International Journal of Biological & Pharmaceutical Science
ISSN (Online): 2208-2166
Volume 11 Issue 02 September 2025
DOI: https://doi.org/10.53555/0dz66a57

IDENTIFYING COMMON PROTEIN TARGET FOR COVID-19 AND EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS USING NETWORK ANALYSIS

Nama Gokul[1], Punitkumar Math[2*], Shanmuga Priya V G[3*]

[1]*M.Sc. Bioinformatics, Department of Life Sciences, Garden City University, Bengaluru, India*

Main Author Email: *namagokul2001@gmail.com*

[2]*M.Sc. Bioinformatics, Department of Life Sciences, Garden City University, Bengaluru, India*

Corresponding Author

Email: punitkumarmath7@gmail.com

[3]*Assistant Professor, Department of Life Sciences, Garden City University, Bengaluru, India*

Co–Corresponding Author

Email: shanmuga.priya@gcu.edu.in

Abstract

Coronavirus Disease 2019 (COVID-19), caused by SARS-CoV-2 infection and a rare autoimmune disorder Eosinophilic Granulomatosis with Polyangiitis (EGPA) share key immune dysregulation mechanisms despite their distinct pathologies. This study uncovers the relationship between genes involved in COVID-19 and EGPA by network analysis approach to identify common potential therapeutic targets for the conditions . By comparing disease-associated genes retrieved from databases CTD, GeneCards and DisGeNET, 154 common genes expressed in both the disease conditions were identified. Protein-Protein Interaction network analysis revealed 10 hub proteins, which are central to immune responses, inflammation, and cytokine signaling pathways. Functional enrichment analyses of these genes using databases Gene Ontology (GO), KEGG, and Reactome, highlight shared pathways such as IL-6 and TNF signaling, which are critical in both diseases. Transcription factor network analysis pinpointed NF-κB as a central regulator of inflammatory responses. This research underscores the interconnectedness of COVID-19 and EGPA, emphasizing potential therapeutic targets like NF-κB for managing inflammation and disease progression in both conditions.

1. Introduction:

The Corona Virus Disease 2019 (COVID-19), caused by coronavirus SARS-CoV-2 infection has led to global health crisis, that overwhelmed healthcare systems worldwide from 2020 to 2023 (Mallah et al., 2021). The COVID-19 presents a range of symptoms from mild respiratory issues such as cough and fever to severe pneumonia and acute respiratory distress syndrome (ARDS) (Mallah et al., 2021). Omicron BA.2 , the variant of SARS-CoV-2 has brought about changes in symptomatology, with a higher prevalence of flu-like symptoms resembling those of common cold and influenza (Shah & Wunderink, 2017).

Another disease called Eosinophilic Granulomatosis with Polyangiitis (EGPA) also known as Churg-Strauss syndrome (CSS), is a rare autoimmune disorder characterized by systemic vasculitis and eosinophilic infiltration into various organs (Nguyen & Guillevin, 2018). This disease progresses through distinctive phases, beginning with allergic symptoms such as asthma and rhinitis and further followed by vasculitis a systemic inflammation condition and tissue damage (Santos et al., 2017). Vasculitis manifestations affect various organs which includes the respiratory, nervous and gastrointestinal systems leading to organ damage. Despite many advancements in understanding and treatment, EGPA remains a challenging condition to manage. Moreover, relapse and complications are posing significant risk to patients health and quality of life (Chakraborty & Aeddula, 2024).

On data mining, numerous studies have shown that a significant proportion of patients suffering from COVID-19 experience persistent symptom such as inflammatory cell accumulation and clot formation in blood vessels, skin rashes and short breath, which resemble manifestations seen in EGPA condition (Daniel et al., 2020). Also, studies show that persistent symptoms in EGPA shares similarities with COVID symptoms (Fliesler, 2022). In COVID-19, the overactive infection leads to widespread inflammation and tissue damage, while in EGPA autoimmune process result in systemic vasculitis and organ dysfunction (Fijolek & Radzikowska, 2023). Recent studies exhibited the formation of clots in the lungs of COVID patients (Polak et al., 2020), which is also a common symptom in EGPA.

Moreover, COVID-19 and EGPA are said to share similarities in their underlying immune pathological mechanisms (Özdemir et al., 2021). Dysregulated immune responses, with notable involvement of TH2-mediated pathways and recruitment of eosinophils to target tissues were the common conditions that occur in both diseases (Antovic et al., 2021).

Given the potential overlap of symptoms and immune regulation between COVID and EGPA, and the potential escalation of EGPA cases after the COVID wave, understanding the underlying interconnectedness between these

conditions has become necessary as it may offer fruitful insights into their pathogenesis and management, guiding the development of targeted therapies and interventions to improve patient's outcomes.
Hence in this study, gene expression in both the disease conditions are compared to get new insights and to identify potential targets to mitigate the conditions.

2. MATERIALS AND METHODS

2.1 Retrieval and Identification of Common Genes in EGPA and COVID-19.

Exploiting comprehensive databases such as CTD (http://ctdbase.org/)(Davis et al., 2021), GeneCards (https://www.genecards.org/) (Safran et al., 2021), and DisGeNET (https://www.disgenet.org/) precisely curated genes associated with EGPA and COVID-19 were retrieved. Top at most 500 genes were extracted from each database that are related to the diseases. Further, common genes associated with COVID and those linked to EGPA were identified and represented in Venn diagram https://bioinformatics.psb.ugent.be/webtools/Venn/).

2.2 Protein-protein interaction (PPI) analysis and network construction

PPI networks can gain deeper understanding of protein functionality. STRING (Szklarczyk et al., 2021) a web based tool was utilized to construct the PPI networks for the common genes. The resulting PPI network was visualized and analysed using Cytoscape software (V3.8.2) (Otasek et al., 2019) (Shannon et al., 2003). Leveraging the cytoHubba (Cline et al., 2007) plugin within Cytoscape, top 10 hub proteins were identified that has highest degree values by employing the degree topological algorithm.

2.3 Functional enrichment analysis

Functional characterization of the 10 hub proteins was performed utilizing Enrichr(https://maayanlab.cloud/Enrichr/), an extensive gene set enrichment web tool(Kuleshov et al., 2016). This approach gives an insight into the biological mechanisms and signalling pathways underlying these diseases.
Gene ontology (GO), a publicly available database under Enrichr was examined to investigate the biological process, cellular component and molecular function of the hub genes to comprehensively delineate their functions (Ashburner et al., 2000). Additionally, Kyoto Encyclopedia of Genes and Genomes(KEGG) pathway analysis (Kanehisa et al., 2021) was employed to identify relevant metabolic pathways associated with the hub genes. Furthermore, to ensure a thorough assessment of relevant pathways, data from WIKIPATHWAYS (Martens et al., 2021), REACTOME (Jassal et al., 2020), and BIOCARTA (Nishimura, 2001) was explored and relatedness between the identified pathways with the EGPA and COVID-19 diseases was scrutinized.

2.4 Transcription factor network analysis

Considering how genes are regulated in different physiological and disease conditions involves studying the interactions between transcription factors(TFs) and genes (Jiang et al., 2022). To explore these interactions, RegNetwork database and NetworkAnalyst 3.0 tool (Zhou et al., 2019) was used to build a network and visualized the results using Cytoscape for a clearer understanding. This analysis was carried out to identify a transcription factor as drug target.

3. RESULTS

3.1 Genes from both COVID and EGPA

Comprehensive search of genes associated with COVID-19 and EGPA were retrieved from databases. Regarding EGPA related genes, from CTD database first 500 genes were retrieved, which are arranged in decreasing order of Inference Score, and from GeneCards and DisGeNET all the 20 and 38 genes were retrieved respectively. Subsequently, the gene sets were merged and duplicates eliminated, resulting in a consolidated list of 540 EGPA-related genes. Similarly, for COVID-19, total of 1,117 genes was collected from the same databases. The two gene sets were compared and 154 common genes between both disease conditions were identified (Figure.1).

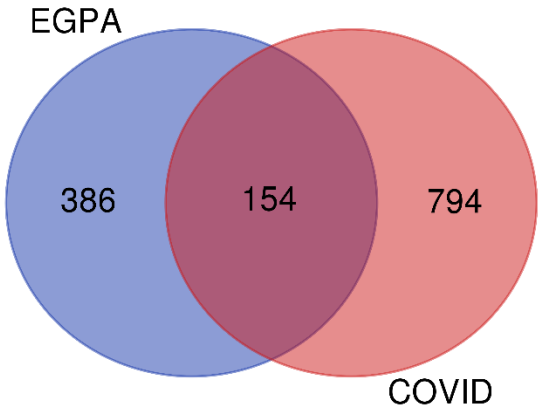

Figure.1 A Venn diagram of common genes. Common 154 genes are identified from 1117 genes of COVID-19 infection and 540 genes of EGPA.

3.2 String analysis and network construction

Input of the common 154 genes into string tool yielded the network that exhibited the interaction among all proteins of these genes as shown in the Figure. 2. This network was exported to Cytoscape and using cytoHubba plugin, top 10 hub proteins were identified based on their degrees, which are JUN, AKT1, TNF, TP53, Alb, IFNG, iL1B, CASP3, STAT3 and IL6. Hub proteins, characterized by numerous interactions with other proteins, also demonstrated interactions among themselves within the PPI network (Figure. 3), indicating their pivotal role in mediating interactions and potentially influencing disease mechanism.

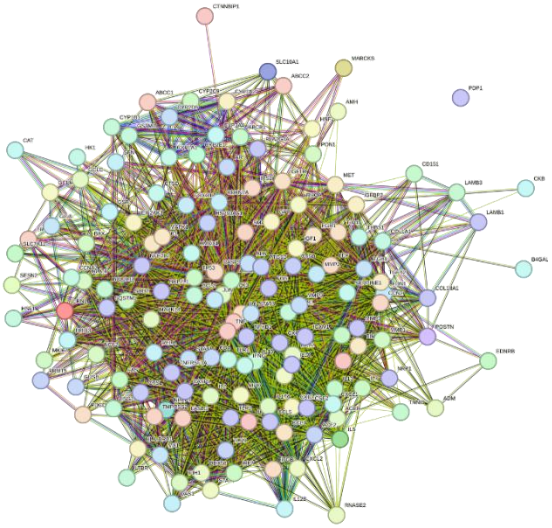

Figure.2 Protein-protein interactions (PPIs) network for common genes from COVID-19 and EGPA

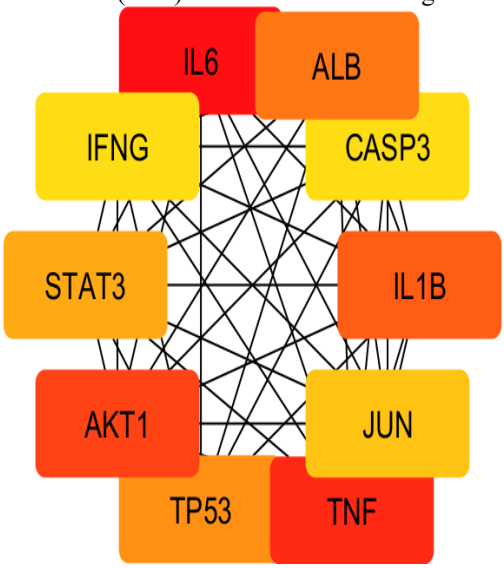

Figure. 3 10 hub proteins from PPI network

3.3 Enrichment Analyses

Insights on GO and pathway enrichment analysis was carried out with Enrichr tool. The GO was used to conduct analysis of common genes, with findings classified into three categories: Biological process, cellular component, and molecular function. The most substantially altered pathway's related with common genes in EGPA and COVID were discovered using the databases: KEGG, WikiPathways, Reactome, and BioCart (Table. 1,2,3,4,5,6,7). These findings are visually represented in bar graphs (Figure.5)

Table. 1 GO – Biological process and the corresponding P-values

GO Biological process		
Index	Name	P-value
1	Positive Regulation Of Macromolecule Metabolic Process (GO:0010604)	7.150e-11
2	Positive Regulation Of Interleukin-6 Production (GO:0032755)	1.721e-10
3	Positive Regulation Of Monooxygenase Activity (GO:0032770)	4.685e-10
4	Positive Regulation Of Gene Expression (GO:0010628)	4.951e-10
5	Positive Regulation Of Nitric Oxide Biosynthetic Process (GO:0045429)	5.498e-10

6	Positive Regulation Of Programmed Cell Death (GO:0043068)	6.406e-10
7	Positive Regulation Of Nitric Oxide Metabolic Process (GO:1904407)	6.413e-10
8	Cytokine-Mediated Signaling Pathway (GO:0019221)	8.542e-10
9	Regulation Of Calcidiol 1-Monooxygenase Activity (GO:0060558)	8.995e-10
10	Regulation Of Interleukin-6 Production (GO:0032675)	1.356e-9

Table. 2 GO- Cellular components and the corresponding P-values

GO Cellular component		
Index	**Name**	**P-value**
1	Endoplasmic Reticulum Lumen (GO:0005788)	0.008387
2	Nucleus (GO:0005634)	0.01146
3	Euchromatin (GO:0000791)	0.02179
4	Intracellular Membrane-Bounded Organelle (GO:0043231)	0.02333
5	Platelet Alpha Granule Lumen (GO:0031093)	0.03252
6	Platelet Alpha Granule (GO:0031091)	0.04363
7	Nuclear Chromosome (GO:0000228)	0.04651
8	Nuclear Lumen (GO:0031981)	0.05554
9	Intracellular Organelle Lumen (GO:0070013)	0.06555
10	Recycling Endosome (GO:0055037)	0.07673

Table. 3 GO -Molecular function and the corresponding P-values

GO Molecular function		
Index	Name	P-value
1	Cytokine Activity (GO:0005125)	0.000001222
2	Transcription Regulatory Region Nucleic Acid Binding (GO:0001067)	0.000003051
3	Receptor Ligand Activity (GO:0048018)	0.00001236
4	Transcription Cis-Regulatory Region Binding (GO:0000976)	0.00005840
5	General Transcription Initiation Factor Binding (GO:0140296)	0.00009715
6	RNA Polymerase II-specific DNA-binding Transcription Factor Binding (GO:0061629)	0.0001654
7	Copper Ion Binding (GO:0005507)	0.0002202
8	Sequence-Specific Double-Stranded DNA Binding (GO:1990837)	0.0002863
9	DNA-binding Transcription Factor Binding (GO:0140297)	0.0003093
10	DNA Binding (GO:0003677)	0.0005441

Table. 4 REACTOME and the corresponding P-values

REACTOME		
Index	Name	P-value
1	Signaling By Interleukins R-HSA-449147	1.421e-14
2	Cytokine Signaling In Immune System R-HSA-1280215	7.452e-13
3	Interleukin-4 And Interleukin-13 Signaling R-HSA-6785807	4.198e-12
4	Interleukin-10 Signaling R-HSA-6783783	4.648e-9
5	Immune System R-HSA-168256	6.919e-9
6	Intrinsic Pathway For Apoptosis R-HSA-109606	1.061e-8
7	Programmed Cell Death R-HSA-5357801	2.801e-8
8	Pyroptosis R-HSA-5620971	2.326e-7
9	Cellular Responses To Stress R-HSA-2262752	4.022e-7
10	Cellular Responses To Stimuli R-HSA-8953897	4.503e-7

Table. 5 BIOPLANT and the corresponding P-values

BIOPLANT

Index	Name	P-value
1	Folate metabolism	1.590e-13
2	Interleukin-27-mediated signaling events	6.190e-13
3	Chagas disease	3.526e-12
4	Interleukin-23-mediated signaling events	4.093e-12
5	Interleukin-5 signaling pathway	1.786e-11
6	Vitamin B12 metabolism	2.433e-11
7	Selenium pathway	5.103e-11
8	TGF-beta signaling pathway	1.176e-10
9	Regular glucocorticoid receptor pathway	2.538e-10
10	Interleukin-2 signaling pathway	4.180e-10

Table. 6 WikiPathway 2023 Human and the corresponding p-values

WikiPathway 2023 Human		
Index	Name	P-value
1	IL 26 Signaling Pathways WP5347	3.462e-17
2	Network Map Of SARS CoV 2 Signaling Pathway WP5115	7.735e-15
3	IL 24 Signaling Pathway WP5413	1.281e-14
4	Hepatitis C And Hepatocellular Carcinoma WP3646	3.280e-14
5	Folate Metabolism WP176	2.559e-13
6	Urotensin II Mediated Signaling Pathway WP5158	2.803e-13
7	Burn Wound Healing WP5055	4.327e-13
8	Acute Viral Myocarditis WP4298	9.479e-13
9	Inflammatory Bowel Disease Signaling WP5198	7.979e-12
10	Spinal Cord Injury WP2431	8.044e-12

Table. 7 KEGG 2021 Human and the corresponding p-values

KEGG 2021 Human		
Index	Name	P-value
1	Lipid and atherosclerosis	6.912e-15
2	AGE-RAGE signaling pathway in diabetic complications	7.476e-15
3	Measles	7.927e-14
4	Inflammatory bowel disease	1.932e-13
5	Hepatitis B	2.360e-13
6	Epstein-Barr virus infection	1.130e-12
7	IL-17 signaling pathway	1.895e-12
8	Human cytomegalovirus infection	2.422e-12
9	Chagas disease	3.130e-12
10	TNF signaling pathway	5.552e-12

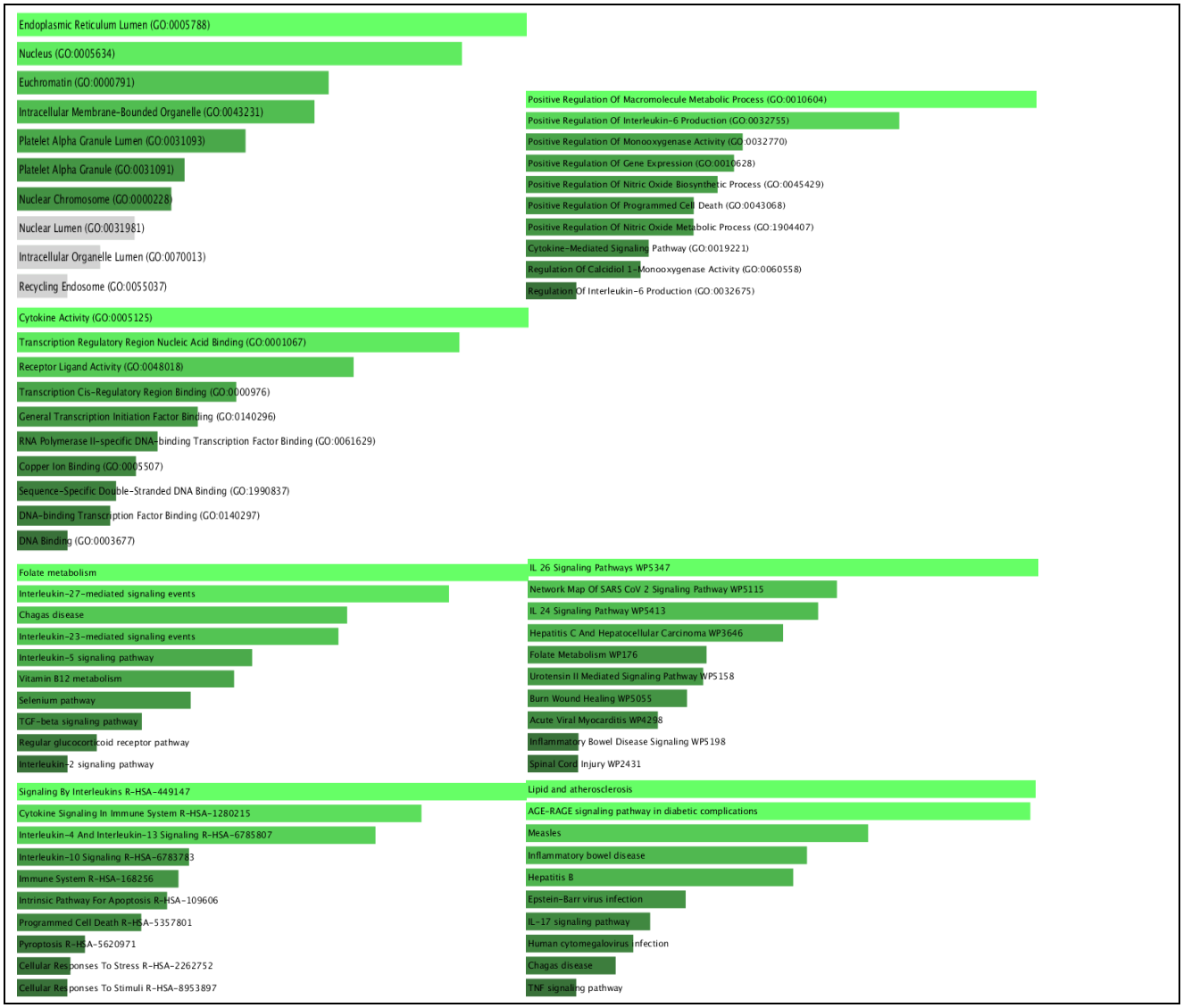

Fig. 4 Gene ontologies of the common genes

3.4 Transcription Factor (TF) -Gene interactions

The interaction between ten common genes and TF genes was analysed using Network Analyst. The TF-gene interaction network consists of 75 nodes and 109 edges. In was detected that TNF has highest degree of 51 degrees and TP53 has a degree of 13 and INF has 10 degree (Figure 6), indicating that they are regulated by many transcription factors.

TFs Foxcl, NFKB1, GATA2,YY1,TFAP2A were selected based on the highest degree values (Table.8) .

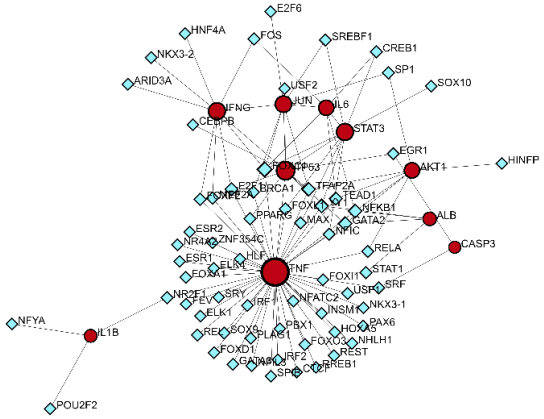

Figure.5 Transcription Factor-Gene interaction

Table.8 Top Transcription Factors and their Degree

SNO	TRANSCRIPTION FACTOR	DEGREE
1	Foxc1	6

2	NFKB1	4
3	GATA2	4
4	YY1	4
5	TFAP2A	4

4. Discussion

This research aimed to uncover genetic relationship between COVID and EGPA using bioinformatics analysis, centered on 154 shared genes that are expressed in both the conditions.

Out of 154 genes, with Protein-Protein Interaction (PPI) network analysis JUN, AKT1, TNF, TP53, ALB, IFNG, IL1B, CASP3, STAT3, IL-6 emerged as central hub proteins due to their elevated degrees of connectivity within the network. Through enrichment analysis it was predicted that hub genes are responsible for pro inflammatory responses, cell proliferation, cell differentiation and immune cell metabolism. Through literature mining it is identified that in both EGPA and COVID-19, interleukin-6 (IL-6) plays a crucial role in immune system activation and inflammation (Tanaka et al., 2014). Role of IL-6 is to increase EGPA condition (Imai et al., 2022) and in severe COVID-19 it fuels the cytokine storm, leading to systemic inflammation and organ dysfunction. The recognition of viral components by pattern-recognition receptors (PRRs) triggers IL-6 release during SARS-CoV-2 infection, exacerbating inflammation. Moreover, IL-6's involvement in initiating adaptive immunity underscores its significance in infection-induced inflammation. Understanding IL-6's complex role in both diseases emphasizes its potential as a therapeutic target for mitigating severity of these disease manifestations (Wang et al., 2022).

The ten hub genes were employed to elucidate Gene Ontology (GO) terms. Regarding the GO biological process, notable terms include Positive regulation of interleukin-6 production, Cytokine-mediated signaling pathway, Positive regulation of programmed cell death. These terms shed light on the intricate immune and inflammatory processes. They signify the dysregulation of immune responses and inflammatory pathways characteristic of EGPA pathology (Gioffredi et al., 2014). In GO molecular function Cytokine a ctivity is seen. The complex cytokine activity observed in both COVID-19 (Tanveer et al., 2022) and EGPA(Isozaki et al., 2020) underlines the critical role of cytokines in disease progression, organ dysfunction, and inflammation, emphasizing the need for understanding their dynamics to develop effective treatment strategies and control viral replication in COVID-19 (Rabaan et al., 2021), as well as to manage eosinophil infiltration, vascular damage, and granuloma formation in EGPA (Fijolek & Radzikowska, 2023).

In reactome analysis, the hub genes were predicted to be involved in common interleukin signaling pathways, including Interleukin-4 and Interleukin-13 signaling, Interleukin-10 signaling, and Cytokine signaling immune pathways and these are observed in both COVID-19 and EGPA, highlighting their significance in regulating immune responses and potentially serving as therapeutic targets for managing inflammation and disease progression in these conditions (Fijolek & Radzikowska, 2023, Jiang et al., 2022).

When considering pathways from both WikiPathways Human and BIOPLANT databases, several overlapping themes emerge. These include pathways related to inflammation, immune response modulation, and metabolic processes. Some common pathways include Folate metabolism, TGF-beta signaling pathway, Interleukin-23-mediated signaling events ,Interleukin-5 signaling pathway, and Interleukin-2 signaling pathway which causes inflamation in covid19(Jiang et al., 2022).

KEGG pathway enrichment analysis was conducted and the top 10 KEGG Human pathways included Lipid and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, and inflammation-related pathways such as TNF signaling pathway, IL-17 signaling pathway, lipid and atherosclerosis, inflammatory bowel disease, and Leishmaniasis. Interestingly, IL-17, a significant regulator of upstream inflammatory pathways, plays a pivotal role in inducing the production of IL-6 (Hwang et al., 2004) (Lee et al., 2008). Elevated peripheral levels of IL-6 have been implicated in initiating EGPA (Rodriguez-Pla et al., 2020).

In the network of interactions between transcription factors and genes, TNF, TP53 and INFG stand out due to their extensive connections with transcription factors. Specifically, TNF is regulated by/ regulates 51 transcription factor genes, while INFG is influenced by 10 transcription factor genes. Elevated levels of TNF in both EGPA (Isozaki et al., 2020) and COVID-19(Mohd Zawawi et al., 2023) are linked with disease progression, contributing to immune dysfunction and addressing long-term complications. As TP53 is a key regulator of cell cycle and apoptosis, there credential as target is questionable (Kastenhuber & Lowe, 2017). Additionally, immunomodulatory factors IFNG plays crucial role in both conditions, influencing immune responses by modulating cytokine patterns, immune balance, and tissue repair processes in both COVID (Todorović-Raković & Whitfield, 2021) and EGPA (Do et al., 2022).

Based on transcription factor network analysis, NFKB is recognized for its essential role in orchestrating the expression of inflammatory proteins, thus serving as a central mediator of inflammation (Liu et al., 2017). It also has high degree of interaction with the hub genes predicted in the study. This strategic selection is underpinned by its critical role in modulating the inflammatory cascade, thereby presenting a compelling target for therapeutic intervention.

5.Conclusion

Our study successfully identified and elucidated the genetic relationships between COVID-19 and EGPA through an extensive bioinformatics analysis of 154 shared genes expressed during both the conditions. By constructing a PPI network, ten hub genes were identified, which are critical in regulating immune response, inflammation, and cell proliferation. These genes highlight the interconnected nature of inflammatory processes in both diseases.

Enrichment and pathway analyses further solidified the role of cytokine signaling, particularly IL-6, which is critical in driving inflammation and immune dysregulation in both COVID-19 and EGPA. IL-6's involvement in the cytokine storm in severe COVID-19 and its exacerbation of EGPA underscores its potential as a therapeutic target in managing both diseases. The presence of overlapping pathways, such as IL-17 and TNF signaling, strengthens the idea that these immune-modulating pathways are pivotal in the pathophysiology of both conditions.

Transcription factor–gene network analysis highlighted TFs Foxc1, NFKB1, GATA2, YY1and TFAP2A to form highly connected nodes, linking them to broad regulatory networks involved in inflammation, immune modulation, and cell death. Based on their functional analysis, NFKB was identified as a promising intervention point for both th disease condition due to its orchestration of inflammatory cascades.

This research contributes to a deeper understanding of the shared molecular mechanisms underlying COVID-19 and EGPA, emphasizing inflammation's central role and offering potential therapeutic targets for managing both conditions.

6.References

1. Mallah, S. I., Ghorab, O. K., Al-Salmi, S., Abdellatif, O. S., Tharmaratnam, T., Iskandar, M. A., Sefen, J. A. N., Sidhu, P., Atallah, B., El-Lababidi, R., & Al-Qahtani, M. (2021). COVID-19: Breaking down a global health crisis. Annals of Clinical Microbiology and Antimicrobials, 20, 35.
2. Shah, R. D., & Wunderink, R. G. (2017). Viral Pneumonia and Acute Respiratory Distress Syndrome. Clinics in Chest Medicine, 38(1), 113–125.
3. Nguyen, Y., & Guillevin, L. (2018). Eosinophilic Granulomatosis with Polyangiitis (Churg–Strauss). Seminars in Respiratory and Critical Care Medicine, 39, 471–481.
4. Santos, Y. A. P., Silva, B. R. A., Lira, P. N. Z. B. A., Vaz, L. C. A., Mafort, T. T., Bruno, L. P., & Lopes, A. J. (2017). Eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome) as a differential diagnosis of hypereosinophilic syndromes. Respiratory Medicine Case Reports, 21, 1–6.
5. Chakraborty, R. K., & Aeddula, N. R. (2024). Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss Syndrome). In StatPearls. StatPearls Publishing.
6. Özdemir, B., Erden, A., Güven, S. C., Armagan, B., Apaydin, H., Karakas, Ö., Akdag, A. G., Ates, İ., Kucuksahin, O., & Omma, A. (2021). COVID-19 and eosinophilic granulomatosis with polyangiitis or COVID-19 mimicking eosinophilic granulomatosis with polyangiitis? Rheumatology International, 41(8), 1515.
7. Antovic, A., Lövström, B., Hugelius, A., Borjesson, O., Bruchfeld, A., & Gunnarsson, I. (2021). Pos1230 Outcome Following Covid-19 Infection in Anti-Neutrophil Cytoplasmic Antibody (anca)-Associated Vasculitis. Annals of the Rheumatic Diseases, 80(Suppl 1), 898–898
8. Fijolek, J., & Radzikowska, E. (2023). Eosinophilic granulomatosis with polyangiitis – Advances in pathogenesis, diagnosis, and treatment. Frontiers in Medicine, 10, 1145257.
9. Polak, S. B., Van Gool, I. C., Cohen, D., von der Thüsen, J. H., & van Paassen, J. (2020). A systematic review of pathological findings in COVID-19: A pathophysiological timeline and possible mechanisms of disease progression. Modern Pathology, 33(11), 2128–2138.
10. Daniel, P., Raad, M., Waked, R., Choucair, J., Riachy, M., & Haddad, F. (2020). COVID-19 in a Patient Treated for Granulomatosis with Polyangiitis: Persistent Viral 32 Shedding with No Cytokine Storm. European Journal of Case Reports in Internal Medicine.
11. Fliesler, N. (2022, April 6). How COVID-19 triggers massive inflammation. Boston Children's Answers. https://answers.childrenshospital.org/covid-19-inflammation/
12. Davis, A. P., Grondin, C. J., Johnson, R. J., Sciaky, D., Wiegers, J., Wiegers, T. C., & Mattingly, C. J. (2021). Comparative Toxicogenomics Database (CTD): Update 2021. Nucleic Acids Research, 49(D1), D1138–D1143
13. Safran, M., Rosen, N., Twik, M., BarShir, R., Stein, T. I., Dahary, D., Fishilevich, S., & Lancet, D. (2021). The GeneCards Suite. In I. Abugessaisa & T. Kasukawa (Eds.), Practical Guide to Life Science Databases (pp. 27–56). Springer Nature.
14. C, Juan Manuel Ramírez-Anguita, Josep Saüch-Pitarch, & Francesco Ronzano. (n.d.). DisGeNET knowledge platform for disease genomics: 2019 update | Nucleic Acids Research | Oxford Academic. Retrieved April 22, 2024
15. Szklarczyk, D., Gable, A. L., Nastou, K. C., Lyon, D., Kirsch, R., Pyysalo, S., Doncheva, N. T., Legeay, M., Fang, T., Bork, P., Jensen, L. J., & von Mering, C. (2021). The STRING database in 2021: Customizable protein–protein networks, and functional characterization of user-uploaded gene/measurement sets. Nucleic Acids Research, 49(D1), D605–D612.
16. Otasek, D., Morris, J. H., Bouças, J., Pico, A. R., & Demchak, B. (2019). Cytoscape Automation: Empowering workflow-based network analysis. Genome Biology, 20(1), 185.
17. Shannon, P., Markiel, A., Ozier, O., Baliga, N. S., Wang, J. T., Ramage, D., Amin, N., Schwikowski, B., & Ideker, T. (2003). Cytoscape: A Software Environment for Integrated Models of Biomolecular Interaction Networks. Genome Research, 13(11), 2498–2504.
18. Cline, M. S., Smoot, M., Cerami, E., Kuchinsky, A., Landys, N., Workman, C., Christmas, R., Avila-Campilo, I., Creech, M., Gross, B., Hanspers, K., Isserlin, R., Kelley, R., Killcoyne, S., Lotia, S., Maere, S., Morris, J., Ono, K., Pavlovic, V., … Bader, G. D. (2007). Integration of biological networks and gene expression data using Cytoscape. Nature Protocols, 2(10), 2366–2382.
19. Kuleshov, M. V., Jones, M. R., Rouillard, A. D., Fernandez, N. F., Duan, Q., Wang, Z., Koplev, S., Jenkins, S. L., Jagodnik, K. M., Lachmann, A., McDermott, M. G., Monteiro, C. D., Gundersen, G. W., & Ma'ayan, A. (2016).

Enrichr: A comprehensive gene set enrichment analysis web server 2016 update. Nucleic Acids Research, 44(W1), W90–W97.
20. Ashburner, M., Ball, C. A., Blake, J. A., Botstein, D., Butler, H., Cherry, J. M., Davis, A. P., Dolinski, K., Dwight, S. S., Eppig, J. T., Harris, M. A., Hill, D. P., Issel-Tarver, L., Kasarskis, A., Lewis, S., Matese, J. C., Richardson, J. E., Ringwald, M., Rubin, G. M., & Sherlock, G. (2000). Gene Ontology: Tool for the unification of biology. Nature Genetics, 25(1), 25–29.
21. Kanehisa, M., Furumichi, M., Sato, Y., Ishiguro-Watanabe, M., & Tanabe, M. (2021). KEGG: Integrating viruses and cellular organisms. Nucleic Acids Research, 49(D1), D545–D551.
22. Martens, M., Ammar, A., Riutta, A., Waagmeester, A., Slenter, D. N., Hanspers, K., A. Miller, R., Digles, D., Lopes, E. N., Ehrhart, F., Dupuis, L. J., Winckers, L. A., Coort, S. L., Willighagen, E. L., Evelo, C. T., Pico, A. R., & Kutmon, M. (2021). WikiPathways: Connecting communities. Nucleic Acids Research, 49(D1), D613 D621
23. Jassal, B., Matthews, L., Viteri, G., Gong, C., Lorente, P., Fabregat, A., Sidiropoulos, K., Cook, J., Gillespie, M., Haw, R., Loney, F., May, B., Milacic, M., Rothfels, K., Sevilla, C., Shamovsky, V., Shorser, S., Varusai, T., Weiser, J., … D'Eustachio, P. (2020). The reactome pathway knowledgebase. Nucleic Acids Research, 48(D1), D498–D503.
24. Nishimura, D. (2001). BioCarta. Biotech Software & Internet Report, 2(3), 117–120.
25. Jiang, Y., Zhao, T., Zhou, X., Xiang, Y., Gutierrez-Castrellon, P., & Ma, X. (2022). Inflammatory pathways in COVID-19: Mechanism and therapeutic interventions. MedComm, 3(3), e154.
26. Zhou, G., Soufan, O., Ewald, J., Hancock, R. E. W., Basu, N., & Xia, J. (2019). NetworkAnalyst 3.0: A visual analytics platform for comprehensive gene expression profiling and meta-analysis. Nucleic Acids Research, 47(W1), W234–W241.
27. Tanaka, T., Narazaki, M., & Kishimoto, T. (2014). IL-6 in inflammation, immunity, and disease. Cold Spring Harbor Perspectives in Biology, 6(10), a016295.
28. Imai, Y., Kondo, Y., Ishigaki, S., Nishina, N., Ota, Y., Hanaoka, H., Kaneko, Y., & Takeuchi, T. (2022). A case of eosinophilic granulomatosis with polyangiitis after prolonged intervals of an anti-interleukin-6 receptor antibody for rheumatoid arthritis. Modern Rheumatology Case Reports, 6(1), 83–86.
29. Wang, X., Tang, G., Liu, Y., Zhang, L., Chen, B., Han, Y., Fu, Z., Wang, L., Hu, G., Ma, Q., Sheng, S., Wang, J., Hu, X., & Shao, S. (2022). The role of IL-6 in coronavirus, especially in COVID-19. Frontiers in Pharmacology, 13.
30. Gioffredi, A., Maritati, F., Oliva, E., & Buzio, C. (2014). Eosinophilic Granulomatosis with Polyangiitis: An Overview. Frontiers in Immunology, 5, 549.
31. Tanveer, A., Akhtar, B., Sharif, A., Saleem, U., Rasul, A., Ahmad, A., & Jilani, K. (2022). Pathogenic role of cytokines in COVID-19, its association with contributing co-morbidities and possible therapeutic regimens. Inflammopharmacology, 30(5), 1503.
32. Isozaki, T., Homma, T., Sagara, H., & Kasama, T. (2020). Role of Cytokines in EGPA and the Possibility of Treatment with an Anti-IL-5 Antibody. Journal of Clinical Medicine, 9(12), 3890.
33. Rabaan, A. A., Al-Ahmed, S. H., Muhammad, J., Khan, A., Sule, A. A., Tirupathi, R., Mutair, A. A., Alhumaid, S., Al-Omari, A., Dhawan, M., Tiwari, R., Sharun, K., Mohapatra, R. K., Mitra, S., Bilal, M., Alyami, S. A., Emran, T. B., Moni, M. A., & Dhama, K. (2021). Role of Inflammatory Cytokines in COVID-19 Patients: A Review on Molecular Mechanisms, Immune Functions, Immunopathology and Immunomodulatory Drugs to Counter Cytokine Storm. Vaccines, 9(5), 436.
34. Fijolek, J., & Radzikowska, E. (2023). Eosinophilic granulomatosis with polyangiitis – Advances in pathogenesis, diagnosis, and treatment. Frontiers in Medicine, 10, 1145257.
35. Jahaj, E., Vassiliou, A. G., Keskinidou, C., Gallos, P., Vrettou, C. S., Tsipilis, S., Mastora, Z., Orfanos, S. E., Dimopoulou, I., & Kotanidou, A. (2021). Evaluating the Role of the Interleukin-23/17 Axis in Critically Ill COVID-19 Patients. Journal of Personalized Medicine, 11(9), 891.
36. Jiang, Y., Zhao, T., Zhou, X., Xiang, Y., Gutierrez-Castrellon, P., & Ma, X. (2022). Inflammatory pathways in COVID-19: Mechanism and therapeutic interventions. MedComm, 3(3), e154.
37. Hwang, S.-Y., Kim, J.-Y., Kim, K.-W., Park, M.-K., Moon, Y., Kim, W.-U., & Kim, H.-Y. (2004). IL-17 induces production of IL-6 and IL-8 in rheumatoid arthritis synovial fibroblasts via NF-κB- and PI3-kinase/Akt-dependent pathways. Arthritis Research & Therapy, 6(2), R120–R128.
38. Lee, J., Wang, P., Kattah, M., Youssef, S., Steinman, L., Defea, K., & Straus, D. (2008). Differential Regulation of Chemokines by IL-17 in Colonic Epithelial Cells. Journal of Immunology (Baltimore, Md. : 1950), 181, 6536–6545.
39. Rodriguez-Pla, A., Warner, R. L., Cuthbertson, D., Carette, S., Khalidi, N. A., Koening, C. L., Langford, C. A., McAlear, C. A., Moreland, L. W., Pagnoux, C., Seo, P., Specks, U., Sreih, A. G., Ytterberg, S. R., Johnson, K. J., Merkel, P. A., & Monach, P. A. (2020). Evaluation of Potential Serum Biomarkers of Disease Activity in Diverse Forms of Vasculitis. The Journal of Rheumatology, 47(7), 1001–1010.
40. Isozaki, T., Homma, T., Sagara, H., & Kasama, T. (2020). Role of Cytokines in EGPA and the Possibility of Treatment with an Anti-IL-5 Antibody. Journal of Clinical Medicine, 9(12), 3890.
41. Mohd Zawawi, Z., Kalyanasundram, J., Mohd Zain, R., Thayan, R., Basri, D. F., & Yap, W. B. (2023). Prospective Roles of Tumor Necrosis Factor-Alpha (TNF-α) in COVID-19: Prognosis, Therapeutic and Management. International Journal of Molecular Sciences, 24(7), 6142.
42. Todorović-Raković, N., & Whitfield, J. R. (2021). Between immunomodulation and immunotolerance: The role of IFNγ in SARS-CoV-2 disease. Cytokine, 146, 155637.
43. Kastenhuber, E. R., & Lowe, S. W. (2017). Putting p53 in Context. *Cell*, 170(6), 1062–1078.

44. Do, H., Ahn, S. S., Pyo, J. Y., Song, J. J., Park, Y.-B., & Lee, S.-W. (2022). Interferon gamma Release Assay Results Are Reliable for Screening for Latent Tuberculosis in Antineutrophil Cytoplasmic Antibody-associated Vasculitis. In Vivo, 36(6), 2884 2889.
45. Liu, T., Zhang, L., Joo, D., & Sun, S.-C. (2017). NF-κB signaling in inflammation. Signal Transduction and Targeted Therapy, 2(1), 1–9.