Original Article

Protein-Protein Interaction Network Study Reveals New Possible Endocrine Disrupting Chemicals (EDC) ‘ Impact on Retinoblastoma

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Abstract:

Background: Retinoblastoma (RB) is a retinal-derived embryonic tumor. The illness severity at the time of presentation affects survival and preserves eyesight. The purpose of this research is to find Retinoblastoma causing genes and EDCs that control gene expression. To uncover genes linked to Retinoblastoma , We utilized the GEO database and a string database to rebuild the protein-protein interaction network. Then, using Cytoscape and the Clusterviz plugin, modules are explored. We utilize the Comptox database to find potential Endocrine Disrupting Chemicals (EDC) then we introduce high-degree EDCs in this network. These findings might aid researchers in better understanding melanoma.

Material and Methods: To further understand retinoblastoma etiology and uncover possible Endocrine Disrupting Chemicals(EDCs), we looked at differential gene expression in retinoblastoma and normal samples. Then we choose differentially expressed genes (DEGs) with an adj P value of less than 0.01. The STRING database was used to create the protein-protein interaction network, which was then presented using the Cytoscape and the Clusterviz plugin was used to explore the modules. The genes in the modules were then investigated for GO and pathway enrichment. EDC-gene interactions for each module’s genes were gathered and reconstructed as a single EDC-gene network.Key words:Retinoblastoma, Protein Protein Interaction Network, systems biology, Endocrine Disrupting Chemicals.

Results: In Retinoblastoma, 347 putative EDCs were discovered to influence gene regulation. The EDC that affects five genes is ethanolamine. For the first time, these EDCs have been suggested as new possible compounds for preventing Retinoblastoma and should be investigated further in clinical trials.

Conclusion: Ethanolamine is a high degree EDC in our network. However, the findings should be experimentally validated to produce better prevention.

Keywords: PPI; Retinoblastoma; EDC; Network.

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Introduction

Retinoblastoma is an unusual childhood eye tumor that develops in the retina. With a frequency of 1/15,000–20,000 live births, it is the most prevalent intraocular cancer in infancy and childhood [1]. Despite a solid knowledge of the aetiology, retinoblastoma mortality remains over 70 % in poor and middle-income nations, where the majority of children are afflicted. Progress is hampered by the lack of public and medical knowledge and rigorous clinical studies to evaluate novel therapies [2]. The fact that retinoblastoma is a malignancy produced by two mutational events is established based on the data from 48 instances and publications. One mutation is transmitted through germinal cells, while the other arises in somatic cells in a dominantly inherited form. Both mutations occur in somatic cells in a nonhereditary form [3]. Retinoblastoma is the most prevalent childhood intraocular malignancy. It is caused by a mutation in the RB1 gene, which was the first discovered tumor-suppressor gene [4-6]. The loss of one RB1 allele in a developing retinal cell causes retinoblastoma tumor formation. Additionally, the loss of the other allele in a developing retinal cell leads to retinoblastoma tumor development. This prototypical cancer has changed the way people think about cancer. There are no confirmed geographic or demographic hotspots for the condition. Large populations with high birth rates, such as those seen in Asia and Africa, have the highest illness load [7]. Retinoblastoma, for example, is the most common eye tumor in Nigeria and one of the five most prevalent pediatric cancers [8, 9]. The most common clinical symptoms of retinoblastoma are leukocoria (white reflection in the pupil) and strabismus. Leukocoria is inconstant at first and observable only at specific angles. Under specific lighting circumstances, this sign can be observed on flash photography. When strabismus is present, it becomes increasingly constant, indicating visual impairment [10].

Endocrine-disrupting chemicals (EDCs) have been linked to a variety of health problems in recent years. Despite a considerable body of research on the specifics of EDCs in various sectors, public worry continues to grow and is exaggerated to some extent by the media. As a result, a thorough understanding of EDCs is required, including scientific findings from prior research and summaries of contemporary EDCs research trends [11-14]. Despite numerous documented cases, EDCs have received little attention due to the low concentrations of identified EDCs and the lack of information on their toxicological importance. On the other hand, some researchers regarded the drugs and drug metabolites to be pollutants in the environment [15]. The Endocrine Disruptor Screening Program (EDSP) was created by the US Environmental Protection Agency (EPA) to develop official screening techniques and toxicity testing procedures for roughly 87,000 chemicals. The European Organization for Economic Co-operation and Development (OECD) has also endeavored to establish a credible technique for confirming EDCs' importance [16]. EDCs are a group of natural and manufactured chemical compounds that imitate or impede the natural activity of the endocrine system in animals and humans, particularly when it comes to reproduction. The presence of trace amounts of EDCs and their variety in diverse aquatic habitats have been identified. EDC measurement and removal are hampered by these features [17].

Advance in systems biology has brought us a variety of analytical means. Many RNA-RNA, RNA-protein, and protein-protein interaction beside other macromolecules interactions in the cells; have been detected in the light of

systems biology method [18-22]. Proposing of the novel panels for early detection of diseases, drug discovery, analyzing signaling networks and metabolomics pathways, and repurposing drugs are attractive subjects in systems biology studies [23-28].

In this study, we reconstruct a network to discover the potential EDCs that may have an impact on Retinoblastoma. For this reason, we discover the genes related to Retinoblastoma and reconstruct the protein-protein interaction network using a string database. Then, modules are created using cytoscape software and clusterviz plugin. As a next step, we find potential EDCs using comptox database and create EDC-GENE network. Finally, we introduce a high degree EDC in this network. We hope these findings help researchers learn more about Retinoblastoma.

Material and Methods

Dataset and preprocessing

The GSE125903 accession number was used to find the expression data in the National Center for Biotechnology Information Gene Expression Omnibus (GEO). The data included valuable information about gene expression fusions, Long Non-coding RNAs, and RNA mutations. Before data preprocessing, non-protein-coding genes were deleted from the original file. ID-free genes were removed once the genes were mapped to their corresponding IDs. For further analysis, genes having adj P value of less than 0.01 were chosen. After preprocessing and eliminating outliers, we reached a sample of top 2000 genes with adj P value less than 0.01. For further investigation, we used all DEGs with adj P value less than 0.01. This dataset contain prepared data like FPKM and we use differential expressed genes to rebuilt PPI network. And DEGs were computed with deseq2 method.

Protein-Protein Interaction Network (PPIN)

Differentially expressed genes with an adj P value of less than 0.01 were chosen to construct the protein-protein interaction network using the STRING database v.11.0. The STRING database[1].brings together all known and anticipated protein-protein interactions, including both physical and functional ones. After that, the data was visualized using Cytoscape v.3.8.2 [2]. ClusterViz employs a variety of methods to carry out cluster analysis. The rapid agglomerate edge clustering (FAG-EC) method was used in this study. Due to its low complexity and high computing power, the FAG-EC method is helpful for analyzing huge protein networks. In this method, we selected the following parameters: Definition In/OutThreshold: 20, Overlapped, and Way: Strong. Finally, we discovered five distinct PPI clusters (i.e., PPI complexes).

We use FAG-EC as clustering algorithm.

Cytoscape is a free and open-source bioinformatics software platform for visualizing and integrating molecular interaction networks with gene expression patterns and other state data. Plugins provide additional functionality.

Gene ontology and pathway enrichment analysis

The modules were chosen for gene ontology (GO) and pathway enrichment analysis of the contained genes. DAVID v.6.8 [3] was used to analyze GO and Reactome pathways.

This open-source database with annotation, visualization, and integrated discovery

1 https://string-db.org/

2 https://cytoscape.org/

3 https://david.ncifcrf.gov/

capabilities (DAVID) is freely available to everyone. It is a web-based resource that enables functional gene/protein interpretation and can be a helpful tool for researchers and scientists.

EDC- Gene interaction network

We created the EDC- gene network for extracted genes after choosing the five most important sub-networks. The findings may be utilized to identify possible EDCs in Retinoblastoma patients. Candidate possible EDCs were suggested using the EDC Gene Interaction database. To find potential EDCs, we needed to build an EDC-gene network and thus used the Comptox dataset to find EDCs for each gene. The CompTox Chemistry dashboard (https://comptox.epa.gov/dashboard) offers a wealth of information on the toxicity of chemicals, their physicochemical features, human exposure, and in vitro bioassay data (agonist, antagonist, up-, and down-regulation) for a total of 883000 compounds (as of August 2020). The Chemical Safety for Sustainability Research Program at the US Environmental Protection Agency developed the CompTox Chemicals Dashboard as part of a series of databases and web applications. The EPA's computational toxicology research efforts to develop creative approaches to improve how chemicals are now evaluated for possible health concerns are aided by these databases and applications. To find critical biological processes that may be disturbed by the chemicals, EPA experts combine breakthroughs in biology, biotechnology, chemistry, and computer science. The combined data aids in the prioritization of chemicals based on their potential health hazards. Thousands of compounds may be examined for possible harm at little cost and in a short period of time using computational toxicology research methodologies.

Results

DEG in Retinoblastoma and normal cases

We analyzed the GSE125903 dataset its platform is Illumina HiSeq 2500 a next-generation sequencing method.to find a list of genes implicated in Retinoblastoma etiology. This dataset contains seven patients and three normal samples.We discovered 2000 significant DE genes (adj P value 0.01) when comparing gene expression levels in Retinoblastoma and normal cases. For identical gene symbols, the average expression was utilized (S1).Analyzing these genes revealed the number of up-and down-regulated genes. According to fold changes, 16649 genes are down-regulated, and 34990 genes are up-regulated.

Clustering and network analysis of the PPI

The PPI network of 2000 genes was obtained from the STRING database (figure 2, S2). Clustering analysis was used to identify highly interactive protein groups. Then, as illustrated in figure 2, five protein modules were discovered [Table 1] (figure 2, S3). We have a large network called PPIN, and some sections of this network is dense, and we want to investigate these areas, which are called modules.

Endocrine-disrupting chemicals (EDCs) identified as a gene activator

The comptox dataset was used to find EDCs that target module genes. In this case, modules genes were initially imported into the comptox dataset individually, and then EDC-gene interactions genes were found for the modules. After collecting EDC-gene interactions for all modules, the complete EDC-gene interactions

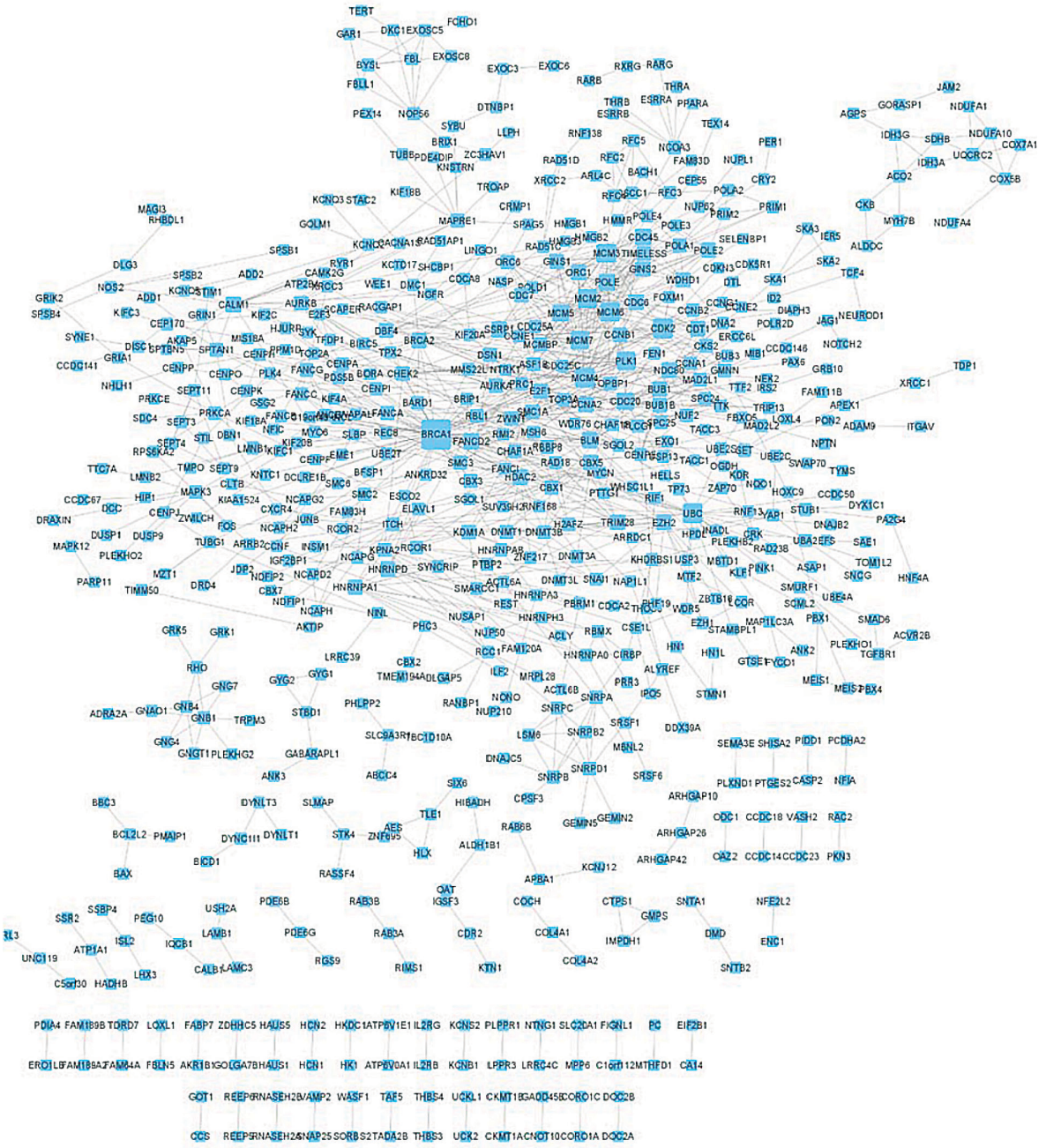

Figure 1: Protein-protein interaction (PPI) refers to the interaction between two proteins. Every node represents a protein, and the edges represent physical interactions that have been empirically verified

were collected and rebuilt as an EDC-gene network. Using this database, we found 347 EDCs for PPI modules (Fig3, S4). . However, no EDC was found for the genes in PPI modules. Then, the cytoscape (Version 3.6) was utilized to visualize these data through an EDC-gene network. Some genes have multiple EDCs in the EDC gene network. Some EDC also controls the expression of more than two genes. As a result, these EDCs play a critical role in the EDC-gene network.

Ethanolamine affects five genes (AURKA1, CDK2, NTRK1, KDR, GRIN1) and is a very potential EDC in our network.

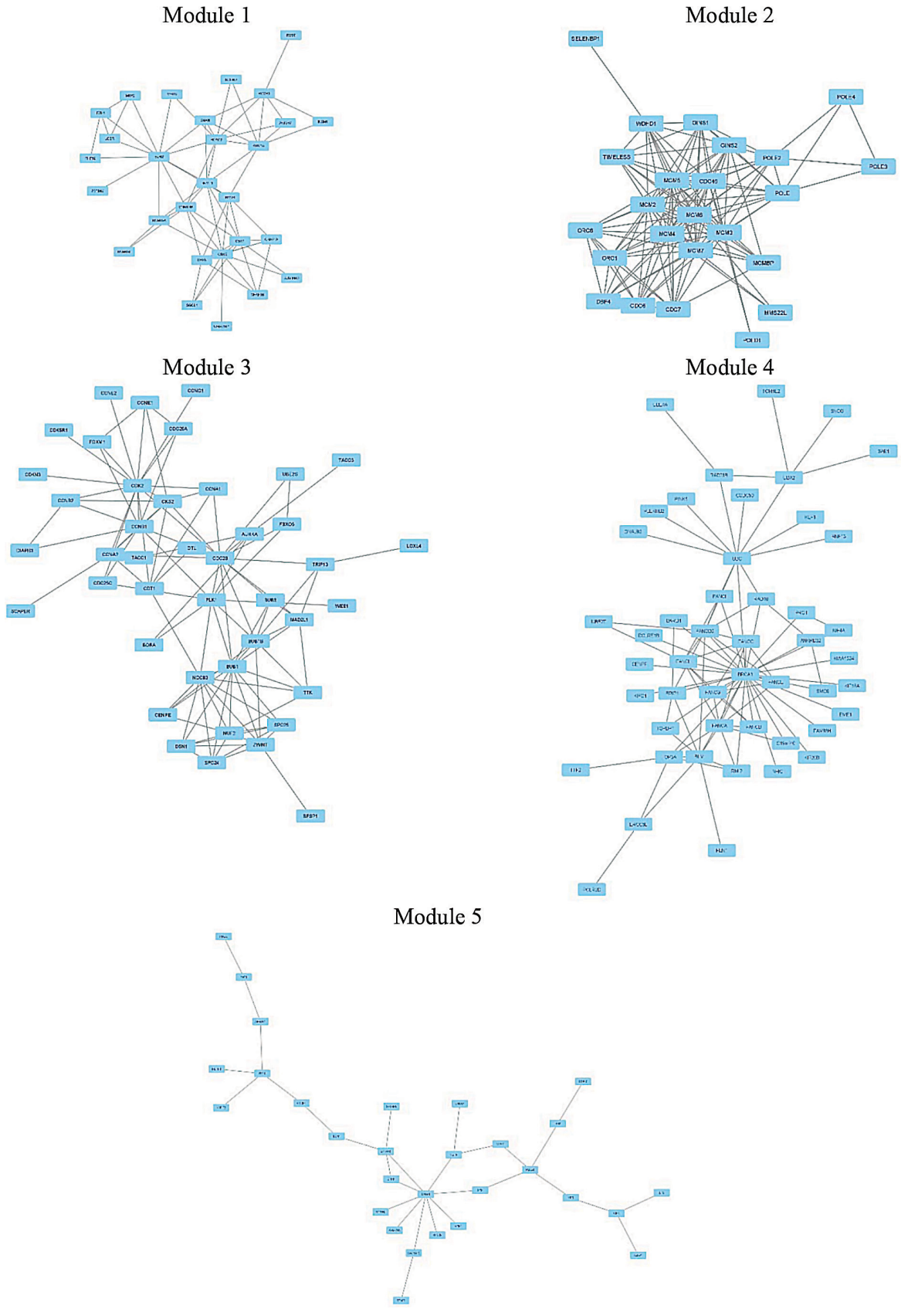

Figure 2: PPI modules were obtained using PPI networks

Table 1: List of each sub-network along with gene names

Cluster	Nodes	Edges	List of genes
1	28	68	DNMT3A, REST, KDM1A, WHSC1L1, EZH2, SNAI1, HDAC2, DNMT1, ZBTB16, SUV39H2, CHAF1B, DNMT3B, CBX3, INSM1, CBX1, CHAF1A, SGOL1, PHF19, LCOR, MTF2, TRIM28, EZH1, ZNF217, RCOR2, RCOR1, CBX5, MYCN, DNMT3L
2	131		MMS22L, POLE, GINS1, MCM4, CDC7, GINS2, ORC6, SELENBP1,
24			POLE2, MCM5, CDC45, ORC1, MCM3, TIMELESS, POLD1, MCM2, POLE4, CDC6, MCMBP, POLE3, WDHD1, MCM7, DBF4, MCM6
3	42	102	TACC1, CDC25A, CDKN3, PLK1, DIAPH3, BUB1B, CDC20, CDC25C, FOXM1, ZWINT, AURKA, BFSP1, CDK5R1, LOXL4, WEE1, SCAPER, CCNA2, CDK2, TRIP13, BUB3, CCNB1, UBE2S, SPC24, CKS2, CDT1, FBXO5, TTK, CCNA1, MAD2L1, SPC25, CCNG1, NUF2, CENPE, NDC80, CCNE2, BUB1, CCNE1, DTL, TACC3, DSN1, BORA, CCNB2
4	48	87	BLM, FANCI, DNAJB2, SMC6, UBC, KIAA1524, BRCA1, RAD18, FANCC, C19orf40, ANKRD32, TTF2, TOM1L2, NFIC, KIFC1, UBE4A, PLEKHB2, KIF18A, FANCL, UBA2, RAD23B, BRIP1, FANCB, PRC1, PINK1, EME1, FAM83H, FANCE, FANCG, CCDC50, TOP3A, KLF1, KIF4A, FANCA, SAE1, UBE2T, RNF13, BARD1, KIF20B, DCLRE1B, ERCC6L, CENPF, RMI2, FEN1, POLR2D, FANCD2, SNCG, TOPBP1
5	29	30	SPTAN1, NDFIP2, NDFIP1, ATP2B4, IRS2, GRB10, NTRK1, KDR, PLCG1, EFS, LINGO1, RYR1, GRIN1, CRK, ASAP1, SPTBN5, SYK, YAP1, ARRDC1, KCNQ5, ITCH, CAMK2G, CALM1, NGFR, INADL, STAC2, CACNA1S, DBN1, CXCR4

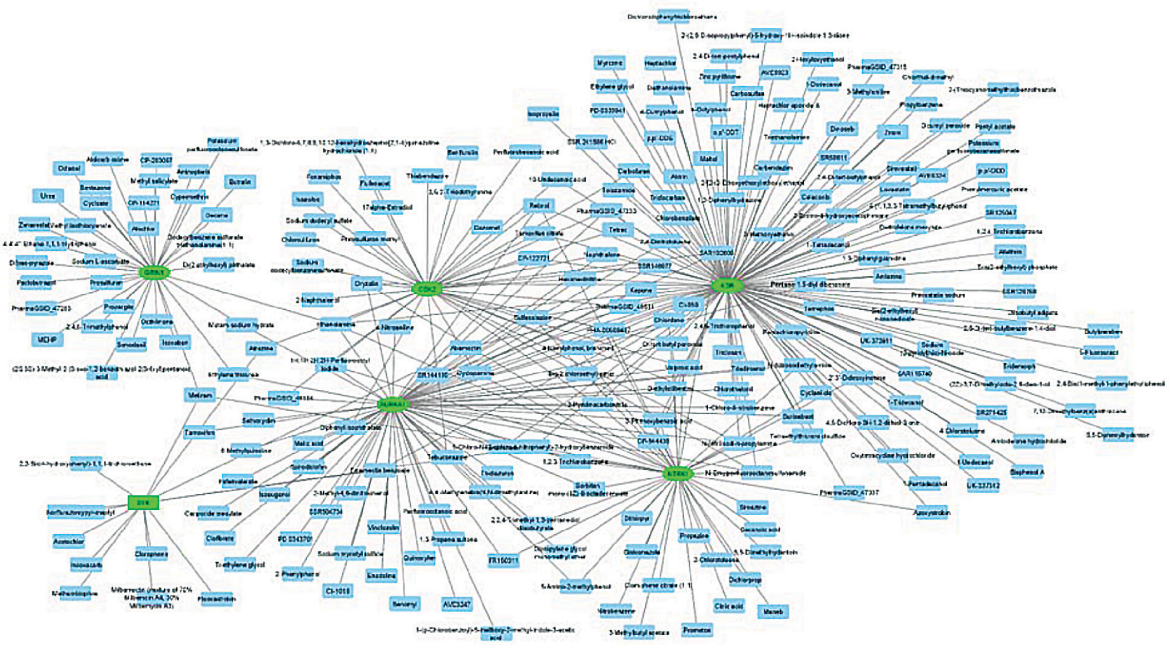

Figure 3: EDC-Gene Interaction Network. The blue round rectangles and green Ellipse nodes are EDCs and PPI module genes, respectively

Table 2: List of EDCs and their interaction with related genes

EDC \ GENE	AURKA1	CDK2	NTRK1	KDR	GRIN1	SYK
Ethanolamine	+	+	+	+	+	-
N-Nitrosodi-n-propylamine	+	+	+	+	-	-
Sulfasalazine	+	+	+	+	-	-
Valproic acid	+	+	+	+	-	-
Oryzalin	+	+	+	+	-	-
Di-tert-butyl peroxide	+	+	+	+	-	-
3-Pyridinecarbonitrile	+	+	+	+	-	-
4-Nonylphenol, branched	+	+	+	+	-	-
N-Ethylperfluorooctanesulfonamide	+	+	+	+	-	-
5-Chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide	+	-	+	+	-	+
Cyclopamine	+	+	+	+	-	-
PHA-00568487	+	+	+	+	-	-
Chlordane	+	-	+	+	-	-
1-Chloro-4-nitrobenzene	+	+	-	+	-	-
Naphthalene	+	+	-	+	-	-
N-Nitrosodiethylamine	+	-	+	+	-	-
3-Phenoxybenzoic acid	+	-	+	+	-	-
Fenaminosulf	+	-	+	+	-	-
CP-122721	+	+	-	+	-	-
CP-544439	+	-	+	+	-	-
PharmaGSID_47333	+	+	-	+	-	-
SSR146977	+	+	-	+	-	-
SAR102608	+	+	-	+	-	-
1H,1H,2H,2H-Perfluorooctyl iodide	+	+	+	-	-	-
PharmaGSID_48511	+	+	-	+	-	-
MetiramMetiram	-	-	+	-	+	+

Ethanolamine is the greatest degree of the EDC node, according to Figure 4 and Table 2. The organic chemical compound ethanolamine (2-aminoethanol, monoethanolamine, ETA, or MEA) has the HOCH2CH2NH2 (C2H7NO) formula [29]. The ethylene oxide reaction to aqueous ammonia generates monoethanolamine, diethanolamine, and triethanolamine. The stoichiometry of the reactants may be used to regulate the product ratio [30].

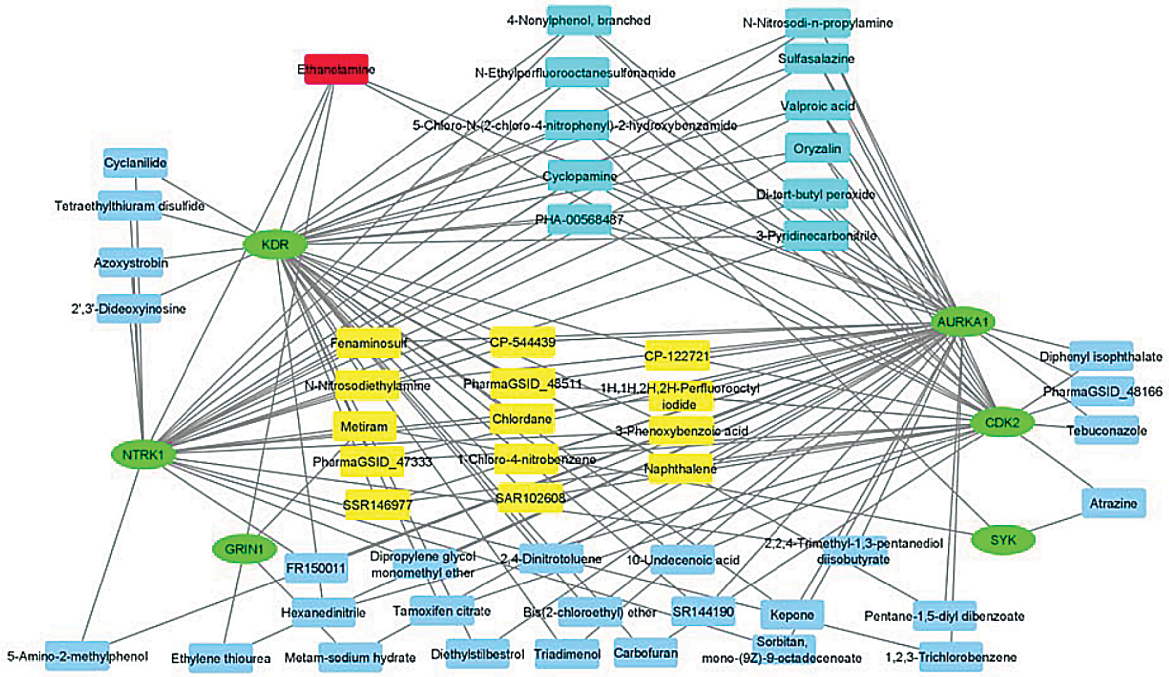

Figure 4: EDC-Gene Interaction Network. The red round rectangles refer to the EDC that affects five genes. The cyan round rectangles refer to the EDC that affects four genes. The yellow round rectangles refer to the EDC that affects three genes. The round blue rectangles refer to the EDC that affects two genes

Gene ontology and pathway enrichment analysis

The DAVID system was used to investigate the biological roles of the genes in clusters at a cellular level. Supplementary file S5 contains the findings of the GO enrichment analysis. According to this file, the most significant terms for PPI modules 1-5 were a structural constituent of cell cycle process, mitotic cell cycle process, DNA metabolic process, cell cycle phase transition, chromosome organization, DNA replication, organelle fission, and cell and nuclear division, respectively.

PPI-modules 1-5 were subjected to a pathway enrichment study using the Reactome. The significant pathways for all four PPI modules are listed in supplementary file S6.

Discussion

We conducted this comprehensive study on retinoblastoma patients and normal groups to identify additional possible EDC for retinoblastoma and better understand the disease's etiology. Based on the findings, 2000 genes were consistently and differently expressed in retinoblastoma and normal cases (with an adj P value of less than 0.01) in both investigations. PPI network analysis was used to find genes that were differentially expressed in Retinoblastoma and normal samples. Then, for further investigation, five protein clusters were identified as complexes of proteins that are more closely linked to Retinoblastoma. The main goal was to find new prospective candidate EDCs for gene regulatory control in Retinoblastoma. Ethanolamine was one of the EDCs found to be linked to five genes in the

EDC- gene network after reconstruction.

Mutational inactivation of both RB1 gene alleles, which map to chromosome 13q14 and encode the tumor suppressor retinoblastoma protein, causes retinoblastoma [31]. Rb is a tumor suppressor oncogene that controls the cell cycle via intricate interactions of numerous kinases and inhibitors on the Rb pathway. Rb activity is activated in the absence of mitogenic cues to prevent cell-cycle progression by inhibiting transcription of the genes needed for S-phase entrance [32, 33].

As shown in Figures 4 and 2, ethanolamine is the more prevalent case in the EDC node. Ethanolamine (2-aminoethanol, monoethanolamine, ETA, or MEA) is a biologically occurring organic molecule with the HOCH2CH2NH2 (C2H7NO) formula [18]. Ethanolamine (EA) provides bacteria with carbon and/or nitrogen to process. The digestive tract, owing to its membrane-rich composition, has higher concentrations of phosphatidylethanolamine (PE). PE is also found in tissues that have membranes rich in phospholipids [34]. In human Y79 retinoblastoma cells, the impact of ethanolamine physiological amounts on choline absorption and incorporation into phosphatidylcholine was studied in a multipotential-undifferentiated retinal cell line (which has maintained many neural features) [35]. Human Y79 retinoblastoma cells, a cultivated cell line of retinal origin that maintains many neural features, were used to study phospholipid production. Ethanolamine is taken up by Y79 cells and used to generate ethanolamine and choline phosphoglycerides through a high-affinity transport mechanism [36].

Conclusion

This study compared 2000 DEGs in Retinoblastoma to normal samples and revealed several disparities. Retinoblastoma genes were found using a network of protein-protein interactions. The resulting network was based on PPI modules genes and EDC-gene interactions. In this study, we used a computational approach and limited experimental resources. Thus, future studies should verify the validity of these EDCs in vitro and in vivo in clinical and experimental trials. Although computational methods are effective for preventive objectives, experimental validation and EDC toxicity tests are necessary to obtain an improved therapy. Future research on retinoblastoma may benefit from the EDCs suggested in this paper.

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Footnotes and Financial Disclosures

Conflict of interest

The authors have no conflict of interest with the subject matter of the present manuscript.