarbons (BaP/BPDE) represent one of the most prevalent and unavoidable environmental pollutants. Epidemiological studies suggest that exposure to PAHs during pregnancy is positively associated with increased miscarriage rates. Based on BPDE-exposed trophoblast cells or HUVECs, placental tissues of BaP-exposed pregnant mouse, and villous or decidual tissues of unexplained miscarriage case-control group, we reach the consistent conclusion. We find that BPDE increases intracellular free Fe^{2+} while down-regulates GPX4, inducing ferroptosis. Similarly, BPDE exposure increases free Fe^{2+} and decreases GPx4 in human HUVECs, leading to endothelial ferroptosis and impaired angiogenesis, ultimately inducing miscarriage. BaP/BPDE up-regulates novel lncRNA lnc-HZ01, which inhibits p53 degradation, inducing apoptosis and miscarriage. Highly expressed lnc-HZ01 suppresses the MEST/Vimentin pathway, suppresses invasion/migration and induces miscarriage. BPDE up-regulates both lnc-HZ03 and miR-hz03, forming a positive feedback loop that activates the p53/SAT1 pathway, accelerates spermidine metabolism, and induces apoptosis. Lnc-HZ03 enhances TRBP transcription to promote miR-hz03 synthesis. BPDE up-regulates p53 to promote lnc-HZ04 transcription, activates the IP3R1/CaMKII/SGCB pathway, and induces apoptosis. BPDE up-regulates lnc-HZ05, suppresses miR-hz05, inhibits the FOXO3a/P21/CDK2 pathway and proliferation. BaP/BPDE induces the up-regulation of novel lnc-HZ06, which enhances IL1B transcription and mRNA stability, ultimately suppresses invasion/migration and promotes apoptosis. BPDE up-regulates lnc-HZ08 and promotes CBL-mediated PI3K ubiquitination and degradation, causing dysfunctions. BPDE-DNA adduct levels in villous tissues are associated with miscarriage; BPDE stimulates lnc-HZ09 transcription and stability, subsequently inhibits invasion/migration. BaP/BPDE up-regulates AhR and thus suppresses BRCA1 transcription, while activates lnc-HZ10 expression levels, forming a feedback loop that impairs homologous recombination repair.[2] Novel lnc-HZ12 is significantly up-regulated in miscarriage villous tissues, blocks chaperone-mediated autophagy degradation of BBC3 to promote apoptosis.[3] BPDE-induced lnc-HZ14 enhances ZBP1 transcription and NLRP3 mRNA stability, inducing pyroptosis. Exosomes mediate remote environmental effects. We find that BaP/BPDE up-regulates novel lnc-HZ11 expression levels and promotes EV-HZ11 secretion (lnc-HZ11-containing exosomes), inhibits recipient invasion/migration. Collectively, our studies demonstrate BaP/BPDE, m6A modification, non-coding RNAs, and key signaling pathway coordinately regulate functions and the occurrence of miscarriage.

NANOPLASTICS

The global microplastics or nanoplastics (MPs/NPs) pollution has emerged as a significant public health concern, with MPs/NPs being successively detected in multiple human organs. Exposure to MPs/NPs is associated with multiple system dysfunctions such as digestive system, reproductive system, nervous system, or immune system. However, there are still few studies on the risk of exposed to MPs/NPs on woman miscarriage. A study has shown that gestational exposure to NPs disrupts fetal development by promoting the placental aging via ferroptosis of syncytiotrophoblast. Our research identifies polystyrene (PS) plastics particles in villous tissues of women with miscarriages, demonstrating their association with miscarriage. PS-NPs-exposed mouse model, PS-NPs-exposed trophoblast cells, and miscarriage case-control study all confirm PS-NPs can induce miscarriage in mice through specific molecular mechanisms: PS-NPs activate autophagy to promote SOX2 degradation while suppress ROCK1 transcription, thereby impair invasion, migration, and migrasome formation, ultimately leading to miscarriage.[4] Furthermore, we detect polystyrene plastics particles in villous tissues of women with unexplained recurrent miscarriage, where these particles induce apoptosis through mitochondrial pathways, consequently causing miscarriage.

HYPOXIA

High-altitude environments, pharmaceuticals, air pollution, stress, anxiety, and female obesity might induce hypoxia, which may lead to adverse pregnancy outcomes in women. Based on hypoxia-treated trophoblast cells, placental tissues of hypoxia-treated pregnant mouse, and villous tissues of unexplained miscarriage case-control group, our research reveals that hypoxia induces ferroptosis and subsequently induce miscarriage through a specific molecular mechanism: a novel lnc-HZ06 forms a positive feedback loop with HIF1α-SUMO to enhance NCOA4 transcription.[5]

METAL

Metal exposure might also induce adverse pregnant outcomes. Epidemiological studies have revealed that exposure to lead, cadmium, or rare earth elements during pregnancy are associated with the occurrence of miscarriage. Since environmental cobalt (Co) exposure causes trophoblast cell hypoxia, we also found that lnc-HZ06 down-regulates HIF1α protein levels in $CoCl_2$-exposed hypoxic human trophoblast cell and villous tissues of miscarriage patients. Copper (Cu), widely utilized in various industries, has been identified as one of the primary metallic pollutants. Our studies using Cu-exposed mouse model demonstrate that copper exposure during pregnancy causes cuproptosis in mouse placental tissue, subsequently induces miscarriage in mice. Furthermore, copper exposure up-regulates lnc-HZ11 expres-

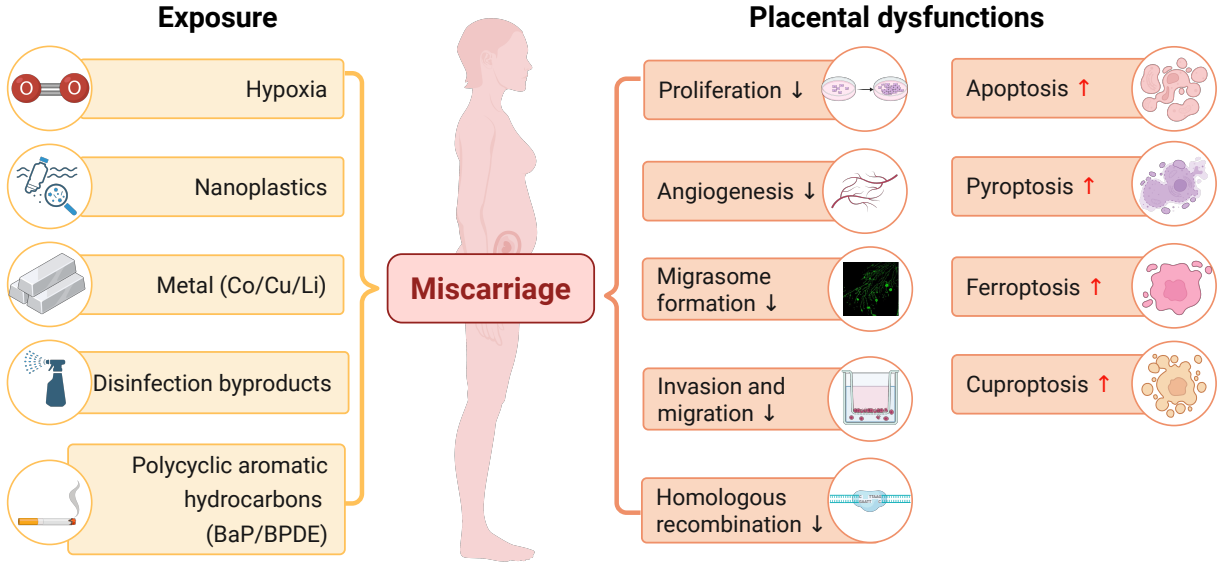

Figure 1. Many environmental toxicants, such as hypoxia, nanoplastics, metals, polycyclic aromatic hydrocarbons (PAHs), and disinfection byproducts, could cause placental dysfunctions to induce miscarriage.

sion, which mediates human trophoblast cell cuproptosis. Lithium (Li) exposure is becoming a new prominent major issue in energy-environment-health ffeld. We find that exposure to 28-fold REED (really environmental exposure dose) of Li is enough to induce mouse miscarriage by altering the structures and functions of placenta.

DISINFECTION BYPRODUCTS

Disinfection byproducts are widely present in tap water. However, its association with miscarriage remains poorly understood. Our research demonstrates that dichloroacetic acid (DCAA) and trichloroacetic acid (TCAA) function as endocrine disruptors that alter the expression levels of hormone and hormone receptors, ultimately inducing miscarriage in pregnant mice.

Collectively, all these environmental toxicants could cause specific placental dysfunction through specific signaling and eventually induce miscarriage. Beyond these environmental toxicants, other factors such as obesity and hyperglycemia, as well as anxiety, depression, chronic stress, and noise pollution, may also constitute significant risk factors for adverse pregnancy outcomes. Since miscarriage occurs post-embryo implantation, the critical reproductive processes including embryo implantation, embryonic development, and oocyte maturation are similarly vulnerable to environmental toxicants. To investigate the environment and female reproduction represents a vital area of scientific inquiry.

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AUTHOR CONTRIBUTIONS

All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.