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Identification and Elucidation of Therapeutic Targets in Nasopharyngeal Carcinoma: A Computational Approach

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ABSTRACT

Nasopharyngeal Carcinoma (NPC) is a malignant epithelial tumor arising from the mucosa of the nasopharynx and has a geographical distribution. It is commonly seen in East and Southeast Asia, South-Central Asia, and North and East Africa. This type of malignancy is highly linked to Epstein-Barr Virus (EBV) infection. It is also characterized by a late diagnosis, high recurrence rate, and low therapeutic treatment options in advanced stages. The purpose of the current study was to find hub genes and possible therapeutic targets for nasopharyngeal carcinomas through bioinformatics approaches. In this study, gene expression data were obtained from the GEO database GSE53819, which consisted of 18 samples of Nasopharyngeal Carcinomas and 18 normal nasopharyngeal samples. Differential gene expressions analysis was done using GEO2R based on an adjusted p-value of <0.05 and fold change logFC >1.5 cut-off values. GO and KEGG pathway enrichment analysis of DEGs was conducted using multi-statistics including Wilcoxon rank-sum test, Fast Gene Set Enrichment Analysis (FGSEA), and Kolmogorov-Smirnov (KS) test in CPA. Construction of Protein-protein Interaction (PPI) network and selection of hub genes were carried out using STRING and Maximal Clique Centrality (MCC), respectively. A total of 11,331 DEGs were initially found, with 250 high-confidence DEGs determined via filtering. Eleven KEGG pathways with significant enrichment were identified, such as cytokine-cytokine receptor interaction, ECM-receptor interaction, focal adhesion, IL-17 signaling pathway, and TNF signaling pathway. Analysis of PPI network was used to select 10 key genes acting as master regulators for NPC, which included IL1B, FN1, CXCL8, CD19, CSF2, IFNG, COL1A1, CXCL10, FCGR3A, and CXCL12. Among these key genes, five hub genes, IL1B (Interleukin-1 beta), FN1 (Fibronectin), CXCL8 (C-X-C motif chemokine ligand 8), CXCL12 (Stromal cell-derived factor 1), and COL1A1 (Collagen alpha-1 [I] chain) play important roles. Topology analysis of network also suggested

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the existence of two oncogenic modules in NPC pathogenesis that included an inflammatory cytokine-chemokine axis (IL1B–CXCL8–CXCL12) and an ECM remodeling axis (FN1–COL1A1). Both two modules can contribute to tumor immune evasion and NPC progression by working together.

Keywords: bioinformatics, differentially expressed genes (DEGs), expression profiles, gene ontology, hub genes, nasopharyngeal carcinoma, therapeutic targets, tumor microenvironment

1. INTRODUCTION

Nasopharyngeal cancer (NPC) begins in the epithelial layer of the nasopharynx and is one of the more frequent head and neck neoplasms [1, 2]. According to statistics, globally, the incidence rate of NPC has traditionally been below 1 case per 100,000 person-years in many regions of the globe [3]. The tumor is especially prevalent in southern China, wherein most of the cases seen are poorly differentiated or undifferentiated in nature, having a high level of malignancy, while those seen in Western countries tend to be well-differentiated tumors with lower malignancy [4]. Geographical distribution for NPC patients is centered on Southeast and East Asia, North Africa, and South-Central Asia [3].

Common symptoms for NPC patients include a cervical mass, nasal blockage, middle ear fluid collection, conductive hearing loss, numbness, and headaches [4, 5]. Imaging workup generally includes both cross-sectional CT and MRI, coupled with histopathological confirmation via endoscopic tumor biopsy [4]. The etiology behind NPC is diverse and includes various factors, such as genetic predisposition, dietary habits, and EBV infection [4, 6]. EBV infection is closely associated with NPC, and affected patients have high levels of immune antibodies against EBV-related proteins, such as VCA-IgA and EA-IgA [6]. NPC is radio-sensitive, so external beam radiotherapy serves as the main form of treatment for the condition [4]. However, NPC patients are usually treated with both chemotherapy and radiation therapy, while surgery is performed in case of salvage only for recurrence, depending on the stage of the disease [4]. The decision regarding the type of treatment to administer depends largely on the staging of the disease by the oncologist [4]. The survival rate for early-stage NPC over a period of five years is around 80%, whereas for advanced-stage disease is roughly 50% [7]. If radiotherapy fails, the tumor persists at the primary location as well as regional lymph nodes, and distant metastases might occur, especially if the cervical lymph nodes had been involved significantly during the initial stages of the disease [4, 8]. Tumor persistence or recurrence occurs at the site of nasopharynx in a small proportion of NPC patients, for which salvage treatment may be an option [4].

During tumor initiation and progression, several genetic and epigenetic mutations cause the pathogenesis of NPC. Among them, DNA methylation modifications have been considered critical epigenetic factors for NPC pathogenesis [1]. Whereas, genome-wide regulation abnormalities and differently-regulated genes obtained from bioinformatics study further prove that this disease is of complex molecular origin [9]. NPC develops due to both genetic predisposition and environmental exposures [4, 6]. Risk factors from the environment include dietary components, such as eating salted fish, as well as certain lifestyle factors. However, genetic susceptibility also plays an important role in the development of the disease [4, 6, 7]. With the help of high-throughput analysis via the use of Gene Expression Omnibus (GEO), it is possible to identify multiple tumor-specific genes in NPC [9]. Unfortunately, although efforts have been made to analyze microarray data, comprehensive gene regulatory network in NPC remains to be established yet.

The current study aimed to identify differentially expressed genes (DEGs) using gene expression profiling data sourced from the GEO database. The identified DEGs were further mapped to respective pathways and screened for the top 10 hub genes that are important in NPC regulation. These findings may contribute to early diagnosis, prognostication, and the identification of novel therapeutic targets for NPC by facilitating key biomarker discovery.

2. MATERIALS AND METHODS

2.1. Data Source

For analysis, gene expression profile, GSE53819 was obtained from GEO database (http://www.ncbi.nlm.nih.gov/geo), which is a publicly accessible database [10]. To access the data, the study applied search criteria focused on primary tumors related to NPC as well as non-cancerous nasopharyngeal tissue samples from *Homo sapiens*. Furthermore, the study utilized Agilent-014850 Whole Human Genome Microarray 4x44K G4112F chip platform (GPL6480). The dataset retrieved for GSE53819 contained 36 samples, consisting of 18 primary tumors associated with nasopharyngeal carcinoma and 18 normal nasopharyngeal tissue samples [9].

2.2. Differential Expression Genes (DEGs)

All the DEGs were detected and analyzed by the online GEO2R platform [11]. The identified DEGs were filtered using specific criteria including a Log Fold Change (logFC) of at least 1.0 and an adjusted p-value of 0.05 or lower. To reduce DEGs screening to a meaningful number, logFC was finally adjusted to greater than 1.5, where the retrieved genes with positive and negative logFC values were upregulated and down-regulated, respectively [1, 9]. Two-step filter criteria were intentionally used to iteratively reduce the DEG list to ensure that only those exhibiting significant and biologically relevant differences in their expression were included for further use in the downstream network and pathway analysis steps.

2.3. Characterization of Differently Expressed Genes (DEGs)

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were conducted using the CPA tool accessible at (http://cpa.tinnguyen-lab.com/) [12]. CPA (Consensus pathway analysis) tool was selected due to the possibility to leverage multiple independent statistical tools to prioritize the biological pathways. Three different methods were used in the current work: the Wilcoxon rank-sum test, FGSEA (Fast Gene Set Enrichment Analysis), and the Kolmogorov-Smirnov test. This made it possible to prioritize the pathways based on the consensus among the three used methods. Additionally, the Database for Annotation, Visualization, and Integrated Discovery (DAVID) were used to validate the findings from the CPA analysis. This online resource compiles biological data and offers a variety of functional annotation details for proteins and genes. Researchers can leverage this platform to obtain information about the role and signaling pathways associated with specific genes. To gain a high-level understanding of gene functions and establish connections between genomic information and large-scale molecular datasets, the researchers also utilized the KEGG database. During the DAVID analysis, a statistical threshold of $P<0.05$ was employed, ensuring that the results obtained were reliable and meaningful [13].

2.4. Protein-protein Interaction (PPI) Network of DEGs

The STRING database, which is accessible online, was employed to identify potential interactions and construct networks [14]. To avoid the false positive interactions, the nodes resulting in a confidence score below 40% were excluded from the network. The minimum confidence level of 0.4 (medium confidence) was chosen. This is because this level is considered to provide an optimal trade-off between the sensitivity and specificity of the interactions identified in cancer-related network biology research. Moreover, it is also considered as the most reliable choice among all other levels available. The dataset prepared in STRING was exported to Cytoscape, where the Cytohubba plugin was used for the identification of top hub genes. The Maximal Clique Centrality (MCC) algorithm was used for hub gene selection as it provides the highest performance compared to other centrality measures when identifying biologically important hub genes in interaction networks [15].

3. RESULTS

All the analyses were carried out on the genome-wide expression profile GEO dataset, GSE53819. For the patients with NPC, the average age recorded in the dataset was 46 years, compared to 45 years for those in the non-cancerous group. Approximately, one-third of the patients in the study were females, and samples were collected before the initiation of any anti-cancer treatment in the People's Republic of China.

3.1. Identification of DEGs

In these analyses, DEGs refer to those genes that can exhibit a notable variation in expression levels (up or downregulation) between the two biological conditions, such as normal tissue and cancer tissue, or between two distinct cell types [13]. To screen the DEGs, the study used Gene Expression Profile GSE53819 from the GEO database. The dataset contained 36 samples that comprised 18 each of nasopharyngeal carcinoma primary tumors and control or normal samples [7]. The detection of DEGs was calculated using a p-value threshold of <0.05, and to analyze a meaningful dataset, later all those genes were filtered with a logFC>1.5. Initially, a total of 11,331 DEGs were calculated, which were reduced to 250 upon the application of a stringent logFC filter, where 213 and 37 genes were found in the up-regulated and down-regulated panels, respectively. Among the notable upregulated genes, LTF (lactotransferrin), C20ORF85

(Chromosome 20 open reading frame 85), and C7 (Complement component 7) showed the highest fold change (logFC) value by 6.249, 5.439, and 5.34. Among the down-regulated genes, HOXB13 (homeobox B13), MMP3 (matrix metallopeptidase 3), MMP1 (matrix metallopeptidase 1), and HOXC8 (homeobox C8) showed the fold change of -6.387,-6.353,-5.36, and -4.481, respectively (Figure 1).

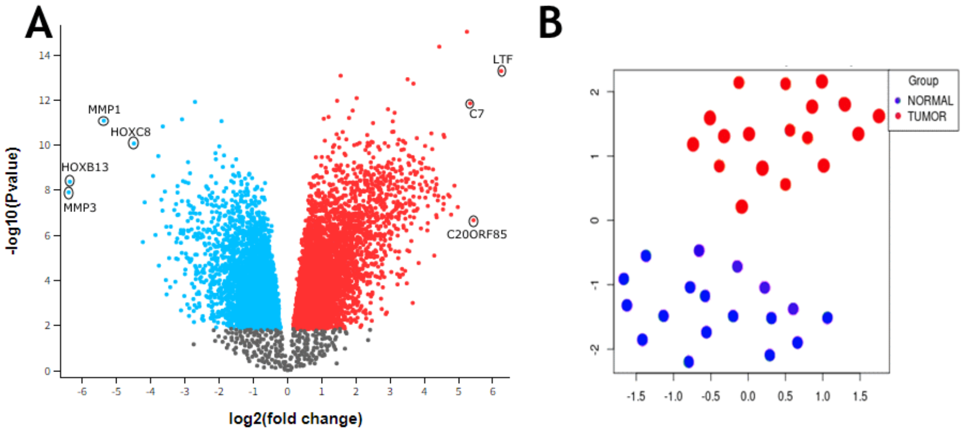

Figure 1. Analysis of Differentially Expressed Genes in the NPC. (A) Volcano Plot of Gene Expression in GSE53819 Dataset. Cyan and Red Represent Down and Upregulated Genes. (B) Uniform Manifold Approximation and Projection (UMAP) of Samples in the GSE53819 Dataset.

In summary, the most significant DEGs were filtered out from the analyzed GSE53819 NPC dataset. It was found that the majority of the genes showed upregulation between cancerous and normal NPC tissues.

3.2. Enrichment Analysis for Gene Ontology (GO) Terms and KEGG Pathways

GO and KEGG pathway enrichment analysis are bioinformatics applications, normally used for the identification of the biological functions and pathways that are enriched. The results can be used to understand and highlight the biological mechanisms underlying a particular condition, such as a disease or a treatment response. GO describes the framework for categorizing molecular roles, biological activities, and cellular structures associated with genes and proteins.

The list of observed DEGs in the NPC was analyzed for pathway enrichment with the application of three statistical tests, the Wilcox, FGSEA, and KS-test. For each analysis, the threshold for significance was set at a False Discovery rate (FDR) of less than 5%. The pathways satisfying all three tests, two tests, and one test were considered highly significant, significant, and less significant, respectively. In total, the study detected eleven KEGG pathways, where eight pathways were found highly significant and three pathways were found significant. The highly significant eight pathways included focal adhesion, human Papillomavirus infection, ECM-receptor interactions, cytokine-cytokine receptor interactions, signaling pathways associated with TNF, rheumatoid arthritis, phagosome processes, and IL-17 signaling pathways. Among the significant pathways, PI3K-AKT signaling, osteoclast differentiation, and AGE-RAGE signaling pathways were detected (Figure 2).

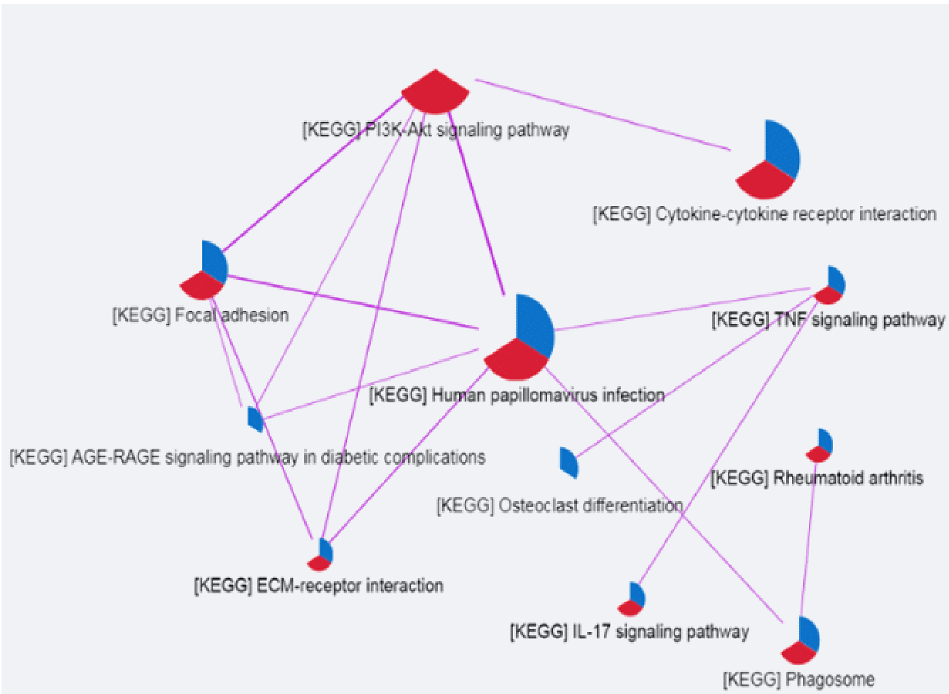

Figure 2. Probing of Target Pathways

Eleven pathways are shown with a circular node having two or three colors. The presence of node colors indicates the statistical significance calculated by Wilcox, FGSEA, and KS-Test. A node with three colors means the satisfaction of three tests and vice versa.

To validate these pathways, the study utilized the DAVID platform (https://david.ncifcrf.gov/) and found a similar result that suggested a cytokine-cytokine receptor pathway with major DEGs contribution (Table 1).

Table 1. Validation of Pathways by DAVID

S. No	Pathway Description	Count	%	*p*-value	P_{BH}-value
1	Cytokine Cytokine Receptor Interaction	49	4.4	1.1E-12	3.3E-10
2	Human Papillomavirus Infection	28	2.5	1.5E-2	1.8E-1
3	PI3K-Akt signaling pathway	26	2.3	7.9E-2	6.4E-1
4	Viral Protein Interaction with Cytokine and Cytokine Receptor	20	1.8	8.4E-7	8.2E-5
5	Chemokine signaling pathway	23	2.0	4.5E-4	11.5E-2
6	Focal adhesion	17	1.5	6.3E-2	5.3E-1
7	ECM-receptor interaction	18	1.6	2.5E-6	1.5E-4
8	IL-17 signaling pathway	19	1.7	1.4E-6	1.1E-4
9	Rheumatoid Arthritis	14	1.2	1.1E-3	2.6E-2
10	Hippo Signaling Pathway	14	1.2	6.9e-2	5.7E-1

To assign a possible biological function, the GO analysis of detected DEGs was performed. The results were organized into three main categories, that is, biological processes, cellular components, and molecular functions. In the category of biological processes, DEGs were enriched in cell adhesion**,** inflammatory response**,** signal transduction**,** immune response**,** cell differentiation**,** cilium movement**,** cell-cell signaling**,** extracellular matrix organization, chemotaxis, and neutrophil chemotaxis. However, it was observed that the majority of the DEGs were picked from the extracellular and perinuclear regions. The DEGs were found to be enriched in a wide array of molecular functions, such as those related to the extracellular matrix, integrin and heparin binding, as well as calcium ion interactions. Moreover, the presence of activities related to cytokines and chemokines, in addition to functions providing tensile strength to the extracellular matrix, was also noted. Furthermore, the DEGs exhibited the potential to bind to CXCR chemokine receptors, proteases, and other receptors (see Table 2).

Table 2. GO Enrichment Analysis of the DEGs Observed in the NPC Patients and Control

Category	Term	*n*	%	*p*-value	P_{BH}-value
GOTERM_BP	Cilium movement	23	2.0	1.5E-16	5.7E-13
	Cell adhesion	74	6.6	9.9E-15	1.8E-11
	Inflammatory response	55	4.9	4.1E-11	5.2E-8
	Signal transduction	98	8.7	6.6E-6	1.4E-3
	Immune response	58	5.2	1.3E-9	1.9E-6
	Cell differentiation	119	5.2	2.6E-9	1.5E-6
	Cell-cell signaling	30	2.7	2.9E-6	8.2E-4
	Extracellular matrix organization	26	2.3	4.6E-7	1.9E-4
	Chemotaxis	21	1.9	2.1E-6	6.5E-4
	Neutrophil chemotaxis	19	1.7	6.5E-8	4.1E-5
GOTERM_CC	Extracellular region	229	20.4	1.7E-31	9.6E-29
	Integral component of plasma membrane	137	12.2	3.1E-14	4.3E-12
	Plasma membrane	356	31.7	9.1E-12	7.2E-10
	Extracellular space	203	18.1	3.6E-26	9.9E-24
	Cell surface	70	6.2	7.8E-10	4.8E-8
	Motile cilium	33	2.9	1.7E-15	3.1E-13
	Extracellular matrix	39	3.5	1.7E-9	9.2E-8
	Axoneme	29	2.6	1.8E-12	2.0E-10
	Axoneme microtubule	15	1.3	5.9E-10	4.1E-8
	9+2 motile cilium	13	1.2	6.7E-12	6.2E-10

Category	Term	*n*	%	*p*-value	P_{BH}-value
GOTERM_MF	Extracellular matrix structural constituent	28	2.5	1.3E-9	1.3E-6
	Integrin binding	26	2.3	6.0E-7	1.0E-4
	Heparin binding	31	2.8	5.1E-9	1.7E-6
	Calcium ion binding	78	6.9	3.3E-9	1.6E-6
	Cytokine activity	28	2.5	1.6E-6	2.0E-4
	Chemokine activity	16	1.4	1.5E-8	3.7E-6
	Extracellular matrix structural constituent conferring tensile strength	12	1.1	4.3E-6	4.8E-4
	CXCR chemokine receptor binding	9	0.8	2.0E-7	4.1E-5
	Receptor binding	41	3.6	3.1e-5	3.1E-3
	Protease binding	15	1.3	1.5e-3	9.6e-2

3.3. Identification of Protein-protein Interactions (PPIs) and Hub Genes

Here, the study aimed for the detection of enriched networks among DEGs to highlight physical or regulatory relationships which can be filtered further for the identification of hub genes. The DEGs interaction network can provide a systems-level understanding of the underlying biological mechanisms of a particular condition and can be used to identify new targets for drug development and biomarker discovery. Subsequently, all identified DEGs were uploaded to the String database. Afterwards, all the experimental and predicted interaction data was mapped which was further used for the NPC network construction. Interactions satisfying the confidence score higher than 0.4, were considered positive interactions, and all the remaining were filtered out. The constructed network contained 119 nodes and 5,040 edges.

In a gene interaction network, hub genes refer to those with a high number of connections or interactions with other genes. Such genes are also seen as master regulators and are significantly associated with disease progression, response, and therapy [14]. This study reported 10 hub genes that retained major connectivity or edges with other candidate genes. These hub genes included IL1B (Interleukin-1 beta), FN1 (Fibronectin), CXCL8 (C-X-C motif chemokine ligand 8) (chemokine interleukin-8/IL-8)), CD19 (B-lymphocyte antigen CD19), CSF2 (Granulocyte-macrophage colony-stimulating factor), CXCL12 - Chemokine (C-X-C motif) ligand 12 (Stromal cell-derived factor 1), isoform (CRA_a), IFNG (Interferon gamma), COL1A1 (Collagen alpha-1(I) chain), CXCL10 (C-X-C motif chemokine 10), and FCGR3A (Low affinity immunoglobulin gamma Fc region receptor III-A). Among them, IL1B and FN1 shared more than 100 connections with other partners, further suggesting a significant role in the NPC (Figure 3).

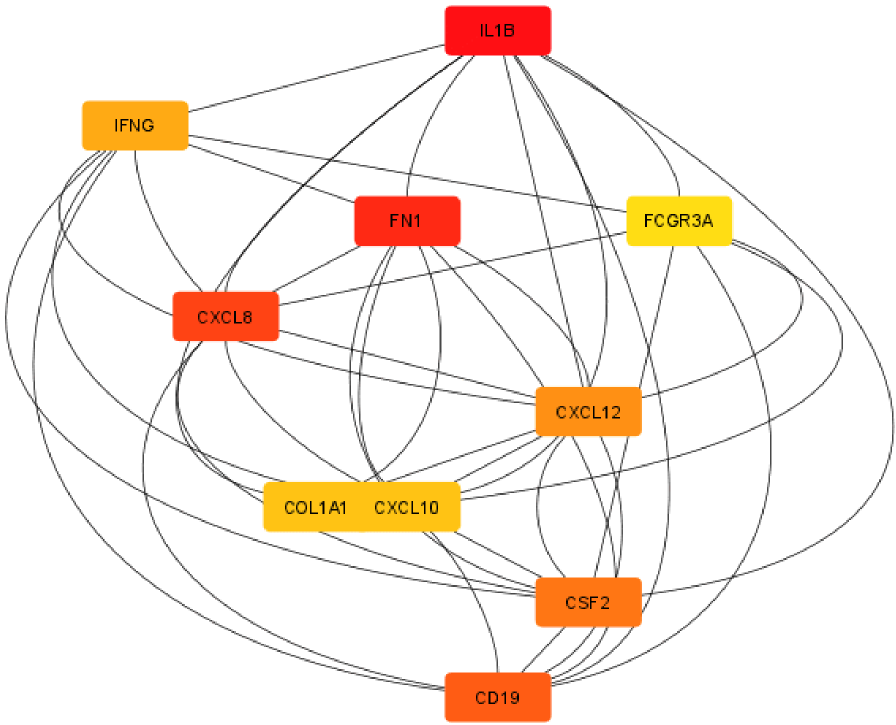

Figure 3. Identification of Hub Genes

The interaction network for hub genes was generated using the STRING database and the Cytoscape software. The network contains the top 10 hub genes. Node depicts the degree of connectivity; red color signifies maximum connectivity.

Subsequently, GO and KEGG pathway analyses were conducted again for these hub-genes that indicated cellular adhesion**,** inflammatory response**,** signal transduction, neutrophil chemotaxis, extracellular region, integrin binding, heparin interactions, binding to calcium ions and components of the extracellular matrix providing structural and tensile strength. The KEGG analysis indicated that these genes are associated with Amoebiasis, cytokine-cytokine receptor interaction, IL-signaling pathways, pathways in Cancer, and AGE-RAGE signaling pathways (Table 3).

Table 3. GO Enrichment and Pathway Analyses for Hub Genes, Detailing the Biological Processes, Cellular Components, and Molecular Functions Involved

Category	Term	*n*	%	*p*-value	Genes
GOTERM _BP	GO:0006955~Immune Response	5	50.0	4.7E-5	FCGR3A,CXCL12,CXCL8,CSF2, IL1B
	GO:0007165~Signal transduction	4	40.0	1.8E-2	CXCL10,CXCL12,CXCL8,IL1B
	GO:0030593~Neutrophil Chemotaxis	3	30.0	6.3E-4	CXCL10, CXCL8, IL1B
	GO:0006935~Chemotaxis	3	30.0	1.4E-3	CXCL10, CXCL12, CXCL8
	GO:0006954~Inflammatory response	3	30.0	1.5E-2	CXCL10, CXCL8, IL1B
GOTERM _CC	GO:0005615~Extracellular space	8	80.0	2.0E-6	COL1A1,CXCL10,FCGR3,CXCL8,CSF2,IFNG, IL1B,FN1
	GO:0005576~Extracellular region	8	80.0	3.8E-6	COL1A1, CXC10, CXCL12, CXCL8, CSF2, IFNG, IL1B, FN1
GOTERM _MF	GO:0005515~protein binding	90	90.0	3.9E-2	COL1A1,CXCL10,FCGR3A,CXCL12,CXCL8,CSF2,IFNG, IL1B, FN19
	GO:0045236~CXCR chemokine receptor binding	30	30.0	1.6E-5	CXCL10, CXCL12, CXCL8
	GO:0008009~Chemokine activity	30	30.0	1.9E-4	CXCL10, CXCL12, CXCL8
	GO:0005178~Int	30	30.0	2.0E-3	CXCL12, IL1B, FN1

Category	Term	n	%	p-value	Genes
	egrin binding				
	GO:0008201~Heparin binding	30	30.0	2.3E-3	CXCL10, CXCL8, FN1
	GO:0005125~Cytokine activity	30	30.0	2.8E-3	CSF2, IFNG, IL1B
KEGG_PATHWAY	hsa05146-Amoebiasis	6	60.0	3.3e-8	COL1A1,CXCL8,CSF2, IFNG, IL1B, FN1
	hsa04060-Cytokine-cytokine receptor interaction	6	60.0	6.5e-6	CXCL10, CXCL12, CXCL8, CSF2, IFNG, IL1B
	hsa05323-Rheumatoid arthritis	5	50.0	1.9E-6	CXCL12,CXCL8,CSF2, IFNG, IL1B
	hsa04657-IL-17 signalling pathway	5	50.0	1.9E-6	CXCL10,CXCL8,CSF2, IFNG, IL1B
	hsa04933-AGE-RANG Signaling Pathway in Diabetic Complications	4	40.0	1.4E-4	CXCL10,CXCL8,IFNG, IL1B

4. DISCUSSION

NPC primarily affects the epithelial cells of the nasopharynx, located in the head and neck region [4, 7]. This condition has been frequently observed in regions including East and Southeast Asia, South Central Asia, and parts of North and East Africa [3]. The current study conducted a thorough bioinformatic analysis of the GSE53819 GEO microarray dataset. This contained microarray expression profiles from 18 NPC tumors and 18 paired normal nasopharynx samples to elucidate the transcriptome profile of NPC and identify therapeutic targets. Upon applying stringent criteria to filter out 11,331 candidate DEGs to 250 high-quality DEGs, 11 significantly enriched KEGG pathways were observed. The most prominently enriched pathways included cytokine-cytokine receptor interaction, ECM-receptor interaction, and IL-17 signaling pathway. Through further analysis utilizing STRING and Cytoscape with CytoHubba app, 10 hub genes (IL1B, FN1, CXCL8, CD19, CSF2, CXCL12, IFNG, COL1A1, CXCL10, and FCGR3A) were successfully identified. Network topology analysis showed that these hub genes were organized into two distinct oncogenic modules, an inflammatory cytokine–chemokine axis (IL1B, CXCL8, CXCL12, CXCL10) and ECM remodeling axis (FN1, COL1A1). This dual module interaction on tumor immune escape and progression represents the primary mechanistic findings in the current study, which is further elaborated below.

Among the hub genes, IL1B (interleukin-1 beta) was observed to have the greatest number of PPIs at 107, making it a master regulator of the NPC transcriptome. IL1B is a pro-inflammatory pleiotropic cytokine known to be expressed excessively in the NPC tumor microenvironment (TME) [16]. Within the TME of NPC, IL1B, which is mainly secreted by tumor-associated macrophages and EBV infected epithelial cells, stimulates the pro-inflammatory signaling via NF-κB and MAPK pathway, recruits neutrophils and myeloid-derived suppressor cells (MDSCs), and promotes the growth of blood vessels within the tumors [16, 17]. Notably, IL1B has been found to attenuate the cytotoxic activity of T cells and NK cells in the tumor microenvironment [18]. Apart from NPC, IL1B is one of the drivers of cancer in various cancers, such as breast, lung, hepatocellular, gastric, cervical cancers, and osteosarcomas [17]. IL1B's position at the center of the PPI network, regulating the expression of CXCL8 and CSF2 downstream, suggests IL1B is an initial signal for inflammatory cytokine chemokine signaling cascades, leading to an immunosuppressive NPC microenvironment. The results are in line with the general notion that chronic inflammation triggered by IL1B plays an important role in the development of infection-related cancers, such as NPC.

The second highest hub gene by degree connectivity is FN1 (fibronectin 1), an epithelial-mesenchymal transition (EMT) related ECM protein with a significant role in mediating cell adhesion, migration, and (EMT). The upregulation of FN1 in NPC tissues has been shown and it has been functionally proved that high levels of FN1 stimulate the migration and invasiveness of NPC cells by upregulating MMP2 and MMP9 while suppressing apoptosis via NF-κB/P65 [18]. Upregulation of FN1 has also been implicated with poor clinical outcome in NPC patients and high probability of developing distant metastasis by immunochemistry and recent identification by serum proteomics as a late-stage NPC biomarker [18, 19]. Moreover, FN1 serves as an essential molecular scaffold, allowing tumor cells to contact the ECM components, which, together with COL1A1, could contribute to promoting pro-invasive ECM remodeling in NPC. It has become clear through the consistent enrichment of FN1 and COL1A1 in GO terms, such as "extracellular matrix structural constituent," "integrin binding," and "ECM organization," among others.

CXCL8, also referred to as Interleukin-8 (IL-8), belongs to the class of ELR motif CXC chemokines that serve as central coordinators of the pro-tumorigenic tumor microenvironment (TME), mediated via CXCR1 and CXCR2 receptors in neutrophils, monocytes, and endothelial cells [20]. Within the context of NPC, CXCL8 mediates tumor sphere formation and tumor sphere growth through the MIF/CXCL8/CXCR2 signaling pathway. Whereas, its levels have been shown to be correlated with NPC susceptibility among populations [21, 22]. Besides, CXCL8 promotes the growth, invasion, and metastasis of NPC cells by recruiting inflammatory cells, such as neutrophils and macrophages, to the tumor microenvironment. Such inflammatory cells further retain the ability to promote proliferation, migration, and invasion of the NPC cells. On a broader scale, increased levels of CXCL8 in the TME contribute to three interconnected pro-tumorigenic processes. These include recruiting immune-suppressing neutrophils and MDSCs; promoting tumor angiogenesis via endothelial CXCR2 signaling and MMP-mediated matrix metalloproteinase-driven extracellular matrix degradation; and enhancing EMT, increasing cancer cell plasticity and invasiveness [20, 23]. This multi-functional role suggests that CXCL8 is a promising therapeutic target in NPC, and its co-expression in our network together with IL1B, whose role as transcriptional inducer of CXCL8 through NF-κB activation is well-established, provides convincing evidence for a functional IL1B to CXCL8 axis.

CD19 was discovered as an important hub gene with significant connectivity and as a surface antigen present on B lymphocytes involved in their development and differentiation [24, 25]. Although CD19 is a known therapeutic target for B-cell disorders, where chimeric antigen receptor T cell (CAR-T) cell approaches are often used for treatment [26], the specific role of CD19 as a key player in NPC etiology needs to be considered carefully. NPC has been shown to exhibit high levels of leukocyte infiltration, such as those of B lymphocytes [6]. Moreover, current data has pointed to the potential dual role of tumor-infiltrating B cells in supporting anti-tumor immune response and participating in cancer immunosuppression via regulatory B cells (Bregs) [6, 27]. Thus, the finding of CD19 as a hub gene can be attributed to the high degree of B cell involvement in the EBV-related NPC microenvironment, without direct implication in epithelial carcinogenesis. The future experiments required to determine the function of CD19 in NPC should involve: (i) analysis by flow cytometry of the number of CD19+ B cell subsets, including B regulatory cells, in NPC tissue compared to normal tissue from the same patient; (ii) co-culture studies to examine the paracrine signaling capacity of primary NPC cells in combination with CD19+ B cells; and (iii) depletion studies using antibodies directed against CD19+ cells in an EBV-associated NPC xenograft mouse model system.

CSF2 is a myelopoietic cytokine coding for granulocyte-macrophage colony-stimulating factor (GM-CSF) and has been shown to play a role in both anti-tumor immunity and immunosuppression [28, 29]. Within the TME, GM-CSF, in high concentration, is a strong inducer of MDSC expansion and migration from the bone marrow into immunosuppressive populations, where they inhibit effector functions of T-cells [29, 30]. CSF2 was upregulated within the NPC dataset, which may be indicative of pathological manipulation of myeloid cell recruitment, leading to the development of an immunosuppressive niche to prevent immune-mediated tumor cell elimination. Notably, both CSF2 and IL1B are co-expressed within the hub gene network, with the notion that GM-CSF signaling significantly upregulates IL1B secretion, as well as the induction of IL1B signaling leads to the accumulation of MDSCs [29, 31].

IFNG encodes Interferon-gamma (IFN-γ), an immunomodulatory cytokine released from activated T cells, natural killer cells, and innate lymphoid cells. In NPC, IFN-γ presents an ambivalent role as an immunologic agent. Even though this protein can activate macrophages and dendritic cells, induce polarization towards the pro-inflammatory phenotype M1, and enhance antigenic presentation in the tumor environment [32], chronic exposure to IFN-γ induces programmed death-ligand 1 (PD-L1) expression on tumor cells via the JAK/STAT1–IRF1 pathway [33]. Regarding EBV-infected NPCs, EBV latent membrane protein 1 (LMP1) signaling via STAT3, AP-1, and NF-κB pathways, combined with independent IFN-γ signaling, contributes to PD-L1 over-expression. Thus, this combination of immunostimulation factors results in conversion of an anti-cancer immune response to an immune checkpoint-based immune escape mechanism [34]. The discovery of IFNG as a hub gene, which shows strong connections with immunostimulating genes (CSF2, CXCL10) as well as with cytokines and chemokines, emphasizes this ambivalent activity of interferon and explains the successful therapeutic potential of anti-PD-1/PD-L1 checkpoint inhibitors in patients with NPC [35].

The protein COL1A1 is responsible for the production of the alpha-1 chain of type I collagen. This represents the most abundant ECM structural protein and acts as a major player involved in the regulation of ECM stiffness and cancer-associated fibroblast (CAF activation [36]. Collagen-rich TME is known to induce immune exclusion due to the formation of physical barriers by T cells and activation of inhibitory receptors [37]. Overexpression of COL1A1 gene in NPCs has been shown to play an important role in tumor progression by way of promotion of NPC development through sponging of miR-1184 to increase the expression of the COL1A1 gene. This results in activation of the downstream PI3K/Akt pathway and promotion of cell proliferation and invasion [38]. Recently, circCOL1A1 was identified to enhance the Warburg effect in NPC cells [39]. At the molecular mechanism level, TGF-β serves as a transcriptional activator of collagen secretion by CAFs and a factor that induces fibrosis and collagen-rich TME and hinders T cell recruitment [37]. The co-expression of COL1A1 and FN1 in GO terms that are related to ECM, along with their simultaneous occurrence in Amoebiasis and ECM-receptor interaction KEGG pathways, implies that there is a concerted effort towards remodeling of the tumor's ECM to make it inhospitable for both the tumor's physical and immune defenses. A treatment approach combining anti-COL1A1-collagen pathway and immunotherapy is thus a potential option, which was confirmed in preclinical cancer models [37].

The FCGR3A gene codes for the Fc gamma receptor IIIa (FcγRIIIa/CD16a), which is present on the surface of natural killer (NK) cells, macrophages, and granulocytes. It participates in antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis through binding to the Fc domain of the IgG antibodies that are attached to their targets [40]. In view of the significant immune infiltrate of NPC tumors, the selection of FCGR3A as an immune hub gene suggests the presence of an expansion of NK cells and monocyte-derived dendritic cell subpopulations within the NPC TME. This can be confirmed based on recently acquired data of single-cell RNA sequencing of NPCs [32]. The considerable antigenic EBV load in NPC and the known effectiveness of EBV-targeted antibodies in this cancer indicate that [6], in addition to other immune processes, the activity of FCGR3A-positive effectors represents an anti-viral response utilized by the NPC TME.

CXCL12, also referred to as SDF-1, is a constitutive CXC chemokine that acts through its primary CXCR4 receptor and decoy CXCR7 receptor. The CXCL12/CXCR4 pathway is crucial in orchestrating the immunosuppressive TME by recruiting CXCR4-expressing regulatory T cells (Tregs), tumor angiogenesis, and EMT/stemness in cancer cells [41]. In NPC, higher CXCL12 levels were associated with late TNM stage, lymph node metastasis, and an immunosuppressive TME characterized by a greater abundance of CXCR4+ Tregs [41]. The underlying mechanisms for CXCL12-induced metastasis in NPC could be related to G protein-coupled CXCR4 signaling. This leads towards intracellular calcium mobilization and subsequent cytoskeletal remodeling to facilitate cell migration and invasion [42]. CXCL10 was identified as another hub gene linked to CXCL12 in our network, which is interesting. This is because, whereas CXCL12 recruits Tregs to suppress the immune system, CXCL10 antagonizes CXCL12 by recruiting CD8+ effector T cells and CD20+ B cells in NPC [43]. Hence, it would be intriguing to examine whether inhibition of CXCL12/CXCR4 signaling using drugs, such as AMD3100 (plerixafor) can reverse the TME in favor of immunity in NPC.

Combined, the findings suggest the existence of two oncogenic modules working in cooperation in NPC: an inflammatory axis comprising cytokines and chemokines and an ECM remodeling axis, both working together to produce a pro-oncogenic microenvironment (see Figure 3). Within the inflammatory module, IL1B is an upstream activator which transcriptionally upregulates CXCL8 and CSF2 genes through NF-κB pathway induction. This leads towards a complex milieu comprising recruitment of MDSCs and neutrophils alongside inhibition of cytotoxic T cells and NK cells. The expression of CXCL12 through its receptor CXCR4 in Tregs causes increased immunosuppression. Whereas, CXCL10 works as an immune stimulator but is repressed by the prevailing immunosuppressive pathways, thus contributing to disease progression. In the ECM remodeling module, FN1 and COL1A1, which are transcriptionally induced by TGF-β, cause ECM stiffening, activation of CAFs, and a physical barrier to immune cell infiltration, as well as survival signaling in NPC cells through integrins. This is an elegant example of how NPC cells exploit a signaling pathway that should prevent tumor formation through its action on PD-L1 using IRF1. This is just one of the many possible treatment strategies for NPC that could arise from this network model. For instance, the inhibition of IL-1β signaling (through anakinra or canakinumab), CXCR4 function (with plerixafor), ECM alteration (with anti-TGF-β), and PD-1/PD-L1 checkpoint inhibitors would provide multiple layers against the redundant immunosuppressive signals in the network.

Table 4. Comparison of Hub Gene Findings with Recently Published Bioinformatics Studies on NPC (2022–2026).

Hub Gene(s)	Study (Year)	Study Type	Dataset	Key Finding vs. Current Study
IL1B,CXCL8, CXCL12	Current study, 2025	Bioinformatics / PPI	GSE53819 (36 samples)	Two oncogenic modules (inflammatory + ECM) identified for first time in NPC
IL1B	Liang et al. [16]	Review of NPC cytokines	Multiple datasets	IL-1β confirmed as key NPC inflammatory biomarker; consistent with IL1B ranking #1 in our PPI.
FN1	Pan et al. [19]	Serum proteomics	Clinical NPC samples	FN1 identified as serum biomarker for late-stage NPC; supports our ECM remodeling axis.
COL1A1	Huang et al. [38]	CircRNA functional study	NPC cell lines	Circ_0000523/miR-1184/COL1A1/PI3K/Akt axis promotes NPC progression; validates our COL1A1 hub.
COL1A1	Zhou et al. [39]	Circular RNA study	NPC cell lines	CircCOL1A1 promotes Warburg effect in NPC; novel mechanism supporting ECM axis.
CXCL12/CXCR4	Yang et al. [41]	Pan-cancer axis review	Multiple datasets	CXCL12/CXCR4 drives Treg recruitment and EMT; confirms our immunosuppressive axis.
CXCL8, CXCL10	Zhang et al. [43]	Immune profiling	NPC tumor tissue	CXCL10 recruits CD8+ T cells; CXCL8 promotes suppression consistent with our dual chemokine hubs.

Hub Gene(s)	Study (Year)	Study Type	Dataset	Key Finding vs. Current Study
IFNG	Ge et al. [33]	PD-L1 regulation	NPC cells + tissue	FOXA1 represses IFN-γ-induced PD-L1; supports IFNG's ambivalent role in our network.
CD19, FCGR3A	Jin et al. [32]	Single-cell RNA-seq	Primary NPC tissue	B cell & NK cell infiltrates confirmed in NPC; validates CD19 and FCGR3A as immune hub genes.

4.1. Conclusion

To conclude, this research employed multiple bioinformatics approaches, namely DEG analysis, enrichment analysis, and PPI networks, to pinpoint ten master genes associated with the development of NPC: IL1B, FN1, CXCL8, CD19, CSF2, CXCL12, IFNG, COL1A1, CXCL10, and FCGR3A. It is interesting to note that for the first time, using the principle of PPI network topology, the existence of two oncogenic modules that play a role in tumor immune evasion was revealed: the inflammatory cytokine–chemokine axis and ECM remodeling axis. Among the ten master genes identified, five genes, including IL1B, FN1, CXCL8, CXCL12, and COL1A1, with the best external validation, provide the most promising prospects in terms of NPC diagnosis and treatment. The combination of these findings with current knowledge about the effect of Epstein-Barr virus (EBV) on the NPC TME can serve as an important starting point for the development of new therapeutic strategies that would address both aspects, that is, immune evasion and ECM remodeling, and tumor progression. Further research should be directed towards the functional validation of the suggested IL1B-CXCL8-CSF2 axis and FN1-COL1A1 ECM axis in NPC cells and in vivo and their clinical utility as NPC biomarkers.

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