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Chapter

Chromium Genotoxicity associated with Respiratory Disease

Jyoti Kant Choudhari, Jyotsna Choubey, Mukesh Kumar Verma, Anand Kumar Jayapal and Biju Prava Sahariah

Abstract

Chromium existing in the biosphere in prominent two forms Cr (III) and Cr (VI) is a well-studied heavy metal. Cr (III) is considered as non-harmful and necessary element in diet whereas Cr(VI) is extremely toxic exerting various negative health impacts on human and other organisms. Mining activity is must for extracting economic minerals and a large number of people are related to these sites as worker or habitants and a major source of chromium exposure. Present chapter discusses genotoxic nature of chromium considering respiratory disease resulted from chromium exposure. The genotoxicity is illustrated in terms of chromium induced differential expressed genes (DEGs), transcription factors and microRNA regulating the DEGs and their gene ontology.

Keywords: Mine tailing, Chromium Toxicity, Genotoxicity, Gene expressions

1. Introduction

For the growth of economy of a country and improving living status of population, industrial functioning is mandatory which is in other hand associated activities including supply of power, raw materials, processing and discharge of waste. For a major section of industries, power supply is from coal or electricity generated from coal, and the raw materials are various form of ores received from mining. Mine tailing is the fine residual mine dump after completion of mining left with dug out soil, scattered residuals and disturbed ecosystem. The major source of chromium in the mine tailings is the residual ores present in traces not extracted with economic point of view and mineral processing chemicals that are left unattended. Chromium (Cr), a valuable element often finds its utility in metallurgical, chemical, and refractory industries due to its pigment property, hardness and persistence. From environment point of view, chromium exists in three oxidative states, elemental chromium (0) that does not exist naturally, whereas trivalent chromium (Cr III) is rather stable followed by hexavalent chromium (Cr VI) based on the different number of electrons and therefore varied properties [1]. Hexavalent chromium is extremely toxic even in low concentration and listed as carcinogenic, hematotoxic and altering genetic material whereas, Cr (III) is regarded as micronutrient in human diet. When Cr is left unattended in mine tailings, it can be transported by

natural means to nearby waterbody, added with acid mine drainage, and surrounding ecosystem expanding the circumference of toxicity exposure [2]. This chapter emphasises on toxicity of hexavalent chromium in genetic level that influence expression of genes, the transcript factors controlling the differentially expressed genes and finally to find out the major indicating and influenced genetic factors with functional analysis of gene ontology for respiratory units of human.

1.1 Source and toxicity of chromium

Toxicity of chromium is directly influenced by the chromium species with valence with number of electrons and thus their properties. The Cr(VI), is a powerful oxidizing agent and plainly toxic to human and other organisms causing adverse effect to blood cells, renal cells, allergic conditions and organs of most part of body failure. Chromium can significantly find its route of exposures through dermal chromium contact in waste sites, inhalation of chromium emissions and ingestion of contaminated water or food grown in chromium contaminated soil. Also, erosion products and emissions from road and cement dust, leather, paints and or any Cr used materials contribute to inhalation of chromium. Dermal ulcers, irritation and sensitization of respiratory/lungs are consecutive result of chromium contact. In the plasma and cells, Cr(VI) readily get reduced to Cr(III), and thereafter excreted in the urine. Trivalent chromium is the form of chromium that is essential to human health and counted as an essential trace mineral in the human diet. Hexavalent chromium is recognised as genotoxic as it can damage genetic information in living cells, causes DNA mutations, and possibly the formation of cancerous tumours. Chromates (chromium salts) formed from hexavalent chromium also finds utilization in manufacture leather products, paints, cement, mortar, anti-corrosives, and other things. They are carcinogenic and allergenic.

1.2 Physiologic effects of chromium exposure in respiratory disease

Occupational exposures often include mixed exposure to both Cr(III) and Cr (VI) [3]. Chromium compounds, when inhaled, causes respiratory tract irritants, resulting in airway irritation, airway obstruction, and lung, nasal, or sinus cancer. Radiographic analysis from several reports revealed enlargement of the hilar region and lymph nodes [4, 5]. Consistent associations have been found between employment in the chromium industries and significant risk for respiratory cancer. Moller et al. [6] reported systemic reactions characterised with anaphylactoid reaction in a young welder having chromium (VI) vapor fume exposures. Following an experiment with sodium chromate inhalation at a concentration of 29 $\mu g/m^3$, formation of static urticaria, angioedema and severe bronchospasm simultaneously with plasma histamine rising in threefold was documented and suggested direct positive leukocyte inhibitory factor of sodium chromate.

A number of nasal mucosa injury cases in Cr (VI) exposed workers at concertation of nearly 20 $\mu g/m^3$ (against US permissible standard 5 $\mu g/m^3$) for 5 months to 10 years characterised with inflamed mucosa and ulcerated/perforated septum was recorded in a study with 43 chrome-plating plants and tanneries in Sweden [7, 8]. Huge number of complaints for nasal irritations was documented in a detail epidemiological study with Tokyo (Japan) housewives residing near chromium slag contaminated construction site [7]. U.S has recommended chromate and chromic acid at workplace to be 5 $\mu g/m^3$ as permissible standard. Gibb et al. [9] observed that with less than 30 days median time for nasal ulceration diagnosis from first exposure, median Cr (VI) concentration matched the Sweden report. Occupational exposure to Cr(III) has also been associated with respiratory effects.

Persons developed coughing, wheezing, and decreased forced volume after an inhalation exposure to a sample of Cr(III) sulfate [10]. Combine effect of Cr(III) and Cr(VI) as total chromium (0.02–0.19 mg total chromium/m^3) investigated among 60 ferrochromium workers squeezed out subjective symptoms of coughing, wheezing, and dyspnea whereas control remained neutral [11]. These symptoms might get puzzled with smoking issue to clarify the accurate problem of the diseases [11]. While considering respiratory issue, animals are also often exposed to chromium similar to the human. Henderson et al. [12] in histological examination with exposure of 0.9–25 mg Cr(III) trichloride for 30 min observed alterations in lung tissues associated with mild inflammation.

2. Chromium-gene interactions in respiratory disease

Comparative toxico-genomics database (CTD, http://ctdbase.org) is a recognised well informed/updated, openly accessible database. It purposes to provide detail knowledge and information about the impacts of exposure of environmental elements (pollutants) on human health.

The core block of the database basically manually curated contains updated information regarding interaction and relationships among chemicals, genes, proteins and their resulted specific disease in terms of functional and pathways to incorporate new hypotheses expressing underlying mechanisms of disease and environmental contamination [13].

3. Results and discussion

In this work, all Chromium- gene /protein interactions for respiratory disease are downloaded from CTD, in which Chromium- gene /protein interactions associated to the following 04 respiratory disease are selected for further analysis according to MESH ID used in CTD— Lung Neoplasma, Pulmonary Fibrosis and Lung disease. Chromium- gene/protein interactions associated to this respiratory disease are collected for further analysis. According to the reference score on relationships between chemicals-genes, genes-diseases and chemicals-diseases [14], lung neoplasms is recognised as most likely having the maximum connectivity with chromium. (**Table 1**). From the identified 168 chromium gene with in respiratory disease, 131 genes are unique.

3.1 Gene function enrichment analysis

KEGG (http://www.genome.jp/) is a knowledge base for systematic analysis of gene functions, linking genomic information with higher-order functional information [15]. For the analysis of Gene Ontology (GO) and Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway analysis, the Database for Annotation, Visualization and Integrated Discovery (DAVID, http://david.abcc.ncifcrf.gov/) is a great option. DAVID provides various functional annotation tools for researchers to understand biological meaning behind large list of genes. [16] Gene ontology (GO) analysis and Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway enrichment analysis can be performed for analysing differentially expressed genes (DEGs) at the functional level based on DAVID Bioinformatics Resources 6.8. $P < 0.05$ as the cut-off criterion. Researchers can upload all DEGs to the online software DAVID to identify overrepresented GO categories and KEGG pathways. The curated genes in CTD for each respiratory disease can be uploaded to DAVID 6.8 Beta (https://da

Disease Name	Inference chromium-interacted genes (n)	Gene count	Inference Score
Lung Neoplasms (Cr VI)	ACE,AKT1,APOA1,APOC3,AR,AVPI1,BCL2L1,BRCA2,CASP8, CCND1,CDKN1A,CDKN1B,CDKN2A,CEACAM1,CHEK2, COL6A1,COX17,CRP,CTNNB1,CWH43,CYP1B1,DPYD,EEF2, EFNB2,EGFR,EGR1,ERBB2,ERBB3,ESR1,FAS,FEN1,FGF9,FOS, GCLC,GPX1,GPX3,GSTM1,GSTP1,HILPDA,HMOX1,HRAS, IDS,IER2,IFNG,IL1B,IL2,IL6,JUN,JUNB,LECT2,MAP2K7, MAPK1,MAPK14,MAPK3,MIR21,MIR494,MMP10,MYC,NOS2, OGG1,PCNA,PDCD4,PRDX1,PRDX6,PRKN,PTMA,SERPINA1, SERPING1,SFTPB,SIDT2,SMC2,SOX2,SOX9,TERT,TFRC, TGFBR2,TNF,TP53,TRP53,USP18,WNT5A	81	74.7
Lung Neoplasms(Cr III)	ACE,AKT1,ANXA2,APOA1,AZGP1,CASP8,CAV1,CDKN1A, CDKN2A,CPE,CYP1B1,FOS,GCLC,GJA1,GPX1,GSTM1, HMOX1,IER2,IFNG,IL10,IL1B,IL6,JUN,MAPK1,MAPK3,MMP1, SFTPB,TGFB1,TLR4,TNF,TP53,TYMS	32	58.22
Pulmonary Fibrosis	ACE2, ACTA2, CAT, CCL11, CCL2, CCL5, CXCL8, EDN1, FAM13A, FN1, FYN, HMGB1, HMOX1, IL1B, IL4, IL6, LAMB1, MMP2, MMP9, MTOR, NFE2L2, PARP1, PDGFB, PTX3, SERPINA1, SOD1,STAT3,TIMP1,TNF	29	25.25
Lung Diseases	ACE, BST1, HARS, HIF1A, IGF1R, INSR, KIT, PDGFRA,PTGS2, SERPINA1,SFTPB,SOD2,TNF,VEGFA	14	7.62
Asthma, Occupational	TGFB1, TNF	02	5.86
Lung Injury	ACE, ACE2, CCL2, CYP1A1, HMOX1, IL6, PARP1, SIRT1, TNF	09	3.12
Nose Neoplasms	MMP2	01	2.55

Table 1.
Selected Respiratory diseases and related chromium-interacted gene.

vid-d.ncif-crf.gov/tools.jsp) with *Homo sapiens* as the background population [17] for GO analysis.

GO analysis results for Cr toxicity in respiratory organs shows that that chromium interacted genes in respiratory disease are involved in the biological processes (BP) such as positive regulation of gene expression, positive regulation of cell proliferation, response to drug positive regulation of protein phosphorylation. (**Table 2**) For molecular function (MF), genes are enriched in identical protein binding, enzyme binding, transcription factor binding and protein phosphatase binding (**Table 2**). In addition, GO cell component (CC) analysis also displayed that the gene are significantly enriched in the extracellular space, protein complex, extracellular region and extracellular exosome (**Table 2**).

Table 3 contains the most significantly enriched pathways of the chromium interacting genes by KEGG analysis. The interacting genes are enriched in Pathways in cancer, Proteoglycans in cancer, HIF-1 signalling pathway and TNF signalling pathways.

3.2 Gene-TFs-miRNAs regulation

The transcription factors (TFs) as well as microRNAs (miRNAs), are recognised for their huge share in transacting and gene regulations with various common logics and regulatory factors for gene regulation in multicellular genomes [18, 19]. The library of ENCODE and ChEA Consensus TFs from ChIP-X in EnrichR (http://amp.pharm.mssm.edu/Enrichr/ [20, 21]) can be used for the possible TFs

Term	Count	P value	FDR	Genes
Biological Process				
Positive regulation of gene expression	26	1.17E-21	2.49E-18	CRP, PDGFB, HIF1A, TNF, GJA1, FGF9, ERBB3, MYC, ERBB2, HRAS, TGFB1, CAV1, STAT3, FN1, MAPK14, MTOR, VEGFA, ACTA2, AR, IL6, IFNG, IL1B, KIT, TP53, TLR4, NFE2L2
Positive regulation of nitric oxide biosynthetic process	14	1.39E-18	1.49E-15	EDN1, INSR, PTGS2, SOD2, ESR1, TNF, EGFR, MTOR, IL6, IFNG, IL1B, AKT1, PTX3, TLR4
Positive regulation of cell proliferation	26	1.23E-15	8.80E-13	CDKN1B, HILPDA, PDGFB, EGFR, IGF1R, EFNB2, FGF9, MYC, MAPK1, SOX9, TIMP1, HRAS, PDGFRA, EDN1, TGFB1, INSR, STAT3, FN1, IL2, TGFBR2, VEGFA, AR, IL6, IFNG, KIT, BCL2L1
Aging	18	1.68E-15	8.89E-13	JUN, TGFB1, OGG1, STAT3, FOS, TYMS, EEF2, TGFBR2, SOD1, GCLC, IL6, CAT, CYP1A1, SERPING1, CCL2, AKT1, TIMP1, NFE2L2
Response to drug	22	2.08E-15	8.89E-13	CDKN1A, JUN, TGFB1, CDKN1B, OGG1, STAT3, APOA1, FOS, TYMS, PTGS2, SOD2, TGFBR2, SOD1, IL4, IL6, IFNG, CCND1, MYC, CAT, CYP1A1, CTNNB1, FYN
Positive regulation of smooth muscle cell proliferation	13	7.81E-15	2.78E-12	JUN, EDN1, PDGFB, PTGS2, TNF, EGFR, MTOR, TGFBR2, IL6, MYC, CCL5, AKT1, HMOX1
Positive regulation of protein phosphorylation	16	1.07E-14	3.27E-12	TGFB1, ANXA2, INSR, TNF, MMP9, EGFR, MTOR, VEGFA, CCND1, CHEK2, IL1B, ERBB2, AKT1, SOX9, HRAS, MAPK3
Term	Count	P value	FDR	Genes
Cellular Component				
Extracellular space	49	1.61E-24	3.37E-22	SERPINA1, CXCL8, TFRC, HILPDA, LECT2, HMGB1, TNF, FGF9, TIMP1, SFTPB, EDN1, ANXA2, GPX3, MMP2, WNT5A, APOA1, MMP9, MMP10, ACTA2, ACE2, AZGP1, IFNG, IL1B, CAT, KIT, SERPING1, CRP, CCL11, GSTP1, PDGFB, EGFR, ERBB3, PRDX1, CCL5, CCL2, HMOX1, TGFB1, ACE, FN1, APOC3, LAMB1, PRDX6, IL2, SOD1, VEGFA, IL4, IL6, CPE, PTX3
Protein complex	21	1.48E-12	1.55E-10	PDGFRA, CDKN1A, FEN1, CDKN1B, PARP1, CDKN2A, OGG1, CAV1, BRCA2, PTGS2, SOD1, ACTA2, AR, MYC, COL6A1, AKT1, MAPK1, CTNNB1, SOX9, TP53, MAPK3
Extracellular region	37	9.09E-12	6.36E-10	CRP, SERPINA1, CCL11, CXCL8, TFRC, PDGFB, HMGB1, TNF, FGF9, CCL5, CCL2, TIMP1, SFTPB, EDN1, TGFB1, ACE, GPX3, MMP2, WNT5A, FN1, APOA1, APOC3, LAMB1, MMP9, MMP10, IL2, SOD1, VEGFA, IL4, ACE2, IL6, AZGP1, IFNG, IL1B, COL6A1, SERPING1, PTX3
Cytosol	49	4.84E-09	2.54E-07	CDKN1A, CDKN1B, FAM13A, SMC2, SOX2, GJA1, CASP8, CCND1, MYC, AKT1, HRAS, GPX1, ANXA2, APOA1, FOS, TGFBR2,

Term	Count	P value	FDR	Genes
				ACTA2, AR, IL1B, DPYD, CAT, TP53, GSTP1, TYMS, USP18, HIF1A, PRDX1, HMOX1, MAPK1, FYN, HARS, MAP2K7, MAPK3, JUN, GSTM1, NOS2, CDKN2A, STAT3, EEF2, MAPK14, PRDX6, MTOR, SOD1, GCLC, PDCD4, CTNNB1, FAS, NFE2L2, BCL2L1
Mitochondrion	26	7.77E-07	2.62E-05	FEN1, GSTP1, OGG1, COX17, TYMS, GJA1, CASP8, MYC, PRDX1, CYP1B1, AKT1, MAPK1, FYN, HARS, MAPK3, GPX1, PARP1, CDKN2A, MMP2, MAPK14, SOD2, SOD1, CAT, CYP1A1, TP53, BCL2L1
Membrane raft	11	7.89E-07	2.62E-05	ACE2, GJA1, CASP8, ANXA2, CAV1, FAS, FYN, EEF2, TNF, EGFR, TGFBR2
Extracellular exosome	40	8.72E-07	2.62E-05	CRP, SERPINA1, PCNA, TFRC, GSTP1, SMC2, GJA1, FGF9, PRDX1, MAPK1, TIMP1, MAPK3, ACE, GPX1, ANXA2, GPX3, INSR, WNT5A, FN1, APOA1, APOC3, LAMB1, EEF2, MAPK14, SOD2, MMP9, PRDX6, SOD1, ACTA2, ACE2, BST1, AZGP1, CEACAM1, IL1B, COL6A1, CAT, SERPING1, CPE, CTNNB1, FAS
Molecular Function				
Identical protein binding	31	2.03E-15	8.34E-13	SERPINA1, PCNA, TFRC, LECT2, PDGFB, TNF, EGFR, IGF1R, CASP8, ERBB3, CHEK2, PRDX1, ERBB2, AKT1, MAPK1, FYN, JUN, PARP1, CAV1, STAT3, FN1, APOA1, SOD2, MMP9, ESR1, SOD1, VEGFA, FAS, PTX3, TP53, BCL2L1
Enzyme binding	22	9.84E-15	2.02E-12	JUN, TGFB1, GSTM1, PCNA, PARP1, CAV1, APOA1, PTGS2, MAPK14, HIF1A, ESR1, EGFR, AR, CCND1, CAT, CYP1A1, AKT1, HMOX1, CTNNB1, FYN, MAP2K7, TP53
Transcription factor binding	15	9.22E-09	1.13E-06	JUN, PARP1, CDKN2A, GPX3, STAT3, HMGB1, FOS, HIF1A, ESR1, AR, CCND1, MYC, MAPK1, CTNNB1, TP53
Protein phosphatase binding	9	1.10E-08	1.13E-06	CEACAM1, CDKN1B, ERBB2, STAT3, CTNNB1, MAPK14, MAP2K7, TP53, EGFR
Protein binding	90	3.45E-08	2.41E-06	CDKN1A, FEN1, CDKN1B, SERPINA1, CXCL8, TFRC, OGG1, HILPDA, HMGB1, BRCA2, TNF, IGF1R, SMC2, SOX2, GJA1, CASP8, CCND1, MYC, CHEK2, AKT1, SOX9, TIMP1, HRAS, PDGFRA, EDN1, PARP1, ANXA2, GPX3, MMP2, WNT5A, APOA1, FOS, MMP9, TGFBR2, ACE2, AR, AZGP1, CEACAM1, DPYD, KIT, SERPING1, TLR4, TP53, AVPI1, CRP, CCL11, PCNA, GSTP1, COX17, PDGFB, PTGS2, USP18, HIF1A, EGFR, EFNB2, ERBB3, TERT, PRDX1, CCL5, ERBB2, HMOX1, MAPK1, FYN, MAP2K7, MAPK3, EGR1, JUN, TGFB1, NOS2, CDKN2A, INSR, CAV1, STAT3, FN1, EEF2, MAPK14, ESR1, PRDX6, MTOR, SOD1, VEGFA, IL4, IL6, CYP1A1, PDCD4, CTNNB1, FAS, PTX3, NFE2L2, BCL2L1
Cytokine activity	12	3.53E-08	2.41E-06	IL4, IL6, EDN1, TGFB1, IFNG, IL1B, WNT5A, TIMP1, HMGB1, TNF, IL2, VEGFA

Term	Count	P value	FDR	Genes
Protein homodimerization activity	21	1.14E-07	6.65E-06	PDGFRA, JUN, TGFB1, GSTM1, NOS2, TFRC, PDGFB, TYMS, PTGS2, SOD1, VEGFA, CEACAM1, TERT, ERBB3, CHEK2, CCL5, KIT, DPYD, CAT, HMOX1, BCL2L1

Table 2.
Gene ontology analysis of Cr interacted genes.

Term	Count	P value	FDR	Genes
Pathways in cancer	41	5.78E-24	5.60E-22	CDKN1A, CDKN1B, CXCL8, GSTP1, PDGFB, BRCA2, PTGS2, HIF1A, EGFR, IGF1R, CASP8, FGF9, CCND1, MYC, ERBB2, AKT1, MAPK1, HRAS, MAPK3, PDGFRA, JUN, TGFB1, NOS2, CDKN2A, MMP2, WNT5A, STAT3, FN1, LAMB1, FOS, MMP9, MTOR, TGFBR2, VEGFA, AR, IL6, KIT, CTNNB1, FAS, TP53, BCL2L1
Proteoglycans in cancer	30	1.79E-21	8.69E-20	CDKN1A, HIF1A, TNF, EGFR, IGF1R, ERBB3, CCND1, MYC, ERBB2, AKT1, MAPK1, HRAS, MAPK3, TGFB1, CAV1, MMP2, WNT5A, STAT3, FN1, MIR21, MAPK14, MMP9, ESR1, MTOR, VEGFA, PDCD4, CTNNB1, FAS, TP53, TLR4
HIF-1 signaling pathway	21	3.91E-18	1.26E-16	CDKN1A, EDN1, CDKN1B, NOS2, TFRC, INSR, STAT3, HIF1A, EGFR, MTOR, IGF1R, VEGFA, IL6, IFNG, ERBB2, AKT1, HMOX1, MAPK1, TIMP1, TLR4, MAPK3
Chagas disease (American trypanosomiasis)	21	2.09E-17	5.07E-16	JUN, TGFB1, ACE, CXCL8, NOS2, FOS, MAPK14, TNF, IL2, TGFBR2, IL6, CASP8, IFNG, IL1B, CCL5, FAS, CCL2, AKT1, MAPK1, TLR4, MAPK3
Bladder cancer	14	1.10E-14	2.13E-13	CDKN1A, CXCL8, CDKN2A, MMP2, MMP9, EGFR, VEGFA, CCND1, MYC, ERBB2, MAPK1, HRAS, TP53, MAPK3
Hepatitis B	21	1.87E-14	3.02E-13	CDKN1A, JUN, TGFB1, CDKN1B, PCNA, CXCL8, STAT3, FOS, TNF, MMP9, IL6, CASP8, CCND1, MYC, FAS, AKT1, MAPK1, HRAS, TP53, TLR4, MAPK3
Prostate cancer	16	1.94E-12	2.69E-11	PDGFRA, CDKN1A, CDKN1B, PDGFB, EGFR, MTOR, IGF1R, AR, CCND1, ERBB2, AKT1, MAPK1, CTNNB1, HRAS, TP53, MAPK3
TNF signaling pathway	17	2.75E-12	3.34E-11	JUN, EDN1, FOS, PTGS2, MAPK14, TNF, MMP9, IL6, CASP8, IL1B, CCL5, FAS, CCL2, AKT1, MAPK1, MAP2K7, MAPK3
Pancreatic cancer	14	7.57E-12	8.16E-11	TGFB1, CDKN2A, STAT3, BRCA2, EGFR, TGFBR2, VEGFA, CCND1, ERBB2, AKT1, MAPK1, TP53, BCL2L1, MAPK3
HTLV-I infection	23	1.29E-11	1.25E-10	PDGFRA, EGR1, CDKN1A, JUN, TGFB1, PCNA, CDKN2A, WNT5A, PDGFB, FOS, TNF, IL2, TGFBR2, IL6, TERT, CCND1, CHEK2, MYC, AKT1, CTNNB1, HRAS, TP53, BCL2L1

Table 3.
Pathway analysis for the chromium interacting genes related to Respiratory Disease.

and related networks. The TargetScan library in EnrichR can be used for the possible miRNA interaction. TFs are identified to be significantly associated with the genes involved in the respiratory disease. TRIM28, NFE2L2, EGR1 GATA2, PPARG,

ZMIZ1 and ESR1 are significant for respiratory disease influencing DEGs. The regulated genes for each of these TFs for chromium toxicity are shown in **Table 4** followed by the miRNAs identified for chromium interacting genes involved in the Respiratory diseases in **Figure 1**.

3.3 Comparable chemicals

Information about biological effects of a chemical at genetic level can be extensively extracted from CTD to create new hypotheses with a lot of interaction pathways and networks among genes-contaminants and diseases [22].

This highly contributes in identifying similar contaminants responsible for specific diseases. Comparable chemicals extracted from CTD for the possible sharing with many of the networks common to chromium in respiratory disease are given in **Table 5**. Mercury, SB 203580, 2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one, 2,3-dimethoxy-1,4-naphthoquinone, were found interacting with 102, 81,77and 61 chromium-iInteracting genes in Respiratory disease.

Term	Overlap	P-value	Adjusted P-value	Combined Score	Gene
TRIM28	9/210	1.02E-05	9.92E-04	82.94725092	EFNB2;EGR1;JUN;PARP1;ERBB3; WNT5A;SOX9;HIF1A;SOD1
NFE2L2	19/1022	3.76E-05	0.001413873	32.51065582	CDKN1A;GSTM1;WNT5A;FN1; PTGS2;ESR1;PRDX6;VEGFA;EFNB2; GJA1;GCLC;PRDX1;DPYD;CAT; CYP1B1;HMOX1;FYN;PTX3;AVPI1
EGR1	10/315	4.37E-05	0.001413873	53.21069483	EGR1;JUN;SERPINA1;STAT3;AKT1; MAPK1;ESR1;MMP9;EGFR;SOD1
GATA2	15/772	1.64E-04	0.003970477	28.45933865	JUN;CDKN1A;EDN1;GPX1;MMP2; LAMB1;FOS;MAPK14;IGF1R;IL4; CHEK2;PDCD4;IDS;IER2;BCL2L1
PPARG	12/535	2.10E-04	0.004075587	31.58677746	EFNB2;PDGFRA;JUN;CDKN1A; CASP8;INSR;HILPDA;CYP1B1;FOS; BCL2L1;SOD1;VEGFA
ZMIZ1	16/914	3.19E-04	0.005162124	23.65905038	EGR1;TGFB1;CDKN1B;GSTP1; MIR21;SOD1;VEGFA;GCLC;MYC; PRDX1;CAT;IDS;MAPK1;CTNNB1; IER2;AVPI1
ESR1	6/154	5.36E-04	0.006683025	48.17527072	EDN1;SERPINA1;STAT3;CYP1B1; FOS;ESR1
CTCF	24/1790	5.51E-04	0.006683025	17.25236108	PDGFRA; EGR1; JUN; EDN1; TGFB1; PCNA; CAV1; APOA1; EEF2; MAPK14; IGF1R; VEGFA; EFNB2; GCLC; IL6; CEACAM1;CASP8; ERBB3;MYC;CYP1B1;MAP2K7;TP53; BCL2L1;NFE2L2
MYC	11/573	0.001387281	0.014951805	20.72253353	GJA1; GCLC; PCNA; TFRC; CCND1; TERT;PARP1;EEF2;TP53;IER2;SOD1
RAD21	17/1265	0.003726145	0.036105828	12.44311845	PDGFRA; JUN; EDN1; PCNA; APOA1; EEF2; MAPK14; SOD2; VEGFA; EFNB2; IL6; CEACAM1; CASP8; MYC; TP53; BCL2L1;NFE2L2

Table 4.
Transcription factors for the chromium interacting genes involved in the Respiratory diseases.

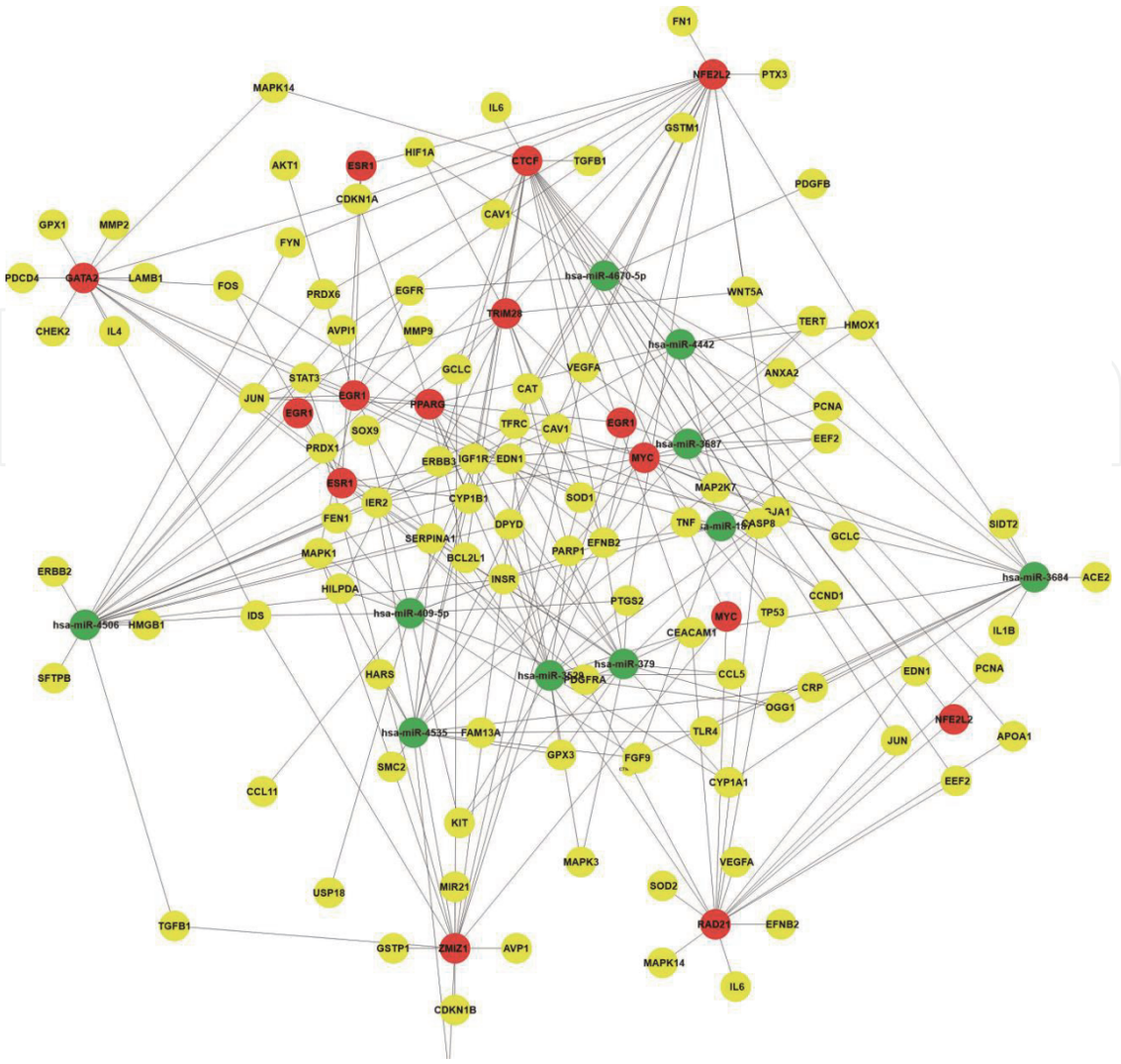

Figure 1.
Gene-TFs-miRNA Interaction Network.

Chemical	CAS RN	Similarity Index	Common Interacting Genes for Respiratory disease
2,3-dimethoxy-1,4-naphthoquinone	6956-96-3	0.174285714	61
Niacin		0.150997151	53
Antimony	7440-36-0	0.143333333	43
Antimony Potassium Tartrate	28300-74-5	0.132183908	46
naringin	10236-47-2	0.131016043	49
SB 203580		0.13022508	81
Mercury	7439-97-6	0.129606099	102
Rutin	153-18-4	0.129518072	43
alpha-Tocopherol	59-02-9	0.126262626	50
cobaltiprotoporphyrin	14325-03-2	0.124338624	47
4-(4-fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl) imidazole		0.122615804	45
Luteolin	491-70-3	0.122395833	47

Chemical	CAS RN	Similarity Index	Common Interacting Genes for Respiratory disease
2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one	154447-36-6	0.122222222	77
Thioctic Acid	62-46-4	0.121890547	49
Cholesterol, Dietary		0.120943953	41
2-(2-amino-3-methoxyphenyl)-4H-1-benzopyran-4-one		0.120385233	75
pyrazolanthrone		0.117117117	65
Docosahexaenoic Acids	25167-62-8	0.117073171	48

Table 5.
Chemicals having comparable sets of interacting genes to chromium.

4. Conclusions

Chromium (VI) is a vital toxic environmental pollutant having various sources including mine tailings. This chapter enlighten respiratory disease accelerated as well as caused due to chromium exposure at genetic level following bioinformatics method that leverages curated data from the public database CTD to generate novel sets of information. This strategy does not require a priori knowledge of the toxicant, biological system, or adverse outcome, and it can be used to identify potential molecular and biological intermediary steps that help fill in knowledge gaps connecting chemical exposures with outcomes for environmentally influenced diseases. With the existed data libraries (mainly CTD, GO, pathway, TFs and miRNA relate databases), bioinformatics web-based tools (David and EnrichR), BPs, CCs, MFs, KEEG signal pathways and gene regulation in the chromium-gene-disease networks were presented. In this study, 127 genes are identified as affected by exposure CR(VI), which are majorly regulated by 10 TFs and 10 very high target miRNAs. The Gene-TFs-miRNAs network recognises maximum interacted genes (EFNB2, IGF1R, CYP1B1, INSR, and VEGFA) and TFs (ZMIZ1, NFE2L2, CTCF and RAD21) and miRNAs (hsa-miR-4506, hsa-miR-379, hsa-miR-3529, hsa-miR-4535, hsa-miR-3684, and hsa-miR-409-5p). The significant biological process (positive regulation of gene expression and positive regulation of nitric oxide biosynthetic process), Cellular Component (extracellular space and protein complex) and Molecular Function (identical protein binding and enzyme binding) are influenced by chromium exposures. From pathway analysis of Cr (VI) influence on respiratory disease, maximum of DEGs are identified to be involved in various pathways in cancer (41 nos.) followed by proteoglycans in cancer (30 nos.), and HTLV-I infection (23 nos.) and so on. Comparable contaminants analysis has recognised Mercury, SB 203580, 2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one and 2-(2-amino-3-methoxyphenyl)-4H-1-benzopyran-4-one to have maximum common DEGs with Cr (VI) exposure.

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