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In silico analysis of genes and molecular pathways involved in the pathogenesis of follicular lymphoma

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Abstract

Background: Follicular lymphoma (FL) is a common form of non-Hodgkin lymphoma, characterized by abnormal B-cell growth within the germinal center. Research has shown the role of genes and molecular pathways in the pathogenesis of FL. However, the main factor of pathogenesis has not been determined. Therefore, in this study, the genes and molecular pathways related to the pathogenesis of FL were evaluated using a systems biology approach.

Materials and Methods: In this study (bioinformatics analysis), the GSE32018 database was used for data analysis. This database was extracted from Gene Expression Omnibus (GEO). The sample of this database was 36, which included normal and FL samples. For this purpose, 23 cases were FL and 13 were healthy samples. Protein-protein interaction (PPI) is performed to show the interaction between DEGs. STRING software is used for this purpose. Associations between the hub genes, transcription factors, and microRNAs were assessed using the miRTarBase and TRRUST databases. The criteria used for data analysis included log fold change greater than one and $p < 0.05$.

Results: After evaluating and analyzing the data, the results showed that 866 DEGs were identified between the control and FL samples. Of this population, 231 cases of UP regulation and 635 cases of downregulation were in FL samples compared to control samples. PPI network and hub gene analyses identified 7 hub genes, including RPL37A, MRPS7, RPS14, RPS28, RPL34, RPS20, and RPS3. According to the results, hsa-miR-191-5p has the highest interactions with hub genes among miRNAs, and KDM5A has the most interactions among TFs.

Conclusion: Identifying genes and molecular pathways can be effective in designing therapeutic strategies and preventing the proliferation of FL cells, thereby increasing patients' survival.

Keywords: Follicular Lymphoma; Molecular Genetics; Bioinformatics

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Introduction

Follicular lymphoma (FL) is a common form of non-Hodgkin lymphoma, characterized by abnormal B-cell growth within the germinal center (1). Despite significant progress in diagnosing and treating FL, there is no comprehensive research on underlying molecular factors driving its development for tailoring personalized therapeutic approaches (2). In this context, unraveling the key genes and molecular pathways involved in FL pathogenesis is of great importance (2). Previous studies have provided valuable insights into the genetic alterations and disrupted signaling pathways associated with FL progression. Using advanced

bioinformatics tools and high-throughput technologies, researchers have identified and characterized these molecular abnormalities (2).

One particularly significant pathway implicated in FL is the B-cell receptor (BCR) signaling pathway. Dysregulation of this pathway has consistently been linked to the initiation and maintenance of FL. Perturbations in critical components, such as CD79A and CD79B (genes encoding BCR accessories), disrupt normal B-cell activation and enhance the survival of malignant cells (3, 4).

Additionally, the overexpression of the BCL2 gene encoding the anti-apoptotic protein of Bcl-2 has emerged as a hallmark genetic alteration in FL. Translocation events involving the BCL2 gene result in elevated levels of Bcl-2 protein, disrupting the cell's usual process of apoptosis and promoting its prolonged survival (5). Furthermore, several other genes and molecular pathways contribute to FL pathogenesis (5). Notably, the amplification of the MYC gene and mutations in epigenetic regulators like EZH2 have been associated with aggressive disease behavior and poorer treatment outcomes (6).

Using genomic data obtained through large-scale sequencing efforts, bioinformatic analyses have opened new horizons to understand the intricate interplay between multiple genes and functional pathways responsible for FL pathogenesis. These computational approaches allow for integrating various omics data, facilitating the creation of a comprehensive landscape, and illustrating the molecular alterations that drive FL (7).

This research is an effort to conduct a bioinformatic analysis that comprehensively explores the involvement of genes and molecular pathways in FL pathogenesis. Using publicly available datasets and employing cutting-edge bioinformatic methods, it is aimed to identify key molecular players, potential targets for therapeutic intervention, and prognostic markers associated with FL. Furthermore, another objective of this research is to unravel the intricate cross-communication and interdependencies between genetic alterations and aberrant signaling pathways, shedding light on the fundamental mechanisms driving FL progression.

Materials and Methods

Determination of GSE and analysis

In this study, the GSE32018 database extracted from Gene Expression Omnibus (GEO) was used for data analysis. The samples of this database were 36, including normal and FL samples. For this purpose, 23 cases were FL and 13 cases were healthy samples. Lymph nodes were analyzed as FL samples for investigation. Boxplots were used to normalize samples in the dataset and visualize the data distribution. The median of each sample group was examined to assess central tendency and detect any potential outliers. R software (version 4.3.1) was used to evaluate differentially expressed genes (DEGs) between two groups. The criteria used for data analysis included log fold change greater than one and $p < 0.05$.

Determination of Gene ontology and KEGG pathway

Gene Ontology (GO) (https://maayanlab.cloud/Enrichr/) was evaluated based on three factors: molecular functions (MF), cellular components (CC), and biological processes (BP). Biological processes associated with DEGs are usually evaluated using GO.

Also, the Kyoto Encyclopedia of Genes and Genomes (KEGG) was analyzed to evaluate molecular pathways related to DEGs. The criteria used for this analysis was $p<0.05$.

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Determination of hub genes based on the PPI network

Protein-protein interaction (PPI) is performed to show the interaction between DEGs. In general, PPI is used to evaluate the relationship between genes or proteins with each other. In addition, hub genes are defined based on the interaction between genes or proteins. STRING software (https://string-db.org/) is used for this purpose. Besides, to determine hub genes, Degree, Betweenness, Closeness, DMNC, MCC, and MNC (version 0.1) associated with DEGs are specified.

Association between hub genes with transcription factors and miRNAs

After determining the hub genes, their relationship with microRNAs (miRNAs) and transcription factors (TFs) is investigated using two databases, i.e., miRTarBase and TRRUST. At first, the interaction between hub genes and microRNAs (miRNAs) was evaluated using the miRTarBase database (https://mirtarbase.cuhk.edu.cn/). The association between hub genes and transcription factors (TFs) was also investigated. TRRUST database (https://www.grnpedia.org/trrust/) was used for this purpose.

Results

Characteristics of DEGs

The boxplot shows the distribution of data within each sample group. It visually represents the median, quartiles, and potential outliers. If the data within each sample group follows a normal distribution, the box plot will exhibit a symmetrical shape with the median line positioned at the center of the box, indicating that the data is evenly distributed around the median. After evaluating and analyzing the data, the results showed that 866 DEGs were identified between the control and FL samples. Of these, 231 cases of UP regulation and 635 cases of downregulation were in FL samples compared to control samples. Fig. 1 illustrates DEGs through the volcano plot.

Gene Ontology enrichment

In terms of BP (Fig. 2a), the DEGs were mainly involved in positive regulation of transcription by RNA polymerase II, cellular response to cytokine stimulus, and regulation of inflammatory responses. Concerning CC (Fig. 2b), they were mainly involved in cell-substrate junction, focal adhesion, and early endosome. Based on MF (Fig. 2c), they were mainly involved in sequence-specific DNA binding, sequence-specific double-stranded DNA binding, and double-stranded DNA binding. Furthermore, regarding the KEGG pathway (Fig. 3a), they were mainly involved in pathways in cancer, cytokine-cytokine receptor interaction, and coronavirus disease. Also, in terms of the Reactome pathway (Fig. 3b), they were mainly involved in the immune system, signaling by interleukins and muscle contraction.

PPI network and hub genes:

Fig. 4 presents the interaction of DEGs based on STRING and Cytoscape analysis in terms of PPI. Also, Fig. 5 shows the interconnected sub-networks represented 2 main clusters. As can be inferred from the analysis results, the main hub genes based on the analysis included RPL37A, MRPS7, RPS14, RPS28, RPL34, RPS20, and RPS3 (Fig. 6).

Association of miRNAs and TF with hub genes:

Based on miRTarBase database analysis, hsa-miR-191-5p as miR had the most interactions with hub genes. However, based on the TRRUST database analysis, KDM5A as a TF had the highest interaction with hubgenes.

Survival analysis of the hub genes

A comprehensive survival analysis of the hub gene was performed using

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PrognoScan, a powerful tool for investigating gene expression patterns and their impact on patient outcomes. This in-depth analysis delved into the intricate relationship between the expression levels of the hub gene and survival time (overall survival, OS) across diverse microarray datasets. By applying stringent criteria, the threshold for significance was established at a Cox p-value of <0.05, ensuring robust statistical significance and reliability in the findings.

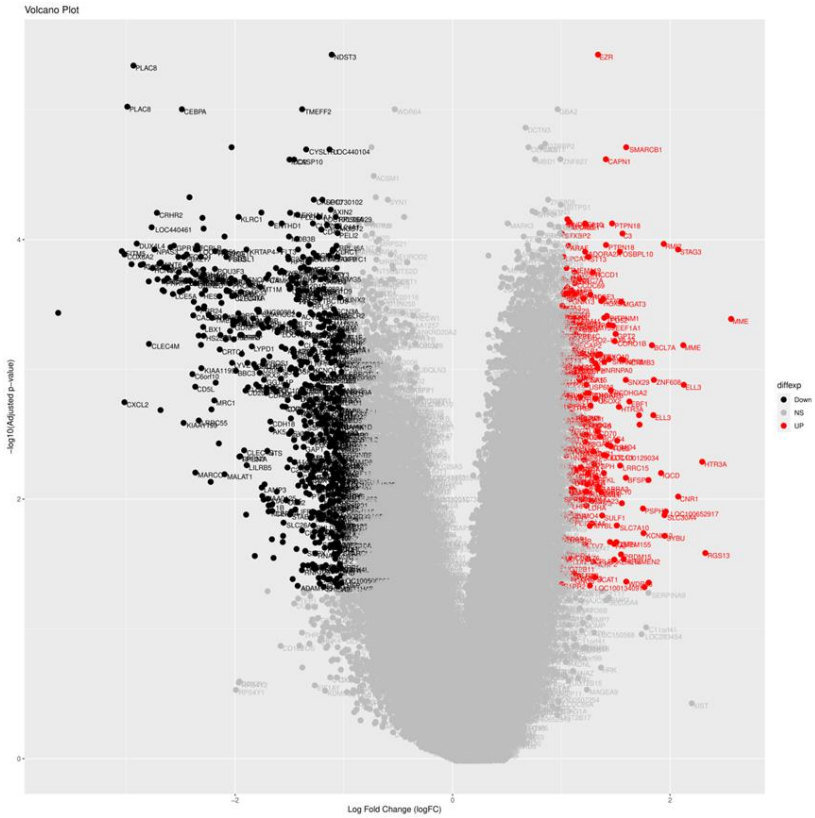

Fig 1. The volcano plot of DEGs; the plot shows the up-and down-regulated genes related to DEGs.

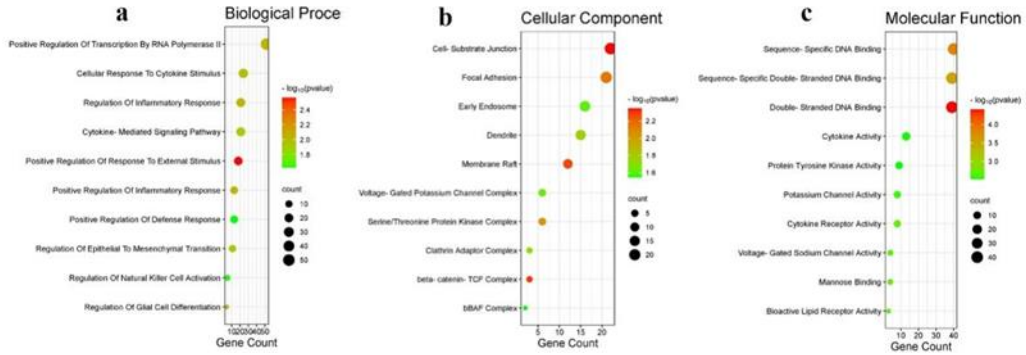

Fig 2. The results of GO enrichment of DEGs; the results of GO enrichment including BP, CC, and MF; a) BP, including inflammation, activation, and cell differentiation; b) CC, including membranes, endormes, and extracellular areas; c) MF, including ion channels, lipid and sugar metabolism, and genome transcription (abbreviations: GO, Gene Ontology; BP, biological process; CC, cellular component; and MF, molecular function)

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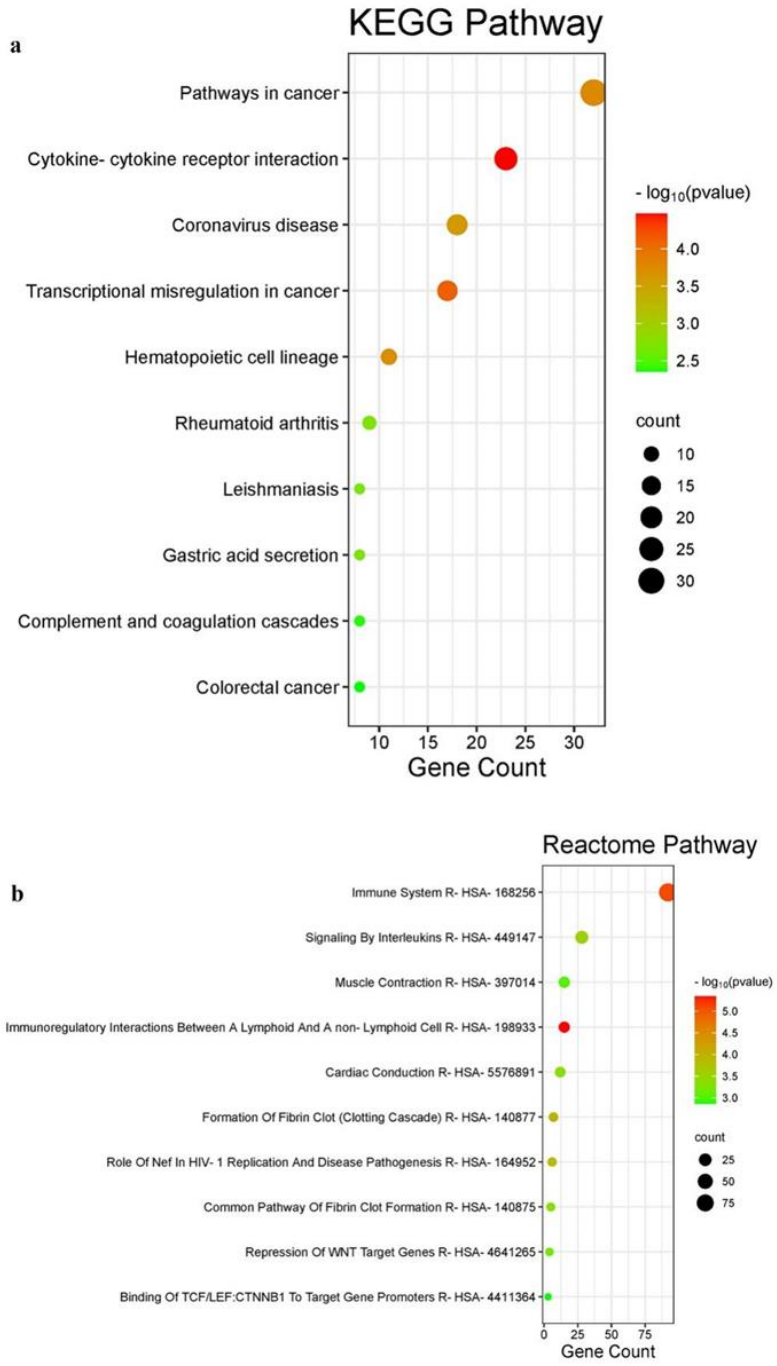

Fig 3. a) KEGG pathways related to DEG; these pathways included cancer, infectious agents, complement and rheumatology diseases and b) the paths involved with the rectome; These pathways included the immune system, heart cells, coagulation pathways, and microbial factors.

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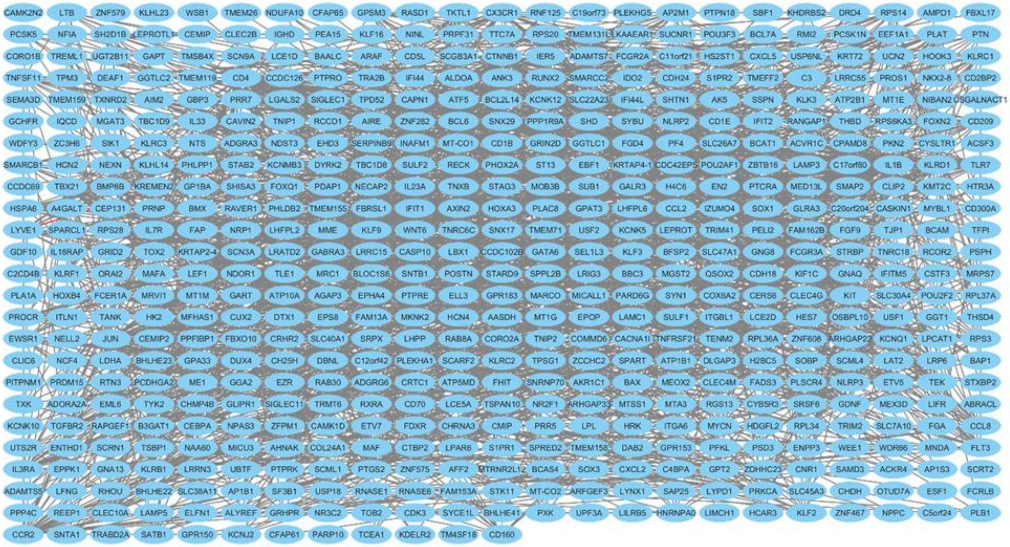

Fig 4. Net interaction between DEGs; the PPI of DEGs was conducted using the STRING database and Cytoscape software. The blue and black colors represent protein and interaction between proteins, respectively.

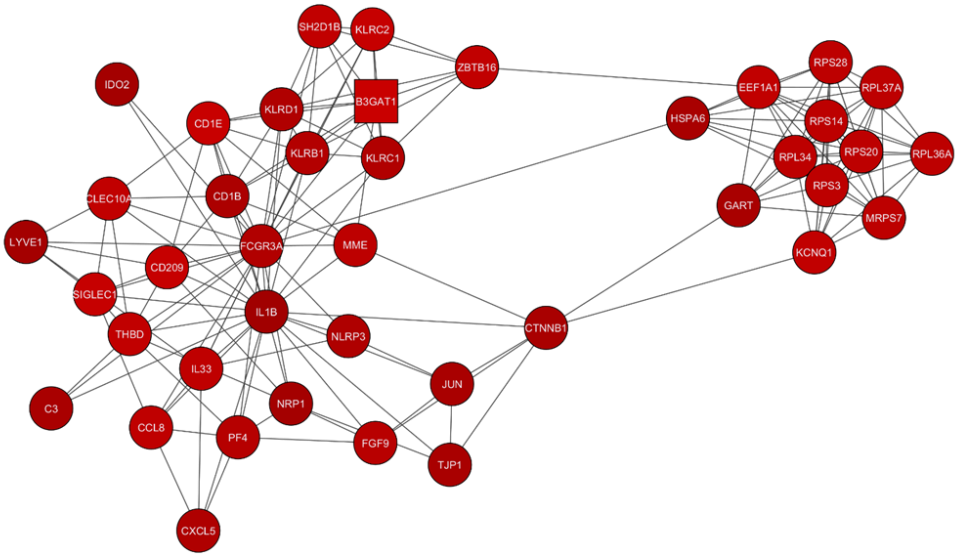

Fig 5. The interaction between sub-network of PPI. Every sub-network has distinct biological function.

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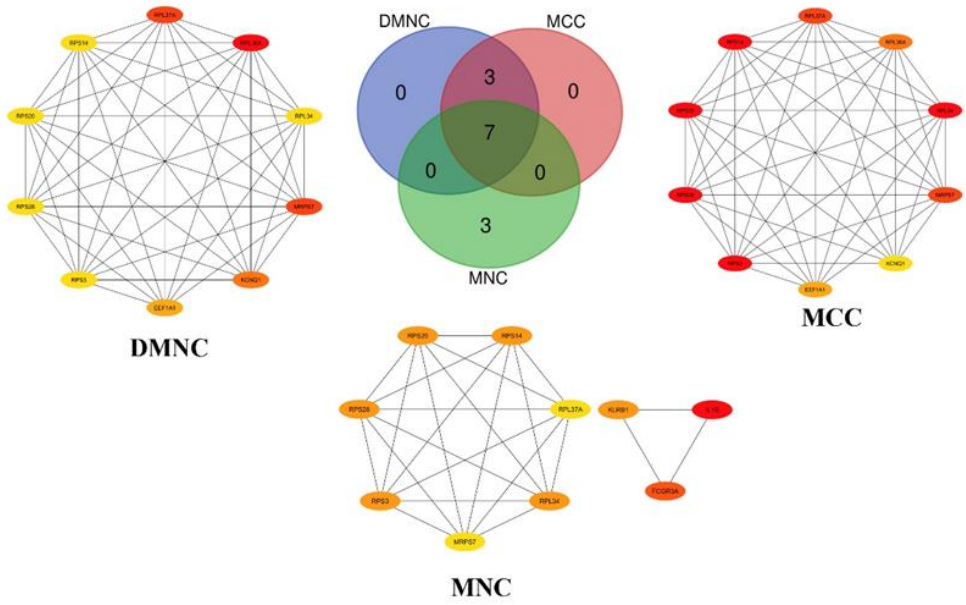

Fig 6. CytoHubba PPI network and Venn diagram for identifying the hub genes

Discussion

FL stands as the second most prevalent subtype of non-Hodgkin lymphoma (NHL) in the United States. It is characterized by its systemic involvement of lymphoid tissues, marked by the infiltration of germinal center B cells, and it is generally categorized as a slow-growing lymphoma (8-10).

Quantitative bioinformatics approaches have been performed to detect genes involved in the pathogenesis of FL. For instance, Zhang et al. showed that FN1, SPARC, POSTN, MMP9, and VCAM1 play an essential role in the pathogenesis and progression of FL (11). In another study, Jiang et al. showed that UBA52, RPL28, and RPL3 genes can be suitable factors for target therapy in FL patients (12).

Genetic changes and mutations are among the common factors contributing to the initiation and progression of FL (10). Molecular signaling pathways play a pivotal role in the pathogenesis of FL. Notably, the PI3K signaling pathway plays a key role in regulating B cell activity by modulating the c-MYC/miR17-92/Pten axis. This pathway leads to the up-regulation of microRNA17-92 by c-MYC, thereby inhibiting Pten and enhancing the activity of the PI3K pathway in tumorigenesis (13, 14). Additionally, miR-17-5p and miR-20-a play a crucial role in regulating E2F1, a direct target of c-MYC, thereby affecting cell cycle control and progression (14, 15).

The pathogenesis of FL is significantly impacted by microRNAs (miRNAs). MiR-155's involvement in FL pathogenesis is attributed to its activation of the PI3K/AKT, NF-KB, and JAK1/STAT3 pathways. It facilitates promoting the growth and survival of FL cells by increasing the expression of Bcl-2 and MYC, while concurrently suppressing apoptosis through MDM2 and ARF (16). Moreover, miR-155 can suppress two tumor suppressor genes, CREBBP and KMT2D and exhibits a direct link between miR-155 levels and the PIK3R1-PDK/AKT-FOXO3α-cMYC axis. This pathway regulates the K-RAS and glucose

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metabolism in cancer cells and can be considered a therapeutic target (16).

Similarly, miR-21 promotes cell growth by down-regulating the expression of PTEN and PDCD4, activating the RasA1/Raf/Mek/Erk and PI3K/Akt/mTOR pathways. It further enhances cell proliferation through the TNFα/TNFR2 pathway, promoting the expression of TRAF2 and NF-KB/JNK while inhibiting apoptosis through the TRADD/FADD/caspase8-3 pathway (17). Besides, miR-146a is known as a tumor-suppressing miRNA that decreases in malignant cells. It effectively inhibits cell growth and survival by reducing the expression of IRAK1 and TRAF6; cited down-regulation is observed via the MAPK and PI3K pathways.

In this respect, has-miR191 can regulate cell growth and survival by targeting MYC and c-Myb. Also, miR-191 increases cell proliferation by activating the ESR1/ESR2 and NDST1 pathways and inhibiting SOCS2, Mxi1, and EGR1. CDKN1A/p21 and SOCS2 expression are directly regulated by miR-20a/miR-20b and miR-194, which are involved in the pathogenesis of FL (2, 17-27). Different miRNAs can generally affect disease progression and severity by regulating the expression of various genes. Activated signaling pathways mediated by miRNAs can be considered therapeutic targets.

Various genes also play a significant role in the development of FL, especially genes associated with B cell development, immune surveillance, and the BCR-NF-KB and JAK/STAT signaling pathways. Mutations in these genes are among the most prevalent abnormalities of FL (28). Genes like MEFB, CARD11, MYD88, STAT3/6, and RRAGC are over-expressed in FL, actively participating in the NF-KB, PI3K/AKT, JAK/STAT, and MAPK signaling pathways in the pathogenesis of FL. In contrast, the expression of EBF1, TNFAIP3, EPHA7, Pten, and SOCS1 genes decreases in FL (2, 6, 17, 27, 29, 30).

Ribosomal proteins, including RPL37A, MRPS7, PRS14, RPS28, RPL34, and RPS20, play crucial roles in various cellular processes such as cell growth, proliferation, survival, epithelial-mesenchymal transition (EMT), cell migration, and invasion. Several signaling pathways govern the expression of these genes at the mRNA level (12, 31-34). For instance, the PI3K/AKT signaling pathway elevates the expression of BCL2, BIRC5, and RPS7 by activating the NF-κB transcription factors. Also, it enhances the expression of CCND2 and MYC through c-Myc activation. MiR-16 and miR-29 target cMYC and are believed to inhibit BCL2 (6).

RPS7 knockdown leads to increased P85α and AKT2 expression, while silencing of RPS7 reduces the levels of ERK1/2, MEK1/2, and P38 and their phosphorylated forms (35, 36). RPL11 suppresses Myc expression, and RPS29 induces apoptosis by regulating P53 and BCL-2. The interaction between GNL1 and RPS20 regulates cell proliferation by activating the mTOR-AKT and ERK-MAPK pathways. Inhibiting RPS20 lowers CDK4, Cyclin-D1, and N-cadherin expression and increases E-cadherin expression. Furthermore, RPS20 knockdown inhibits cellular proliferation, migration, and invasion by suppressing the MAPK/AKT/ERK/JNK/P38 pathway (37-40).

RPL37A, PRS15, and RPS20 regulate the Mdm2-P53-MdmX axis, leading to P53 activation and Mdm2 E3 ligase inhibition, thereby causing cell cycle arrest and death (33). RPL34 plays a pivotal role in tumor progression by increasing the expression of oncogenes in the MAPK/ERK and Myc pathways and reducing the expression of pRB and P53 (41). Reduced RPL34 inhibits cell proliferation, cellular migration, metastasis, and EMT by

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activating the JAK2/STAT3 pathway. Underexpression of RPL34 also inhibits Cullin-Associated NEDD8-Dissociated Protein1 (CAND1) regulation. This regulation controls proteins related to the cell cycle, metastasis, and lymphoma-genesis (42, 43). FL progression can be prevented by blocking the activation of genes and molecular signaling pathways that lead to metastasis, proliferation, and migration.

This study used microarray data to investigate follicular lymphoma's molecular pathways and hub genes. While microarray analysis offers valuable insights into the gene expression patterns associated with follicular lymphoma, it has some inherent limitations, particularly regarding sample size.

Given the restricted sample size in this study, further experimental validation is required to corroborate our findings. In this respect, additional experimental validation (qRT-PCR and Western blotting) is recommended.

Conclusion

Understanding the connections between signaling pathways and miRNAs in FL is crucial for developing new and more effective treatments. One approach to target signaling pathways in FL is using miRNA inhibitors. MiRNA inhibitors are molecules that can bind to miRNAs and prevent their binding to target mRNA. Another approach for this purpose is to use drugs targeting the involved genes in these pathways, such as those targeting the PI3K/AKT or MAPK/p38 pathways. These drugs may offer greater efficacy than current FL treatments and potentially fewer side effects. Nevertheless, further research is necessary to evaluate these new drugs' safety and efficacy in FL patients.

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Authors' contribution

H.R design the study. B.Sh, N.K, F.Gh, A.R.R.A, write the manuscript. M.H.M and Sh.Gh revise the manuscript. E.K analysis data.

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Not applicable

Availability of data and materials

Data availability is the corresponding author's responsibility.

Ethics approval and consent to participate

IR.IUMS.REC.1402.179

Conflict of interest

The authors declare that they have no conflict of interest.

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