Original Article

Identification of Potential Biomarkers and Treatment Targets in Retinal Detachment

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Abstract

Background: Retinal detachment (RD), separation of the neurosensory retina away from its underlying layer of support tissue (retinal pigment epithelium), can be a severe eye condition that affects on vision and can lead to blindness if not treated. Understanding the pathological mechanism of RD help us to the treatment of RD patients.

Material and Methods: In this study, the gene expression profile was downloaded from the GEO database and were analyzed in the samples of patients with RD and control cases. Then, the STRING online database was used for the reconstruction protein-protein interaction network, and then the important signaling pathways and critical biomarkers involved in RD were assessed by resulting network analysis and extraction of functional modules. Furthermore, we used the miRWalk online database to extract miRNAs related to identified genes. Finally, the DGIdb online database was used for extracting drug-target interactions.

Result: We extracted differentially expressed genes (DEGs) using the independent t-test with adj.P.Val<.05 and |log2-fold change|>=2. So, 196 DEGs were obtained for RD (36 and 160 genes were identified as down and upregulated genes, respectively). There is significant evidence that activation of the phototransduction cascade, interferon signaling, immune response, and cytokine signaling in the immune system are involved pathways that have a significant role in RD. as well as our finding indicates that up-regulation of HLA-C, HLA-A, HLA –B and HLA –E involved in the inflammatory response and C1QA, C1QB the members of the complement pathway are strictly correlated with RD. Subsequently, the PPI network was extracted from STRING. This network showed 196 genes and 183 interactions and alsoextracted three functional modules from the PPI network. Then, we used the miRWalk database and extracted 30 miRNAs. Finally, we proposed three miRNAs for the treatment of RD.

Conclusion: Our results indicate activation of some inflammatory signaling and cell death in RD. Hence, we suggested some mRNAs,miRNAs, and drugs as potential biomarkers and therapeutic targets in RD.

Keywords: Retinal Detachment; System Biology; Biological Networks.

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Introduction

Retinal detachment is a disorder of the eye in which the retina peels away from its underlying layer of support tissue, resulting in a gradual degeneration of photoreceptor (PR) cells [1]. If not treated, it will lead to blindness [2].

RD occurs when the adhesion forces between neurosensory retinal detachment (NSR) and retinal pigment epithelium (RPE) are affected. The accumulation of fluid under the retina is a common feature that is involved in all types of RD [3, 4].

There are four major types of RD including: 1-Rhegmatogenous retinal detachment (RRD): a break in the retina leading to penetration under the vitreous retina identifies the most common type of RD [5], 2-Traction retinal detachment (TRD) [6], exudative, 3-Transudative or serous retinal detachment (SRD): a very rare RD serous, due to inflammatory or exudative conditions of the retina [7], and 4-Combined traction-rhegmatogenous retinal detachment (TRRD) [8, 9].

RD has been treated with surgery so far [10]. However, despite retinal reconnection after surgery, in many cases, it has been associated with vision loss or severe vision loss due to loss of photoreceptor cells [11]. Within a few days, retinal regeneration and apoptosis occur [12]. RD causes pronounced stress to PR cells, resulting in their eventual death [13]. In addition to the loss of photoreceptors, an inflammatory response occurs during RD that leads to proliferative vitreous retinopathy (PVR), a clinical consequence of the formation of contractile cell membranes at both the retinal and vitreous levels [14]. PVR associated with severe RD involves both inflammatory and immune responses, so we can say that immune response and the death of photoreceptor cells play significant role in RD [15].

Several studies have documented that in addition to activating innate immune responses in RD, high levels of cytokines and growth factors have been observed in the vitreous of RD patients [16].

Among the various mechanisms of cell death in RD-related photoreceptor death,such as mediated by the intrinsic pathway, the complement system, the immune response, and endoplasmic reticulum stress-mediated cell death, programmed necrosis and cytokine signaling in the immune system were mentioned [12, 17].

Systems biology is a multidisciplinary field focusing on complex interactions within biological systems [18-21]. It uses the computational and mathematical analysis and modeling of complex biological systems [22]. Hence, we used systems biology approaches to identify new potential pharmacological targets and molecular mechanisms of RD.

In this study, the gene expression dataset was downloaded from the GEO database [23], then we extracted DEGs between control and RD samples. Furthermore, the STRING [24] online database was used to reconstruct protein-protein networks. Subsequently, the critical functional modules related to signaling pathways and key biomarkers involved in RD were identified, and candidate miRNAs and drugs were proposed for the treatment of RD. So, in this study, bioinformatics analyses were used to identify some biomarkers that could be used efficiently in combination with surgery to improve further and final outcome [23-26].

Material and Methods

Dataset Collection

A microarray experiment is used to evaluate the difference in gene expression in both control and RD states. In this study, the microarray experiment is not done experimentally.

Therefore, gene expression omnibus (GEO) database has been used to extract the preliminary data from microarray. The expression of genes extracted from GSE28133 about 38 surgical specimens (samples) was analyzed, 19 represent biopsies from patients with retinal detachment (RD) and 19 represent control samples without retinal detachment [15]. The experiment type was expression profiling by array, and the platform accession number for this analysis was GPL570 (Affymetrix human genome U133 plus 2.0 array).

Differential expressed genes (DEGs) Analysis

In this study, we used the Affymetrix gene chip system as a commercial microarray platform that allows whole genome gene expression analysis for a wide variety of experimental organisms, and also the robust multi-array average expression measure (RMA) package in R was used for normalization of raw data. In this study, the raw data of GSE28133 consists of 38 samples, and the data related to GPL570 with 54675 rows were downloaded. In this study, the"Limma" R package from the bioconductor project was used to identify differentially expressed genes between control and RD samples, then differentially expressed genes (DEGs) were detected by using the independent t-test with adj.P.Val<.05 and log2-fold change (log2FC) absolute value greater than 2 and less than -2 (The common criteria for LogFC is equal to 1).

Protein-Protein Interaction (PPI) Network

Intracellular biological networks typically consider multiple interactions and molecular components within a cell. A network is a set of nodes and a set of directed or undirected edges between the nodes, which can help to understand how cellular behaviors by the connection between the molecules. Different types of mathematical structures called graphs can demonstrate intracellular molecular biological networks.

In this study, human-specific interactions of protein-protein interaction (PPI) were obtained from Search Tool for the retrieval of interacting genes/proteins (STRING) (version 11. 0) with considering parameters such as experiments and databases and also 0.9 for the minimum required interaction score.

Moreover, the list of interacting genes/proteins obtained from STRING was imported in Cytoscape (v.3.9.1) for extracting, visualizing, and analyzing the data [27]. Molecular components in this generated network are demonstrated as nodes, and the interactions between these nodes as edges. Then the network analyzer, a plugin in Cytoscape, was used for topological analysis and interactive visualization. Also, to identify functional modules within the network, a Cytoscape plugin, called cluster maker, was used. This plugin provides different algorithms such as K-means was used for performing cluster analysis to identify modules in the network [28].

Enrichment analysis

To identify the best and key cluster from the 3 proposed clusters, we used a gene ontology approach based on 4 categories, including biological process, pathway, drug-gene associations, and disease. So, GO enrichment analysis of the modules genes was performed by using the Toppgene database (https://toppgene.cchmc.org/) [29].

Identification of human gene-disease associations

In this study, we used the DisGeNET database for the extraction of human gene-disease associations [30] and the genes of each module were checked for disease with the DisGeNET

Table 1: Dataset. Demographic features of Individuals in the study

Transcriptomic Analysis of Human Retinal Detachment Reveals Both Inflammatory Response and Photoreceptor Death				
GSE28133				
Source name	Organism	Sample type	Number of sample	Total RD duration
control	Homo sapiens	RNA	19	0 weeks
retinal detachment	Homo sapiens	RNA	19	3weeks-1 year

database.

Identification of miRNA-mRNA network

miRWalk (http://mirwalk.umm.uni-heidelberg.de) is an open-source online database that generates validated and predicted miRNA of known genes of human and some species. We used mirWalk to extract miRNAs, in other words, we entered 196 DEGs as input, then obtained miRNAs that interacted with these DEGs. Finally, the miRNA-mRNA bipartite network was drawn using cytoscape.

Identification of drug-target network

The Drug-Gene Interaction Database (DGIdb) (www.dgidb.org) is an online database that generates information on drug-gene interactions from sources, including publications, databases, and other web-based resources. We used DGidb to extract drugs of candidate module genes.

Results

Normalization

As mentioned above, the raw data of GSE28133 consists of 38 samples, and data related to GPL570 with 54675 rows were downloaded (Supplementary Files 1 and 2). The information about data of GSE28133 composed of 38 samples is presented in Table 1. As well as RMA package was used for

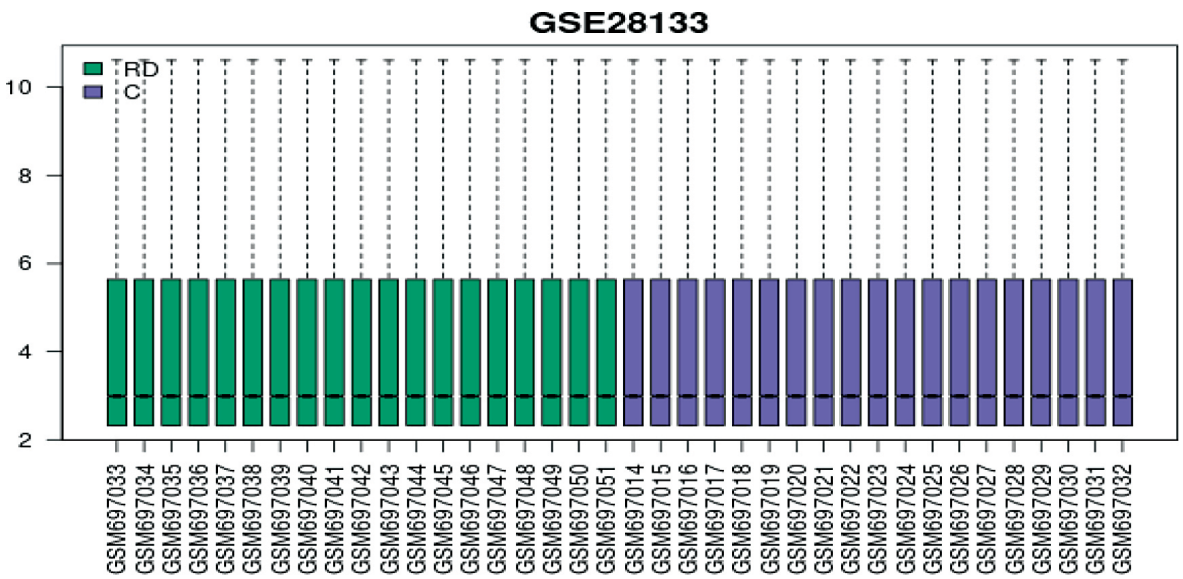

Figure 1: Post-normalized gene expression box plots. The plot shows data after log transform and normalization. The horizontal axis represents the samples which colored according to groups and median-centered values are indicative that the data are normalized and cross-comparable

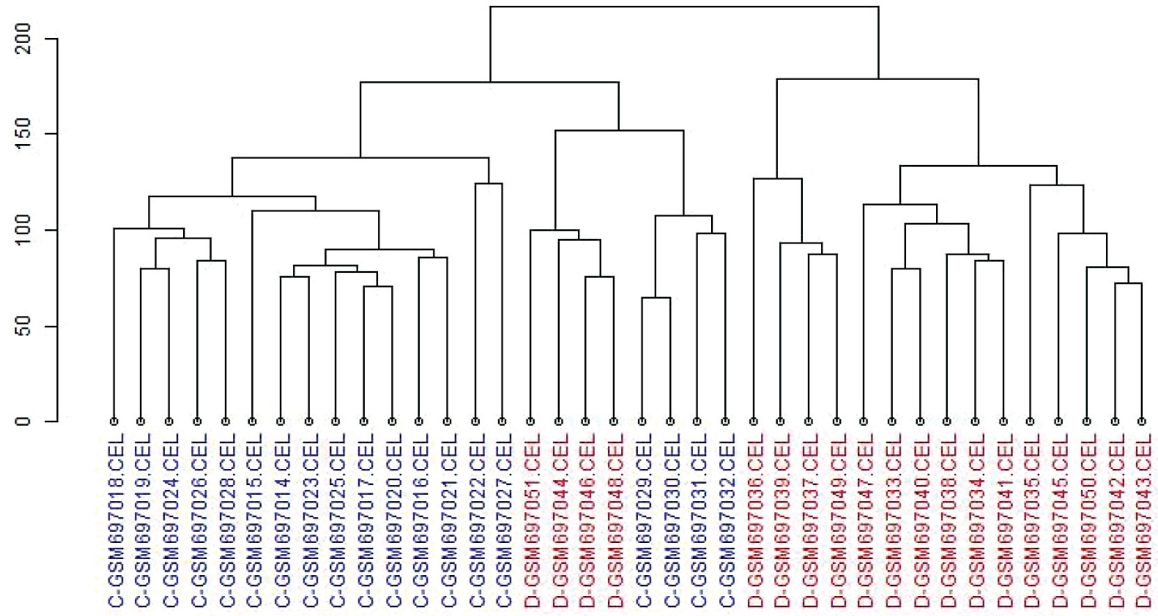

Figure 2: The hierarchical clustering of the RD and control samples. Blue and red samples represent control and RD samples, respectively

the normalization of the raw data, which is provided in supplementary file 3. In the next step, the boxplot, and hierarchical clustering plots were used for quality control (QC) of data. These plots can help toassess normalization status and sample groupings, they can help to determine the suitability of the study for further analysis and whether to apply any adjustments to the test. Quality control (QC) plots for the raw dataset (GSE28133) shows that RD and control samples are in the normal range, and there is no outlier data.

Boxplot was used to view the distribution of the values of the selected samples. All selected

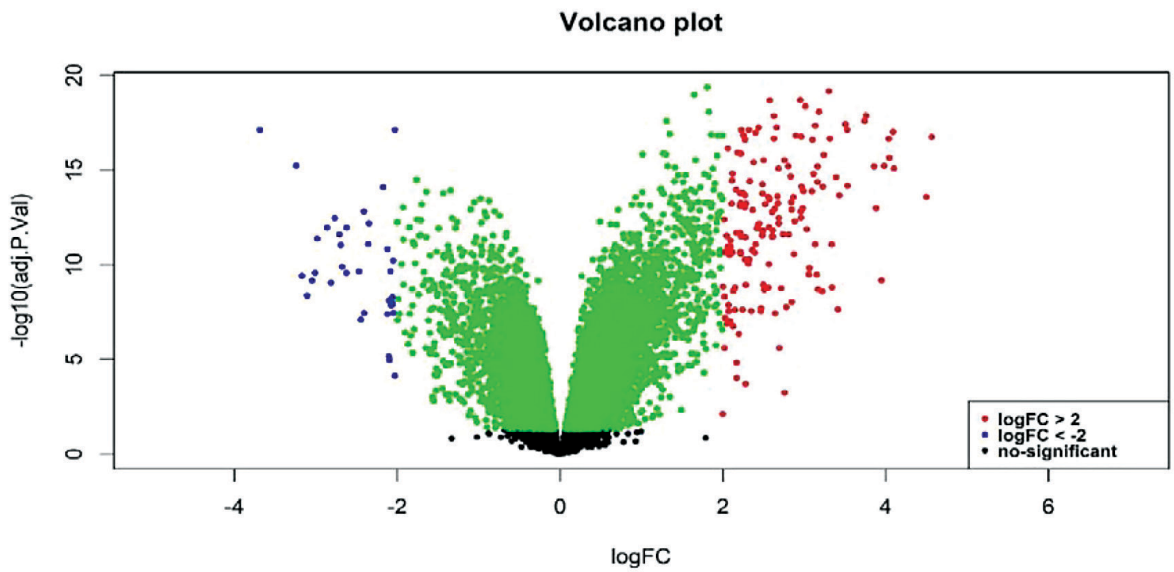

Figure 3: Highlighted genes are significantly differentially expressed at a default adjusted p-value cutoff of 0.05 (red = upregulated logFC >= 2, blue = downregulated logFC <= 2)

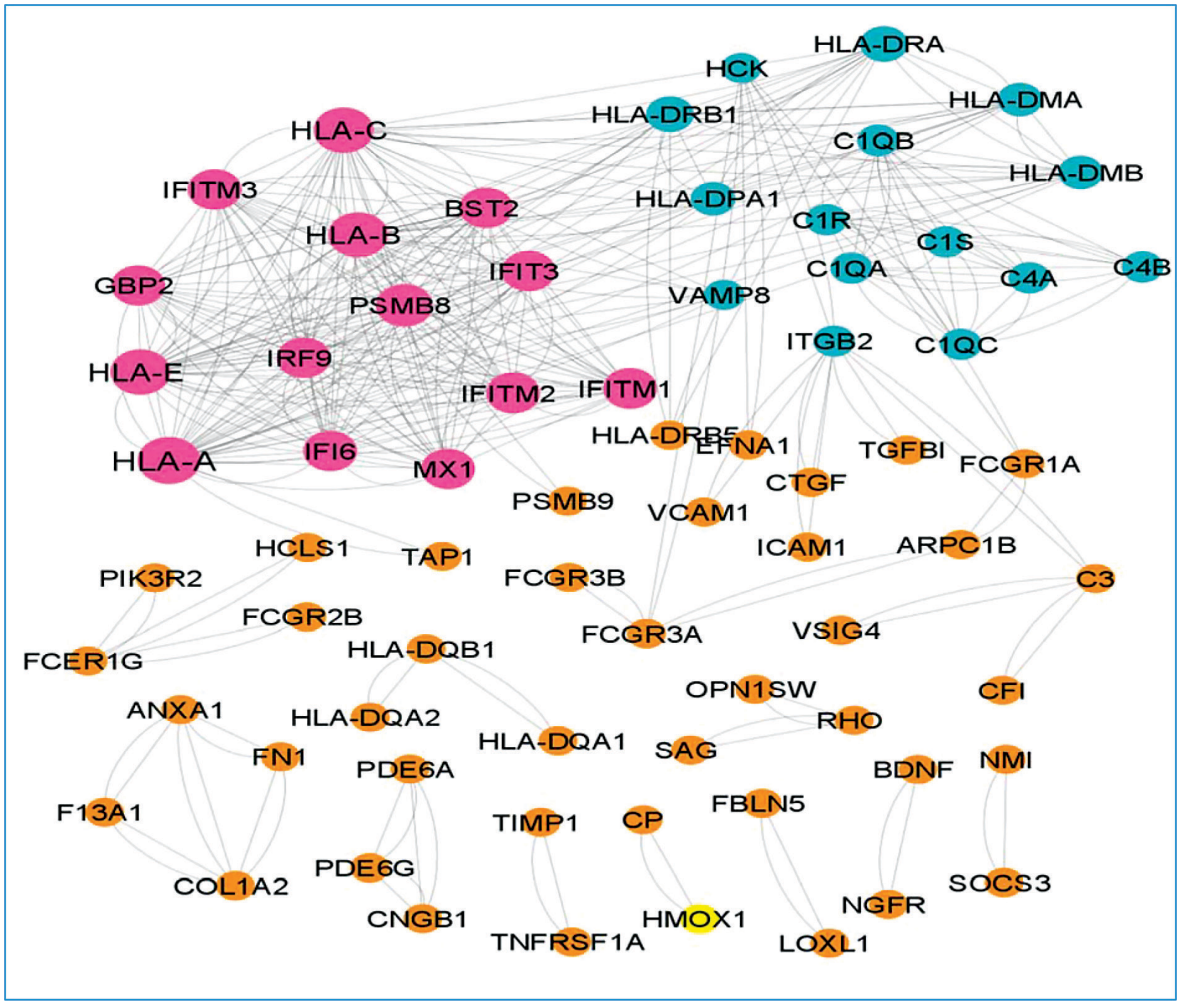

Figure 4: Reconstruction the PPI Network which is composed of 3 functional modules, cluster02 (pink), cluster01 (orange) and cluster00 (blue)

Samples have identical value distributions which are illustrated in Figure 1.

The hierarchical clustering of the samples and their related clinical information is shown in Figure 2. There is no outlier sample (which was far from others based on the gene expression profile).

DEG Identifications

As mentioned above, we use the GSE28133 dataset to identify the DEGs of RD, for this purpose "Limma" R package from the bioconductor project was used to identify differentially expressed genes between normal and RD samples. In the next step, the file of DEGFullFC consists of all DEGs provided in Supplementary file 4. Ultimately, to enhance data quality, the gene expression dataset was filtered for the putative contaminants the by using the independent t-test with adj.P.Val<0.05 and log2-fold change (log2FC) absolute value greater than 2 and less than -2. Therefore, the final differentially expressed genes were identified by microarray experiment. Therefore 196 DEGs are obtained for RD (supplementary file 5). Finally, 36 and 160 genes were identified as down and up regulated genes, respectively.

Figure 3 shows the volcano plot, which displays statistical significance (-log10 P value) versus

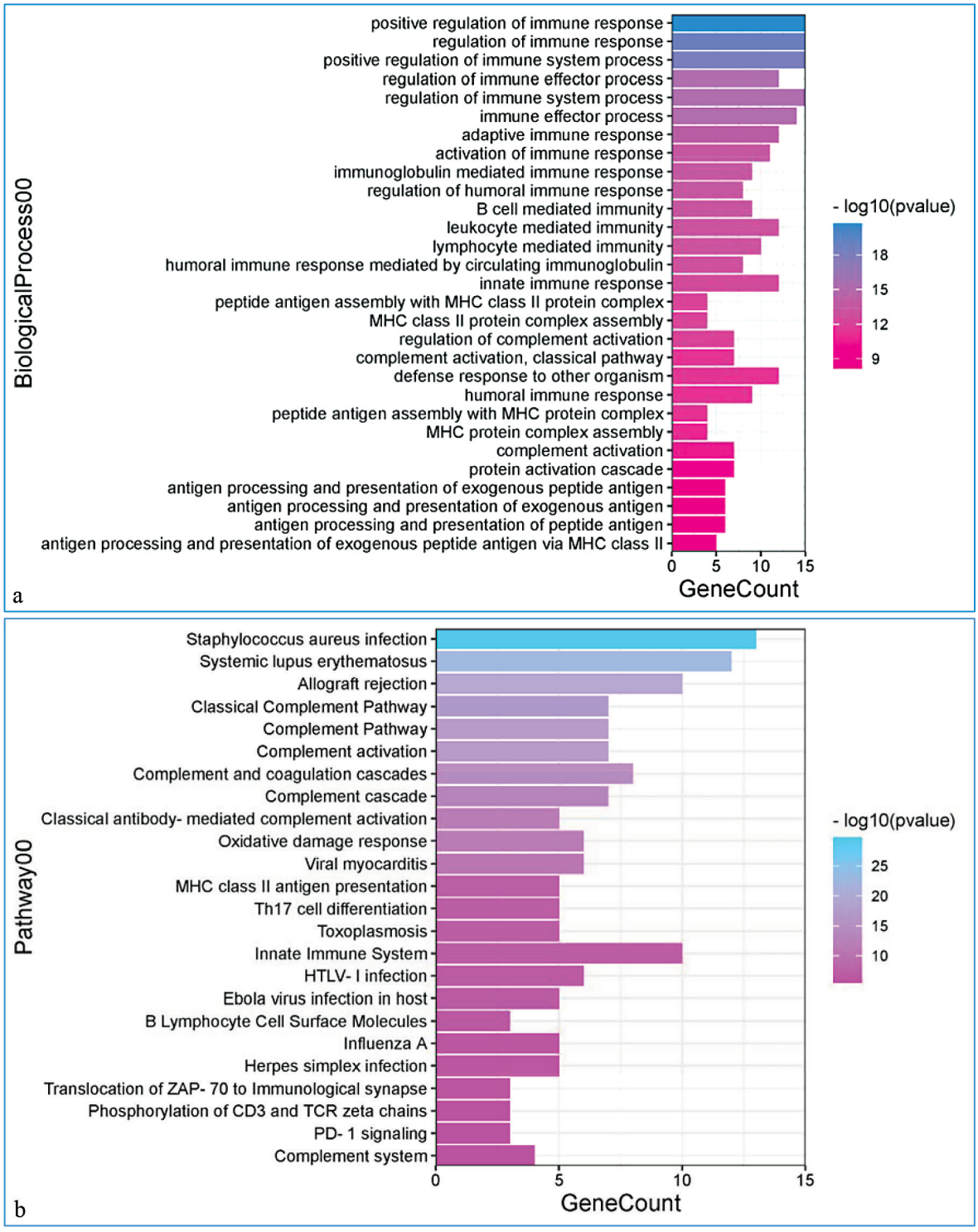

Figure 5: Gene ontology functional enrichment of differentially expressed genes based on each cluster a) Biological Processes for cluster00- b) Pathway for cluster00.

magnitude of change (log2 fold change) and is helpful for visualizing differentially expressed genes.

Reconstruction PPI Network

The protein-protein interaction network was extracted based on the 196 differentially

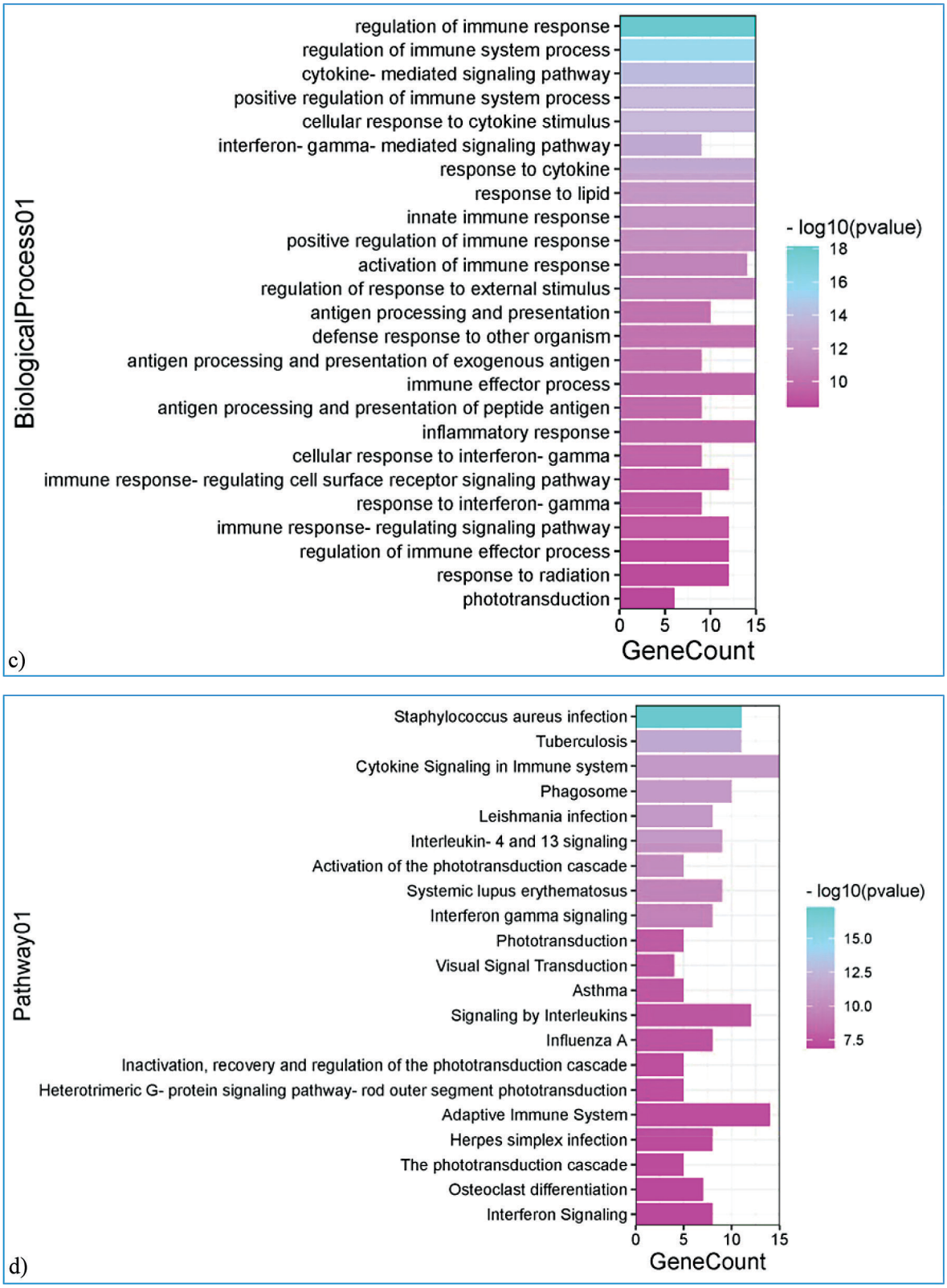

Figure 5: c) Biological Processes for cluster01. d) Pathway for cluster01- e) Biological Processes for cluster02- f) Pathway for cluster02

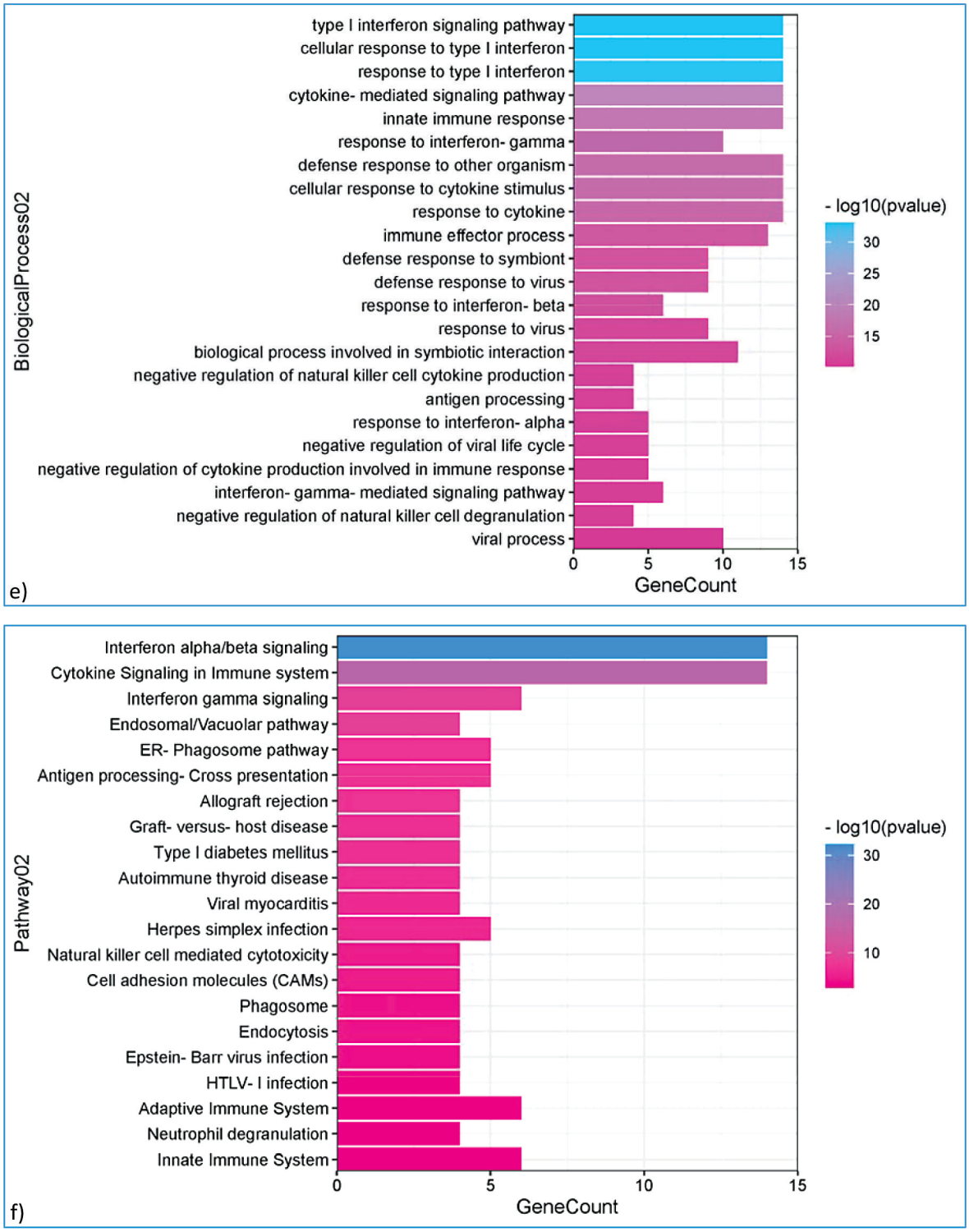

Figure 5: e) Biological Processes for cluster02- f) Pathway for cluster02

expressed genes and the interactions among their corresponding proteins provided in STRING with high confidence of 0.9 and considering parameters such as experiments and databases. The PPI network consists of 196 genes and 183 interactions among them and it is provided in (Supplementary File 6) Eventually, the PPI network was analyzed with

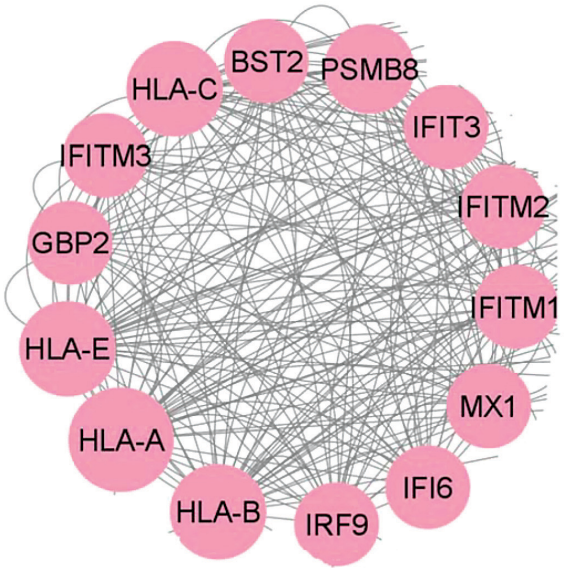

Figure 6: Cluster 02 that consists hub genes which play major role in diagnosing the Retinal Detachment

Cytoscape software, network analyzer a plugin of Cytoscape was used for the computation a comprehensive set of network topological parameters including degree distribution, the shortest path lengths between any two nodes, the mean path length, the network diameter, density, different centrality measures, heterogeneity and clustering coefficient (Supplementary File 7). Genes with the highest degree of connectivity in the network are considered hub genes and are expected to exhibit higher biological significance than the other genes in the network. The nodes with no connection have been deleted.

Identification of Functional modules

The identification of functional modules for the PPI network, may provide more precious insights into the molecular mechanisms underlying the development and progression of RD. K-means, a clustering algorithm in the clusterMaker plugin of Cytoscape, was applied to identify modules in the network. The result has shown that the PPI network is composed of 3 functional modules (first module 00 in blue, second module 01 in orange and third module 02 in pink), as is present in Figure 4. According to this study, there is three modules in the PPI network which contain 43, 15and 14 nodes (Supplementary file 8). The ToppGene database was used to detect the functional enrichment of each cluster of genes based on biological processes, disease, drug-gene associations, and involved pathways. The result is listed in Supplementary files 9, 10, and 11. We put the DEGs of each cluster in ToppGene to detect the functional cluster which has most associated with the RD. According to the results obtained from Toppgene, gene list enrichment analysis was performed. To get an understanding of the biological processes and pathways active or activated in the RD, the Toppgene GO terms in different biological processes and pathways are shown in figure 5. The results showed that the most significant GO terms for DEGs in biological processes were regulation of the immune response, activation of immune response, regulation of complement activation, immune effector process, antigen processing, interferon signaling pathway, and cytokine-mediated signaling pathway, respectively. The pathway analysis showed that the DEGs in patients with RD were significantly enriched in Antigen processing-cross presentation, cell adhesion molecules (CAMs), Activation of the photo transduction cascade, staphylococcus aureus infection, autoimmune thyroid disease and cytokine signaling in immune system. For validation of the clusters has the most significant GO terms, all terms which consist of biological processes, disease, drug-gene associations, and involved pathways have been searched in the literatures. So the cases which have already been reported in the articles were extracted. Eventually, the results of literature mining reveal that cluster 02 has

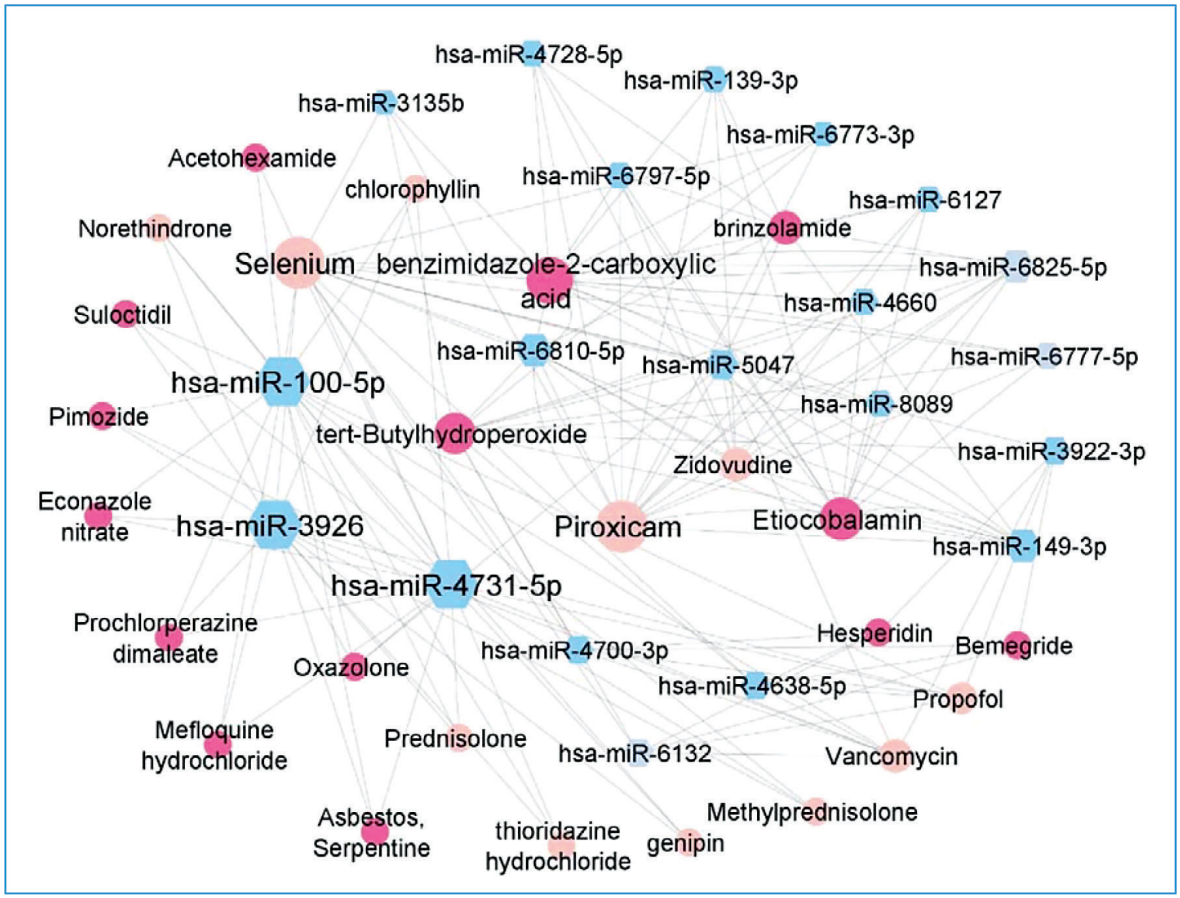

Figure 7: Drug-Gene-miRNA Interaction Network. Final network was designed to detect hub genes for identifying drug molecules and related miRNA for RD. The pale pink circles represent reported drugs and other represent novel drugs and also pale blue hexagons represent reported miRNA. The nodes with no connection have been deleted

the most significant association with the RD which consists of 14 nodes HLA-A, HLA-E, HLA-B, HLA-C, PSMB8, BST2, GBP2, IFITM2, IRF9, IFI6, IFITM3, IFIT3, IFITM1, MX1 play a major role in diagnosing the RD (Figure 6).

Eventually, searching for disease in the DisGeNET for each module demonstrated that module 02 (pink) has the most significant association with the RD, the information about this result is presented in Supplementary file 12.

miRWalk database

In this study, the miRWalk database [31] was used to extract miRNA related to cluster 02. For this aim, Target miRNAs were predicted using the TargetScan database, miRDB and,miRTarBase then further filtration of these data based on the score of 1, eventually 29 miRNAs were identified (Supplementary file 13).

Identification of Drug Candidates

Eventually, a list of the drug-gene associations for cluster 02 which consists of genes with the highest degree of connectivity in the network and related miRNA was prepared (Supplementary file 14). So, this list was loaded into Cytoscape software for visual analysis then the final network was designed

to detect hub genes for identifying drug molecules and related miRNA for RD. This network consists of 152 nodes and 175 edges, which are shown in Figure 7.

The Figure 7 reveals the association of some of the drugs with miRNAs target genes such as HLA-A, HLA-E, HLA-B, HLA-C, IFITM3, and IFIT3 which are involved in RD (Supplementary file 14).

Furthermore, on performing a review of the literature on each miRNA base on the miRWalk database, we observed that 3 of the 29 miRNAs have been reported to play a role in RD and 16 of the 31 drugs have been reported.

Discussion

RD is the most common cause of blindness. The detached retina occurs when the thin layer behind the eye (retina) becomes loose. It needs to be treated as soon as possible to stop it before vision loss. RD has been treated with surgery so far. However, there is no definitive treatment for this disease.

In the previous study reported that inflammatory and immune responses are involved in RD [15, 32]. In this study, the key signaling pathways and target genes associated with RD were recognized by using the reconstruction of the PPI network, functional modules, and mentioned databases.

Interferons (IFNs) are a group of signaling proteins made and released by host cells (a virus-infected cells) in response to the presence of several viruses. Interferons are glycoproteins that are known as cytokines, and have antiviral, antiproliferative, and immunomodulatory functions [33].

According to various studies, the reported incidence of IFN-associated retinopathy ranges from 18 % to 86 %. IFNγ regulated retinal pigment epithelial fluid transport and IFNγ receptors are mainly localized to the basolateral membrane of human retinal pigment epithelium (RPE) [33]. Also in some studies reported that IFN-β signaling limited chronic inflammation and pathological angiogenesis in eye disease [34]. These results demonstrate a protective role for IFN signaling in regulating retinal hydration in inflammatory disease processes [35], in this study, in cluster 01 and 02, some of the signaling pathways and biological processes were related to interferon signaling. PSMB8, HLA-A, HLA-B, HLA-C, IFITM1, IFI6, GBP2, IFITM3, IRF9, BST2, IFIT3, IFITM2, MX1, and HLA-E are involved for this process in cluster 02 and NMI, FCGR1A, HLA-DQA1, HLA-DQA2, HLA-DQB1, VCAM1, HLA-DRB5, ICAM1, SOCS3 in cluster 01.

According to various studies, an inflammatory response is a part of the reaction to the retinal detachment that may effect vision after surgical repair(1). This includes heightened intracellular cytokine responses [36]. So, RD leads to the activation of innate immune responses and inflammatory gene expression. Several studies have documented elevated levels of cytokines and growth factors in the vitreous of RD patients. Inflammation and high levels of growth factors in the vitreous are two factors thought to be involved in the onset of proliferative vitreous retinopathy (PVR) in patients with RD [37]. In this study, in the clusters 01 and 02, some of the signaling pathways and biological processes were related to cytokine signaling in the immune system. We detected HLA-A, HLA-B, HLA-C, IFITM1, IFI6, GBP2, IFITM3, IRF9, BST2, IFIT3, IFITM2, MX1, HLA-E directly linked to this process in cluster 02 and PSMB9, NMI, HMOX1, TNFRSF1A, FN1, FCER1G, FCGR1A, TIMP1, ANXA1, HLA-DQA1, HLA-DQA2, HLA-DQB1, F13A1, VCAM1,

HLA-DRB5, ICAM1, SOCS3, COL1A2 in cluster 01.

Interestingly, we found cluster00, including VAMP8, C1QA, C1QB, ITGB2, C1QC, C1R, C1S, HCK, C4A, C4B, HLA-DMA, HLA-DRA, and HLA-DRB1 was strictly correlated with the immune response in RD.

Some of the up-regulated genes were related to an inflammatory process and complement activation, with the highest fold changes including the members of the complement pathway C1QA, C1QB in cluster 00, and C3 in cluster 01.

The enrichment result shows that all clusters with the highest enrichment scores correspond to immune response and antigen processing. Thus, the enrichments demonstrate the existence of an immune response in RD. As a result, our finding shows that up-regulation of HLA-C, HLA-A, HLA –B, and HLA –E is involved in the inflammatory response.

The photoreceptor markers RHO, and OPN1SW were down-regulated in cluster 01. Previous studies show that various mechanisms, including glycolysis, photoreceptor death, and Wnt and MAPK signaling, are activated during or after the RD to promote retinal cell survival [5]. Activation of the phototransduction cascade was the most significantly enriched process in the RD. We detected five proteins, including SAG, PDE6A, PDE6G, CNGB1, and RHO which are directly linked to phototransduction in cluster 01.

In the human genome, expression of up to 60 % of protein-coding genes may be regulated by miRNAs, indicating their pervasive role in multiple biological functions and be involved in many diseases. And also, miRNAs are linked with several diseases. Due to their biological importance, they are recognized as novel disease biomarkers and potential therapeutic targets for developing new interventions [38-41].

Furthermore, 3 of the 20 miRNAs such as hsa-miR-6777-5p, hsa-miR-6825-5p, and hsa-miR-6132 have been reported to play a role in eye disease, including glaucoma [42] and diabetic retinopathy and age-related macular degeneration [42]. The following miRNAs were found to be novel miRNAs that have not been yet linked to eye disease and RD including: hsa-miR-8089, hsa-miR-139-3p, hsa-miR-4728-5p, hsa-miR-6127, hsa-miR-6797-5p, hsa-miR-3135b, hsa-miR-6773-3p, hsa-miR-4660, hsa-miR-3926, hsa-miR-100-5p, hsa-miR-4731-5p, hsa-miR-149-3p, hsa-miR-6810-5p, hsa-miR-6825-5p, hsa-miR-5047, hsa-miR-3922-3p, hsa-miR-4638-5p and hsa-miR-4700-3p. These miRNAs can target HLA-A, HLA-E, HLA-B, HLA-C, IFITM3, and IFIT3 which have a critical role in RD.

Moreover, our study showed these miRNAs being involved in some pathways such as immune responses, interferon signaling, inflammatory process, and cytokine signaling in the immune system.

In this study, other interesting finding was detected in eye disorder and RD. These drugs can target HLA-A, HLA-E, HLA-B, HLA-C, IFITM3, and IFIT3, which play an essential role in the early diagnosis of RD.

We observed that 10 of 32 drugs had been reported to play a role in eye disease and RD [43- 48]. The following drugs were found to be novel drugs that have not been yet linked to RD including: benzimidazole-2-carboxylicacid, etiocobalamin, brinzolamide, bemegride, hesperidin, suloctidil, prochlorperazine dimaleate, econazole nitrate, mefloquine hydrochloride, methylprednisolone and pimozide.

Our finding indicates that most of the diseases involved in the inflammatory response and immune response. For validation of which clusters have the most significant association

with RD and eye disease, DisGeNET databases were used. The third cluster (02) was closest to the RD of the three clusters . These diseases can target HLA-A, HLA-E, HLA-B and HLA-C, which are involved in the inflammatory response and immune responses and have a critical role in the diagnosis of RD. Our finding demonstrated that these biomarkers have the highest degree of connectivity in the network and were considered hub genes, and can be expected to exhibit higher biological significance than the other genes in the network. So we can suggest HLA-A, HLA-E, HLA-B, and HLA-C as potential biomarkers in RD.

Conclusions

Our results indicate that the immune system, interferon signaling, cytokine signaling, and photo transduction pathways are involved in RD. These pathways activate some inflammatory signaling responses, and photoreceptor cell death in RD. Finally, we suggested some mRNAs,miRNAs, and drugs as potential biomarkers and therapeutic targets in RD.

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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.