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

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

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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 aims of this study are to determine the molecular mechanisms that influence infertility and embryonic development in PID with CT and NG infections.

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. Finally, new drug candidates were repurposed using the drug-gene interaction database.

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.

Keywords: Pelvic inflammatory disease, Infertility, Bacterial infections, Protein-protein interaction network, Gene regulatory network, Computational biology.

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Резюме

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

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. Новые кандидаты на лекарственные препараты были перепрофилированы с использованием базы данных взаимодействия лекарственных препаратов и генов.

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,

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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.

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1 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 (1). 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 (2). 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 (3).

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 percent 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 (4). 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 (5). 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 (6). Several research groups have observed that a decrease in ciliary beat

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frequency occurs in various contexts before the visible damage to the epithelial surface (7).

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 (8). 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 (10) analyzed blood samples from patients with pelvic inflammatory disease infected with CT and GC infections (GSE110106) (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE110106). We separated the differentially expressed genes (DEGs) based on $|\log2FC>0.5|$ and the P-value<0.05 of this dataset using GEO2R. The workflow study is represented in **Figure 1**.

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

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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 (Cutoff=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.

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 $|\log2FC>0.5|$ and the P-value <0.05, revealed 338 (146 up-regulated and 192 downregulated) and 70 (37 upregulated and 33 down regulated) differentially

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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. **Figures 2A and 2B** 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 sub-networks, MYC and JAK2 were identified as seed nodes (**Table 2** and **Figures 3A and 3B**).

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

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GRN of CT compromised 2611 nodes, and 23439 edges. The GRN of NG showed 2178 nodes and 10630 edges. The common nodes with 5% degree and 5% betweenness centrality 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 **(Figures 4A and 4B).**

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 **(Figure 4C).**

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.

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 (PID) is a clinical syndrome that affects the female reproductive system, encompassing the uterus, vagina and fallopian tubes. It is

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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 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 GC and CT infections. These are shown women with GC 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 (IFN-β), 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

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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

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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

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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

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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

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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 (NFkB) 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). *C. trachomatis* 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 *C. trachomatis* 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

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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, including*RPL13, 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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Ethical approval

All the experimental procedures in this study were approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (ethical code: IR.SBMU.RETECH.REC.1401.781).

Consent to participate

Not applicable.

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

SF, DZ, PT, MSH, and TZ: writing manuscript; DZ and ZH: data collection and analysis.

Data availability

All relevant data can be found within the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Supplementary Information

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The online version contains supplementary material.

List of Abbreviations

CT	Chlamydia trachomatis
DEGs	Differentially expressed genes
D-DT/MIF-2	D-dopachrome tautomerase
GEO	Gene Expression Omnibus
GRN	Gene-regulatory network
IMPDH2	Inosine-5'-monophosphate dehydrogenase 2
IFN-β	Interferon-β
IL-6	Interleukin-6
MCODE	Molecular Complex Detection
MMF	Mycophenolate mofetil
MIF	Migration inhibitory factor
NG	Neisseria gonorrhoeae
NFAT5	Nuclear factor of activated T cells
NF-κB	Nuclear factor-κB
PID	Pelvic inflammatory disease
PPIN	Protein-protein interaction network
TFI	Tubal factor infertility
UPR	Unfolded protein response

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ТАБЛИЦЫ

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
GC		
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

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JAK2	10	0.068586

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
GC				
1	10.8	11	62	RPL7A, RPL3, EEF1G, RPL35, RPL22, RPS17, TPT1, MYC, RPS18, RPL13, RPL14
2	4	4	7	CISH, JAK2, BCL2, IL7R

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

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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

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

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hsa05200	Pathways in cancer	0.14024

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Supplementary Table S1

DEGs/Chlamydia trachomatis	DEGs/Neisseria gonorrhoeae
RNA28S5	AGTPBP1
EIF5A	RPL13
HINT3	BCL2
IL7R	MFSD14B
CD74	DDIAS
TPI1	RPL35
FXYD5	MYC
FCRLA	JAK2
SNHG7	NBN
RPL13AP6	ZFC3H1
DGKA	RPS18
CD37	SNORA8
AES	RPL22
PFN1	RPL7A
UCP2	TPT1
PRF1	MAL
ARPC4	ARPC2
VEGFB	CISH
ACTG1	BAZ1A
COPE	SGK223
CHCHD10	MLLT6
FCER2	RAC1
CD79B	HMGB2
C17orf49	RPL3
UBA1	PRPF4B

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PTPRCAP	CXCR2P1
BIN1	CIAO1
VPREB3	ANKRD13A
XRCC6	SAT1
TECR	NELL2
CD3E	SNORA25
CXCR5	RPL14
RSL1D1	MAN1C1
CD52	FAM111A
RPS4X	RPL13AP5
MAL	GLRX
FLT3LG	NDUFB3
APRT	HNRNPA1P10
PIK3R1	HIST1H2BD
DDIT4	MFN2
BLOC1S1	PRMT5
LOC407835	UBE2C
KRTCAP2	ZNF91
BANF1	IL7R
GZMM	SOCS2
MTA2	RPL13AP6
C19orf43	RPS17
ROMO1	RMI1
PA2G4	SPOCK2
PGAM1	MAX
MLF2	SNRPN
TRAPPC6A	GP6
RALY	LTB

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PVRIG	N4BP2L2
RPL36	CCDC65
ITGA5	GLOD4
ATP6V0D1	XIST
CD79A	CCT3
HLA-DOB	NFAT5
RPS9	ABCA1
SERPINA10	LINC01420
GIMAP5	NFATC2IP
SLC25A3	CASP4
EEF1G	TXN
EEF1D	SMCHD1
TMEM238	CXXC5
ZNF581	EEF1G
MAP2K2	
BIRC3	
CD3G	
CALR	
GNAI2	
GPSM3	
IMPDH2	
LAMTOR1	
APH1A	
CD4	
SSR2	
ERGIC3	
HNRNPR	
APEX1	

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SLC9A3R1	
ECH1	
PPA1	
RPL13	
SELPLG	
RBM3	
SNRPF	
RPL12	
CD96	
ARHGDIA	
GPR183	
LSM4	
OXA1L	
SIRPG	
CXXC5	
ITM2C	
RPS3A	
PEX11B	
TNRC6B	
SSR4	
SAMM50	
VPS51	
AIP	
PFDN1	
EIF3I	
LSM2	
ATP5D	
SGSH	

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CAPZB	
POLR2F	
RWDD1	
CD27	
SKAP1	
HSP90AB1	
TOMM22	
PPP1CA	
C1QBP	
RNF115	
P2RY8	
SUMF2	
CRTAP	
IFFO2	
SGK223	
HNRNPA1P10	
IDH3G	
C19orf53	
RPS5	
VAMP8	
MRPL34	
ENSA	
CD99	
NDUFB7	
WDR1	
RPLP0	
ZEB2	
AMY2A	

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SHOC2	
WDR26	
PPT1	
SLC25A44	
FCGR2A	
UBA6	
DMTF1	
TDP2	
ROCK1	
CBL	
ARFGEF1	
ASAP1	
STK3	
EDEM3	
NBPF3	
RMI1	
SENP6	
CPQ	
CHSY1	
ARGLU1	
OLIG1	
TLR8	
PHF21A	
SACM1L	
WIPF1	
TRIM33	
ZNF654	
AHCTF1	

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FRAT2	
USP8	
CHMP5	
FPR1	
SLFN11	
PNISR	
NFAT5	
ALPK1	
CCNL1	
RNF149	
TANK	
VCPKMT	
RCBTB2	
DENND5A	
7-Sep	
RAX2	
ARID4B	
TMED7	
DICER1	
CEACAM3	
PDPK1	
RNPC3	
MCL1	
TIA1	
SORL1	
IRAK3	
IL18RAP	
MED23	

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FAM129A	
HNRNPH3	
PPP4R1	
TRPM6	
CLK1	
PRPF4B	
RHOB	
MTMR6	
FAM160B1	
GK	
BNIP2	
USP15	
CAPZA1	
ZNF217	
LAMP2	
RAB33B	
TLR5	
RNASEL	
WAC	
ZSWIM6	
SYNJ1	
LOC401357	
SOD2	
TOP1P2	
PPM1A	
SLK	
IFRD1	
N4BP2L2	

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RASSF2	
GCA	
NEDD9	
ATP2B1	
KIAA1551	
HEBP2	
FCHO2	
ATXN1	
BIRC2	
CLK4	
SPOPL	
MARCKS	
RSRP1	
RBM47	
SCARNA9	
SLC4A7	
SLC22A4	
PHIP	
LUC7L3	
ATP11B	
UBE4A	
KLF4	
VCAN	
ZFC3H1	
LILRB3	
JMJD1C	
NPL	
LMO2	

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IL1RAP	
PNN	
FBXO38	
SRSF11	
RAPGEF2	
AQP9	
FAM214A	
SRPK1	
MXD1	
SIPA1L2	
KCNJ15	
DPYD	
FNDC3B	
TMEM154	
ABCA1	
APAF1	
GPCPD1	
OGT	
C9orf72	
KLHL2	
WSB1	
RTN3	
SNAP23	
F5	
F2RL1	
SP3	
PICALM	
P2RY13	

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PPP1R12A	
BAZ2B	
GNA13	
ACSL4	
OSBPL8	
CD44	
HNRNPA2B1	
NFXL1	
BASP1	
FAM198B	
NFKBIZ	
HECA	
XIST	
BCL6	
DUSP6	
DDX6	
CREB5	
LRRK2	
LY96	
LCOR	
BAZ1A	
ANXA2P1	
LYST	
SNORA12	
ADM	
ZFP36L1	
TLR1	
ACSL1	

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MBNL3	
YOD1	
SNORD13	

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РИСУНКИ

Figure 1. Workflow of study.

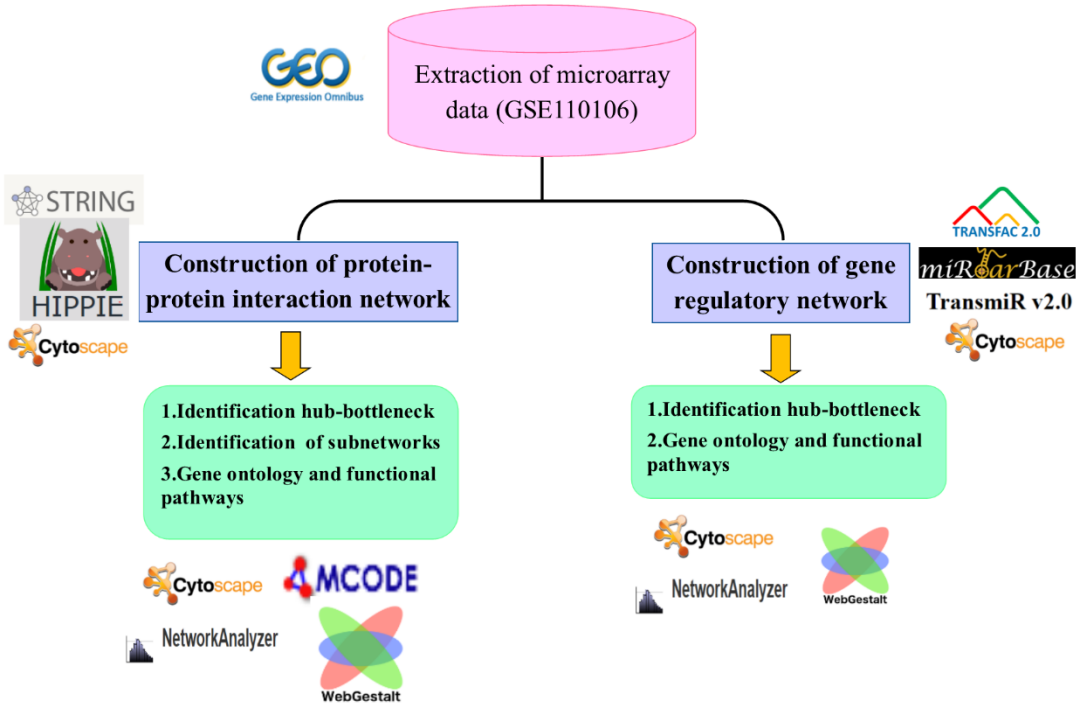

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Figure 2. PPIN. A) The results of shared nodes with the highest degree and betweenness Centrality in PPIN of CT **(A)** and NG **(B)**. The nodes with big size and dark color have highest degree.

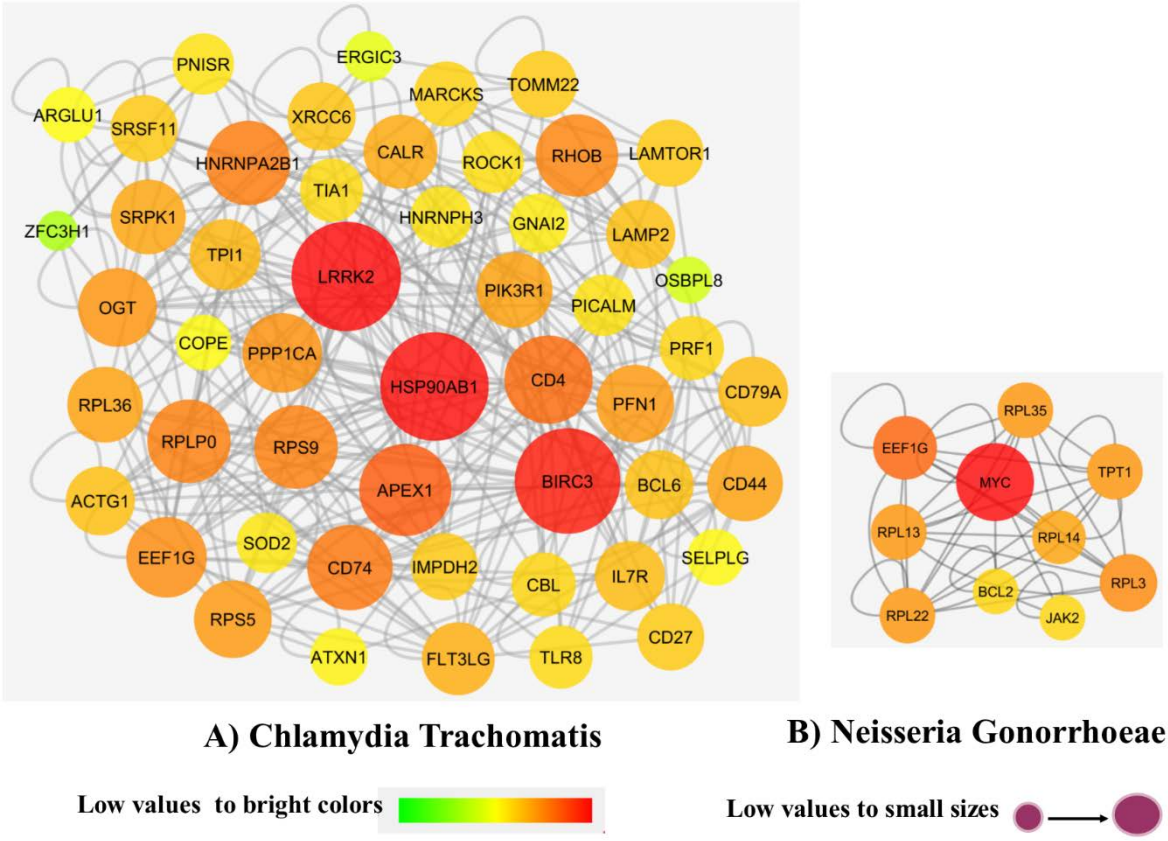

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Figure 3. The subnetwork obtained from the MCODE app with score >3 in PPIN CT **(A)** and NG **(B)**.

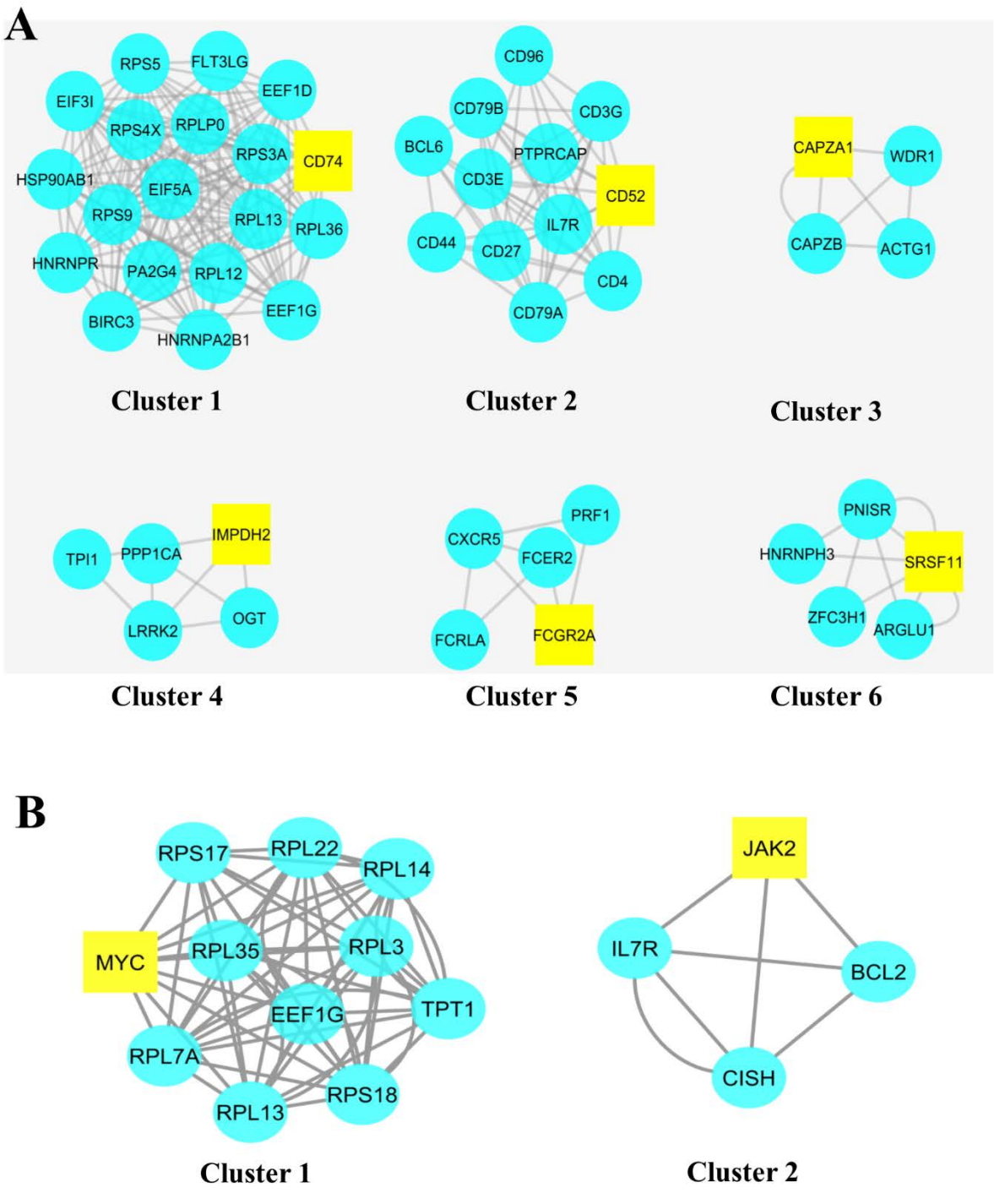

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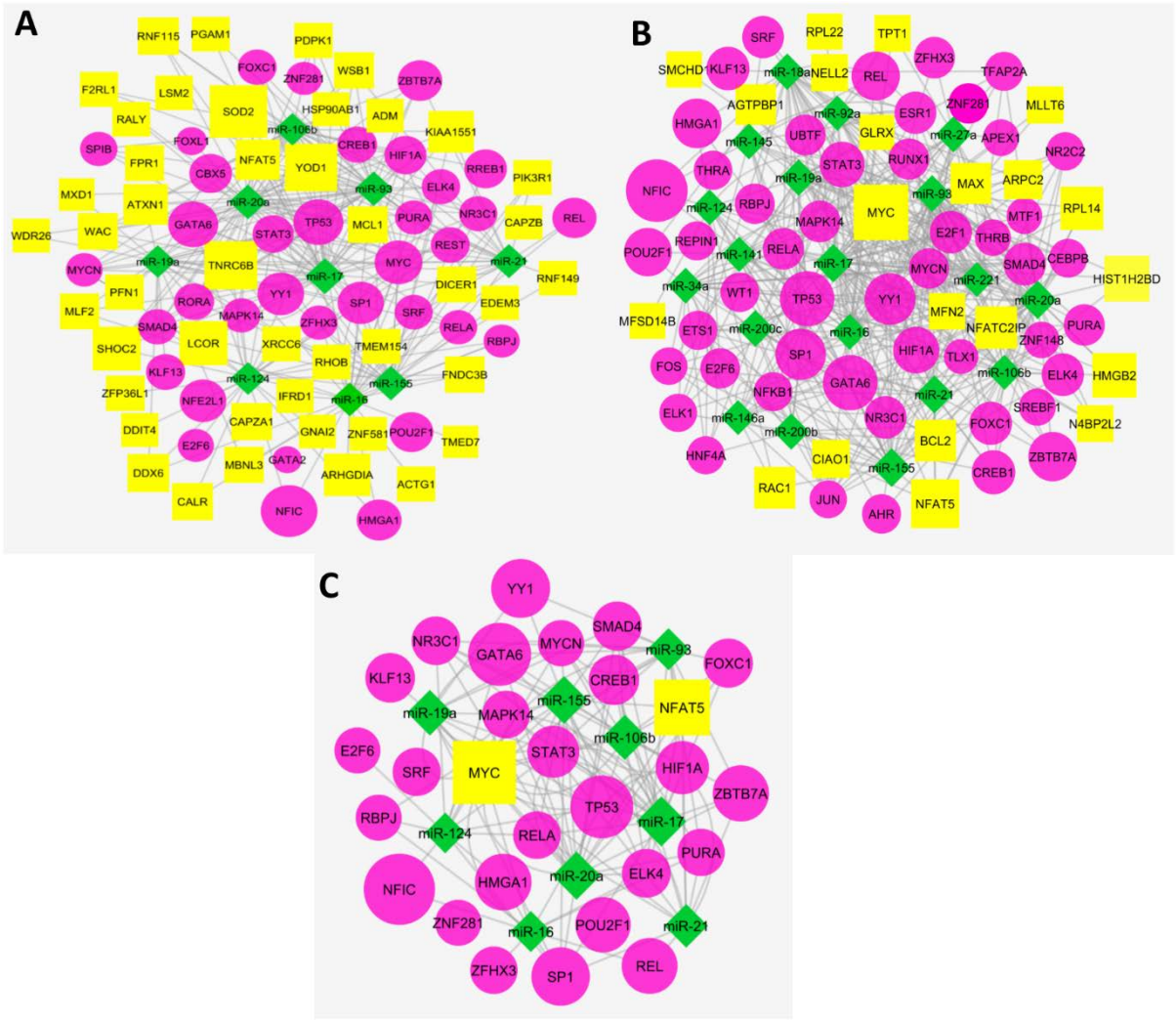
Figure 4. GRN. The results of shared nodes with the highest degree and betweenness Centrality in GRN of CT **(A)**, NG **(B), and (C)** share nodes between GRN of CT and NG infections**.** Nodes with bigger sizes have the highest degree. The miRNAs, TFs, and genes are shown with yellow, pink, and yellow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



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ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

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Блок 3. Метаданные статьи

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

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

Сокращенное название статьи для верхнего колонтитула:
PELVIC INFLAMMATORY DISEASE AND INFERTILITY
ВОСПАЛИТЕЛЬНЫЕ ЗАБОЛЕВАНИЯ ОРГАНОВ МАЛОГО ТАЗА И БЕСПЛОДИЕ

Keywords: Pelvic inflammatory disease, Infertility, Bacterial infections, Protein-protein interaction network, Gene regulatory network, Computational biology.
Ключевые слова: воспалительные заболевания органов малого таза, бесплодие, бактериальные инфекции, сеть белок-белкового взаимодействия, сеть регуляции генов, вычислительная биология.

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