American Journal of Immunology

Editorial

An Immunological Argument for One Health

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Article history
Received: 10-01-2023
Revised: 19-01-2023
Accepted: 19-01-2023

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Abstract: Human exposure to heavy metals is associated with higher rates of immunological deficiencies, autoimmunity, and cancer. Chronic exposure to lead contributes to abnormalities in immunomodulation while cadmium is linked to breast, prostate, and lung cancers. Prenatal exposure to these metals impacts both the development and function of immune cells. The concept of one health underscores the importance of the interface between human, animal, and environmental health. Herein, we highlight heavy metal exposure via honey consumption as an example of the critical intersection of these factors as they relate to immunological impacts and downstream pathologies.

Keywords: Heavy Metals, Lead, Cadmium, Autoimmunity, Tumorigenesis

Introduction

A one health approach to public health research accounts for the critical intersection of human, animal, and environmental factors which impact human health. This often misunderstood approach can be better understood using a simple example that highlights the overlapping, upstream role of these factors with their potential life-threatening downstream impacts on the immune system. For example, consider the common use of honey as a food item. Honeybees forage pollen from an environmental setting inevitably contains trace levels of Cadmium (Cd) and lead (Pb) (Bartha *et al*., 2020; Quinto *et al*., 2016; Samarghandian *et al*., 2017). Such heavy metals become concentrated in trophic chains and, although they rarely reach levels of acute toxicity in single exposures, chronic exposure-even that is well below the maximum recommended limits-can poses a serious risk to human health as a result of bioaccumulation (Rehman *et al*., 2018). For instance, long-term exposure to Cd and Pb contributes to immunological deficiencies, autoimmunity, and a range of cancers (Achanzar *et al*., 2001; Benbrahim-Tallaa *et al*., 2009; Luevano and Damodaran, 2014; Mishra, 2009; Akesson *et al*., 2008; Zhou *et al*., 2020). Other health issues associated with cumulative exposure include cardiovascular disorders, renal damage, diabetes, and neuronal disorders (Rehman *et al*., 2018).

Consumption of heavy metal-containing foods is of particular risk to developing children. For example, weekly servings of honey may contain 25% or more of the Provisional Weekly Tolerable Intake (PWTI) for Pb as defined by the Joint Food and Agriculture Organization-World Health Organization Expert Committee on Food Additives (JECFA) (Bartha *et al*., 2020; Quinto *et al*., 2016; Samarghandian *et al*., 2017). Honey from some regions also contains high levels of Cd (Bartha *et al*., 2020; Quinto *et al*., 2016). While childhood exposure to Pb is associated with a host of neurological and downstream cognitive disorders (Eid and Zawia, 2016), prenatal exposure to Cd has been shown to adversely impact the development and activity of immune cells (Hanson *et al*., 2012). Teratogenic in nature, Cd exposure can have severe adverse consequences for both the placenta as well as the developing embryo (Geng and Wang, 2019). Combinatorial exposure to both Pb and Cd amplifies their neurotoxicological impacts through an epigenetic mechanism that is associated with a host of neurodegenerative diseases (Zhou *et al*., 2020).

Immunological Impacts of Pb/Cd Exposure

Chronic exposure to Pb is associated with the underlying mechanisms of Alzheimer's, multiple sclerosis, and amyotrophic sclerosis (Waterman *et al*., 1994; Mishra, 2009).

Cumulative exposure to Pb contributes to such neurodegenerative diseases by initiating pathways that lead to autoimmunity against native proteins of the nervous system (Waterman *et al*., 1994). Consumption of Pb has also been shown to impact mucosal-derived gut immunity by reducing expression of the cytokine, TGF-β, and disruption in oral tolerance (Goebel *et al*., 2000). Pb exposure has been shown to further disrupt the ratios of CD4 + versus CD8 + circulating immune cells such that Pb-exposed individuals manifest significantly lower than normal CD4 + cells (Fischbein *et al*., 1993; Ündeğer *et al*., 1996; Li *et al*., 2005) and higher than normal CD8 + cells (Sata *et al*., 1997). Exposure to Pb is also associated with reduced populations of CD16 + cells (Sata *et al*., 1997). Finally, concerning immunological impacts, Pb exposure has been linked to type I hypersensitivity (Min *et al*., 2008; Min and Min, 2015).

Long-term exposure to Cd has been linked to chronic inflammation and downstream renal tubular dysfunction, pneumonitis, and liver dysfunction (Hossein-Khannazer *et al*., 2020). Cd is also associated with a host of immunological aberrations that ultimately contribute to preeclampsia (Zhang *et al*., 2016). Although Cd has been touted for its ability to stimulate the immune system, this dubious benefit is the result of its involvement in the ERK1/2 signal cascade and the downstream amplification of monocytes differentiation (Ober-Blöbaum *et al*., 2010). Thus, any Cd-mediated enhancement of immunity comes at the price of elevated levels of pro-inflammatory cytokines.

Pb/Cd Exposure and Cancer

Although there is limited evidence linking Pb exposure to gliomas and stomach and lung cancer (Englyst *et al*., 2001; Fu and Boffetta, 1995; Steenland *et al*., 2019), Pb is considered only moderately mutagenic (Steenland and Boffetta, 2000). Instead, reducing DNA repair is a contributing factor to cancers initiated by other causes. Individuals who have experienced exposure to Pb often exhibit higher rates of chromosomal abnormalities, often a precursor to tumorigenesis, as a result of inefficient DNA repair (Steenland and Boffetta, 2000).

Conversely, Cd exposure is highly associated with a range of cancers. Chronic exposure to Cd transforms healthy breast tissue into malignant anchor-independent, malignant cells (Benbrahim-Tallaa *et al*., 2009). When these cells are introduced into mice, they develop into highly invasive, metastatic carcinomas exhibiting anaplasticity and the absence of both ER-α and HER2. Two cellular indicators associated with breast stem cells, p63 and CK5, are overexpressed (Benbrahim-Tallaa *et al*., 2009). Chronic exposure to Cd also transforms healthy prostate cells and chronic inhalation of Cd induces pulmonary adenocarcinomas (Achanzar *et al*., 2001; Luevano and Damodaran, 2014). Lifetime exposure to Cd in women causes a higher risk for endometrial cancer (Akesson *et al*., 2008). On a molecular level, Cd functions in tumorigenesis through several pathways, most notably, by inhibiting the binding efficiency of p53 and by acting as an endocrine disruptor and initiating estrogen receptor mediated proliferation (Luevano and Damodaran, 2014; Achanzar *et al*., 2001).

Conclusion

It is impossible to fully separate the milieu of variables present in the intersecting chain from environmental pollutant to an entomological carrier and ultimately to an adverse human health outcomes. Here, a simple act of honey collection and consumption becomes a matter of immunological disorder and tumorigenesis. One health research encourages the collaborative efforts of human, animal, and environmental health researchers when it comes to understanding and solving the gray areas that exist at the links of such chains.

Author's Contributions

Mark Brown: Conceived and wrote the first draft of the paper, revised, and approved the final manuscript.

Mai Awad: Helped write the first draft of the paper, revised, and approved the final manuscript.

Christian Schmidt: Provided critical analysis and assisted in reviewed, revised, and improved the paper and approved the final manuscript.

Ethics

MAB, MMA, and CS report no conflicts of interest concerning this report. CS is a member of the editorial board of the American Journal of Immunology and is waived from the article processing fee for this contribution.

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