S, Najafi A, Masoudi-Nejad A. An efficient hybrid feature selection method to identify potential biomarkers in common chronic lung inflammatory diseases. Genomics. 2020;112(5):3284-93.

5. Rabinowitz YS. Keratoconus. Survey of ophthalmology. 1998;42(4):297-319.

6. Rabinowitz YS, Dong L, Wistow G. Gene expression profile studies of human keratoconus cornea for NEIBank: a novel cornea-expressed gene and the absence of transcripts for aquaporin 5. Invest Ophthalmol Vis Sci. 2005;46(4):1239-46.

7. Maghsoudloo M, Azimzadeh Jamalkandi S, Najafi A, Masoudi-Nejad A. Identification of biomarkers in common chronic lung diseases by co-expression networks and drug-target interactions analysis. Mol Med. 2020;26(1):9.

8. Valgaeren H, Koppen C, Van Camp G. A new perspective on the genetics of keratoconus: why have we not been more successful? Ophthalmic Genet. 2018;39(2):158-74.

9. Barbaro V, Di Iorio E, Ferrari S, Bisceglia L, Ruzza A, De Luca M, et al. Expression of VSX1 in human corneal keratocytes during differentiation into myofibroblasts in response to wound healing. Invest Ophthalmol Vis Sci. 2006;47(12):5243-50.

10. Kabza M, Karolak JA, Rydzanicz M, Szczesniak MW, Nowak DM, Ginter-Matuszewska B, et al. Collagen synthesis disruption and downregulation of core elements of TGF-beta, Hippo, and Wnt pathways in keratoconus corneas. Eur J Hum Genet. 2017;25(5):582-90.

11. Mas Tur V, MacGregor C, Jayaswal R, O'Brart D, Maycock N. A review of keratoconus: Diagnosis, pathophysiology, and genetics. Surv Ophthalmol. 2017;62(6):770-83.

12. You J, Corley SM, Wen L, Hodge C, Hollhumer R, Madigan MC, et al. RNA-Seq analysis and comparison of corneal epithelium in keratoconus and myopia patients. Sci Rep. 2018;8(1):389.

13. Abedi Z, MotieGhader H, Maghsoudloo M, Goharrizi MASB, Shojaei A. Novel potential drugs for therapy of age-related macular degeneration using Protein-Protein Interaction Network (PPIN) analysis. Journal of Ophthalmic and Optometric Sciences. 2019;3(4).

14. Ghorbani M, Pournoor E, Maghsoudloo M. Transcriptomic Analysis of Human Retina Reveals Molecular Mechanisms Underlying Diabetic Retinopathy in Sexually Divergent Manner. Journal of Ophthalmic and Optometric Sciences. 2020;4(2).

15. Hosseini SS, Abedi Z, Maghsoudloo M, Goharrizi MASB, Shojaei A. Investigation of genes associated with primary open-angle glaucoma (POAG) using expression profile analysis. Journal of Ophthalmic and Optometric Sciences. 2019;3(3).

16. Maghsoudloo M, Azimzadeh Jamalkandi S, Najafi A, Masoudi-Nejad A. Identification of biomarkers in common chronic lung diseases by co-expression networks and drug-target interactions analysis. Molecular Medicine. 2020;26(1):1-19.

17. Darabi M, Masoudi-Nejad A, Nemat-Zadeh G. Bioinformatics study of the 3-hydroxy-3-methylglotaryl-coenzyme A reductase (HMGR) gene in Gramineae. Molecular biology reports. 2012;39(9):8925-35.

18. Ghasemi M, Seidkhani H, Tamimi F, Rahgozar M, Masoudi-Nejad A. Centrality measures in biological networks. Current Bioinformatics. 2014;9(4):426-41.

19. Cesana M, Cacchiarelli D, Legnini I, Santini T, Sthandier O, Chinappi M, et al. A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA. Cell. 2011;147(2):358-69.

20. Tan JY, Sirey T, Honti F, Graham B, Piovesan A, Merkenschlager M, et al. Extensive microRNA-mediated crosstalk between lncRNAs and mRNAs in mouse embryonic stem cells. Genome Res. 2015;25(5):655-66.
21. Luo S, Lu JY, Liu L, Yin Y, Chen C, Han X, et al. Divergent lncRNAs Regulate Gene Expression and Lineage Differentiation in Pluripotent Cells. Cell Stem Cell. 2016;18(5):637-52.
22. Kouhsar M, Azimzadeh Jamalkandi S, Moeini A, Masoudi-Nejad A. Detection of novel biomarkers for early detection of Non-Muscle-Invasive Bladder Cancer using Competing Endogenous RNA network analysis. Scientific reports. 2019;9(1):1-15.
23. Ahmadi H, Ahmadi A, Azimzadeh-Jamalkandi S, Shoorehdeli MA, Salehzadeh-Yazdi A, Bidkhori G, et al. HomoTarget: a new algorithm for prediction of microRNA targets in Homo sapiens. Genomics. 2013;101(2):94-100.
24. Motieghader H, Kouhsar M, Najafi A, Sadeghi B, Masoudi-Nejad A. mRNA–miRNA bipartite network reconstruction to predict prognostic module biomarkers in colorectal cancer stage differentiation. Molecular BioSystems. 2017;13(10):2168-80.
25. Maghsoudloo M, Noroozizadeh MH. A gene selection approach for Diabetic retinopathy microarray data classification using Ant Colony Optimization. Journal of Ophthalmic and Optometric Sciences.3(4):1-10.
26. Norouzi M, Maghsoudloo M, Hafez M. Collagen Cross-Linking Therapy on Important Functional Genes Involved in Keratoconus Patients Using Protein-Protein Interactions (PPI) Network and Differential Expression Analysis. Journal of Ophthalmic and Optometric Sciences Volume. 2019;3(3).
27. Cheng L, Wang P, Tian R, Wang S, Guo Q, Luo M, et al. LncRNA2Target v2.0: a comprehensive database for target genes of lncRNAs in human and mouse. Nucleic Acids Res. 2019;47(D1):D140-D4.
28. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res. 2003;13(11):2498-504.
29. Tian R, Wang L, Zou H, Song M, Liu L, Zhang H. Role of the XIST-miR-181a-COL4A1 axis in the development and progression of keratoconus. Mol Vis. 2020;26:1-13.
30. Loukovitis E, Sfakianakis K, Syrmakesi P, Tsotridou E, Orfanidou M, Bakaloudi DR, et al. Genetic Aspects of Keratoconus: A Literature Review Exploring Potential Genetic Contributions and Possible Genetic Relationships with Comorbidities. Ophthalmol Ther. 2018;7(2):263-92.
31. Yuan S, Li D, Ma M, Zhou L, Ma Z, Shi B, et al. Evaluating the association between MPDZ-NF1B rs1324183 and keratoconus in an independent northwestern Chinese population. BMC Ophthalmol. 2022;22(1):129.
32. Alaei S, Sadeghi B, Najafi A, Masoudi-Nejad A. LncRNA and mRNA integration network reconstruction reveals novel key regulators in esophageal squamous-cell carcinoma. Genomics. 2019;111(1):76-89.
33. Mortezaei Z, Lanjanian H, Masoudi-Nejad A. Candidate novel long noncoding RNAs, MicroRNAs and putative drugs for Parkinson's disease using a robust and efficient genome-wide association study. Genomics. 2017;109(3-4):158-64.

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Conflict of interest:

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

Original Article

Protein-Protein Interaction Network Analysis and Drug Repurposing for Uveal Melanoma Patients

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Abstract

Background: Uveal melanoma is the most prevalent melanoma in adults. This malignancy arises from melanocytes. Patients with uveal melanoma were investigated according to their metastases and non-metastases status to propose candidate drugs.
Material and Methods: The studied data set included 63 patients (24 females and 39 males), among whom 35 patients were with metastases and 28 patients were without metastases. By comparing the metastases and non-metastases cases, 2000 genes were chosen as practical genes. A co-expression network was constructed, and protein complexes were extracted to find effective gene modules. Then drug-gene networks were constructed to find essential drugs.
Results: The STRING database was utilized to construct a co-expression network. Then, protein complexes were extracted using the MCODE clustering algorithm. Four meaningful modules were chosen for the next step. Afterward, drug-gene subnetworks were constructed and illustrated, and high degree drugs were chosen as effective drugs for this disease.
Conclusion: As a result, 12 important drugs were introduced as the proposed candidate drugs. By detailed investigation of the obtained results, drugs that were not previously reported were introduced as new drugs, which would be studied experimentally in future works. These were Bortezomib, Oprozomib, Clofarabine, ME-344 and NV-128.
Keywords: Protein-Protein Interaction Network; Uveal Melanoma; Drug Repurposing; Drug-Gene; Metastasis.

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Introduction

Although uveal melanoma is a rare tumor, it is the most prevalent non-dermal melanoma and primary malignancy of the eye in adults. This tumor develops from melanocytes which are located at various anatomic locations [1]. According to global studies, there are approximately 7095 new cases each year [2]. By considering the range of 6-100, the mean age of this disease is 60 years, but the incidence rate for both males and females is almost the same, with slight predominance among males [3]. Analyzing 4070 patients with primary uveal melanoma over 36 years between 1973 and 2008 using the Surveillance, Epidemiology, and End Results (SEER) program database of the United States National Cancer Institute revealed 5.1 cases per million per year [4]. According to UM's clinical and histopathological characteristics, 103 samples with the clinical diagnosis were studied and analyzed due to their pathological features. Results demonstrate that UM is more common in western countries than in Asian Indians. Younger persons are more exposed to this disease and usually res of mixed cell types [5]. According to another clinical study, UM patients were examined retrospectively, and the results showed that there isn't yet sufficient progress in the diagnosis of this disease. All the available information is a systematic collection of data and tumor tissue and molecular biology of UM [6]. The type of tumors was classified as T1, T2, T3, and T4 according to the size of the tumor. This measurement was calculated by width and height, usually called thickness. The detailed information of this classification is demonstrated by a table in canser.net [7]. Reviewing the previous studies demonstrated valuable progress in early diagnosis and then early treatment. According to the advances in this field, treating smaller tumors increases the survival hope rate. Considering these achievements, early treatment of small melanomas results in local disease control and prevention of metastases, ultimately causing the patient's survival [8].

One of the most important research projects to analyze the gene expression levels and clinical features related to the patients is called weighted gene co-expression network analysis (WGCNA) [9-12]. This protocol has been used for many studies. In one of these studies, they found four significant modules, hub genes and vital genes, targeted in the progress of uveal melanoma. Modules were chosen according to clinical traits [13]. Another study employed gene expression data from The Cancer Genome Atlas (TCGA) database. Eight co-expression modules were extracted using WGCNA, and prognostic markers of uveal melanoma were identified to better manage this disease. Pathway enrichment analysis demonstrated that genes in the obtained modules were significantly enriched in the progression process and tumorigenesis [14]. Another investigation suggested a framework constructed by gene modules in uveal melanoma and contributed to a greater understanding of these modules by functional analysis. Furthermore, some studies helped develop more effective strategies for diagnosing uveal melanoma by extracting vital molecular mechanisms and cellular pathways. According to their results, hub genes were introduced as prognostic markers, which have an essential role in the recurrence of UM [15, 16]. There are studies that utilized Protein-Protein Interaction Network in their studies. As an example, one of them studied age-related macular degeneration (AMD) and their related drugs [17]. Another used PPI in studying Keratoconus (KC) by investigating RNA-Seq data. Finally, effective genes effective in treatment were identified

using hub genes obtained from PPI network and transcription factor (TF) genes [18]. Due to the relation between vision loss and diabetes, there are several articles that studied diabetes. One of them, utilized microarray data to select the effective genes using Ant Colony Optimization has achieved a high precision rate [19]. Another one used mRNA expression profiles to show the effect of gender factor in the onset and progression of diabetic retinopathy [20]. In relation to eye-related diseases, we can refer to Glaucoma which is recognized as cause of blindness. This was studied using PPI network and module extraction to obtain effective genes. Then candidate pathways were introduced using GO enrichment which can be considered in therapeutic measures [21-24]. Most uveal melanoma patients encounter metastatic tumors, mainly in the liver. In the present study, we used co-expression network reconstruction to repurpose drugs related to UV. For this purpose, uveal melanoma samples containing metastases and those without metastases were examined. By extracting modules of the obtained network, the effective genes were extracted. The results detected important biomarkers which can lead to the early diagnosis of this cancer. Detected biomarkers were utilized to construct a bipartite Drug-Gene network, leading to the proposal of potential drugs according to the goal of this study. The utilized dataset is different from that of the previous studies and was obtained from the Genome Expression Omnibus [25] using the GSE22138 accession number. This dataset is Expression Data from uveal melanoma primary tumors. Below we present a complete description of the dataset utilized and the methods used for this study.

Material and Methods

The proposed methodology in this study was divided into several steps and used different platforms.

Preprocessing

The dataset used in this study was obtained from Genome Expression Omnibus with the GSE22138 accession number. First of all, GEO2R [25], a web-based data analysis tool, was utilized. Using this tool, genes whose expression was significantly different between patients with metastases and those without metastases were chosen to be used in the remainder of the study. After sorting the genes by their P values, the genes whose P value were smaller than 0.001 were chosen. Finally, they were filtered, and 2000 genes were chosen for the rest of the study. The Supplementary file contains a list of differentially expressed genes utilized in this study.

PPI network construction STRING

A co-expression network related to the selected genes was constructed in the next step. To reconstruct this network, we used STRING [26] site. A co-expression network with the experimental connections was constructed. Then, these connections were represented as a co-expression network using Cytoscape.3.7.0. [27].

Module detection

Then, subnetworks or modules were extracted using the MCODE clustering algorithm, one of the clustering algorithms in ClusterViz [28]. There are four parameters associated with the MCODE algorithm, namely, "DegreeThreshold," "NodeScoreThreshold," "K-CoreThreshold," and "MaxDepth". The values of 2, 0.2, 2, and 100 were selected for these parameters, respectively.

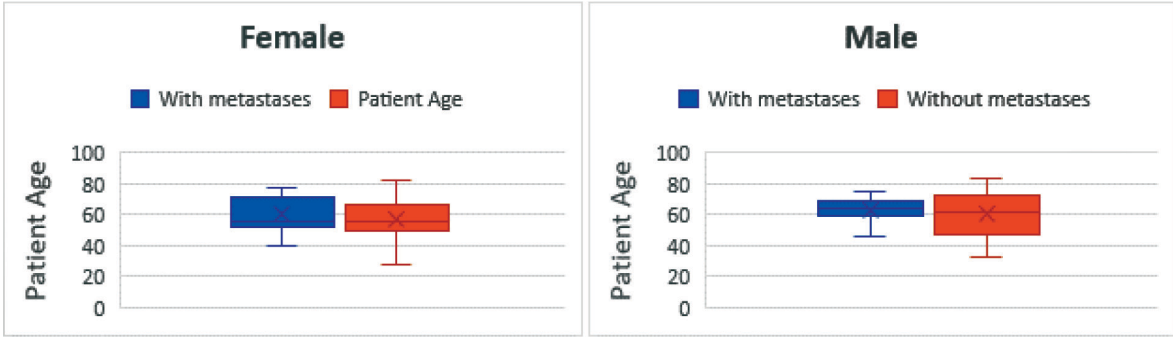

Figure 1: Dispersion of samples according to their age and gender

DGIdb

Finally, a drug-gene network was constructed by DGIdb that represents drug-gene interactions extracted from different resources. DGIdb 3.0 [29] provides a valuable database by updating resources and adding new resources. Accordingly, this database was utilized for constructing a drug-gene bipartite network.

Results

Data description

Figure 1 illustrates the range and dispersion of samples in terms of their age and gender, and table 1 depicts the number of patients regarding their metastases status.

According to the box charts provided in figure 1, the age of the patients was in the range of 28-84. The blue boxes and the orange ones are related to the patients without metastases and the patients with metastasis, respectively.

PPI network construction

By preparing 2000 genes that were more effective in metastases of uveal melanoma, a co-expression network was constructed using the STRING database. Cytoscape illustrated this network. Figure 2 presents the extracted network.

The green rectangles and the edges represent the genes and the connection between the genes, respectively. The obtained co-expression network will utilize to extract vital modules in the following.

Extracting modules

Subsequently, the essential modules as protein complexes were extracted using the MCODE clustering algorithm. The important modules are the ones that include nodes with a higher degree or, in other words, include hub genes. Among the obtained clusters, the meaningful ones were chosen as protein complexes. Hence, four meaningful modules were demonstrated in figure 3. table 2 lists the genes associated with these modules.

As depicted in figure 3, the first and second clusters contain 35 and 12 nodes, respectively.

Table 1: The number of data samples according to their gender and metastases status

Gender	With Metastases	Without Metastases	Total
Female	13	11	24
Male	22	17	39
Total	35	28	63

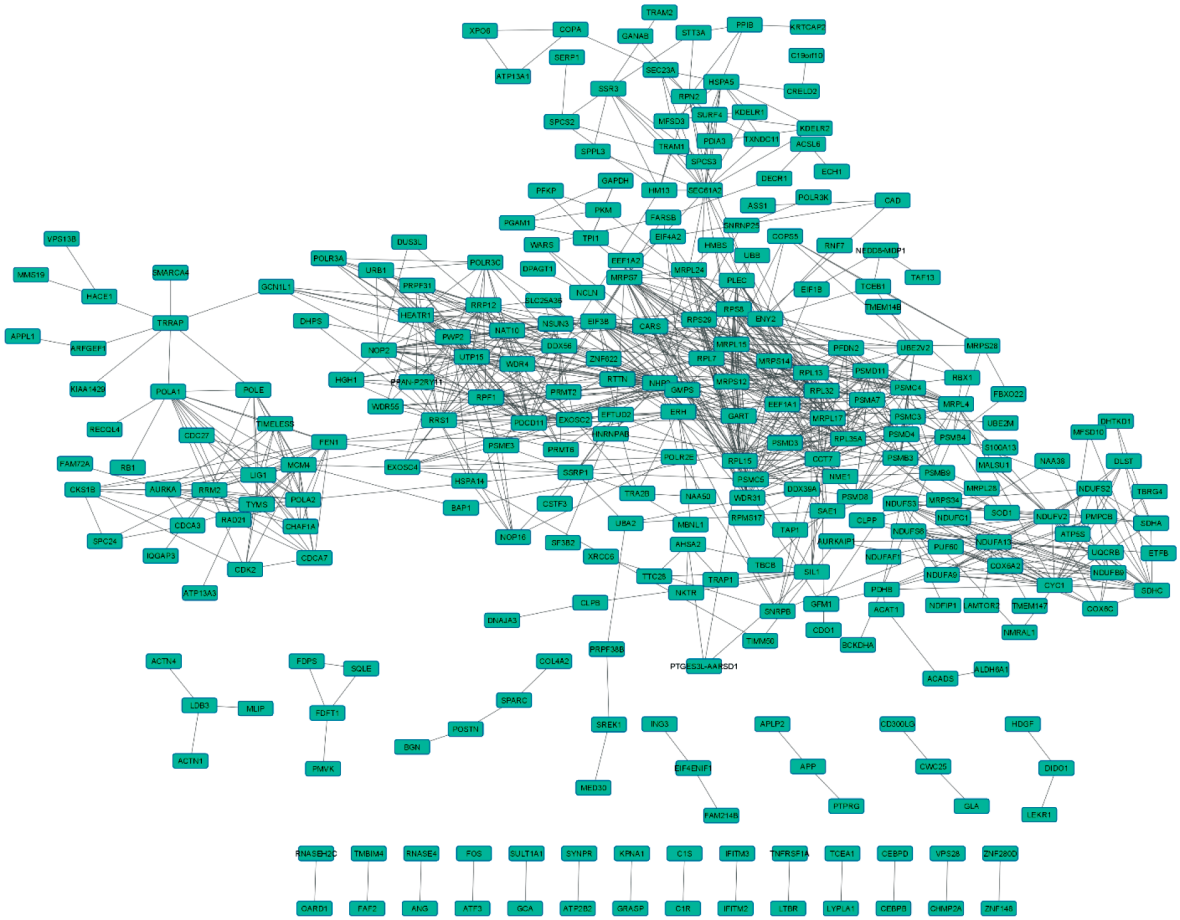

Figure 2: The co-expression network extracted by the selected genes

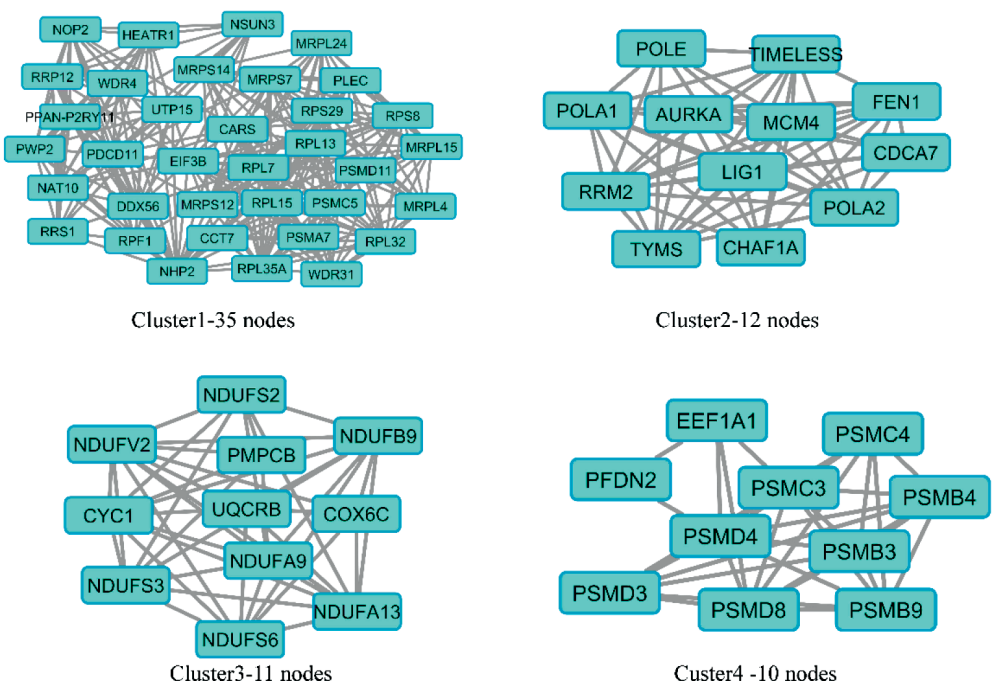

Figure 3: The extracted protein complexes using the MCODE clustering algorithm

Table 2: List of genes related to each module

List of Clusters	List of related Genes
Cluster1	RPS29, RPL32, RPS8, NSUN3, CCT7, WDR4, PWP2, UTP15, MRPS14, PPAN-P2RY11, HEATR1, RRP12, RPF1, PDCD11, NHP2, RRS1, PSMD11, CARS, MRPS7, MRPL4, PSMC5, NAT10, RPL13, RPL15, PSMA7, PLEC, RPL7, MRPL15, EIF3B, MRPL24, WDR31, NOP2, DDX56, MRPS12, RPL35A.
Cluster2	MCM4, FEN1, LIG1, TYMS, RRM2, POLE, AURKA, CDCA7, POLA2, TIMELESS, CHAF1A, POLA1.
Cluster3	NDUFA9, NDUFS2, NDUFS6, NDUFB9, UQCRB, COX6C, CYC1, PMPCB, NDUFA13, NDUFS3, NDUFV2
Cluster4	PSMC3, PSMB3, PSMD3, PFDN2, PSMB4, EEF1A1, PSMC4, PSMD8, PSMB9, PSMD4.

The third and fourth clusters also comprise 11 and 10 nodes, respectively. The names of these genes related to each separate module are listed in table 2.

Drug-gene bipartite network

In the next step, to achieve the goal of this study, bipartite networks were constructed by obtaining the drugs that targeted the selected genes. Thus, four bipartite drug-gene networks were chosen, and drugs with a high degree targeted more genes in each gene complex. Then, the subnetworks of those bipartite networks were constructed and illustrated in figure 4.

According to figure 4, the green rectangle nodes and the yellow oval nodes represent the genes and the drugs, respectively. The high degree drugs were chosen due to their relationship with more genes; therefore, they are the most meaningful drugs related to this disease. The high degree drugs include Bortezomib, Carfilzomib, Ixazomib Citrate, Oprozomib, Clofarabine, Cytarabine, Fludarabine, Gemcitabine Hydrochloride, ME-344, Metformin Hydrochloride, NV-128, Marizomib.

Discussion

In this section, to represent an effective result, the obtained drugs were studied in the literature in detail to prove the correctness of the accomplished method and propose candidate drugs. Afterward, to represent a more detailed investigation, focus on the most important gene and related drugs.

The first drug, Bortezomib, is a proteasome inhibitor that plays a therapeutic role in many cancers, especially in uveal melanoma [30]. Another study also reported that Bortezomib decreased cell proliferation in uveal melanoma [31]. Investigating the relationship between Bortezomib and metastatic malignant melanoma revealed that although this drug has displayed an anticancer role concerning melanoma tumors, it was not so effective when used alone [32, 33]. The next one Carfilzomib, was analyzed concerning its role in replaced/refectory multiple myeloma (RRMM), indicating an influential role in improving survival outcomes [34, 35]. Therefore, this candidate drug was not directly related to UM in the previous experimental studies. The next drug, Cytarabine, was recognized as one of the chemotherapeutic agents in

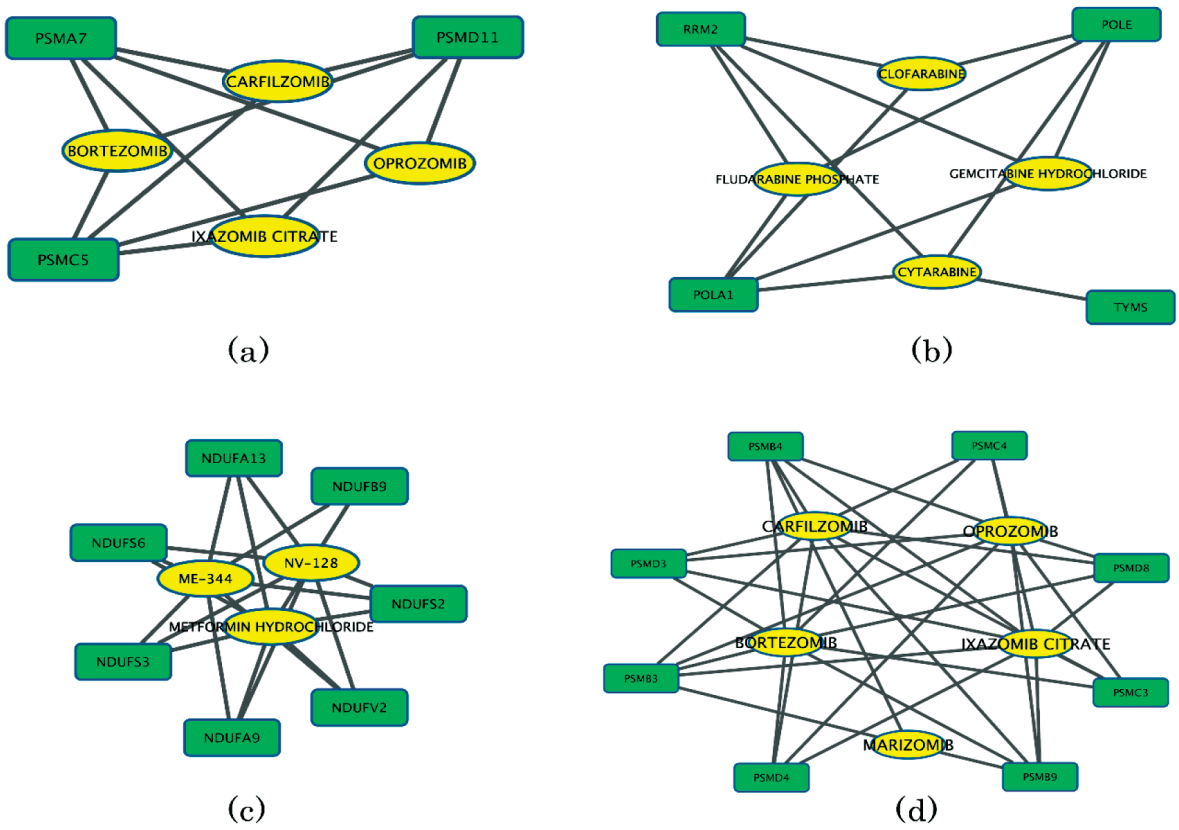

Figure 4: Bipartite drug-gene sub-networks for four protein complexes

eye cancers [36]. Another study demonstrated the effect of Cytarabine and Gemcitabine in uveal melanoma cells [37]. The next candidate drug, FLUDARABINE, was associated with metastases uveal melanoma according to a review study [38]. Based on the treatment of metastatic uveal melanoma, another study used Fludarabine in patients' treatment to complete their experiments [39]. Gemcitabine Hydrochloride as the next drug was proposed in combination with other drugs for UM [40, 41]. Another drug called Metformin Hydrochloride was considered necessary in treating cancers, especially melanoma [42]. Investigating the relationship between metformin hydrochloride and UM, a study reported the potential role of Metformin in eye tissue therapies [43]. According to a paper published about drug development, Marizomib was identified as related drug associated with melanoma [44, 45]. According to a comprehensive review of experimental studies, some of the obtained drugs were related to UM. In contrast, some were related to eye cancer cells but not directly related to UM. This study, as potential candidates, introduced the drugs that were not reported as UM-related in the investigated studies. Of course, they were related to many other cancers but not exclusively to UM. Thus, the present study determined Bortezomib, Oprozomib, Clofarabine, ME-344, and NV-128 as new drug candidates.

To evaluate the results from the biological point of view, we consider the most critical gene among the obtained genes. The genes whose adjusted P value was smaller than 0.05 were biologically important. Among the genes related to the obtained clusters (Figure 3), only the adjusted P value of NDUFB9 was smaller than 0.05. So NDUFB9 with adjusted

P value=0.019 is introduced as a vital gene between metastasis and non-metastasis samples in UM.

According to previous studies, NDUFB9 was already introduced as a prognostic gene in UM by performing research in the literature. This study revealed its results using protein-protein analysis [46, 47]. Another study states NDUFB9 has an important role in causing complex I deficiency [48]. The encoded protein obtained from this gene is a subunit of mitochondrial oxidative phosphorylation complex I. according to GeneCards, Mitochondrial Complex I Deficiency, Nuclear Type 24, and Mitochondrial Complex I Deficiency, Nuclear Type 1 is the disease associated with NDUFB9 [49].

In the following, according to the Drug-Gene bipartite networks illustrated in figure 4 and the proposed drugs, two drugs called ME-344 and NV-128 are related to NDUFB9. By choosing this gene as a vital gene obtained by the proposed method, ME-344 and NV-128 were also attracting more attention to be investigated in experimental studies.

Conclusion

This study aimed to propose potential candidate drugs related to metastatic uveal melanoma. The effective genes among the samples with metastases and without metastases were selected. These selected genes constructed a co-expression network. Then, the influential gene groups were determined by extracting protein complexes obtained by meaningful modules. Bipartite drug-gene subnetworks related to each protein complex were illustrated separately. Hence, the important drugs were analyzed using previously published experimental studies, and new potential drugs related to metastatic uveal melanoma were introduced. Ultimately, in this study, Bortezomib, Oprozomib, Clofarabine, ME-344, and NV-128 were presented as potential candidates.

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References

1. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. Cancer: Interdisciplinary International Journal of the American Cancer Society. 1998;83(8):1664-78.

2. Kivelä T. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. BMJ Publishing Group Ltd; 2009.

3. Singh AD, De Potter P, Fijal BA, Shields CL, Shields JA, Elston RC. Lifetime prevalence of uveal melanoma in white patients with oculo (dermal) melanocytosis. Ophthalmology. 1998;105(1):195-8.

4. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. Ophthalmology. 2011;118(9):1881-5.

5. Biswas J, Kabra S, Krishnakumar S, Shanmugam MP. Clinical and histopathological characteristics of uveal melanoma in Asian Indians. A study of 103 patients. Indian journal of ophthalmology. 2004;52(1):41-4.

6. Cerbone L, Van Ginderdeuren R, Van den

Oord J, Fieuws S, Spileers W, Van Eenoo L, et al. Clinical presentation, pathological features and natural course of metastatic uveal melanoma, an orphan and commonly fatal disease. Oncology. 2014;86(3):185-9.
7. Canser.net. Available from: https://www.cancer.net/cancer-types/eye-cancer/stages-and-grades.
8. Kaliki S, Shields C. Uveal melanoma: relatively rare but deadly cancer. Eye. 2017;31(2):241-57.
9. Motieghader H, Kouhsar M, Najafi A, Sadeghi B, Masoudi-Nejad A. mRNA–miRNA bipartite network reconstruction to predict prognostic module biomarkers in colorectal cancer stage differentiation. Molecular BioSystems. 2017;13(10):2168-80.
10. MotieGhader H, Masoudi-Sobhanzadeh Y, Ashtiani SH, Masoudi-Nejad A. mRNA and microRNA selection for breast cancer molecular subtype stratification using meta-heuristic based algorithms. Genomics. 2020;112(5):3207-17.
11. Ghasemi M, Seidkhani H, Tamimi F, Rahgozar M, Masoudi-Nejad A. Centrality measures in biological networks. Current Bioinformatics. 2014;9(4):426-41.
12. Kouhsar M, Azimzadeh Jamalkandi S, Moeini A, Masoudi-Nejad A. Detection of novel biomarkers for early detection of Non-Muscle-Invasive Bladder Cancer using Competing Endogenous RNA network analysis. Scientific reports. 2019;9(1):1-15.
13. Shi K, Bing Z-T, Cao G-Q, Guo L, Cao Y-N, Jiang H-O, et al. Identify the signature genes for diagnose of uveal melanoma by weight gene co-expression network analysis. International journal of ophthalmology. 2015;8(2):269.
14. Ni Y, Zhang Z, Chen G, Long W, Tong L, Zeng J. Integrated analyses identify potential prognostic markers for uveal melanoma. Experimental Eye Research. 2019;187:107780.
15. Yang M, Wan Q, Hu X, Yin H, Hao D, Wu C, et al. Coexpression modules constructed by weighted gene co-expression network analysis indicate ubiquitin-mediated proteolysis as a potential biomarker of uveal melanoma. Experimental and Therapeutic Medicine. 2019;17(1):237-43.
16. Wan Q, Tang J, Han Y, Wang D. Co-expression modules construction by WGCNA and identify potential prognostic markers of uveal melanoma. Experimental eye research. 2018;166:13-20.
17. Abedi Z, MotieGhader H, Maghsoudloo M, Goharrizi MASB, Shojaei A. Novel potential drugs for therapy of age-related macular degeneration using Protein-Protein Interaction Network (PPIN) analysis. Journal of Ophthalmic and Optometric Sciences. 2019;3(4).
18. Norouzi M, Maghsoudloo M, Noroozizadeh MH. Collagen Cross-Linking Therapy on Important Functional Genes Involved in Keratoconus Patients. Journal of Ophthalmic and Optometric Sciences.3(3):1-15.
19. Maghsoudloo M, Noroozizadeh MH. A gene selection approach for Diabetic retinopathy microarray data classification using Ant Colony Optimization. Journal of Ophthalmic and Optometric Sciences Volume. 2019;3(4).
20. Ghorbani M, Pournoor E, Maghsoudloo M. Transcriptomic Analysis of Human Retina Reveals Molecular Mechanisms Underlying Diabetic Retinopathy in Sexually Divergent Manner. Journal of Ophthalmic and Optometric Sciences. 2020;4(2).
21. Hosseini SS, Abedi Z, Maghsoudloo M, Goharrizi MASB, Shojaei A. Investigation of genes associated with primary open-angle glaucoma (POAG) using expression profile analysis. Journal of Ophthalmic and

Optometric Sciences. 2019;3(3).
22. Ahmadi H, Ahmadi A, Azimzadeh-Jamalkandi S, Shoorehdeli MA, Salehzadeh-Yazdi A, Bidkhori G, et al. HomoTarget: a new algorithm for prediction of microRNA targets in Homo sapiens. Genomics. 2013;101(2):94-100.
23. Alaei S, Sadeghi B, Najafi A, Masoudi-Nejad A. LncRNA and mRNA integration network reconstruction reveals novel key regulators in esophageal squamous-cell carcinoma. Genomics. 2019;111(1):76-89.
24. Mortezaei Z, Lanjanian H, Masoudi-Nejad A. Candidate novel long noncoding RNAs, MicroRNAs and putative drugs for Parkinson's disease using a robust and efficient genome-wide association study. Genomics. 2017;109(3-4):158-64.
25. Barrett T, Wilhite SE, Ledoux P, Evangelista C, Kim IF, Tomashevsky M, et al. NCBI GEO: archive for functional genomics data sets—update. Nucleic acids research. 2012;41(D1):D991-D5.
26. Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J, et al. STRING v11: protein–protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic acids research. 2019;47(D1):D607-D13.
27. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome research. 2003;13(11):2498-504.
28. Wang J, Zhong J, Chen G, Li M, Wu F-x, Pan Y. ClusterViz: a cytoscape APP for cluster analysis of biological network. IEEE/ACM transactions on computational biology and bioinformatics. 2014;12(4):815-22.
29. Cotto KC, Wagner AH, Feng Y-Y, Kiwala S, Coffman AC, Spies G, et al. DGIdb 3.0: a redesign and expansion of the drug–gene interaction database. Nucleic acids research. 2018;46(D1):D1068-D73.
30. Velho T, Kapiteijn E, Jager M. New therapeutic agents in uveal melanoma. Anticancer research. 2012;32(7):2591-8.
31. Wang JZ, Lin V, Toumi E, Wang K, Zhu H, Conway RM, et al. Development of new therapeutic options for the treatment of uveal melanoma. The FEBS Journal. 2021.
32. Markovic SN, Geyer SM, Dawkins F, Sharfman W, Albertini M, Maples W, et al. A phase II study of bortezomib in the treatment of metastatic malignant melanoma. Cancer. 2005;103(12):2584-9.
33. Su Y, Amiri KI, Horton LW, Yu Y, Ayers GD, Koehler E, et al. A phase I trial of bortezomib with temozolomide in patients with advanced melanoma: toxicities, antitumor effects, and modulation of therapeutic targets. Clinical Cancer Research. 2010;16(1):348-57.
34. Zhou X, Flüchter P, Nickel K, Meckel K, Messerschmidt J, Böckle D, et al. Carfilzomib based treatment strategies in the management of relapsed/refractory multiple myeloma with extramedullary disease. Cancers. 2020;12(4):1035.
35. Conticello C, Martino EA, Del Fabro V, Sapienza G, Calafiore V, Garibaldi B, et al. Impact of Cumulative Dose of Carfilzomib in Combination with Lenalidomide and Desamethasone in Relapsed Refractory Myeloma Patients: A Retrospective Real Life Survey of the Sicilian Myeloma Network. American Society of Hematology Washington, DC; 2018.
36. Dolland R. Chemotherapy in eye cancer. Continuing Medical Education. 2013;31(4):138-42.
37. Neale M, Myatt N, Cree I, Kurbacher C, Foss A, Hungerford J, et al. Combination chemotherapy for choroidal melanoma: ex

vivo sensitivity to treosulfan with gemcitabine or cytosine arabinoside. British journal of cancer. 1999;79(9):1487-93.
38. Orloff M. Clinical Trials in Metastatic Uveal Melanoma: Immunotherapy. Ocular Oncology and Pathology. 2021:1-9.
39. Chandran SS, Somerville RP, Yang JC, Sherry RM, Klebanoff CA, Goff SL, et al. Treatment of metastatic uveal melanoma with adoptive transfer of tumour-infiltrating lymphocytes: a single-centre, two-stage, single-arm, phase 2 study. The Lancet Oncology. 2017;18(6):792-802.
40. Corrie P, Shaw J, Spanswick V, Sehmbi R, Jonson A, Mayer A, et al. Phase I trial combining gemcitabine and treosulfan in advanced cutaneous and uveal melanoma patients. British journal of cancer. 2005;92(11):1997-2003.
41. Schmittel A, Scheulen ME, Bechrakis NE, Strumberg D, Baumgart J, Bornfeld N, et al. Phase II trial of cisplatin, gemcitabine and treosulfan in patients with metastatic uveal melanoma. Melanoma research. 2005;15(3):205-7.
42. Jaune E, Rocchi S. Metformin: Focus on melanoma. Frontiers in endocrinology. 2018;9:472.
43. de Andrade BDM, Lasiste J, Miyamoto D, Rezende CP, Mastromonaco C, Burnier MN. Metformin inhibits survival, migration, and vascular endothelial growth factor production in uveal melanoma cells. Investigative Ophthalmology & Visual Science. 2017;58(8):3964-.
44. Zhang X, Linder S, Bazzaro M. Drug development targeting the ubiquitin–proteasome system (UPS) for the treatment of human cancers. Cancers. 2020;12(4):902.
45. Millward M, Price T, Townsend A, Sweeney C, Spencer A, Sukumaran S, et al. Phase 1 clinical trial of the novel proteasome inhibitor marizomib with the histone deacetylase inhibitor vorinostat in patients with melanoma, pancreatic and lung cancer based on in vitro assessments of the combination. Investigational new drugs. 2012;30(6):2303-17.
46. Choi S, Ha M, Lee JS, Heo HJ, Kim GH, Oh S-O, et al. Novel prognostic factor for uveal melanoma: bioinformatics analysis of three independent cohorts. Anticancer Research. 2020;40(7):3839-46.
47. Masoudi-Sobhanzadeh Y, Omidi Y, Amanlou M, Masoudi-Nejad A. DrugR+: a comprehensive relational database for drug repurposing, combination therapy, and replacement therapy. Computers in biology and medicine. 2019;109:254-62.
48. Haack TB, Madignier F, Herzer M, Lamantea E, Danhauser K, Invernizzi F, et al. Mutation screening of 75 candidate genes in 152 complex I deficiency cases identifies pathogenic variants in 16 genes including NDUFB9. Journal of medical genetics. 2012;49(2):83-9.
49. GeneCards Organization. 1996-2022.

Footnotes and Financial Disclosures

Conflict of interest:

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