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Invited article

Disruption of iron homeostasis and resultant health effects upon exposure to various environmental pollutants: A critical review

Wenli Guo[1,**], *Jie Zhang*[1,**], *Wenjun Li*[2], *Ming Xu*[1,*], *Sijin Liu*[1,*]

1. *State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China. E-mails: biogwl@126.com, sdzhangjie1989@163.com*
2. *School of Stomatology, Wuhan University, Wuhan 430072, China*

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ABSTRACT

Environmental pollution has become one of the greatest problems in the world, and the concerns about environmental pollutants released by human activities from agriculture and industrial production have been continuously increasing. Although intense efforts have been made to understand the health effects of environmental pollutants, most studies have only focused on direct toxic effects and failed to simultaneously evaluate the long-term adaptive, compensatory and secondary impacts on health. Burgeoning evidence suggests that environmental pollutants may directly or indirectly give rise to disordered element homeostasis, such as for iron. It is crucially important to maintain concerted cellular and systemic iron metabolism. Otherwise, disordered iron metabolism would lead to cytotoxicity and increased risk for various diseases, including cancers. Thus, study on the effects of environmental pollutants upon iron homeostasis is urgently needed. In this review, we recapitulate the available findings on the direct or indirect impacts of environmental pollutants, including persistent organic pollutants (POPs), heavy metals and pesticides, on iron homeostasis and associated adverse health problems. In view of the unanswered questions, more efforts are warranted to investigate the disruptive effects of environmental pollutants on iron homeostasis and consequent toxicities.

Introduction

Nowadays, *ca*. 24% of diseases and 23% of the deaths of human beings can be attributed to environmental factors, based on the world health organization (WHO) report (WHO, 2006), in which environmental pollutants emerge as the greatest danger to public health. Although epidemiological studies have provided a great deal of evidence on the relationship between environmental pollutants and diseases, the pathogenic effects of environmental pollutants have not been fully understood due to their complicated biological activities. Upon exposure, the human body will adapt or implement numerous pathways to compensate for alterations induced by environmental pollutants. To reveal

* *Corresponding authors*. E-mails: mingxu@rcees.ac.cn (Ming Xu), sjliu@rcees.ac.cn (Sijin Liu).
** These authors equally contribute to this work.

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these underlying pathogenic mechanisms, numerous *in vitro* and *in vivo* studies have been carried out to gain knowledge about the exposure risk of environmental pollutants and their health effects.

In terms of health effects of environmental pollutants, some aspects should be carefully and systematically considered. (1) The effects of environmental pollutants on disease initiation are more likely to be indirect rather than direct (Porta, 2006). For example, it was reported that persistent organic pollutants (POPs) in adipose tissue indirectly influenced breast cancer development and/or progression (Reaves et al., 2015). (2) The exposure conditions of pollutants in the natural environment and human body are complicated. Environmental factors, individual conditions, and interactions of multiple pollutants should be considered. Moreover, the exposures to pollutants are life-course environmental exposures, referred to as the exposome (Lioy and Rappaport, 2011), and both internal and external factors contribute to environmental pollutant-induced health effects. (3) Environmental pollutants could possibly induce or enhance the initiation and/or development of various diseases through epigenetic changes, including DNA methylation, histone modification and non-coding RNA mediated mechanisms (Hou et al., 2012; Vaiserman, 2014). It has been reported that polychlorinated biphenyls (PCBs) have the ability to activate androgen receptor (AR) transcriptional activity, and this action is assisted by the histone demethylase Jarid1b (Casati et al., 2013). (4) Environmental pollutants can cause metabolic disruption in the human body, such as with iron metabolism, resulting in significant health risk (Casals-Casas and Desvergne, 2011).

Iron is a necessary chemical element, involved in a wide spectrum of fundamental biological processes, such as DNA replication, iron–sulfur synthesis, and energy metabolism (Torti and Torti, 2013). Iron homeostasis is concertedly governed under normal settings, and disordered iron metabolism can lead to a wide array of diseases, including cancers. Misregulation of intracellular iron metabolism has been demonstrated to contribute to malignant phenotypes in tumors. Clinical studies also reported that excessive body iron burden could increase the risk of tumor occurrence (Torti and Torti, 2013; Y. Yu et al., 2007). Excess iron could accelerate tumor initiation and progression by enhancing the formation of free radicals, and by functioning as a necessary nutrient that fosters tumor cell proliferation as well (Torti and Torti, 2013). Moreover, recent studies by our group and others demonstrated that environmental pollutants, including PCBs, cadmium (Cd) and chlorpyrifos (CPF), could alter the expression levels of hepcidin (the central regulator of iron absorption) and ferroportin (FPN, the only regulator of iron exportation), and thus disrupt the hepcidin-FPN signaling (Qian et al., 2015; Sun et al., 2014, 2015; L. Wang et al., 2013a). Finally, it should be stressed that the effect of pollutant-induced disruption to iron homeostasis could be a long-term and secondary event; however, it also occurs as an acute and direct one. For example, we demonstrated that PCB-77 exposure in mice could consistently repress hepatic hepcidin expression by more than 65% at 6, 12, and 24 hr, compared with untreated mice. Similarly, alterations of FPN were also found with cadmium and CPF after a short time exposure. These preliminary data suggest that environmental pollutants have the potential to directly disorder iron homeostasis, which warrants careful attention in future studies.

In the current review, we recapitulate the potential detrimental effects of environmental pollutants on iron metabolism, and highlight the corresponding mechanisms responsible for cellular responses (Table 1). The improved understanding of environmental pollutant-mediated imbalance of iron metabolism will assist in elucidating their potential adverse effects on health.

1. Iron homeostasis and health effects

Iron is an essential biometal necessary for most forms of life. Iron plays a crucial role in various biological processes, because it is a necessary component of iron-containing proteins, including enzymes responsible for DNA replication and repair, cell cycle control, and mitochondrial energy metabolism (Duce et al., 2010; Ganeshaguru et al., 1980). Iron also contributes to cellular signaling, such as in cell survival and inflammation (Xiong et al., 2014). However, excessive iron has the potential to induce adverse effects on human health, due to its ability to gain and lose electrons, to participate in redox cycling and to generate free-radical species (Torti and Torti, 2013). The Fenton reaction is the major route responsible for iron-induced radical production. In this chemical reaction, ferrous iron reacts with hydrogen peroxide to produce $^{\cdot}OH$ radical by donating an electron ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\cdot}OH + {}^{-}OH$). Therefore, excessive iron generates increased radical species, resulting in oxidative damage to DNA, lipids and proteins (Dizdaroglu et al., 1991; Inoue and Kawanishi, 1987).

To balance the absorption, transport, storage and utilization of iron in the body, systemic iron homeostasis is fine-tuned through various signaling pathways. The disruption of cellular signaling for iron homeostasis can cause iron deficiency or iron overload, which are deleterious to health. On one hand, iron deficiency can incur anemia, which is a major issue of public health for children and pregnant woman, especially for those in low- and middle-income countries (Pasricha et al., 2013). On the other hand, excess iron burden is considered to contribute to a wide spectrum of cancer types including breast cancer, lung cancer, prostate cancer, gastrointestinal cancer, hepatocellular cancer, and hematological malignancies (Torti and Torti, 2013; Zhang and Zhang, 2015). Greatly increased risk of hepatocellular, colorectal and breast cancers has been observed in hereditary hemochromatosis patients (HFE C282Y homozygotes) with iron overload, compared to individuals without the HFE variant (Osborne et al., 2010).

Hepcidin-FPN signaling is one of the key mechanisms responsible for iron supply, utilization, recycling and storage. Hepcidin, a 25 amino acid peptide, is mainly derived from hepatocytes, and it fundamentally equilibrates systemic iron homeostasis. The expression of hepcidin is primarily regulated by iron status, hypoxia, anemia and inflammation (Ganz, 2013). FPN is the only known iron exporter in mammals, and its concentration is mainly controlled by the binding of hepcidin. Our recent studies demonstrated that, following exposure to environmental pollutants, the hepcidin-FPN axis is misregulated in administrated animals along with disordered systemic iron homeostasis, which will be discussed in more detail in the following sections.