In silico toxicogenomic data-mining to unraveling the influence of lead and cadmium co-exposure on molecular mechanisms involved in the development and progression of Hypertension

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Research Article

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Abstract

Heavy metals, generally characterized by high densities and atomic weights, are ubiquitous in the environment and are of public health concern due to the several health issues they pose to humans. Of all heavy metals, lead and cadmium among others are known to be capable of inducing multiple health effects even at a low rate of exposure. Hypertension (HYP), a major cause of death and a risk factor for other cardiovascular diseases, is known to be caused by both lead and cadmium. While the mechanism underlying the development of HYP induced by independent exposures to lead and cadmium have been well studied, the mechanism underlying the induction and progression of HYP upon lead and cadmium co-exposure remains mildly explored. Hence, this study aimed to elucidate the molecular mechanisms using an *in silico* toxicogenomic approach. The set of genes affected by both metals were identified using the Comparative Toxicogenomics Database (CTD) while HYP targets were retrieved from the GeneCards database. The shared genes between the metals and the disease were identified and subjected to further analyses. The results of our analyses revealed the signaling pathways that are dysregulated by lead and cadmium co-exposure while oxidative stress, inflammation, and endothelial dysfunction were revealed as processes pertinent to the induction and progression of HYP by lead and cadmium co-exposure. Biomarkers that could be used for prognosis evaluation were also identified. Ultimately, this study supports and advances the growing body of findings on the roles played by lead and cadmium co-exposure in inducing HYP.

1.0 Introduction

Over the years, the risk of exposure to various toxic substances has tremendously increased due to various industrial, geogenic, and anthropogenic activities. These toxic substances include heavy metals such as Arsenic (As), Lead (Pb), Cadmium (Cd), and Mercury (Hg). Heavy metals are ubiquitous and are widely distributed in the environment due to technological applications among other factors [1]. Based on biological utility, heavy metals are classified into essential and non-essential. The essential heavy metals are required by living organisms in minimal concentrations and they play important biochemical and physiological functions such as serving as cofactors for several enzymes. Conversely, non-essential heavy metals are known to possess no known beneficial effect on living organisms [1, 2]. Both essential and non-essential heavy metals are known to pose dose- and duration-dependent detrimental effects to human health, this is due to their ability to interact with cellular organelles and components such as the mitochondria, deoxyribonucleic acid (DNA), and proteins. Hence, this results in the disruption of normal biological and physiological processes including DNA damage, cytotoxicity, apoptosis, and carcinogenesis [3]. Notably, heavy metal toxicity has been implicated in the etiology of cardiovascular, neurological, autoimmune, and respiratory diseases [4].

Of all heavy metals, Pb and Cd pose a great challenge to human health due to their concentrations in the environment and non-biodegradability [5]. Interestingly, Pb and Cd are ranked second and seventh respectively on the priority list of dangerous substances by the United States Agency for Toxic Substances and Disease Registry (ATSDR) [6]. Pb and Cd, which exist in water, soil, and air are transferred

to the human body via ingestion and inhalation of contaminated food and air. Upon entrance to the human body, they are distributed by the red blood cells and proteins which cause various damages including blood pressure changes that result in HYP [5]. Noteworthy, while some areas possess low individual concentrations of heavy metals which correspond to lower chances of inducing toxicity, a combined exposure to a mixture of heavy metals could still result in detrimental effects [7]. For example, Zhouab et al., [8] demonstrated that Pb, Cd, arsenic, and mercury co-exposure led to higher neurotoxic effects compared to the effects induced by co-exposure to three or fewer of the same metals. Similarly, Javorac et al., [9] reported that oxidative status induced by exposure of rats to metal mixtures was absent during treatment with the individual metals.

Several studies have investigated the roles and mechanisms of Pb and Cd in inducing blood pressure changes and HYP. Chen et al. reported that blood Cd level was associated with elevated blood pressure. They also reported that an increase in blood Cd level was concomitant with an increase in the prevalence of HYP in the studied population[10]. Furthermore, Eum et al., [11] reported that Cd toxicity results in HYP via the inhibition of endothelial nitric oxide synthase and the suppression of vascular relaxation induced by acetylcholine. They also reported that Cd mediates the production of cytokines and induces endothelial damage. Similarly, Robles et al., [12] reported that Pb treatment was associated with increased generation of reactive oxygen species (ROS) which might have led to the inactivation of nitric oxide (NO) in Pb-induced hypertensive animals. This is corroborated by a study by Alghasham et al., [13], in which they reported that Pb decreased the plasma levels of nitric oxide, which functions as a vasodilator in hypertensive patients and a positive correlation between blood pressure and blood Pb levels. Studies have also investigated the effects of Pb and Cd co-exposure. Andjelkovic et al., [5] reported that a mixed treatment of Wistar rats with Pb and Cd resulted in a high plasma advanced oxidation protein product level (AOPP), signifying oxidative damages. They also reported that the co-exposure of Cd and Pb resulted in a higher negative effect in plasma compared to the individual metals. While numerous studies have been conducted to demystify the roles of Pb and Cd in the etiology of cardiovascular diseases, the mechanism by which the co-exposure to both metals induces HYP in humans remains a mystery [13]. Hence, this necessitates further attempts aimed at unraveling their mechanism as etiological agents of HYP.

Advances in bioinformatics have powered the breaking of limitations of conventional toxicology through the ability to investigate the impact of toxicants at the molecular level. Hence, providing biomarkers of toxicants for further *in vitro* and *in vivo* evaluation. Using a toxicogenomic approach, this study aims to unravel the molecular mechanism via which Pb and Cd co-exposure induce and aggravate HYP.

2.0 Materials And Methods

2.1 Retrieval of Pb and Cd gene targets

The genes that are affected by Pb and Cd toxicity were retrieved from the Comparative Toxicogenomics Database (CTD, http://ctdbase.org/) (accessed May 8, 2022) using the keywords “lead” and “cadmium”

respectively. CTD is a freely accessible database that holds relevant data on relationships between chemicals present in the environment, genes, and diseases [14–16]. CTD provides manually curated information about the interactions between chemicals and genes/proteins, chemicals and diseases, and genes and diseases.

2.2 Retrieval of HYP gene targets

The gene targets of HYP were retrieved from the GeneCards database (https://www.genecards.org/) [17]. GeneCards is a freely available, searchable integrative database that provides comprehensive information on all annotated and predicted human genes and their associations with various diseases.

2.3 Identification of shared targets

The MyVenn analysis tool of the CTD database (http://ctdbase.org/tools/myVenn.go) was utilized to identify the gene targets of lead and cadmium relevant to HYP. This tool effectively identifies the standard genes in a given list and filters out non-genes present in the given datasets.

2.4 Construction of Protein-protein interaction (PPI) network

To explore the interaction between the shared targets of lead, cadmium, and HYP, the String database (https://string-db.org/) [18] was employed to construct the PPI network of the shared targets, with Homo sapiens selected as the organism of interest and a medium confidence score of 0.4, as the minimum required interaction score.

2.5 Gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis

To access the biological roles and signaling pathways that are disrupted due to co-exposure to both Pb and Cd, the ShinyGo v0.76 web server (https://bioinformatics.sdstate.edu/go/) [19] was employed to perform the GO and KEGG pathways analysis of the common targets. Furthermore, the enrichment plots of the significant GO and pathways of the target genes were generated using the graphing tool on the same web server.

3.0 Results

3.1 Retrieval of Pb and Cd gene targets

Following extensive data mining activity on the CTD, the gene targets of lead and cadmium were curated. Interestingly, 3, 123 genes and 3, 175 genes were retrieved as Pb and Cd targets respectively.

3.2 Retrieval of HYP gene targets

Using the keyword “HYP” on the GeneCards database, 9, 408 unique genes that have been implicated in the development of HYP were retrieved. Subsequently, the RNA genes and other non-genes were filtered

out. This resulted in the identification of 8, 727 unique genes with standard IDs.

3.3 Identification of shared targets

Pb and Cd genes that are disrupted for the induction of HYP following co-exposure were identified using the MyVenn tool of CTD. The gene IDs of HYP, lead, and cadmium were uploaded to the server. The identified 512 shared targets (Fig. 1) were considered the genes that are disrupted for the induction of HYP following Pb and Cd co-exposure..

3.4 Construction of PPI network

To understand the relationship between the shared genes in the biological milieu, StringDB was employed to generate a PPI network of the 512 common targets. Interestingly, only 496 targets showed interactions based on the PPI network analysis. Visualization and further analysis of the generated PPI network using Cytoscape v3.9.1 showed the network possessed 496 nodes and 10,985 edges (Fig. 2). Subsequently, the CytoHubba plug-in of Cytoscape was utilized to derive the top 10 targets of the network based on the degree of interactions (Fig. 3). These targets can be considered the essential targets via which co-exposure to lead and cadmium disrupt normal biological and physiological activities of the body.

3.5 GO and KEGG pathway analysis

Enrichment analysis of the common targets was performed using the ShinyGo v0.76 webserver. The GO analysis revealed the various functions that are played by the genes at the molecular level. Interestingly, the genes were enriched in biological processes such as response to lead ion, response to cadmium ion, response to cell death, response to oxygen-containing compound, and response to oxidative stress. Similarly, the molecular functions of the genes include oxidoreductase activity, antioxidant activity, ubiquitin-like protein ligase binding, hormone activity, and protein kinase activity. Furthermore, the targets were also found to be cellular components of the mitochondrion, blood microparticle, cell surface, lysosome, and platelet alpha granule. Based on the false discovry rate (FDR) cutoff of 0.05, the top 10 results of the GO analysis were further selected for visualization (Fig. 4).

Identification of the potential signaling pathways disrupted as a result of the co-exposure revealed the HIF-1 signaling pathway, chemical carcinogenesis, PI3K-Akt signaling pathway, Mineral absorption pathway, and P53 signaling pathway as the potential pathways in which the shared are enriched. The top 20 pathways were identified and visualized based on an FDR cut-off of 0.05 (Fig. 5).

4.0 Discussion

Heavy metals are highly notorious for their ability to induce numerous forms of toxicity-associated burdens in humans, especially at elevated levels of exposure. While several experimental and computational studies have accessed the effects and mode of action of many heavy metals including lead and cadmium on the biological system, studies on the mechanism and the ability of co-exposure to these metals to result in some diseases and trigger an additive or synergistic effect have been mildly

explored. To this end, this study was aimed at unraveling the molecular mechanism via which Pb and Cd co-exposure results in the development of HYP.

The set of genes whose biological activities or expression are affected by Pb and Cd were retrieved from the earlier stated CTD while the set of genes implicated in the development and progression of HYP were also retrieved from the GeneCards database. Further analysis performed revealed the 512 genes that are co-affected by Pb and Cd in their pathogenesis of HYP. The set of genes includes genes that control important biological processes such as cell cycle, cell death, inflammation, protein folding, and many others.

Interestingly, the set of the mutual genes are genes that are affected by independent exposure to Pb and Cd. Hence, this suggests that co-exposure to Pb and Cd could pose an additive or synergistic effect on the pathogenesis of HYP. For example, the activity of blood ALAD, which provides instructions for making heme, is known to be inhibited by lead and contributes to the retention of lead in the blood [20]. Similarly, cadmium was reported to decrease the blood activity of ALAD in humans with a greater risk associated with an increased dose [21].

ACE plays a significant role in the renin-angiotensin system which is responsible for the control of blood pressure via the regulation of body fluids volume. This enzyme converts angiotensin I to angiotensin II, a process that leads to the constrictions of blood vessels [22]. Júnior et al. reported that cadmium poses a dose/duration-dependent effect on ACE activity. They reported that acute exposure to low doses of cadmium increases ACE activity while chronic exposure to low doses reduces its activity [23]. Contrastingly, a study by Broseghini-Filho et al. showed that acute cadmium exposure inhibits the activity of ACE in the serum, aorta, and lung while promoting the retention of the metal in the associated tissues. The inhibition was proposed to be via competitive replacement of zinc at the active site of ACE [24]. Furthermore, Carmignani et al. [25] reported an increase in the activity of ACE following acute lead exposure, a result which is also consistent with the findings of Sharifi et al. [26]. While no study has reported the effect of Pb and Cd co-exposure on ACE activity, from the results of this study, it can be inferred that co-exposure to both metals could be capable of altering the expression and activity of ACE based on the concentration and duration of exposure.

Co-exposure to Pb and Cd is known to promote systemic inflammation [27]. They also induce oxidative stress via the generation of free radicals and depletion of the body's antioxidant level [28, 29]. Several studies have reported an increased level of inflammation in hypertensive patients. Xiao et al. reported several biomarkers of inflammation are elevated in HYP [30]. Our study revealed several pro- and anti-inflammatory markers which are targeted by Pb and Cd in HYP. These markers include IL10, TNF, IL2, IL4, IL6, CRP, IL1B, and IL17 among many others [31]. Cadmium activates inflammatory response via the upregulation of NF-Kβ, IL6, TNFα, and IL-1β among others. Conversely, the ability of lead to alter the expression of pro- and anti-inflammatory cytokines is heavily dependent on the concentration [32]. It could be inferred that Pb and Cd co-exposure would both contribute to the increased progression of HYP either via the stimulation of the expression of pro-inflammatory cytokines or/and the increased

generation of ROS either directly or indirectly. This claim is supported by a study by Zhang et al.[33] in which they reported that Pb and Cd co-exposure were associated with increased systemic immune inflammation. They also reported that both Pb and Cd can be immune inflammation biomarkers.

Additionally, Pb and Cd are capable of disrupting the balance between oxidant and antioxidant levels which play a vital role in the remission of oxidative stress [33]. While a study has reported that co-exposure to Pb and Cd increased the expression of oxidative stress genes such as SOD, GPx, and HSP. This study found that co-exposure to Pb and Cd could potentially alter the expression and activities of GSTA1, GSTM1, GSTO1, GSTP1, GSTT1, HSP90AB1, HSP90B1, HSPA1A, HSPA5, HSPA8, HSPA9, HSPB1, and HSPD1 in the context of HYP development and progression.

To further understand the complex relationship between genes dysregulated Pb and Cd co-exposure in HYP, the PPI network of the 512 shared targets was constructed and analyzed while GO and KEGG analyses were also performed. The top 10 targets via which Pb and Cd co-exposure disrupt the normal biological and physiological activities of the body were then identified and the biological activities of the targets among others were also revealed. The top 10 targets include GAPDH, ALB, AKT1, TP53, TNF, IL6, EGFR, CTNNB1, MYC, and CASP3.

Based on FDR values, lipid and atherosclerosis, pathways in cancer, AGE-RAGE signaling pathway, HIF-1 signaling pathway, and human cytomegalovirus infection were the top five pathways that are dysregulated by Pb and Cd co-exposure in HYP development and progression.

Both advanced glycation end products (AGEs) and their cell receptor (RAGE) have been reported to be well involved in the stiffing of the arteries while the expression of AGEs and RAGE are also known to be elevated in hypertensive patients [39, 40]. The results of this study show that AGEs and RAGE are also involved in the development and progression of HYP as a result of Pb and Cd co-exposure. The interaction of AGEs with RAGE facilitates the expression of inflammatory cytokines, increase the production of ROS via the nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase, and activates the nuclear factor kappa-B (NF-κB) which results in the contraction of arterial walls. The activation of NF-κB leads to the generation of pro-inflammatory cytokines, which results in an elevated inflammatory response, a biological process that has been reported to be dysregulated in hypertensive patients [30].

Several accumulating evidence suggest that the activation of Hypoxia-inducible factor 1α (HIF-1α) is associated with arterial HYP and acts as a pathogenic mechanism for several diseases [41]. HIF plays an essential role in the response of cells to low oxygen levels and is responsible for the activation of specific genes in hypoxic conditions [42]. The deletion of HIF-1α has been reported to combat HYP induced as a result of hypoxia. Hence, the results of this study reveal HIF signaling pathway can be regarded as a dysregulated pathway in Pb and Cd-induced HYP. There exists an association between signaling pathways that are dysregulated by Pb and Cd co-exposure. This is evident from the number of genes that intercorrelate between the pathways, hence, depicting that the development and progression of Pb and Cd co-exposure-induced HYP are dependent on the dysregulation of many interacting pathways.

Conclusion

Summarily, this study attempted to elucidate the molecular mechanism via which Pb and Cd co-exposure induce HYP. This study reveals the set of genes whose dysregulation by Pb and Cd co-exposure results in the induction and progression of HYP. Our study also reveals the signaling pathways via which the HYP-inducing effect of Pb and Cd co-exposure is mediated, with the most significant signaling pathways being the lipid and atherosclerosis signaling pathways. Furthermore, the stimulation of inflammation, oxidative stress, and mediating endothelial dysfunction was revealed to be an important process in Pb and Cd co-exposure mediated HYP while the inflammatory and stress markers that could be used for prognosis evaluation were revealed. While the results of this study provide insights into some of the dysregulation caused by Pb and Cd co-exposure for HYP induction and progression, further *in vitro* and *in vivo* studies are needed to support the results.

Declarations

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Competing Interest

The authors declare that there are no relevant financial or non-financial interests to disclose.

Author's Contributions

Oluwatoyin. Folake Olukunle and Victor Omoboyede contributed to the study conception and design.
Victor Omoboyede

performed material preparation, data collection, analyses and wrote the first draft of the manuscript and Oluwatoyin. Folake

Olukunle commented on previous versions of the manuscript. The two authors read and approved the final manuscript.

Data Availabitity

The datasets generated during the current study are not publicly available because the manuuscript is yet to be reviewed but are available from the corresponding author on reasonable request.

Ethics Approval

This is an *in silico* study. The University Research Ethics Committee has confirmed that no ethical approval is required.

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Figures

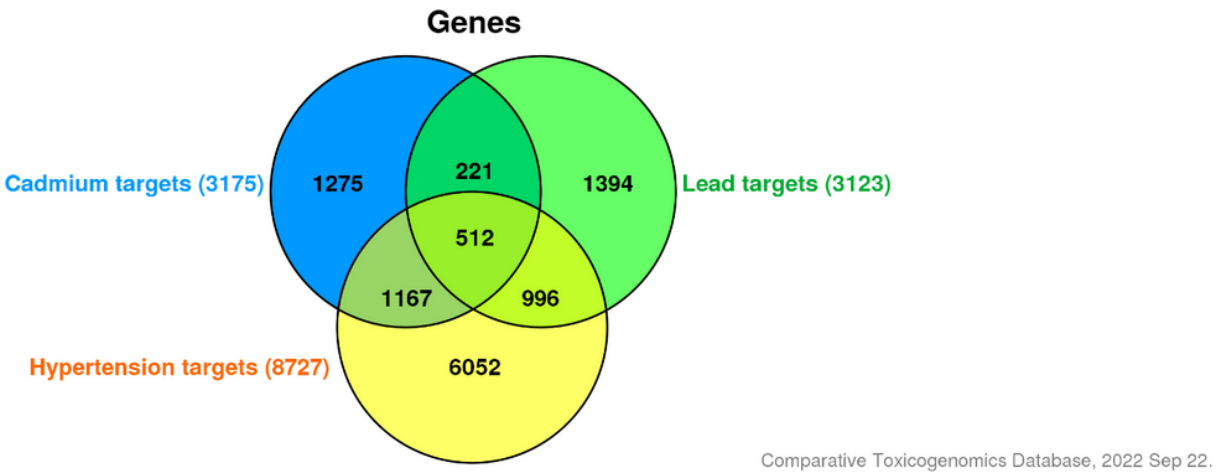

Figure 1

A Venn diagram depicting the number of genes that were retrieved for Pb, Cd, HYP, and the number of interacting genes.

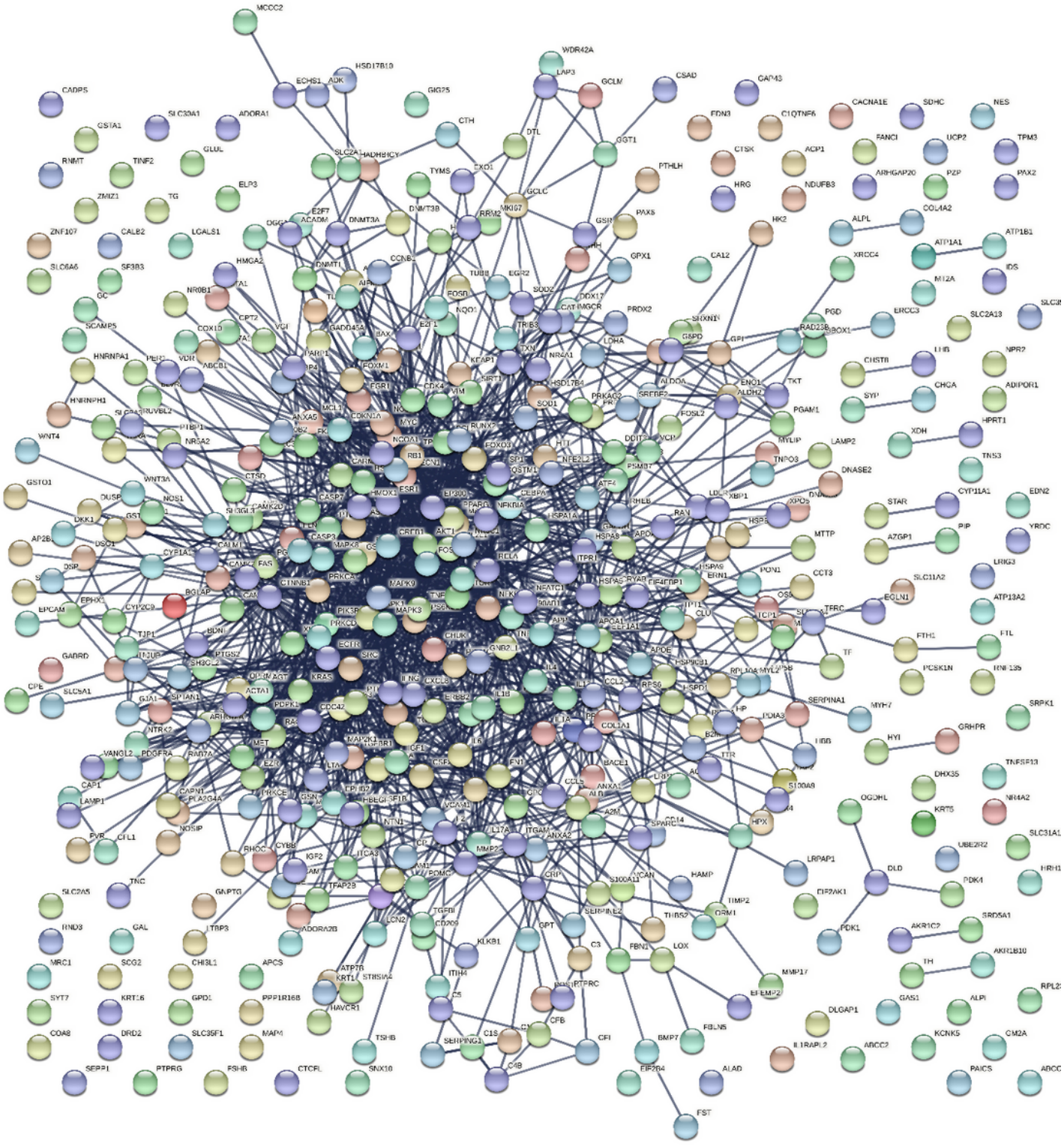

Figure 2

PPI network of the 512 shared targets constructed using string.

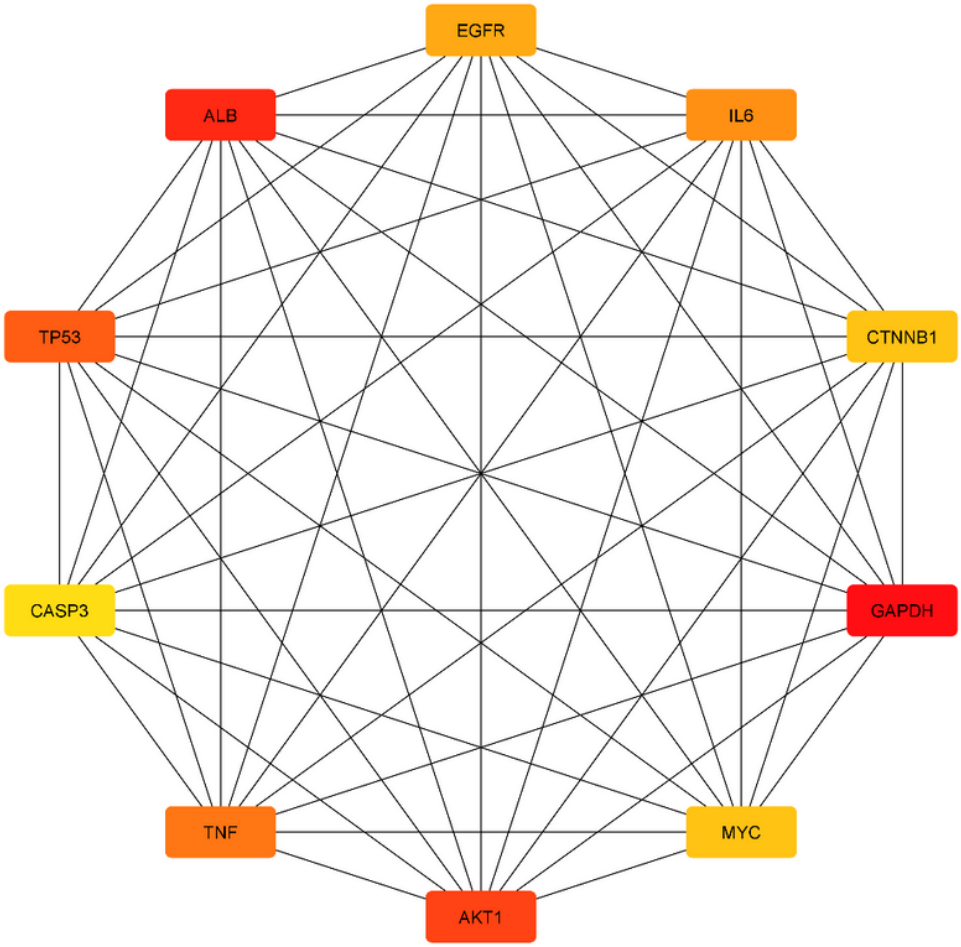

Figure 3

The top ten targets of the PPI network selected based on the degree of interactions using CytoHubba plug-in of cytoscape.

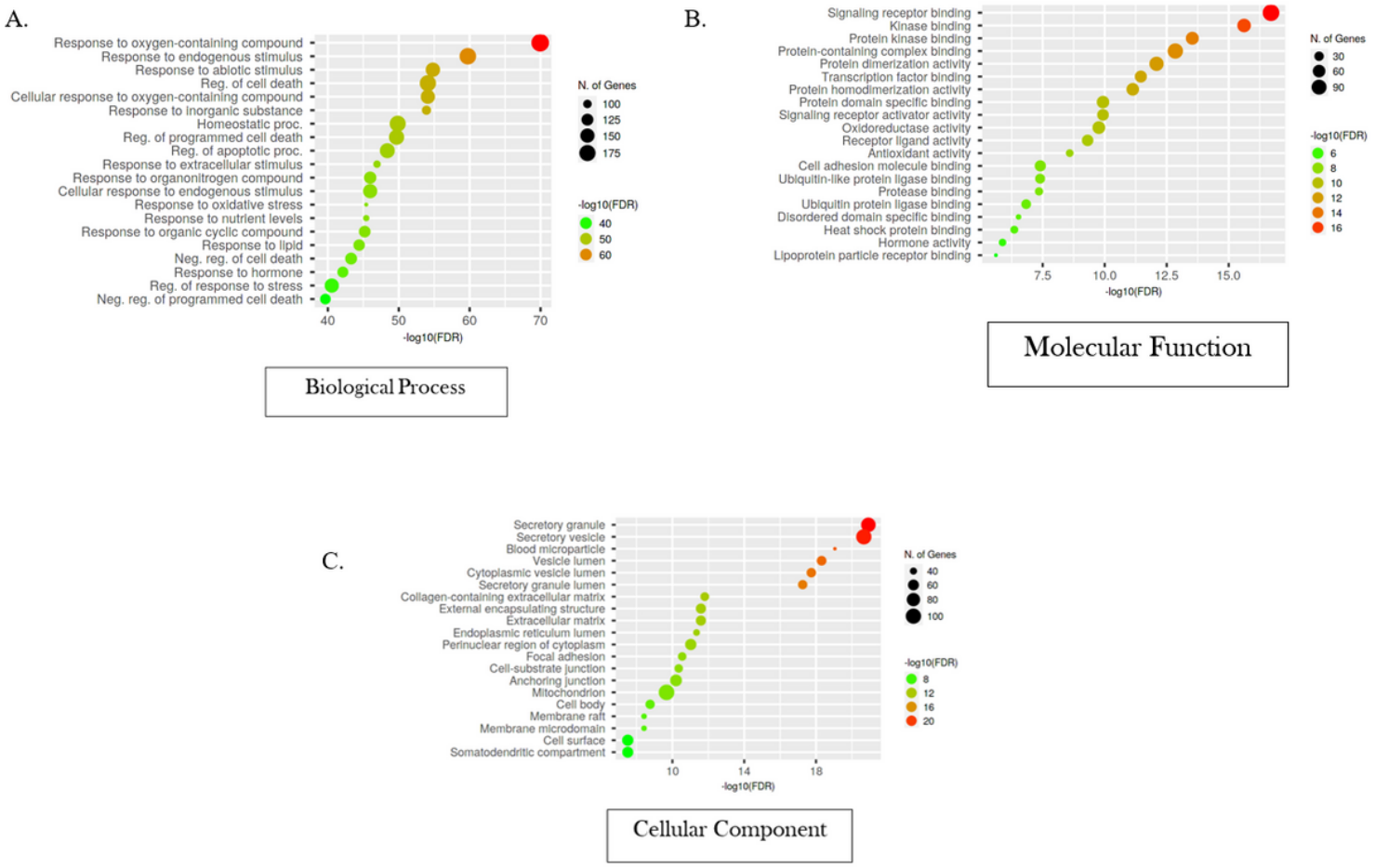

Figure 4

The Gene ontology functional annotation analysis of the targets of Pb and Cd in HYP. A. Biological process in which the targets are enriched. (b) Molecular function of the targets. (c) Cellular components of the targets.

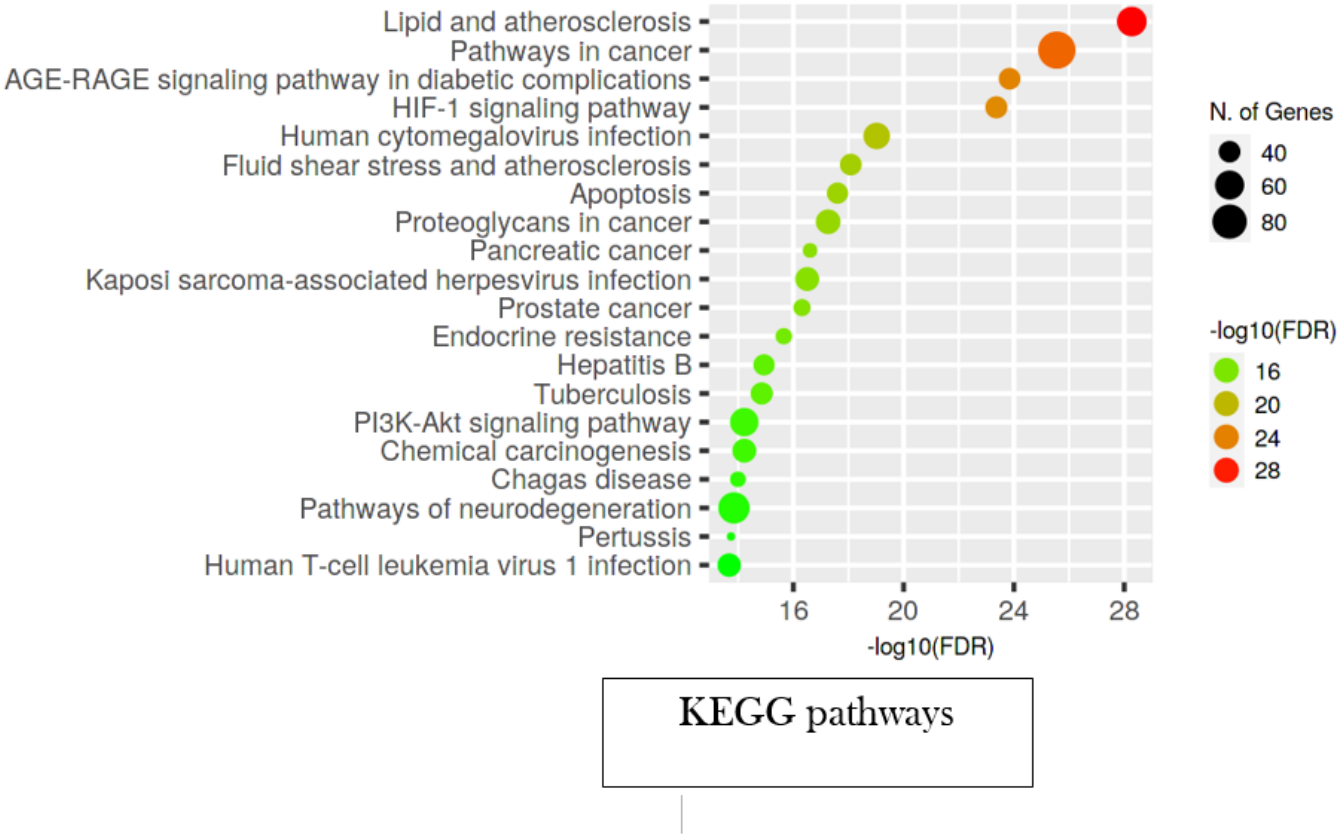

Figure 5

The top 20 KEGG pathways in which the shared targets are enriched