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Original Article

Network and pathway analysis for Cesium in *Homo sapiens*

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ABSTRACT: Cesium is an alkali metal whose physiological roles and toxic effects have not been reported until date. In contrast, radio cesium has long lasting half-life of at least 30 years which can be toxic and hazardous to health. Radio isotope of cesium is usually used for nuclear energy production and recently incidence of nuclear power plant in Japan caused havoc to their local environment. To elucidate the possible interactions of cesium with proteins or genes in human body, we have applied some recently developed computational tools in this present study. Our results show that cesium has either some positive or negative interactions with 10 human proteins and subsequently these 10 proteins have been found to interact with 99 other human proteins through the application of bioinformatics tools. All of these proteins are involved in cellular, molecular and biological functions in human body. We need to conduct further study to know the specific functions of all these proteins so that further experiments can be conducted in laboratory to find out the possible effects of radio-cesium in rat models.
KEYWORDS: Cesium, cellular component, gene ontology, human health, proteins

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INTRODUCTION

Cesium (Cs) is not categorized as heavy metal, but it is one of the heaviest stable alkali metal which has several applications, such as in atomic clocks or as gradient centrifugation reagents[1]. The concentration of natural cesium in air and water though very low at less than 1ng and 1µg per cubic meter of air and water, respectively, the mean consumption of cesium by an individual ranges to about 10µg of cesium per day in food and water about 0.025µg per day through inhalation. Concentration of cesium in plant and animals can thus vary from 1–300ng/g.

However, due to the high density[2] and low toxicity[3] of cesium brines, it has become popular for the deep drilling operations. At a global scale, consumption of cesium rose sharply during the 1950s in accordance to increase in electronic applications, which were succeeded by peaks in cesium consumption between the 1960s till the 1980s, followed by subsequent fall in consumption of cesium in the 1990s. Majority of this cesium consumption took place in the United States in the area of developmental research. In addition, radioactive cesium has also been detected in surface water and in many types of food. This includes breast milk and pasteurized milk. Canada is known to hold the largest reserve of cesium, followed by Namibia, Zimbabwe, Afghanistan and India, respectively[2].

On the contrary, radio-cesium has longer half-life; for example, Cs-134 and Cs-137 have half-life

approximately 2.07 and 30.17 years, respectively[1]. In the last few decades, nuclear accidents such as Chernobyl and Fukushima showed the major risk of contamination of radio-cesium in environment which has attracted public attention[1]. Because, the large amount of radio-cesium always remains in the neighboring area of nuclear reactors' meltdown site, which makes the large area of land unsuitable for inhabitants[4].

Cesium is easily taken up by plant roots from the contaminated soil and later transferred in other parts of the plants including edible portions of animals and humans[5]. This process easily facilitates the entry of radio-cesium in food chain[6]. In the human system, cesium being readily absorbed in the small intestine and is subsequently secreted by the distal nephron and its ingestion is heavily linked to the levels of both intracellular and extracellular potassium. Cesium, upon entering into the body as halides, either in its natural or radioactive form is almost fully absorbed and is distributed all over the body, in appreciably higher concentrations in kidneys, skeletal muscles, liver and erythrocytes[8, 10]. Primarily, cesium is excreted through kidneys, in the form of urine, via mechanisms that are similar to the excretion of potassium[8].

Cesium, like potassium, enters cells and helps to maintain a balance of electrical charges between the inside and outside of cells so that cells can perform tasks that depend on those electrical charges. This includes cells like muscle cells and nerve cells which require changes in membrane potential for proper functioning.[7, 8]

Several studies have indicated that the toxicity to cesium is strictly dose dependent, though information about its acute and chronic toxicity remains unavailable. Though theoretical or clinical evidences to approve of cesium vulnerability to cancer cells remain missing, treatments involving cesium or radio-cesium may pose severe health hazards[7].

So far no direct link or interactions of radio-cesium with human diseases, more precisely genes and proteins, have been reported. This study is thus aimed at establishing a computational approach to elucidate the interaction of cesium with human genes or proteins in order to specify the exact pathways that might be targeted by cesium. In addition, this study is focused on establishing the protein-protein network between the proteins interacting with cesium and other human proteins followed by gene ontology based characterization of the overall proteins. Moreover, this approach will aid in the detection of the target of heavy metals in human system at the same time.

MATERIAL AND METHODS

Network retrieval

The interaction of cesium with human (*Homo sapiens*) proteins was searched through STITCH 4.0 (http://stitch.embl.de/) web server (Kuhn et al. 2013). This tool congregates the builds up of a unified network based on the origins of protein–chemical interactions from experimental databases, pathway databases, drug–target databases, text mining and drug–target predictions[9]. The interaction between CsCl and human proteins was checked at a high confidence level of 0.7 in order wipe out any weaker protein-ligand interaction that might have been predicted.

The list of human (*Homo sapiens*) proteins interacting with cesium was considered further to identify the protein-protein interaction (PPI) also in the same species. PPI was done through STRING 9.1 (http://string-db.org/) web server[11], which returns all the known and predicted protein interactions based on direct (physical) and indirect (functional) associations.

Sequence retrieval

The sequences of proteins which were listed through PPI were downloaded in FASTA format from NCBI protein (http://www.ncbi.nlm.nih.gov/protein) database [Supplementary file 1]. Repetition was avoided during sequence retrieval.

Prediction of gene ontology

Gene ontology of these sequences was done through Blast2GO software. This tool was used for functional annotation and analysis of protein sequences. The correlation of sequences in biological process and molecular function; and the presence in cellular component were analyzed. The annotation parameters for the Blast2GO software include: the selection of appropriate search database, frequency and identity coverage of blast

results along with the extension of the query-hit match, validity of the annotations that had been transferred with the involvement of motif annotation. Gene ontology terms, enzyme codes (EC), InterPro IDs, and KEGG pathways are the specific vocabularies that are supported by the Blast2GO software [12].

RESULT AND DISCUSSION

Cesium interaction network

Cesium being abundant in the form of cesium chloride, an interaction network for this purpose was established on the basis of evidence derived from experiments, databases and literature mining by STITCH 4.0. It identified 10 potential targets of our desired molecule as well as some potential protein-protein interaction among these target proteins. The proteins found to interact with cesium chloride along with their respective functions and interaction scores are listed in table 1 which is shown below.

Table 1. List of interacting proteins with CsCl detected through STITCH 4.0 along with their brief description.

Interacting proteins	Short descriptions	Interaction Score
GNAI1	Guanine nucleotide binding protein (G protein)	0.929
FTL	Ferritin, light polypeptide	0.907
KDR	Kinase insert domain receptor	0.907
DYNLRB1	Dynein, light chain, roadblock-type 1	0.900
VEGFC	Vascular endothelial growth factor C	0.900
POLB	Polymerase (DNA directed), beta	0.900
GRIK1	Glutamate receptor, ionotropic, kainate 1	0.865
ACY3	Aspartoacylase (aminocyclase) 3	0.853
KCNJ6	Potassium inwardly-rectifying channel, subfamily J, member 6	0.851
IGK	Immunoglobulin kappa constant	0.844

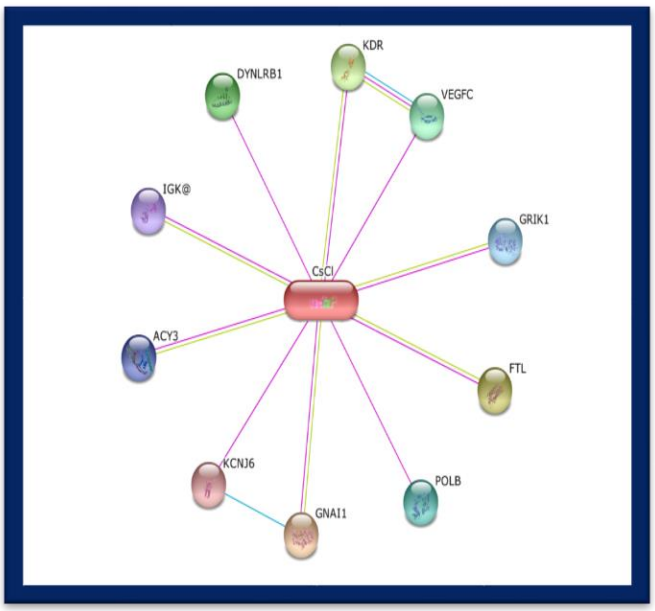

Figure 1. Interactions of CsCl with *Homo sapiens* protein targets detected through STITCH 4.0.

Strong interactions as indicated by the high scores for the respective ligand-protein binding were found. Additionally, a relatively strong protein-protein interaction between the proteins KDR and VEGFC was predicted on the basis of thicker lines linking the respective proteins.

Protein-Protein Interaction study

STRING 9.1 revealed the protein-protein interaction between the proteins interacting with cesium and other human proteins. Protein-protein interactions which are pivotal for the proper maintenance of any cellular function and the properties of proteins are often rigorously affected by the nature of the other proteins with which it interacts[13]. Since the biology of human system is

so complex where it works based on the interaction rather than direct targeting of molecular, we looked for interacting proteins of human origin based on primary targets. From this protein-protein interaction (PPI) study, we have identified a total of 99 interacting molecules to interact with the selected proteins. The list of these 99 proteins along with their NCBI accessions and number of constituent amino acid residues is provided in Supplementary Table 1. Figures 2, 3 and 4 depict the interaction between each of the 10 individual proteins interacting with cesium and the other human specific proteins.

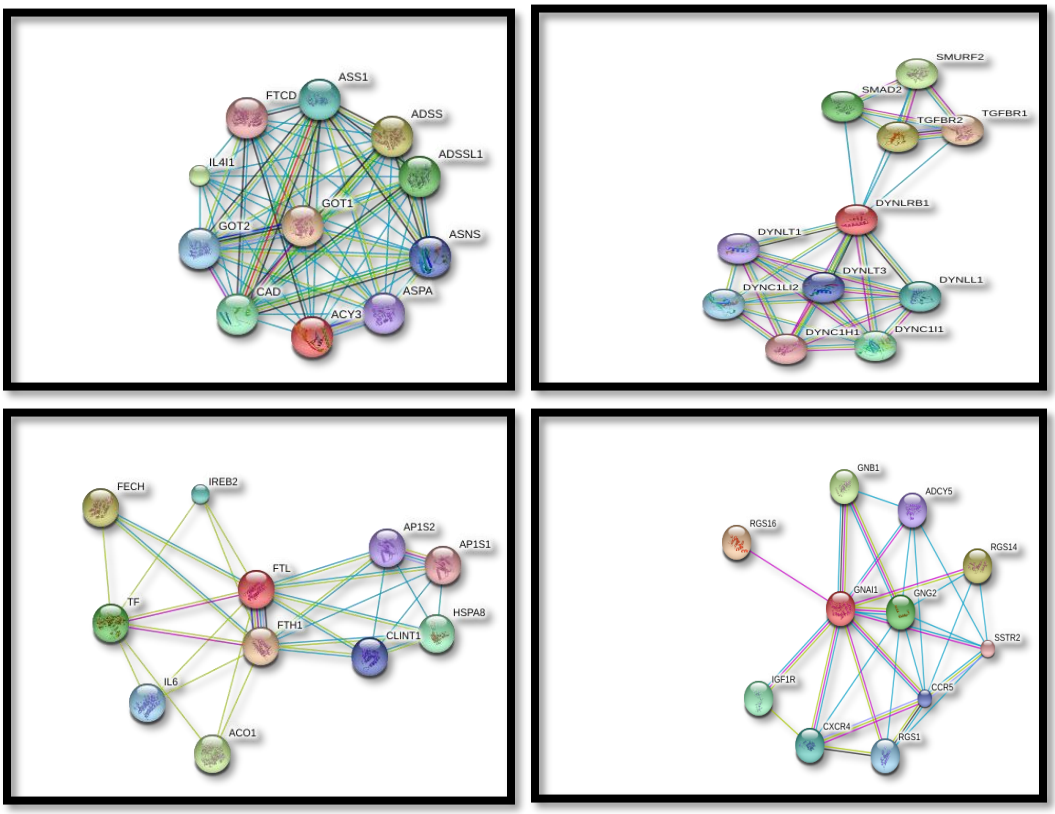

Figure 2. Interaction of the proteins ACY3 (top-left), DYNLRB1 (top-right), FTL (bottom-left) and GNAI1 (bottom-right) with other human specific proteins.

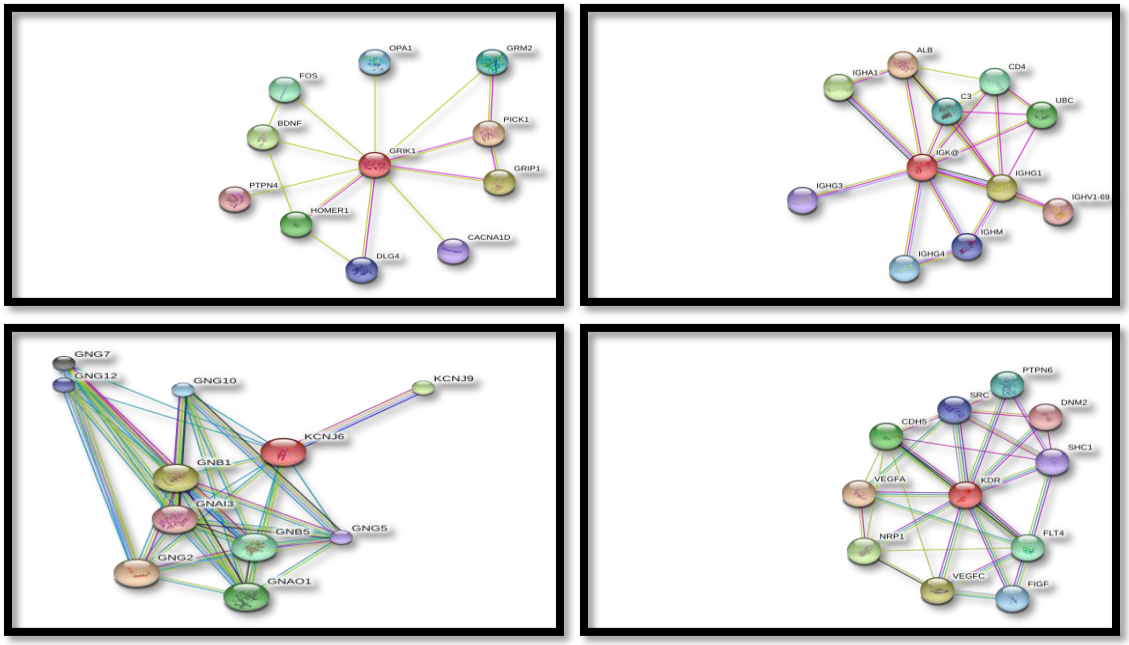

Figure 3. Interactions of the proteins GRIK1 (top-left), IGK (top-right), KCNJ6 (bottom-left) and KDR (bottom-right) with different human proteins

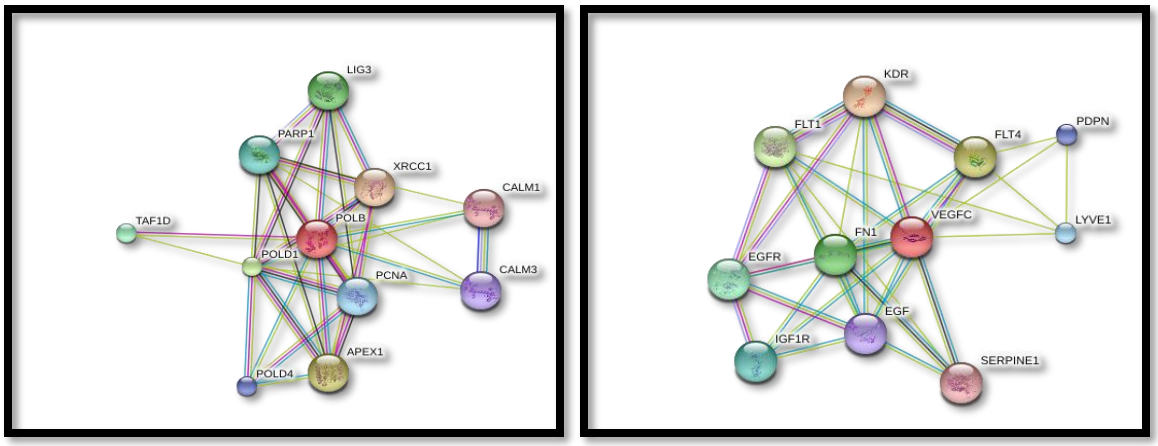

Figure 4. Interactions of proteins POLB (left) and VEGF (right) with different human proteins.

Functional annotations of the proteins

Gene Ontology (GO) is referred to as being an international standard classification system for gene function, which provides a set of specified vocabulary intended for the intensive description of the property of genes and gene products. In our study, the characterization of the proteins interacting with cesium and other human proteins with which they are involved protein-prtoein interactions, information about the molecular functions of these proteins, the cellular component they occupy and their corresponding biological functions had been elucidated. Figure 5 shows a graphical representation of the various biological functions of these proteins.

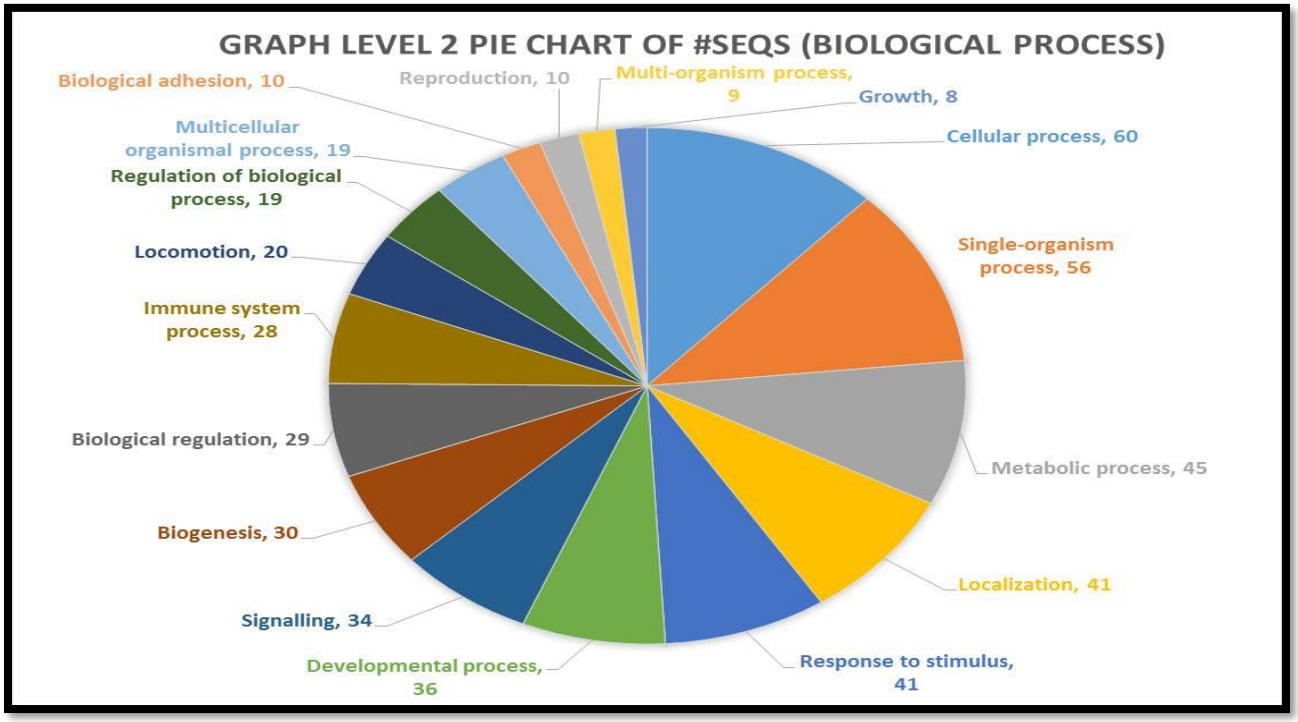

Figure 5. Graphical representation of the different biological processes with which these proteins are involved. The area occupying a greater proportion in the pie chart indicates the prevalence of those particular functions and vice versa. Hence, the biological function of being involved with various cellular processes is the most distinct while the biological process of growth is the least noticeable.

Figure 6 and 7 project cellular components they occupy and the molecular functions of these proteins , respectively.

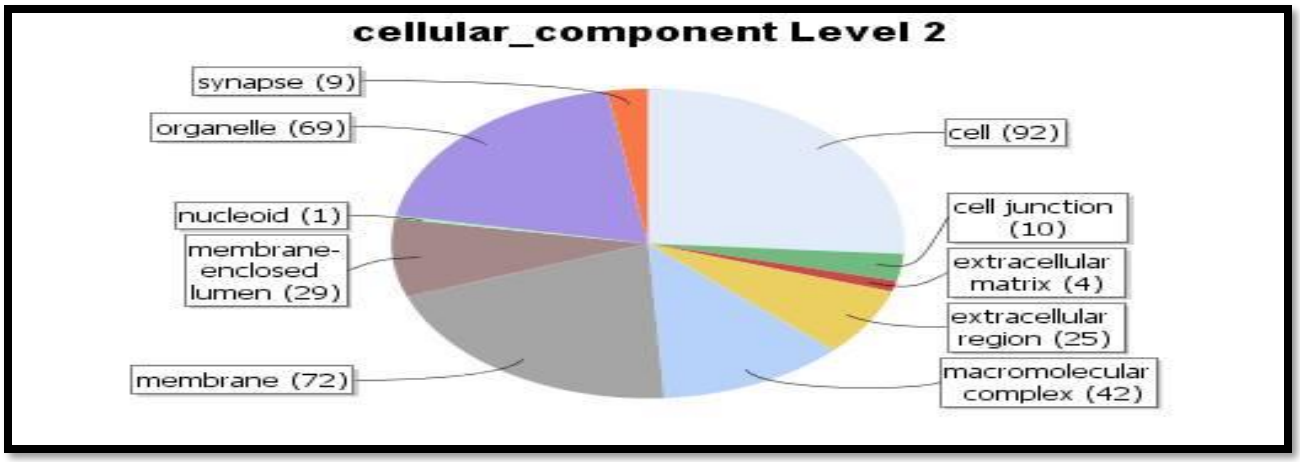

Figure 6. Graphical representations of the different cellular components localized by the proteins. Majority of the proteins are seen to occupy the regions within the cell and regions on the cell membrane, while least number of proteins are seen to occupy the extracellular matrix and the nucleoid regions.

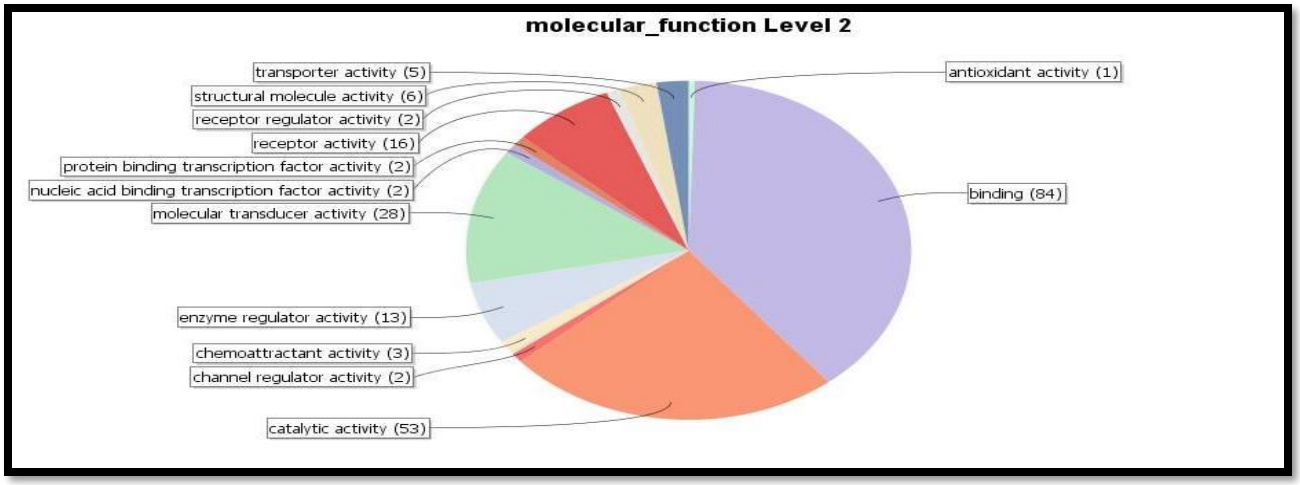

Figure 7. Graphical representation of the various functions exhibited by the proteins. Functions such as: binding and catalytic activity are the most predominant while the function of antioxidant activity is the least prominent.

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CONCLUSION

In our present study, we have identified some proteins of human body which are interacted with cesium. We found total 99 proteins by applying different bioinformatics tools and all of these proteins are directly and indirectly affected by cesium in human health. We could not mention here about the common functions of these proteins and further study is needed to characterize all of these proteins. Intriguingly, our study revealed that cesium can interact with some proteins that have potential cellular, molecular and biological functions. Our study clearly revealed that cesium might bring some life threatening non-contagious diseases to human body. Bangladesh is an overpopulated country and the industrialization has been increasing day by day. As a result, the industrial area is becoming water, soil and air polluted with some metals like the cesium. We should take the awareness and necessary steps to keep free of our evergreen environment. We should need to take necessary actions to keep pollution free in our environment.

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Supplementary Table 1. List of interacting proteins by STITCH 9.1 for collecting sequences

Target proteins	NCBI accession	Amino acid residues
RGS16	O15492	202
RGS14	O43566	566
GNB1	CAG33065	340
GNG2	NP_001230703	71
IGF1R	NP_000866	1367
CXCR4	NP_001008540	356
RGS1	Q08116	209
CCR5	AAB57793	352
ADCY5	O95622	1261
SSTR2	NP_001041	369
FTH1	AAH66341	183
FECH	NP_001012533	429
ACO1	NP_001265281	889
TF	AIC55219	698
HSPA8	EAW67540	646
IREB2	NP_004127	963
IL6	CAG29292	212
CLINT1	NP_001182484	643
AP1S2	NP_003907	157
AP1S1	NP_001274	158
VEGFA	NP_001020537	412

VEGFC	AAX43222	420
NRP1	NP_003864	923
CDH5	P33151	784
FLT4	NP_891555	1363
PTPN6	NP_536859	624
FIGF	O43915	354
SRC	NP_938033	536
SHC1	NP_001123512	584
DNM2	NP_001005361	870
TGFBR1	P36897	503
TGFBR2	NP_001020018	592
SMURF2	NP_073576	748
SMAD2	AAC39657	467
DYNC1I1	NP_004402	645
DNYLL1	NP_001032584	89
DYNC1LI2	O43237	492
DYNLT3	NP_006511	116
DYNLT1	P63172	113
DYNC1H1	NP_001367	4646
KDR	NP_002244	1356
FLT4	NP_891555	1363
FLT1	EAX08432	1338
FN1	NP_997647	2477
EGFR	NP_005219	1210
IGF1R	NP_000866	1367
LYVE1	NP_006682	322
PDPN	NP_006465	238
EGF	NP_001954	1207
SERPINE1	P05121	402
XRCC1	CAG33009	633
APEX1	NP_001231178	318
POLD1	NP_001243778	1107
LIG3	NP_039269	1009
TAF1D	AAH01972	278
PARP1	NP_001609	1014
PCNA	CAG46598	261
POLD4	NP_066996	107
CALM3	EAW57426	149
CALM1	NP_008819	149
PICK1	BAA89294	415

GRIP1	NP_066973	1076
BDNF	NP_001137282	329
HOMER1	NP_004263	354
FOS	CAG47063	380
GRM2	NP_000830	872
OPA1	NP_570849	997
DLG4	NP_001356	767
CACNA1D	NP_000711	2181
PTPN4	P29074	926
GOT1	AAC32851	413
ADSS	NP_001117	456
IL4I1	NP_001244947	589
ADSSL1	NP_954634	500
CAD	NP_004332	2225
ASS1	NP_000041	412
GOT2	EAW82989	430
ASNS	NP_899199	561
ASPA	CAG46706	313
FTCD	NP_996848	541
ALB	NP_000468	609
IGHG1	AAA70227	237
IGHA1	CAC20453	353
UBC	NP_066289	685
CD4	NP_000607	458
C3	NP_000055	1663
IGHG4	CAC20457	327
IGHM	NP_001269071	470
IGHG3	CAC10247	362
IGHV1-69	CEF92754	117
GNG2	NP_001230703	71
GNB1	CAG33065	340
KCNJ9	AAF89098	393
GNAO1	NP_620073	354
GNB5	O14775	395
GNG7	NP_443079	68
GNG10	NP_001185593	68
GNG12	EAX06486	72
GNG5	NP_005265	68
GNAI3	NP_00647	354