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A network biology-based approach to evaluating the effect of environmental contaminants on human interactome and diseases

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ABSTRACT

Environmental contaminant exposure can pose significant risks to human health. Therefore, evaluating the impact of this exposure is of great importance; however, it is often difficult because both the molecular mechanism of disease and the mode of action of the contaminants are complex. We used network biology techniques to quantitatively assess the impact of environmental contaminants on the human interactome and diseases with a particular focus on seven major contaminant categories: *persistent organic pollutants (POPs), dioxins, polycyclic aromatic hydrocarbons (PAHs), pesticides, perfluorochemicals (PFCs), metals,* and *pharmaceutical and personal care products (PPCPs)*. We integrated publicly available data on toxicogenomics, the diseasome, protein–protein interactions (PPIs), and gene essentiality and found that a few contaminants were targeted to many genes, and a few genes were targeted by many contaminants. The contaminant targets were hub proteins in the human PPI network, whereas the target proteins in most categories did not contain abundant essential proteins. Generally, contaminant targets and disease-associated proteins were closely associated with the PPI network, and the closeness of the associations depended on the disease type and chemical category. Network biology techniques were used to identify environmental contaminants with broad effects on the human interactome and contaminant-sensitive biomarkers. Moreover, this method enabled us to quantify the relationship between environmental contaminants and human diseases, which was supported by epidemiological and experimental evidence. These methods and findings have facilitated the elucidation of the complex relationship between environmental exposure and adverse health outcomes.

1. Introduction

Humans are exposed to a range of ubiquitous environmental contaminants, which poses a major risk to human health (Gross and Birnbaum, 2017). Studies conducted over the last few decades have revealed the relationships between environmental contaminants, genes, and diseases. For example, dioxins and polycyclic aromatic hydrocarbons (PAHs) cause several types of cancer (Kim et al., 2013; Tavakoly Sany et al., 2015); metallic elements damage multiple organs and cause ailments such as pneumonia, depression, skin lesions, and cancer (Tchounwou et al., 2012); and the persistent exposure to pesticides results in endocrine disruption and polyneuropathy in humans (Hernández et al., 2013). The data on the association between contaminants, genes, and adverse outcomes obtained from previous studies have been curated and deposited in the Comparative Toxicogenomics Database (CTD) (Davis et al., 2017).

The quantification of the association between exposure to individual chemicals and human health outcomes could help guide public health efforts by enabling the intervention in the use of high-risk agents (Braun et al., 2016). However, it is often difficult to evaluate the involvement of contaminants in human disease development because their effects are complex and often indirect (Briggs, 2003). The molecular

Abbreviations: AHR, aryl hydrocarbon receptor; AR, androgen receptor; As, arsenic; BaP, benzo[a]pyrene; CASP, caspase; CRISPR, clustered regularly interspaced short palindromic repeats; CTD, Comparative Toxicogenomics Database; CYP, cytochrome P450; CXCL8, chemokine (C-X-C motif) ligand 8; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; ER, estrogen receptor; FDA, Food and Drug Administration; HCB, hexachlorobenzene; IARC, International Agency for Research on Cancer; KS, Kolmogorov-Smirnov; PAHs, polycyclic aromatic hydrocarbons; PARP1, poly (ADP-ribose) polymerase 1; PBBs, polybrominated biphenyls; PBDEs, polybrominated diphenyl ethers; PCB, polychlorinated biphenyls; PCDD, polychlorinated dibenzo-*p*-dioxins; PCDF, polychlorinated dibenzofurans; PFCs, perfluorochemicals; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PFOSF, perfluorooctanesulfonyl fluoride; POPs, persistent organic pollutants; PPAR, peroxisome proliferator-activated receptor; PPCPs, pharmaceutical and personal care products; PPI, protein–protein interaction; PXR, pregnane X receptor; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TNF, tumor necrosis factor; US EPA, US Environmental Protection Agency

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mechanisms of action of contaminants in inducing human diseases are still poorly understood in the context of the human interactome. From this perspective, network science (Barabási, 2013) and network biology (Barabási and Oltvai, 2004) are useful because networks describe the relationships among elements (nodes) and provide simple and powerful tools for the description and analysis of complicated data sets. In particular, recent computational approaches of network science have successfully used large-scale data on drug-disease associations and disease-gene associations to better understand drug-disease interactions (Goh et al., 2007; Reyes-Palomares et al., 2013; Yıldırım et al., 2007). Yıldırım et al. (2007) constructed drug-target networks that described the relationship between approved/experimental drugs and their target proteins, and systematically evaluated the effects of drugs on the human interactome and diseases using data of essential genes and protein–protein interactions (PPIs). The network-based approach has also been used to obtain comprehensive information on the relationship between contaminants and biological functions. Darabos et al. (2016) investigated the relationships between environmental pollutants and biological pathways to identify candidate biological pathways that might be disrupted by exposure to environmental contaminants. However, the human disease-inducing effects of environmental pollutant are still not fully characterized.

In this study, we quantitatively evaluated the impact of environmental contaminants on the human interactome and diseases using techniques based on network biology and inspired by Yıldırım et al. (2007). We collected datasets on chemical-gene, gene-disease, and chemical-disease associations and then manually classified the chemical compounds into the following seven categories based on the major chemical contaminants, persistent organic pollutants (POPs), dioxins, PAHs, pesticides, perfluorochemicals (PFCs), metals, and pharmaceutical and personal care products (PPCPs). Moreover, we quantified the relationships between chemicals and disease-associated genes in a human PPI network using complex network analysis. In particular, we demonstrated the different effects of the chemicals in each category on human disease development.

2. Materials and methods

2.1. Dataset of chemical-gene interactions

We obtained the dataset of chemical-gene interactions (chemical targets) from the CTD database (ctdbase.org) (Davis et al., 2017) on July 06, 2017. The dataset contained 12,373 chemical entries. The chemical-target network was represented as a bipartite network in which an edge was drawn between a gene and the chemical compounds that targeted it.

2.2. Classification of chemical compounds

The chemicals included in this study were selected based on the availability of curated data linked to genes and chemicals, the seriousness of known health effects, and scientific data that suggested exposure risks in humans. We extracted 535 substances that targeted human proteins and classified the substances into the following seven chemical contaminant categories: *POPs, dioxins, PAHs, pesticides, PFCs, metals,* and *PPCPs*, as well as *US Food and Drug Administration (FDA)-approved drugs*. These categories were defined based on the following criteria. However, it should be noted that a chemical compound could be classified into multiple categories.

2.2.1. POPs

The *POP* category was defined based on Annex A of the Stockholm Convention on Persistent Organic Pollutants (UNEP, 2009) and includes organochlorine pesticides (e.g. dieldrin, dichlorodiphenyldichloroethylene (DDE), dichlorodiphenyltrichloroethane (DDT), endosulfan, heptachlor, hexachlorobenzene (HCB), and lindane), polybrominated biphenyls (PBBs), polychlorinated biphenyls (PCBs), and polychlorinated dibenzo-*p*-dioxins and dibenzofuranes (PCDD/Fs) that are commonly known as dioxins, polybrominated diphenyl ethers (PBDE) (tetra-, penta-, hexa-, and hepta-brominated diphenyl ethers), perfluoroalkyl substances (PFOS, its salts, and perfluorooctanesulfonyl fluoride [PFOSF]). Of these chemicals, we extracted 77 available substances from the CTD database.

2.2.2. Dioxins

According to the US Environmental Protection Agency (US EPA) (US EPA, 2004), we categorized the following chemicals as dioxins and dioxin-like compounds: 10 PCDFs, 7 PCDDs, and 12 PCBs. In this study, 12 dioxin-like compounds including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) were available in the CTD database and were classified into the *dioxin* category.

2.2.3. PAHs

PAHs are a large category of chemicals comprising two or more fused aromatic rings. We focused on PAHs in the priority-pollutant lists of the US EPA and the European Food Safety Authority (EFSA) (EFSA, 2008; US EPA, 2014). Eighteen substances including benzo[a]pyrene (BaP) were available in the CTD database and were further analyzed.

2.2.4. Pesticides

This category was based on the Updated Tables, January 2017, of the Fourth National Report on Human Exposure to Environmental Chemicals, 2009 (CDC, 2017); in particular, we considered the substances assigned to the following categories as pesticides: insect repellents and metabolites, carbamate pesticide metabolites, organochlorine pesticide metabolites, organophosphorus insecticides, pyrethroid metabolites, and organochlorine pesticides and metabolites. Finally, 18 substances including DDE and DDT were available in the CTD database and were included in our analysis.

2.2.5. PFCs

PFCs were defined as chemical substances assigned to the perfluoroalkyl polyfluoroalkyl categories of the Fourth Report (CDC, 2017). Eight available substances including perfluorooctanoic acid (PFOA) and PFOS were identified in the CTD database and were included in our analysis.

2.2.6. Metals

The substances assigned to the metal and metalloid category in the Fourth Report (CDC, 2017) and the heavy metal category in the CTD database (Davis et al., 2017) were included in this category. A total of 74 substances such as arsenic (As), copper (Cu), and zinc (Zn) from the CTD database were analyzed in this study.

2.2.7. PPCPs

Despite the absence of a consensus on the definition of PPCPs, in this study they were defined as substances assigned as personal care and consumer product chemicals and metabolites in the CDC Updated Tables of the Fourth Report (CDC, 2017) and several previous studies (Batt et al., 2016; Howard and Muir, 2011; Tanoue et al., 2015). We analyzed 18 substances that included acetaminophen and ibuprofen, which were available in the CTD database.

2.2.8. FDA-approved drugs

For comparison with a previous study (Yıldırım et al., 2007), we also considered approved drugs. We identified FDA-approved drugs from the DrugBank database (drugbank.ca) (Law et al., 2014) on May 1, 2017. We included 331 substances such as fluorouracil that were available in the CTD database in the analysis.