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DECIPHERING CRUCIAL GENES IN PELVIC INFLAMMATORY DISEASE AND THEIR RELATIONSHIP WITH INFERTILITY THROUGH SYSTEMS BIOLOGY STUDIES

F. Saberi[a], Z. Dehghan[b], T. Pilehchi[a], Sh. Mehdinejadiani[c], Z. Taheri[d], H. Zali[a]

[a] *Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[b] *Shiraz University of Medical Sciences, Shiraz, Iran*
[c] *University of Calgary, Calgary, Canada*
[d] *University of Pavia, Pavia, Italy*

Abstract. *Background.* Pelvic inflammatory disease (PID) is an infection of the female reproductive system. PID is usually caused by infection with *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG). Women with PID have an increased risk of becoming infertility. The aim of this study was to determine the molecular mechanisms that influence infertility and embryonic development in PID with CT and NG infections. *Materials and methods.* Microarray data were extracted from the Gene Expression Omnibus (GEO), and the protein-protein interaction network was constructed using Cytoscape software. Network analysis was performed to identify hub-bottlenecks and sub-networks. The functional mechanisms for critical genes were identified using the webgestalt server. *Results.* RPL13, EEF1G, JAK2, MYC, IL7R, CD74, IMPDH2, and NFAT5 were identified as crucial genes in protein-protein interactions and gene regulatory networks in CT and NG infections of PID. Ribosome, hematopoietic cell lineage, platelet activation, and Chagas disease, JAK-STAT pathway, eukaryotic translation elongation, Rap1 pathway, apoptosis, protein processing in the endoplasmic reticulum, progesterone-mediated oocyte maturation, and Epstein–Barr virus infection were identified as significant signaling pathways involving in CT and NG infections. *Conclusion.* Our model suggests novel critical genes, and functional pathways involved in CT and NG infections, establishing a link between these infections and infertility. However, further studies *in vitro* and *in vivo* are needed.

Key words: *pelvic inflammatory disease, infertility, bacterial infections, protein-protein interaction network, gene regulatory network, computational biology.*

СИСТЕМНАЯ БИОЛОГИЯ В РАСШИФРОВКЕ КРИТИЧЕСКИХ ГЕНОВ В ВОСПАЛИТЕЛЬНЫХ ЗАБОЛЕВАНИЯХ ОРГАНОВ МАЛОГО ТАЗА И ИХ СВЯЗИ С БЕСПЛОДИЕМ

Сабери Ф.[1], Дехган З.[2], Пилехчи Т.[1], Мехдинеджадиани Ш.[3], Тахери З.[4], Зали Х.[1]

[1] *Медицинский университет имени Шахида Бехешти, Тегеран, Иран*
[2] *Университет медицинских наук Шираза, г. Шираз, Иран*
[3] *Университет Калгари, г. Калгари, Канада*
[4] *Университет Павии, г. Павия, Италия*

Резюме. *Введение.* Воспалительные заболевания органов малого таза (ВЗОМТ) — это инфекция женской репродуктивной системы. ВЗОМТ обычно вызываются инфекцией *Chlamydia trachomatis* (CT) и *Neisseria gonorrhoeae*

Адрес для переписки:
Хакиме Зали
Медицинский университет имени Шахида Бехешти,
Тегеран, Иран.
Тел.: +98 21 22439848. E-mail: Hakimehzali@gmail.com

Contacts:
Hakimeh Zali
Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Phone: +98 21 22439848.
E-mail: Hakimehzali@gmail.com

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(NG). Женщины с ВЗОМТ имеют повышенный риск развития бесплодия. Целью данного исследования является определение молекулярных механизмов, которые влияют на бесплодие и эмбриональное развитие при ВЗОМТ с инфекциями CT и NG. *Материалы и методы.* Данные микрочипов были анализированы при помощи Gene Expression Omnibus (GEO), а сеть белок-белковых взаимодействий была построена с помощью программы Cytoscape. Сетевой анализ был выполнен для выявления узловых точек и подсетей. Функциональные механизмы для критических генов были идентифицированы с помощью сервера webgestalt. *Результаты.* RPL13, EEF1G, JAK2, MYC, IL7R, CD74, IMPDH2 и NFAT5 были идентифицированы как важные гены во взаимодействиях белок-белок и сетях регуляции генов при ВЗОМТ с инфекциями CT и NG. Важные сигнальные пути, вовлеченные в инфекции CT и NG, были ассоциированы с рибосомами, гемопоэтическими клеточными линиями, активацией тромбоцитов и болезнью Шагаса, путем JAK-STAT, эукариотической элонгацией трансляции, путем Rap1, апоптозом, процессингом белков в эндоплазматическом ретикулуме, прогестерон-опосредованным созреванием ооцитов и инфекцией вирусом Эпштейна–Барр. *Заключение.* Наша модель позволяет предложить новые критические гены и функциональные пути, вовлеченные в инфекции CT и NG, устанавливая связь между этими инфекциями и бесплодием. Однако необходимо проведение дальнейших исследований *in vitro* и *in vivo*.

Ключевые слова: *воспалительные заболевания органов малого таза, бесплодие, бактериальные инфекции, сеть белок-белкового взаимодействия, сеть регуляции генов, вычислительная биология.*

Introduction

Pelvic inflammatory disease (PID) is known as a poly-microbial infection of the upper reproductive tract that predominantly affects sexually active young women, particularly those with multiple partners [4]. The diagnosis of PID is based on various clinical symptoms, including lower abdominal pain, purulent vaginal discharge, abnormal uterine bleeding, and an elevated body temperature. A bimanual pelvic examination supports the diagnosis of PID through defining features such the presence of cervical motion tenderness, uterine tenderness, and adnexal tenderness [34]. The data show that, multiple types of organisms can contribute to the etiology of PID, emphasizing the importance of considering a broader range of pathogens in the diagnosis and treatment of this disease. There is evidence supporting the significant involvement of *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) in the development of PID. Both are Gram-negative pathogens that can survive both extracellularly and intracellularly [7].

The consequences of PID can have various long-term effects. Women with PID have an increased risk of infertility due to tubal factor infertility (TFI), with around 20% of women affected by it. This complication. Scarring of the fallopian tubes can lead to blockages or damage in the fallopian tubes, making it more difficult for the egg to reach the uterus for fertilization. Another possible complication of PID is the increased risk of ectopic pregnancy, in which the fertilized egg implants outside the uterus, typically in the fallopian tubes [14]. The percentage of tubal factor infertility attributed to CT infection may vary (estimates range from 10% to 50%), depending on the specific serologic tests used for estimation [1]. The primary concern regarding the damage caused by NG infection is the death of ciliated epithelial cells. These cells play a crucial role in fertility by facilitating the transport of the fertilized ovum towards the uterus. When ciliated cells are affected and lose their function, it significantly increases the risk of tubal factor infertility and ectopic pregnancy [27]. Several research groups have observed that a decrease in ciliary beat frequency occurs in various contexts before the visible damage to the epithelial surface [28].

Over the past two decades, systems biology has emerged as a novel and comprehensive approach to the study of biology. This interdisciplinary field has significantly improved our understanding of the molecular mechanisms underlying various diseases [37]. By integrating and analyzing complex biological data at multiple levels, including genomics, proteomics, and metabolomics, systems biology has provided valuable insights into the intricate pathways of disease. This approach has paved the way for discoveries and therapeutic strategies in the field of biology [9]. The molecular mechanisms involved in infertility and embryonic development in PID are still not fully understood. Therefore, in this study, we constructed protein-protein interactions and gene regulatory networks to understand critical genes and molecular mechanisms involved in CT and NG infections in PID.

Material and methods

Collection and processing of data. The microarray dataset related to pelvic inflammatory was extracted from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo). Zheng L. et al. in 2018 [49] analyzed blood samples from patients with pelvic inflammatory disease infected with CT and NG infections (GSE110106) (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc = GSE110106). We separated the differentially expressed genes (DEGs) based on $\left|\log_2 FC > 0.5\right|$ and the P-value < 0.05 of this dataset using GEO2R. The workflow study is represented in Fig. 1 (cover II).

Construction of protein-protein interaction network (PPIN). The STRING and HIPPIE databases were separately used to map the interaction of DEGs related to CT and NG. These networks obtained from each database were then merged separately in the Cytoscape software for both infections.

Topological analysis. The Network Analyzer app was then used to analyze networks degree, betweenness centrality, clustering coefficient, shortest path, network density and diameters. Finally, the common nodes between PPINs of both infections with a degree ≥ 10 and a betweenness centrality ≥ 0.01 were determined using a Venn diagram. These nodes were used for further analysis.

Detection of clusters in PPINs. The Molecular Complex Detection (MCODE) app was used to detect highly interconnected network regions (clusters) and seed nodes in the PPI networks of both infections. The default settings of the MCODE app (cut off = 0.2, K-Core = 2, and Max-Depth = 100) were used for the extraction of clusters. The subnetworks with a score > 3 were chosen as significant clusters.

Construction and analysis of gene-regulatory network (GRN). The four relationships, miR-gene, miR-TF, TF-gene, and miR-TF were created using miRTarBase, TRANSFACT, and Transmir databases. These relationships were input into Cytoscape software and visualized as GRNs. The Network Analyzer app was then used to extract the properties of networks, including degree, and betweenness centrality. Finally, common nodes with a degree of 5% and a betweenness centrality of 5% were identified in GRNs of all infections and common nodes between both infections were determined using the Venn diagram. These nodes were used for further analysis.

Table 1. The list of hub-bottlenecks in *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) infections

Genes	Degree	Betweenness centrality
CT		
LRRK2	70	0.080949
HSP90AB1	69	0.075475
BIRC3	66	0.078461
APEX1	52	0.102002
CD4	48	0.047645
CD74	45	0.057007
HNRNPA2B1	44	0.019454
RPLP0	43	0.017128
RPS9	43	0.014556
RHOB	42	0.041998
NG		
MYC	26	0.506756
EEF1G	19	0.128775
RPL3	16	0.123235
RPL35	15	0.070224
TPT1	15	0.041017
RPL13	15	0.035638
RPL22	15	0.028137
RPL14	14	0.035638
BCL2	10	0.112867
JAK2	10	0.068586

Functional pathways analysis. The common nodes with the highest degree, and betweenness centrality in PPIN and GRN, as well as cluster nodes were selected for functional pathways. The nodes were enriched using the webgestalt tool.

Results

Raw data collection and processing. Analysis of dataset GSE110106 with GEO2R, applying filters of $\left|\text{log2FC} > 0.5\right|$ and the P-value < 0.05, revealed 338 (146 up-regulated and 192 downregulated) and 70 (37 upregulated and 33 down regulated) differentially expressed proteins in CT and NG, respectively. All DEGs are listed in Supplementary Table S1.

Construction of PPIN. The STRING and HIPPIE databases were used for the drawing of PPIN. These networks were merged and visualized for both CT and NG infections using Cytoscape software, separately. The CT PPIN had 277 nodes and 1817 edges and the NG PPIN showed 45 nodes and 151 edges.

Topological analysis. The network analyzer plugin was used to evaluate the topological network properties and determine the critical nodes (hub and bottleneck). The topological network properties related to PPIN of CT included: clustering coefficient of 0.262, shortest path of 95%, network density of 0.042, and diameter of 8. For the topological network properties PPIN of NG had a clustering coefficient of 0.360, shortest path of 95%, network density of 0.121, and diameter: 5. Fig. 2A and 2B (cover II) show the two infection subnetworks, containing common genes with a degree ≥ 10 and a betweenness centrality ≥ 0.01 as hub-bottlenecks. Table 1 depicts and characterizes them by their degree and betweenness centrality). In addition, the 16 common nodes (IL7R, PRPF4B, HNRNPA1P10, RMI1, SGK223, ZFC3H1, NFAT5, N4BP2L2, ABCA1, XIST, CXXC5, MAL, EEF1G, RPL13AP6, RPL13, and BAZ1A) between PPIN of both infections were identified using a Venn diagram.

Sub-networks detection. The extraction of clusters by the MCODE app in the Cytoscape software resulted in 6 and 2 clusters with a score > 3 for CT and NG, respectively. The seed nodes in the CT sub-networks included: CD74, CD52, CAPZA1, IMPDH2, FCGR2A, and SRSF11. In the NG subnetworks, MYC and JAK2 were identified as seed nodes (Table 2 and Fig. 3A and 3B, cover III).

Construction of GRN. The four relationships (miRNA→gene, TF→gene, miRNA→TF, and TF→miRNA interactions) were merged to create GRN in Cytoscape software. The GRN of CT compromised 2611 nodes, and 23 439 edges. The GRN of NG showed 2178 nodes and 10 630 edges. The common nodes with 5% degree and 5% betweenness cen-

Table 2. Summary of cluster characteristics of CT and NG protein-protein interaction networks identified using the MCODE app.

Cluster	Score	Nodes	Edges	Node IDs
CT				
1	16.889	19	159	PA2G4, RPL36, BIRC3, RPS9, HNRNPR, RPS3A, RPLP0, RPL13, FLT3LG, RPL12, CD74, EIF5A, RPS4X, HNRNPA2B1, RPS5, HSP90AB1, EEF1G, EEF1D, EIF3I
2	9.455	12	54	CD4, CD79B, CD96, CD3G, CD79A, CD3E, CD52, CD27, CD44, IL7R, BCL6, PTPRCAP
3	4	4	7	ACTG1, CAPZB, CAPZA1, WDR1
4	3.5	5	7	TPI1, LRRK2, PPP1CA, IMPDH2, OGT
5	3.5	5	7	FCGR2A, FCRLA, FCER2, CXCR5, PRF1
NG				
1	10.8	11	62	RPL7A, RPL3, EEF1G, RPL35, RPL22, RPS17, TPT1, MYC, RPS18, RPL13, RPL14
2	4	4	7	CISH, JAK2, BCL2, IL7R

trality between the GRN of CT and NG infections included 89 nodes (45 genes, 9 miRNAs, and 35 TFs) and 470 edges for CT 89 nodes (21 genes, 19 miRNAs, and 49 TFs) and 435 edges for NG, respectively (Fig. 4A and 4B, cover III).

The intersection GRN between both infections showed 39 nodes (2 genes, 9 miRNAs, and 26 TFs), and 139 edges. This common network includes NFAT5, and MYC genes, miR-93, miR-155, miR-19a, miR-106b, miR-124, miR-17, miR-20a, miR-21, and miR-16 miRNAs, and 26 TFs (Fig. 4C, cover III).

Gene ontology and functional pathways analysis. The functional pathway analysis for hub-bottleneck and cluster nodes was performed for both infections with webgestalt. In CT, Pathway analysis revealed that ribosome, hematopoietic cell lineage, platelet activation, and Chagas disease are important pathways. Among the hub-bottleneck and cluster nodes in the PPIN of NG, the ribosome and the JAK-STAT signaling pathway are the most important pathways. Common nodes between both infections are involved in eukaryotic translation elongation, and disease pathways. Table 3 shows the top results of gene pathway analysis.

Table 3. Functional pathways obtained by webgestalt server for hub-bottleneck and clusters nodes and common nodes between both infections in PPIN of CT and NG infections

ID	Term	FDR
CT		
hsa03010	Ribosome	2.42E-05
hsa04640	Hematopoietic cell lineage	3.77E-05
hsa04611	Platelet activation	0.000142
hsa05142	Chagas disease (American trypanosomiasis)	0.000522
NG		
hsa03010	Ribosome	2.95E-11
hsa04630	JAK-STAT signaling pathway	8.78E-06
Common nodes between both infections		
R-HSA-156842	Eukaryotic Translation Elongation	1
R-HSA-1643685	Disease	1

For hub-bottleneck in GRN of CT, five major signaling pathways are Rap1 signaling pathway, apoptosis, protein processing in endoplasmic reticulum, progesterone-mediated oocyte maturation, and Chagas disease. In GRN of NG, hub-bottleneck nodes are involved in colorectal cancer, small cell lung cancer, Epstein–Barr virus infection, amyotrophic lateral sclerosis (ALS), and pathways in cancer. Table 4 shows the analysis pathways associated with hub-bottleneck GRN in both infections.

Discussion

Pelvic inflammatory disease is a clinical syndrome that affects the female reproductive system, encompassing the uterus, vagina and fallopian tubes. It is characterized by pelvic pain, typically presenting as lower abdominal pain, and tenderness in the uterine, cervical or adnexal [11]. The sexually transmitted organisms CT and NG are the most well-known pathogens associated with PID patients [12]. PID can lead to inflammation, damage and scarring in the reproductive organs, potentially resulting in the blockage of fallopian tubes, hindering egg fertilization, and impeding the transportation of the fertilized egg into the uterus for implantation. These complications can

Table 4. Functional pathways identified by the Webgestalt server for hub-bottleneck GRN of CT and NG infections

ID	Term	FDR
CT		
hsa04015	Rap1 signaling pathway	0.13726
hsa04210	Apoptosis	0.13726
hsa04141	Protein processing in endoplasmic reticulum	0.16986
hsa05215	Prostate cancer	0.16986
NG		
hsa05210	Colorectal cancer	0.02424
hsa05222	Small cell lung cancer	0.02424
hsa05169	Epstein–Barr virus infection	0.13008
hsa05014	Amyotrophic lateral sclerosis (ALS)	0.13008
hsa05200	Pathways in cancer	0.14024

lead to critical outcomes, such as infertility and ectopic pregnancy [13]. Although PID is usually treated with antibiotics, chronic infections prove extremely challenging to address. Therefore, it is important to identify critical genes and molecular mechanisms for untreatable PID cases.

The study by Zheng et al. (2018) reported immunologic reactions in NG and CT infections. These are shown women with NG and/or CT-induced PID have an increased expression of myeloid cell genes and inhibition of protein production, mitochondrial oxidative phosphorylation, and T-cell specific genetic material [10]. However, the present study is an *in silico* analysis that predicts critical genes and functional mechanisms of PID with CT and NG infections using PPIN and GRN, and explores the relationship of these genes to infertility and embryonic development. Some critical genes identified in PPIN and GRN related to these infections include RPL13, EEF1G, JAK2, MYC, IL7R, CD74, IMPDH2, and NFAT5.

RPL13, EEF1G and IL7R emerged as important genes in the PPINs of both infections. RPL13 (ribosomal protein L13) is a component of the 60S subunit of ribosomal organelle responsible for protein synthesis. Increased expression of RPL13 has been demonstrated to activate antiviral innate immune signaling pathways, leading to up-regulation of nuclear factor-κB (NF-κB), interferon-β (IFNβ), and the pro-inflammatory cytokine interleukin-6 (IL-6) [14]. EEF1G encodes the elongation factor 1-gamma subunit of the elongation factor-1 complex, involved in the delivery of aminoacyl-tRNAs to the ribosome during the protein synthesis process. Thus, elongation factor-1 complex and its subunits may have a function in non-translational processes [15]. Furthermore, additional studies on the role of EEF1G in PID are needed. IL7R is a heterodimer composed of the interleukin-7 receptor-α (CD127) and the common-γ chain receptor (CD132), playing various roles in the development, homeostasis and function of lymphocytes [16]. Deficiency in IL-7R in mice resulted a decreased in endometrial innate immunity, leading to increased susceptibility of the endometrium to CT infections [17]. Zhang et al. found that progenitors of the $CD127^+$ uterine natural killer lineage were absent in the early post-implantation phase of mouse gestation, suggesting that the decidualized endometrial stroma has important immune-regulatory properties [18]. Therefore, the down-regulation of $CD127^+$ could have an impact on embryo implantation in PID patients. An aspect that has not yet been investigated.

JAK2 and *MYC* emerged as important genes in the NG sub-networks. JAK2 (Janus kinase 2) is a non-receptor tyrosine kinase involved in the JAK/STAT signaling pathway, which is involved in immune response, cell growth, and differentiation [19]. Lad et al. demonstrated that the expression of JAK2 was increased in CT-infected human cervical adenocarcinoma HeLa 229 cells, suppressing the growth of Chlamydia [20]. JAK2 expression is also implicated in the regulation of early preimplantation development. Evidence indicates that JAK2 is overexpressed in unfertilized oocytes of mice, and then gradually decreases until the four-cell stage, persisting at low levels until the blastocyst stage [21]. Altered JAK2 expression in PID may impair embryo development and implantation. MYC, also known as c-Myc, encodes a nuclear phosphoprotein acting as a transcription factor that plays a role in metabolism, apoptosis, cell cycle progression and cell transformation. In Xenopus, maternal c-Myc is involved in oogenesis, early embryonic development, and transition to the midblastula. The level of maternal c-Myc protein in a mature oocyte is higher than in a somatically growing cell and is maintained only during the cleavage phase of the embryo. However, the level of c-Myc protein is reduced during the cleavage phase until the mid-blastula stage [22]. Therefore, a change in maternal c-Myc level during gestation may affect early embryonic development in PID patients.

CD74 and IMPDH2 were critical genes in the CT sub-networks. The CD74 gene encodes the gamma chain of class II HLA histocompatibility antigen (also called invariant chain) which has a diverse range of biological functions, including antigen presentation, development of T- and B-cell, macrophage inflammation, dendritic cell motility and thymic selection. It can also act as a receptor for bacterial proteins, macrophage migration inhibitory factor (MIF) and D-dopachrome tautomerase (D-DT/MIF-2) [23]. Ietta et al. demonstrated that CD74 is expressed in placental tissues throughout the first trimester of pregnancy. They also indicated that the MIF/CD74 axis is involved in the maintenance of trophoblast homeostasis under hypoxia/re-oxygenation conditions in placental explant cultures from the first trimester of pregnancy [24]. In contrast, Al Abdulmonem showed that the CD74 isoforms in first-trimester trophoblast cells, JEG-3 and ACH-3 P are not expressed under normal conditions. However, bacterial lipopolysaccharide-induced the expression of the intracellular CD74 isoform in JEG-3 and ACH-3 P cells. It is likely, that the absence of the cell surface CD74 isoform on trophoblast cells protects the fetus from miscarriage [25]. IMPDH2 (inosine-5’-monophosphate dehydrogenase 2) is a rate-limiting enzyme involved in the *de novo* biosynthesis of guanine nucleotides. Rother et al. demonstrated that CT regulates the host’s glucose and nucleotide metabolism to control its infection processes. IMPDH2 is an important pharmacological target that can be inhibited by mycophenolate mofetil (MMF). Consequently they showed that inhibition of IMPDH2 by MMF prevents the growth of CT in human HeLa and murine MLE 12 cells as well as in the mouse lung infection model [26]. IMPDH aggregates under certain circumstances to form cytoophidium, a non-membranous, filamentous macrostructure, in various cells such as oocytes and their associated somatic cells in the ovary. It has been reported that IMPDH is involved in cGMP production to maintain oocyte meiotic arrest and oocyte–follicle developmental synchrony in mouse ovaries [27]. Ni et al. observed a reduction in the expression of IMPDH2 in mice, accompanied by the formation of cyto-ophidia in growing oocytes and granulosa cells of pre-ovulatory follicles after a luteinizing hormone surge, naturally synchronizing with oocyte meiosis resumption. Additionally, they found that the expression of IMPDH2 is associated with oocyte meiotic and development of embryos beyond the 4-cell stage [27]. Therefore, the dynamic changes in IMPDH2 expression may be disturbed in PID patients.

NFAT5 and MYC are critical genes in the GRN of both infections. The nuclear factor of activated T cells (NFAT5) is an important transcription factor involved in the maintenance of cellular homeostasis, playing crucial roles in the survival, proliferation, migration, and activation of T cells and macrophages [28]. A study by Hu Tao et al. (2019), reported that NFAT5 is regulated by the p53/mir-27a signaling axis and promotes the proliferation of mouse ovarian granulosa cells proliferation through the Wnt signaling pathway [29].

Functional enrichment analysis identified the ribosome, hematopoietic cell lineage, platelet activation, Chagas disease, JAK-STAT signaling pathway, eukaryotic translation elongation, disease, Rap1 signaling pathway, apoptosis, protein processing in endoplasmic reticulum, progesterone-mediated oocyte maturation, and Epstein–Barr virus infection pathways as functional pathways in initiation these infections.

The functional enrichment analysis identified significant signaling pathways, including the ribosome, hematopoietic cell lineage, platelet activation, and Chagas disease in PPIN of CT infections. Additionally, the ribosome and JAK-STAT signaling pathway were identified as significant pathways in PPIN of NG infections. The ribosome signaling pathway was shared by both infections. While the ribosome signaling pathway primarily plays a role in protein synthesis, it also contributes to immune regulation. Dysregulation of ribosome function may contribute to inflammation [30]. Furthermore, it was found that the translation of ribosomal proteins is regulated during activation of human dendritic cells by lipopolysaccharide, a component of the outer membrane of Gram-negative bacteria [31]. Proteomics and bioinformatics analyses have revealed that the ribosome signaling pathway also contributes to early pregnancy loss [32]. Therefore, further studies on the ribosome pathway and pregnancy loss in PID patients are needed. The hematopoietic cell lineage pathway is involved in the production of platelets, red blood cells and white blood cells such as neutrophils, monocytes and lymphocytes, which participate in inflammatory responses. It has been shown that bacterial infections could exacerbate this pathway [33]. It has been reported that platelet adhesion was significantly increased in CT-infected endothelial cells [34]. The decrease in maternal platelet count at the maternal-placental interface in the first trimester is crucial for normal placental development [35]. Meanwhile, the mean values for platelet volume, platelet distribution width and red blood cell distribution width are higher in women with first-trimester recurrent pregnancy loss than in healthy women [36]. The mean platelet volume is also lower in PID patients compared to healthy individuals [37]. This indicates the importance of platelet activation during pregnancy in patients with PID. On the other hand, CT is an obligate intracellular bacterium [12]. Several cellular processes associated with Chagas disease, including immune responses, cellular signaling pathways, and inflammatory pathways, are also associated with PID [38]. The JAK-STAT signaling pathway plays a crucial role in the regulation of immune responses and inflammatory reactions [39]. NG has been shown to modulate the JAK-STAT signaling pathway, evading host immune defenses and establishing infection [40]. The maternal JAK/STAT signaling pathway also plays a role in pregnancy. In rats, the maternal JAK/STAT signaling pathway is involved in the modulating immunological response and the interaction between the uterus and embryo during the implantation period [41]. Therefore, alteration of the JAK/STAT pathway could impair embryo implantation and development in women with PID. The eukaryotic translation elongation pathway is involved in the elongation of the growing polypeptide chain during the protein synthesis process [42]. It is emphasized that bacterial infections control host translation and protein synthesis to trigger immune responses and influence immunity-related inflammation [43]. Translational changes are also crucial for the development of oocytes and early embryos [44]. Therefore, the eukaryotic translation elongation pathway in PID might influence oocyte and early embryo development, a topic that has not been investigated yet.

Rap1 signaling pathway, apoptosis, protein processing in endoplasmic reticulum, progesterone-mediated oocyte maturation, Chagas disease and Epstein–Barr virus are significant pathways in GRN of both infections. Repressor activator protein 1 (Rap1), as a small GTPase, is essential for structural integrity and length of telomere. However, it also induces the production of pro-inflammatory cytokines via nuclear factor kappa B (NF-κB) signaling in cells, such as macrophages [45]. A study conducted by Yin Cai showed that the presence of Rap1 was positively associated with the advancement and progression of the inflammatory disease [46]. Studies have shown that different stages of CT infection regulate different host cell signaling pathways, including Rap1, which may play an important role in modulating infection with this microorganism and host cell survival [47]. CT impairs apoptosis in infected cells by blocking the release of mitochondrial cytochrome C and subsequently inhibiting the cell death caspase [47]. They also inhibit host cell apoptosis through both host cell-derived anti-apoptotic factors and the chlamydial protease-like activity factor (CPAF). This strategy maintains the intracellular environment for the persistence and development of chronic infection, including pelvic inflammatory disease [48].

The unfolded protein response (UPR) is triggered by CT through chlamydial effector proteins (CT228 and Tarp (and T3SS effector-mediated activation of MHC-II. This process of UPR contributes to the replication and pathogenesis of this intracellular parasite. The purpose of the UPR is to establish the initial anti-apoptotic baseline state and restore cellular homeostasis, ensuring successful development of the infection [49]. Progesterone levels are elevated during pregnancy and ensure the establishment development and maintenance of a normal pregnancy by suppressing various inflammatory pathways. Dysregulation of progesterone, crucial for the development of the mammary gland, ovarian and the function of uterine leads to poor pregnancy outcomes. However, progesterone enhances susceptibility to chlamydia infections through immunosuppression in the uterus and the vagina and proliferation of pathogens [50]. Epstein–Barr infection is possibly associated with autoimmune ovarian insufficiency, as this virus prevents the maturation of oocytes [51].

Conclusion

Our study identified crucial genes and molecular mechanisms involved in the pathogenesis of CT and NG infections in PID. We used PPIN and GRN to identify hubs and bottlenecks, includingRPL13, EEF1G, JAK2, MYC, IL7R, CD74, IMPDH2, and NFAT5 that are involved in the pathogenesis of PID. The functional pathways regulated by critical genes include the ribosome, hematopoietic cell lineage, platelet activation, Chagas disease, JAK-STAT signaling pathway, eukaryotic translation elongation, disease, Rap1 pathway, apoptosis, and protein processing in the endoplasmic reticulum, progesterone-mediated oocyte maturation, and Epstein–Barr virus infection. Given the limited treatment options for the chronic form of the disease and the emerging problems related to infertility, the identification of important genes and functional signaling pathways in this disease could make an important contribution to its treatment and the resolution of infertility problems. While some of our results are consistent with previous studies, we recommend *in vitro* and *in vivo* studies to validate our findings.

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Additional information

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Авторы:

Сабери Ф., Студенческий исследовательский комитет, кафедра медицинской биотехнологии, Школа передовых технологий в медицине, Исследовательский центр клеточной и молекулярной биологии, Медицинский университет имени Шахида Бехешти, Тегеран, Иран;
Дехган З., кафедра сравнительных биомедицинских наук, Школа передовых медицинских наук и технологий, Университет медицинских наук Шираза, Шираз, Иран; Центр исследований аутоиммунных заболеваний, Университет медицинских наук Шираза, Шираз, Иран;
Пилехчи Т., Студенческий исследовательский комитет, кафедра медицинской биотехнологии, Школа передовых технологий в медицине, Исследовательский центр клеточной и молекулярной биологии, Медицинский университет имени Шахида Бехешти, Тегеран, Иран;
Мехдинеджадиани Ш., факультет ветеринарной медицины, Университет Калгари, г. Калгари, Канада;
Тахери З., кафедра биологии и биотехнологии, Университет Павии, г. Павия, Италия;
Зали Х., доктор философии, кафедра тканевой инженерии и прикладных клеточных наук, Школа передовых технологий в медицине, Медицинский университет имени Шахида Бехешти, Тегеран, Иран.

Authors:

Saberi F., Student Research Committee, Department of Medical Biotechnology, School of Advanced Technologies in Medicine, Cellular and Molecular Biology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran;
Dehghan Z., Department of Comparative Biomedical Sciences, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran; Autoimmune Diseases Research Center, Shiraz University of Medical Sciences, Shiraz, Iran;
Pilehchi T., Student Research Committee, Department of Medical Biotechnology, School of Advanced Technologies in Medicine, Cellular and Molecular Biology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran;
Mehdinejadiani Sh., Faculty of Veterinary Medicine, University of Calgary, Calgary, Canada;
Taheri Z., Department of Biology and Biotechnology, University of Pavia, Pavia, Italy;
Zali H., PhD, Department of Tissue Engineering and Applied Cell Sciences, School of Advanced Technologies in Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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Иллюстрации к статье «Системная биология в расшифровке критических генов в воспалительных заболеваниях органов малого таза и их связи с бесплодием» (авторы: Ф. Саберн, З. Дехган, Т. Пилехчи, Ш. Мехдинеджадиани, З. Тахери, Х. Зали) (с. 664–672)

Illustration for the article “Deciphering crucial genes in pelvic inflammatory disease and their relationship with infertility through systems biology studies” (authors: Saberi F., Dehghan Z., Pilehchi T., Mehdinejadiani Sh., Taheri Z., Zali H.) (pp. 664–672)

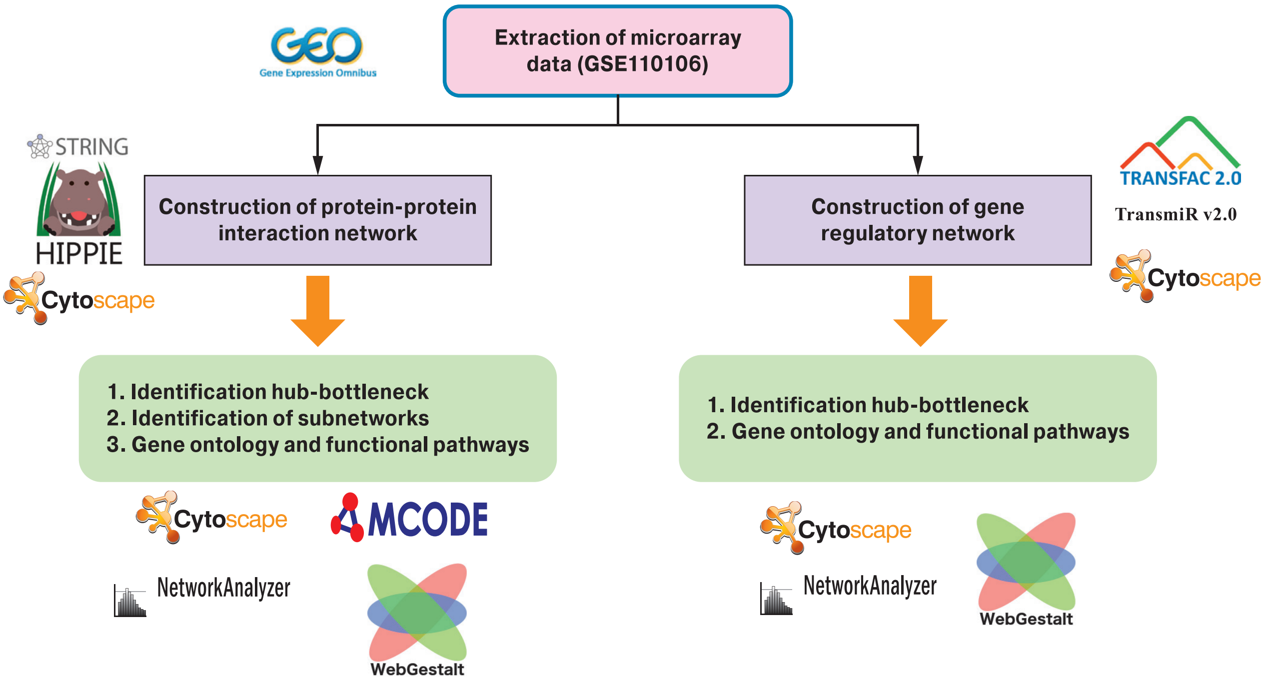

Figure 1. Workflow of study

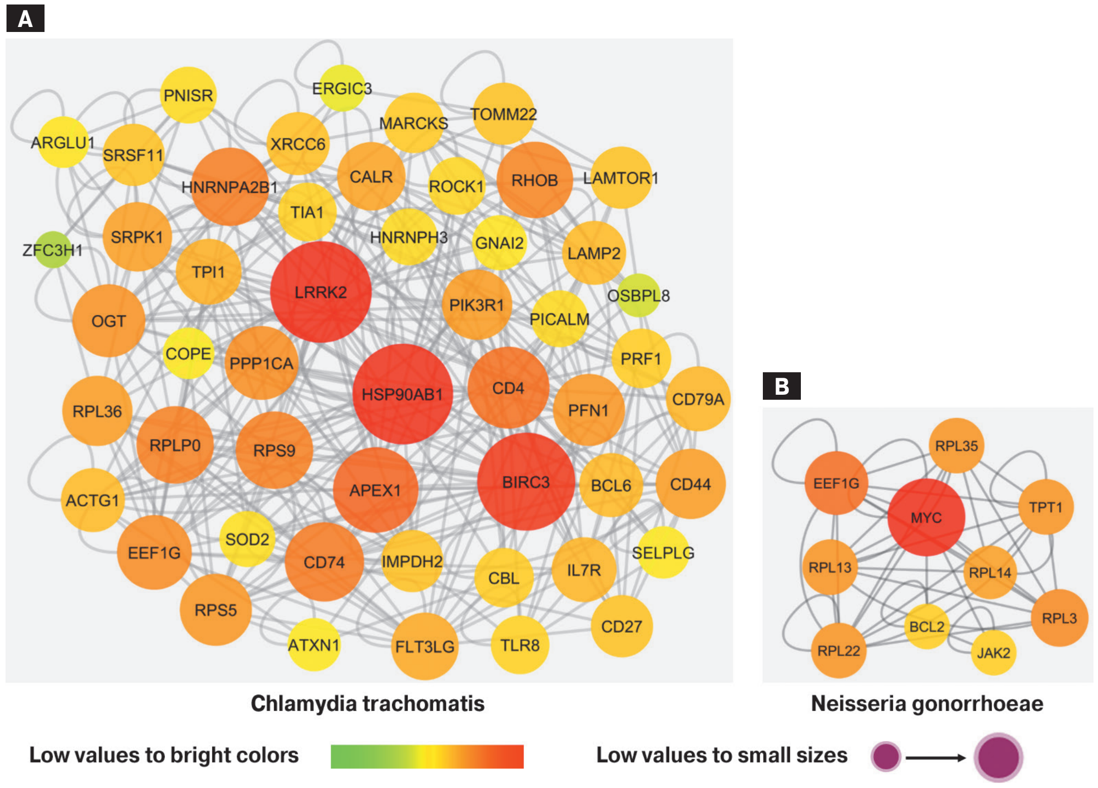

Figure 2. PPIN. A) The results of shared nodes with the highest degree and betweenness Centrality in PPIN of CT (A) and NG (B). The nodes with big size and dark color have highest degree

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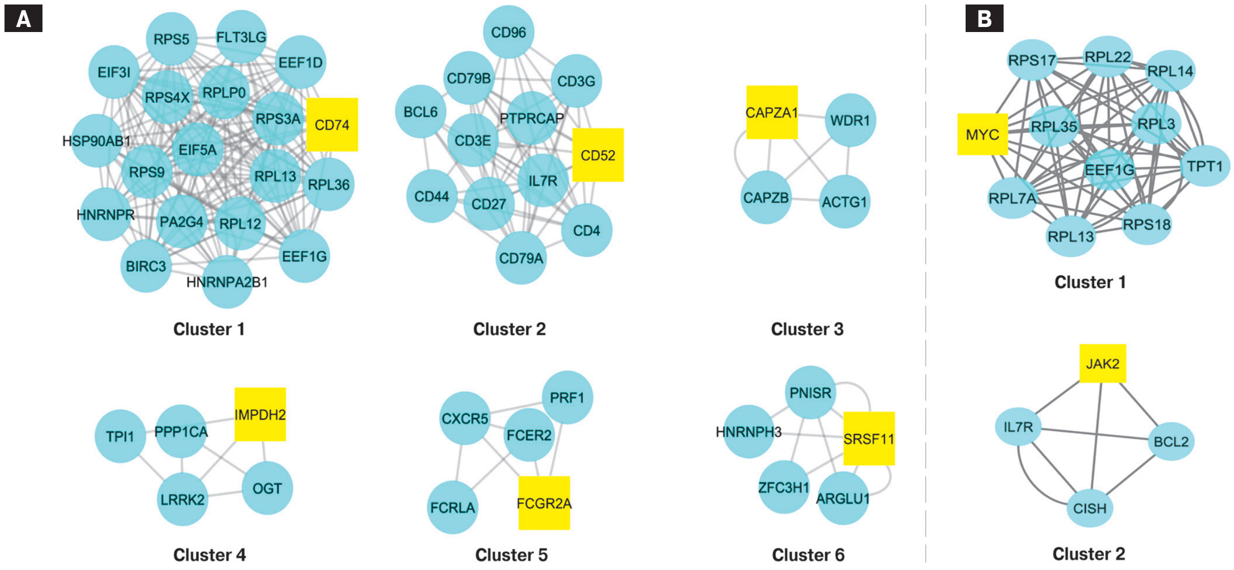

Figure 3. The subnetwork obtained from the MCODE app with score > 3 in PPIN CT (A) and NG (B)

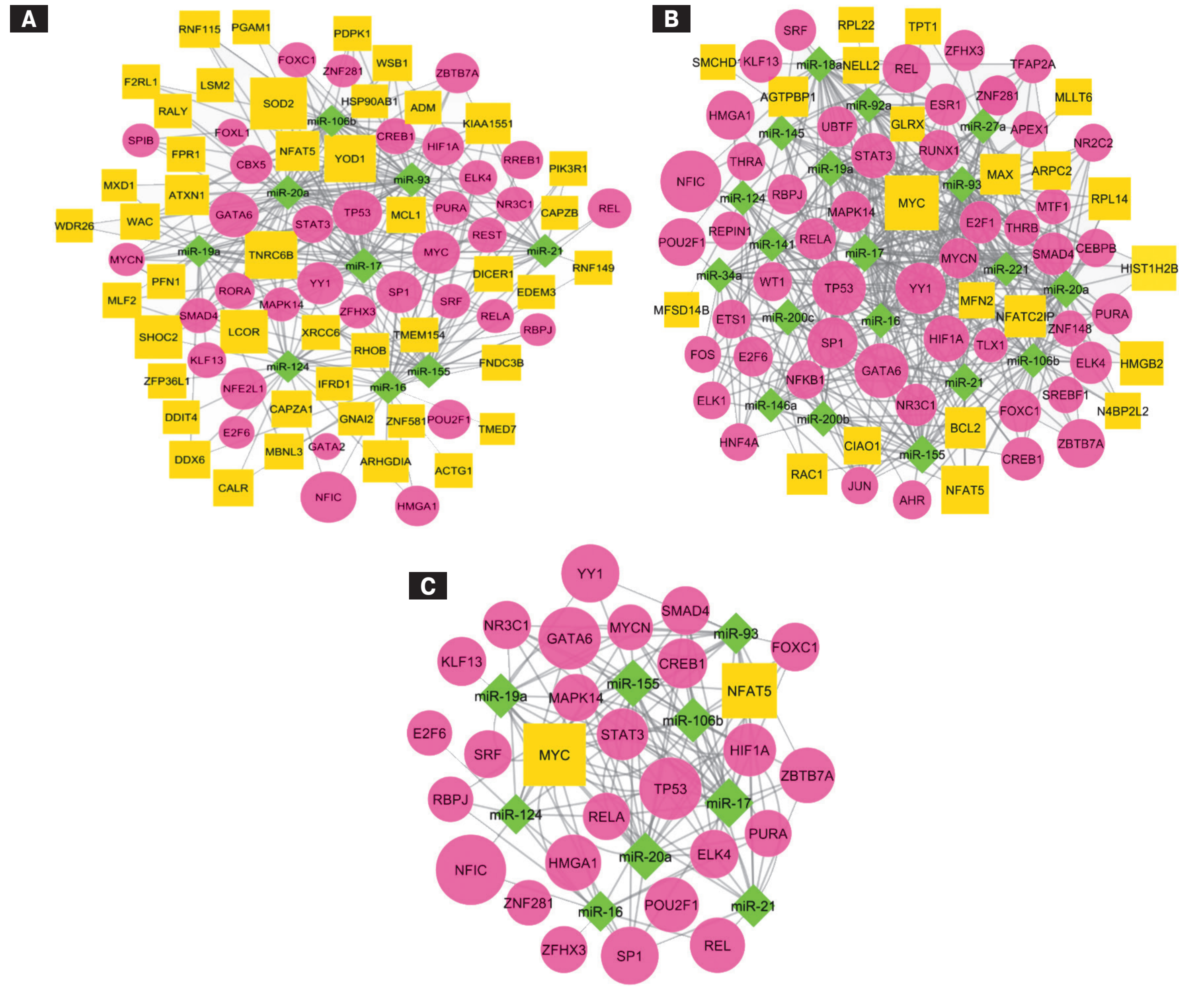

Figure 4. GRN. The results of shared nodes with the highest degree and betweenness Centrality in GRN of CT (A), NG (B), and (C) share nodes between GRN of CT and NG infections. Nodes with bigger sizes have the highest degree. The miRNAs, TFs, and genes are shown with yellow, pink, and yellow colors, respectively