



Correlation between microRNAs- 604, 1302-3p and IL-37 Expression in Iraqi Patients with Toxoplasmosis

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ABSTRACT

Background: *Toxoplasma gondii* is an obligate intracellular protozoan parasite with a unique global prevalence and is the causative agent of toxoplasmosis. MicroRNAs are key epigenetic elements crucial that modulate the immune response by influencing cytokine expression.

Objectives: To investigate serum levels of IL-37 alongside the expression of microRNAs miR-604 and miR-1302-3p in Iraqi patients with toxoplasmosis, and to evaluate their potential correlations and regulatory relationships.

Methods: A total of 200 non-pregnant women were enrolled in the present study, consisting of 100 toxoplasmosis- positive and 100 healthy controls. Toxoplasmosis status was determined via serological screening using a rapid diagnostic test (TORCH) and ELISA for IgM, IgG antibodies. For the molecular analysis, total RNA was extracted from whole blood samples and reverse-transcribed into cDNA. Quantitative real-time PCR (RT-qPCR) was then performed on both groups to quantify the expression levels of microRNA-604 and microRNA-1302-3p.

Result: The expression levels of both microRNA-604 and microRNA 1302-3p were significantly reduced in toxoplasmosis patients compared to the control group in patients (relative expression: 2.1896 ± 1.12221 ng/L vs. 1.6384 ± 1.09466 for microRNA-604; 4.0896 ± 1.42896 vs. 2.5764 ± 1.16224 for microRNA 1302-3p). Conversely, serum levels of IL-37 were significantly higher in the patient group (295.0604 ± 45.79983 ng/L) compared to the control group (36.7183 ± 3.83299 ng/L).

Conclusion: Our findings demonstrate that miRNA-604 and 1302-3p are downregulated in toxoplasmosis patients, a state associated with the marked induction of pro-inflammatory cytokine IL-37. These altered expression profiles suggest a coordinated role in the pathogenesis of toxoplasmosis, highlighting their potential utility as novel diagnostic biomarkers or therapeutic targets.

Keywords: Toxoplasmosis; cytokine; IL-37; miRNA-604; microRNA-1302-3p

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INTRODUCTION

Toxoplasmosis is a globally prevalent zoonotic infection caused by the obligate intracellular parasite *Toxoplasma gondii* (*T. gondii*), which infects a broad range of mammalian and avian hosts. Felids, including domestic cats and other members of the family Felidae, serve as the definitive hosts (1). In most animals, infection occurs through the ingestion of food and water contaminated with oocysts shed in cat feces (2). These oocysts are environmentally resilient and can persist under a wide range of conditions for prolonged periods. In humans, the primary routes of infection include the consumption of tissue cysts in undercooked meat, ingestion of sporulated oocysts from contaminated food or water (3), and congenital transmission via placental transfer of the actively replicating tachyzoite stage (4). In immunocompetent individuals, *T. gondii* infection typically remains asymptomatic. However, in immunocompromised hosts, the parasite can reactivate or progress to severe opportunistic disease, manifesting as encephalitis, as well as behavioral and psychiatric disorders (5). Additionally, chronic toxoplasmosis has been associated with psoriasis (6), diabetes mellitus (7), and end-stage renal disease in hemodialysis patients (8). Congenital infection poses a particularly serious risk: when primary maternal infection occurs during pregnancy, transplacental transmission of tachyzoites can lead to fetal complications, including spontaneous abortion, hydrocephalus, deafness, blindness, stillbirth, and variable degrees of physical or mental disability (9). Diagnosis relies on a combination of molecular and immunological techniques (10).

The relationship between host immune responses and *T. gondii* immune evasion is highly complex. To survive and replicate within host cells, the parasite employs a range of sophisticated strategies to subvert host defenses (11). One such mechanism involves the modulation of autophagy; consequently, by interfering with both canonical and

noncanonical autophagy pathways, *T. gondii* prevents its own destruction by host cells (12). Furthermore, the parasite utilizes specialized effector secretion systems to deliver proteins across the host cell membrane, facilitating nutrient acquisition and successfully manipulating host cellular functions (13). Additionally, excretory–secretory products released by the parasite have been shown to affect human immunocompetent cells. Collectively, these evasion mechanisms enhance parasite survival and contribute to the establishment of chronic infection (14).

Cytokines are key mediators of intercellular communication and play an essential regulatory role in the immune system. They are secreted by a wide range of cell types in response to diverse stimuli. However, understanding the nature of host responses during *T. gondii* infection is complicated by the functional pleiotropy and redundancy of cytokines, as well as the complexity of their interactions in experimental models (15).

More than 30% of human mRNAs are negatively regulated at the post-transcriptional level through binding of microRNAs (miRNAs) to the 3' untranslated region (3' UTR) of target transcripts. These small non-coding RNAs, typically 21–23 nucleotides in length, function as post-transcriptional gene regulators via the miRNA-induced silencing complex (miRISC), which can interfere with the expression of cytokine-encoding genes (16). Furthermore, MicroRNAs play crucial roles in numerous pathophysiological processes, including immune responses, inflammation and oxidative stress (17). In particular, miRNAs are pivotal for the negative regulation and functional modulation of anti-inflammatory cytokines, especially during excessive inflammatory responses, thereby shaping immune cell behavior and potentially exacerbating inflammatory conditions (18). Interleukin-37 (IL-37) is a member of the IL-1 family of cytokine family, encoded by a gene located on the long arm of human chromosome 2. It is characterized by an anti-inflammatory β -trefoil fold (cysteine-knot structure) and

exists in multiple splice variants, designated IL-37a through IL-37e (17). The biological activity of IL-37 is mediated through its interaction with both IL-1 receptor 8 (IL-1R8) and the IL-18 receptor α -chain (IL-18R α), forming a receptor complex that inhibits downstream pro-inflammatory signaling pathways (18). In contrast to the anti-inflammatory properties of IL-37, most cytokines—with the notable exception of other IL-1 family members such as IL-1, IL-18, and IL-33—exert pro-inflammatory functions and are synthesized in response to pathogen invasion and tissue injury. In the context of COVID-19, aberrant expression of IL-37 has been significantly associated with clinical outcomes, with predictions suggesting that severe disease may result from an inadequate IL-37-mediated anti-inflammatory response (19). Furthermore, recent studies have indicated that IL-37 can facilitate tumor progression, particularly in colitis-associated cancer (CAC), by impairing antitumor immune responses (20).

The primary objectives of this study were to investigate serum IL-37 levels in Iraqi patients with toxoplasmosis and to measure the expression levels of two specific microRNAs, miR-604 and miR-1302-3p, within the same cohort. The selection of miR-604 and miR-1302-3p was informed by our previous experimental screening, which revealed a significant correlation with IL-37 levels, suggesting a previously uncharacterized regulatory role for these miRNAs in the IL-37-associated immune response to *Toxoplasma gondii* infection. This rationale is further supported by established literature demonstrating that IL-37 expression is directly modulated by various microRNAs in other pathological contexts. For example, miR-335 and miR-657 have been shown to target IL-37 in asthma and tuberculosis, respectively (21, 22). Furthermore, in silico analysis using target prediction tools (e.g., TargetScan, miRDB) has identified potential binding sites for miRNAs within the 3'UTR of the IL37 gene, providing a bioinformatic

foundation for our investigation (23). On this basis, we hypothesized that miR-604 and miR-1302-3p may exert a similar regulatory function on IL-37, potentially revealing a novel immunomodulatory mechanism in human toxoplasmosis.

MATERIALS AND METHODS

Sample collection and processing

Blood samples (5 mL) were collected from each participant (patients and controls), with ages ranging from 16 to ≥ 50 years, during the period from November 1, 2023, to September 30, 2024. Participants were recruited from Imamein Kadhimein Medical City, Al-Alawiya Teaching Hospital, and Al kawashif Laboratory. The TORCH rapid diagnostic test was used for preliminary detection of toxoplasmosis. Following collection, each blood sample was divided into two aliquots: the first was transferred to an Eppendorf tube for subsequent molecular analysis, and the second was placed into a plain tube for serum separation. After complete clotting, the latter was centrifuged at 3000 rpm for 5 minutes at room temperature. The resulting serum was carefully isolated, aliquoted, and stored at -20°C until the immunological assessment.

Serological study

- Determination of IgM, IgG antibodies

Serum levels of anti-*T. gondii* IgG and IgM antibodies levels were determined using available ELISA kits (Foresight, Germany), following the manufacturer's instructions.

- Determination of serum IL-37 levels

Serum IL-37 concentrations were measured using a commercial human IL-37 ELISA Kit (Elascience, USA). Briefly, serum samples previously stored at -20°C were thawed, and the assay was performed according to the manufacturer's instructions.

Molecular Study

- Total RNA Extraction

- Total RNA, including small RNA fractions,

was extracted from whole blood samples using TRIzol reagent. Briefly, 1 mL of whole blood was mixed with 750 μ L of Trizol in a microcentrifuge tube and thoroughly homogenized. The samples were then stored at -20°C until further processing for miRNA extraction.

- Assessment of RNA quantity and purity

The concentration and purity of extracted total RNA were assessed using the QubitTM RNA HS Assay Kit (Q32852; Thermo Fisher®, USA), following the manufacturer's instructions. miRNA concentrations across all samples ranged from 10 pg/ μ L to 100 ng/ μ L, demonstrating a pronounced selectivity of the assay for miRNA over other RNA species.

- Quantification of Micro-RNAs expression by qRT-PCR

miRNA expression levels were quantified using quantitative real-time PCR (qRT-PCR) and normalized to the internal reference gene U6 snRNA. Relative expression was calculated using the $2^{-\Delta\Delta\text{Ct}}$ method, and data are presented as dimensionless fold change values.

- Primer sequences for miRNA-604 and miRNA- 1302-3p

Specific primers for miRNA-miRNA-604

and miRNA-1302-3p were designed and synthesized by Applied Biological Materials (Macrogen, South Korea). The primers exhibited melting temperatures ranging from 60 to 95°C , with amplicon sizes between 75 and 150 base pairs and primer lengths ranging from 19 to 26 nucleotides. The names and sequences are listed below.

Statistical Analysis

Statistical analyses were performed IBM SPSS Statistics version 29. Differences between group means were compared using the independent Student's t-test. Graphical data were generated using GraphPad Prism 9 software. Continuous variables are presented as mean $\pm$ standard error of the mean (SEM). Pearson correlation analysis was performed to assess the relationships between studied markers. Correlations are reported as the Pearson correlation coefficient (r) and the corresponding p-value. Receiver operating characteristic (ROC) curve analysis was employed to calculate the area under the curve (AUC), serving as an indicator of test reliability, and to determine the specificity and sensitivity of these assays. A p-value of <0.05 was considered statistically significant (24).

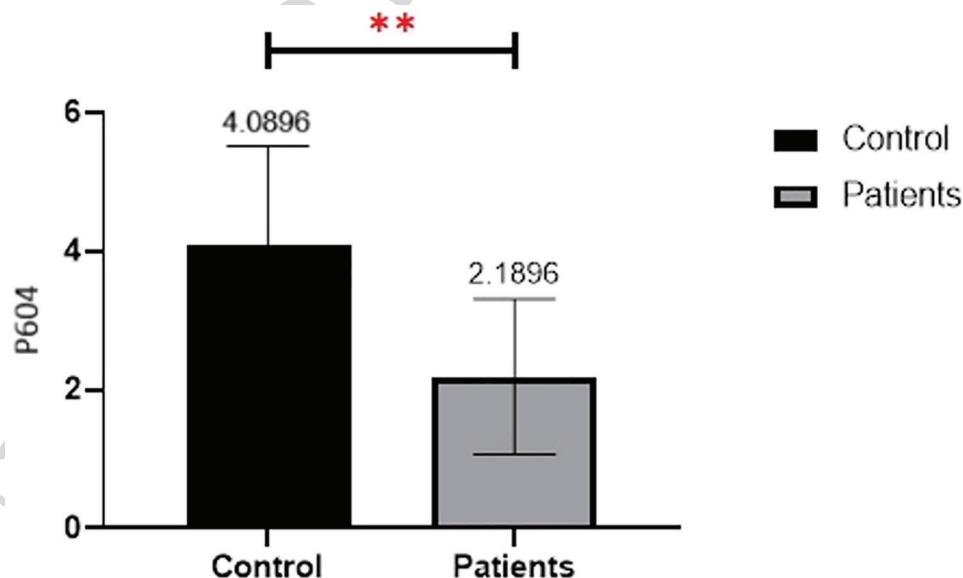


Figure 1. Relative expression of miR-604 in whole blood samples from toxoplasmosis patients compared with healthy controls. Bars represent the mean fold change ($2^{-\Delta\Delta\text{Ct}}$) for each group, normalized to U6 snRNA. Error bars indicate Standard deviation (SD). Statistical significance was determined using an independent t-test ($P = 0.001$).

RESULTS

Expression level of miRNA-604 in Toxoplasmosis patients and healthy controls

We evaluated the expression levels of miRNA-604 in whole blood samples obtained from 50 patients with toxoplasmosis and 50 healthy controls. As presented in Fig. 1, miR-604 expression levels were significantly different between the two groups ($P=0.001$). Notably, miR-604 expression was decreased in the patient group (2.1896 ± 1.12221 -fold change) compared with the control group (4.0896 ± 1.42896 -fold change).

As shown in Figure 2, ROC curve analysis revealed that miRNA-604 had an AUC of 0.69 at a cut-off value of 3.5800, a sensitivity of 62%, and a specificity of 84%.

Similarly, dysregulated expression of miR1302-3p was observed in the patient group (1.6384 ± 1.09466 -fold change), compared with the control group (2.5764 ± 1.16224 -fold change); the levels of miR1302-3p difference between groups was statistically significant ($P=0.01$, Figure 3).

Furthermore, ROC analysis indicated that miR-1302-3p expression was a good predictor

with an optimal cut-off threshold at $Ct = -3.120$ (dimensionless fold change), an AUC of 0.802, a specificity of 88%, and a sensitivity of 68% (Figure 4).

IL-37 serum concentrations in toxoplasmosis patients and controls

Serum levels of IL-37 were assessed and compared between toxoplasmosis patients and healthy control group. The findings revealed that IL-37 levels were significantly elevated in the patient group compared with the control group ($P < 0.001$). As illustrated in Figure 5, the mean serum concentration of IL-17 in patients was $(295.0604 \pm 45.79983 \text{ ng/L})$, whereas that in the control group was $36.7183 \pm 3.83299 \text{ ng/L}$.

Correlation between MicRNA-604, MicRNA-1302-3p, and IL-37 levels

Pearson's correlation coefficient was used to examine the relationship between MicRNA-604, MicRNA-1302-3p, and IL-37 serum levels. The results revealed a significant negative correlation between IL-37 and both MiR 604 and MiR 1302-3p ($r = -0.342$, $P < 0.001$ and $r = -0.247$, $P = 0.013$, respectively), as shown in Table 1.

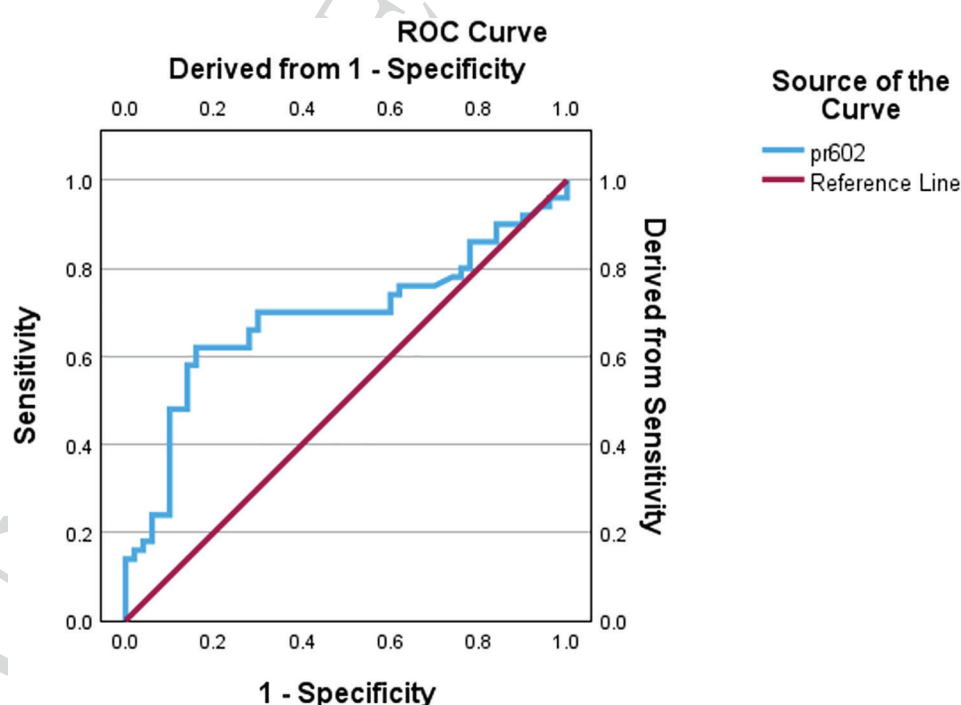


Figure 2. Receiver operating characteristic (ROC) curve analysis of miRNA-604 expression levels for distinguishing between toxoplasmosis patients from healthy controls.

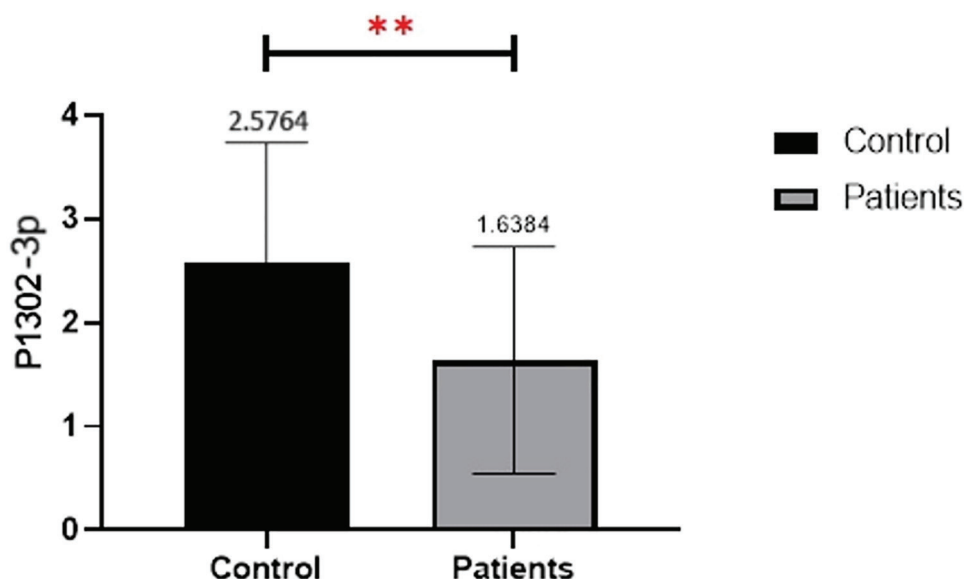


Figure 3. Relative expression of miR-1302-3p in whole blood samples from toxoplasmosis patients compared with healthy controls. Bars represent the mean fold change ($2^{-\Delta\Delta Ct}$) for each group, normalized to U6 snRNA. Error bars indicate Standard deviation (SD). Statistical significance was determined using an independent t-test ($P = 0.01$).

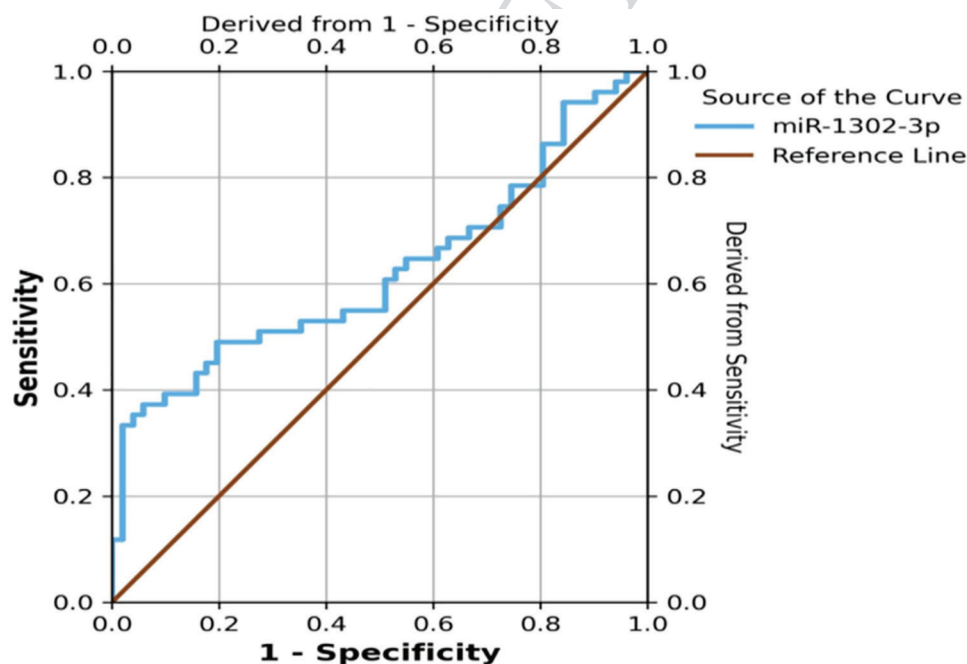


Figure 4. Receiver operating characteristic (ROC) curve analysis of miRNA-1302-3p expression levels for distinguishing toxoplasmosis patients from healthy controls.

Table 1. Specific primer sequences for miRNA-604 and miRNA-1302-3p

miR-604	5'-AGGCTGCGGAATTCAGGAC-3'	19
miR-1302-3P	5'-TTGGGACATACTTATGCTAAA-3'	21
miRU6 F.P.	5'- AGAGAAGATTAGCATGGCCCT-3'	22
Universal R. transcription p	5'-CAGGTCCAGTTTTTTTTTTTTTTTVN-3'	26
miRNA-universe R.P.	5'- GCGAGCACAGAATTAATACGAC-3'	22

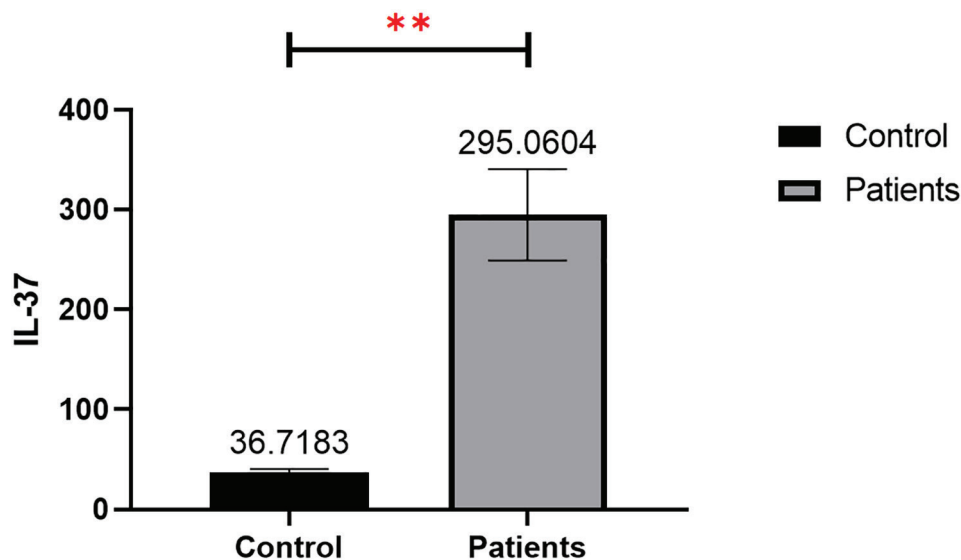


Figure 5. Serum concentrations of IL-37 (ng/L) in toxoplasmosis patients compared with healthy controls. Data are presented as mean $\pm$ standard deviation (SD).

Table 2: Pearson Correlation analysis of MicRNA-604, MicRNA-1302-3p, and serum L-37 levels in toxoplasmosis patients and healthy controls

Correlations			
		IL-37	MIR-1302-3p
MIR-604	r	-0.342**	0.096
	p	<0.001	0.341
MIR-1302-3p	r	-0.247*	--
	p	0.013	

** Significant correlation at $p < 0.01$. * Significant correlation at $p < 0.05$.

DISCUSSION

Toxoplasma gondii, the causative agent of toxoplasmosis, exhibits a complex life cycle involving both definitive and intermediate hosts, which contributes to its widespread global distribution. As an obligate intracellular pathogen, the parasite resides within a membrane-bound parasitophorous vacuole, from which it subverts multiple host cellular processes to ensure its survival and replication (25).

miRNA-mediated post-transcriptional gene regulation represents one of the more intricate mechanisms controlling the differentiation, proliferation, maturation, and activation of B and T lymphocytes at multiple levels. Numerous studies have demonstrated that host miRNAs play critical roles in both

innate and adaptive immunity, including the modulation of cytokine production (26). To the best of our knowledge, this study is the first study conducted in Iraq to investigate the role of miRNA-604, miRNA-1302-3p, and their target IL-37 in the pathogenesis of Toxoplasmosis.

The present study investigated whether miR604 and miR1303-3p are involved in inflammatory diseases through their immunoregulatory roles. The results demonstrated significant differences in the expression of both microRNAs in whole blood samples from the patient group compared with controls. Specifically, miRNA-604 expression was lower in toxoplasmosis patients than in controls. Similarly, miRNA-1302-3p expression was reduced in the patient group relative to the control group.

Our findings are supported by previous reports demonstrating negative regulation of other miRNAs, with lower expression levels observed in patients compared with healthy controls. For instance, a study conducted in Brazil showed that *T. gondii* may manipulate host gene expression, thereby modifying immune response pathways, including those associated with apoptosis and cytokine production. More broadly, intracellular parasites such as *T. gondii* are known to employ sophisticated strategies to manipulate host gene expression at multiple levels, thereby enhancing their capacity to infect and replicate within target cells, including epithelial, hepatic, and certain immune cells (27).

Zeiner *et al.* were the first to demonstrate that *T. gondii* effectors are responsible for alterations in host expression of the miR-17 ~ 92 and miR-106b ~ 25 families, which are upregulated following infection in primary human foreskin fibroblasts (HFFs) (28). Furthermore, certain miRNAs within the miR-17~92 cluster, including miR-19a, miR-19b, and miR-20a have been implicated in a novel apoptotic regulatory mechanism through inhibition of the pro-apoptotic molecule BIM, thereby enabling *T. gondii* to evade immune responses and facilitate its dissemination within the host (29). Notably, *T. gondii* induces a strong IFN- γ -mediated immune response, which plays a critical role in controlling acute infection and suppressing chronic persistence (30). Despite the potent IFN γ mediated host defense, *T. gondii* efficiently subverts this response by blocking the IFN- γ -induced transcriptional program, affecting at least 127 identified responsive genes in human fibroblasts. This suppression is achieved through inhibition of Signal Transducer and Activator of Transcription 1 (STAT-1) via mechanisms that are independent of the well characterized effector proteins ROP16 and GRA15. Remarkably, *T. gondii* interferes with STAT1 dynamics by preventing its dissociation from DNA, thereby impairing the cyclical transcriptional reactivation required for sustained IFN γ

dependent gene expression (31). Additionally, *T. gondii* infection epigenetically alters the TNF α , IFN γ , and NF κ B pathways, potentially disrupting monocyte activation and differentiation. Research using murine macrophages has demonstrated that *T. gondii* secretes the effector *Toxoplasma gondii* inhibitor of STAT1 activity, TgIST, which translocates to the nucleus and forms a complex with STAT-1 and Mi-2/NuRD chromatin remodeling complex, thereby, suppressing the transcription of IFN- γ -response genes (32). Similarly, several studies indicate that *Cryptosporidium parvum* employs host miRNAs to enhance its survival. *C. parvum* infection specifically inhibits the production of miR-98 and the let-7 family, leading to the activation of suppressor of cytokine signaling 4 (SOCS4), which functions as a negative regulator of cytokine signaling (33). These findings are consistent with those reported in the study (34), which demonstrated that reduced microRNA expression can modulate host cell behavior and macrophage function in the context of intracellular parasitic infection. One potential explanation for the decreased miRNA levels observed in toxoplasmosis could be the miRNA-silencing mechanism employed by several parasite types, including *Toxoplasma gondii*. This mechanism plays a crucial role during parasitic infection by modulating host immune responses, thereby facilitating parasite survival, pathogenesis, and long-term persistence (35).

The current investigation demonstrated that the mean serum concentration of IL-37 was markedly elevated in *Toxoplasma gondii* infection compared with healthy controls. To further explore the regulatory relationship between the studied miRNAs and their target, we assessed the expression of miRNA-604 and miRNA-1302-3p in relation to IL-37 levels. Correlation analysis revealed a significant inverse association between IL-37 and both miRNAs, suggesting that downregulation of these miRNAs may contribute to the elevated IL-37 production observed in infected individuals.

Our findings suggest that the downregulation of miRNA-604 and miRNA-1302-3p may represent a regulatory mechanism contributing to the elevated IL-37 levels observed in chronic toxoplasmosis. Given that IL-37 functions fundamentally as an anti-inflammatory cytokine, its increased expression is interpreted as a compensatory host immune response aimed at dampening persistent infection-induced inflammation. However, in the context of chronic *Toxoplasma gondii* infection, this anti-inflammatory response may be insufficient to adequately control inflammation, potentially contributing to the immunopathology associated with chronic Toxoplasmosis.

Although no previous studies have directly demonstrated a regulatory role for miR-604 and miR-1302-3 in IL-37 expression, our findings suggest a possible link between these microRNAs and IL-37 levels in patients with toxoplasmosis. The observed correlations may indicate that these miRNAs participate in immune modulation during infection, potentially through indirect regulation of pathways associated with IL-37 production or secretion. This is consistent with previous reports showing that other microRNAs, such as miR-335 and miR-657, can influence IL-37 expression in various inflammatory and autoimmune conditions.

This scientific background supports our hypothesis that miR-604 and miR-1302-3 may represent novel regulatory elements in IL-37-related immune responses, particularly in the context of toxoplasmosis. Further molecular and bioinformatic analyses are warranted to elucidate their exact mechanisms of action.

Infections can modulate host miRNA expression through transcriptional, translational, and immune response pathways. Alterations in miRNA profiles may arise from changes in cellular development, apoptosis, the cell cycle progression, host immunological responses, and intrinsic defense mechanisms. In particular, acute infections often trigger extensive inflammation and tissue damage, which can in turn reshape the miRNA

landscape of infected hosts (36). These observations provide a broader context for our findings, in which specific miRNAs—namely miR604 and miR13023p—were differentially expressed in toxoplasmosis patients, potentially reflecting infection-driven immune modulation.

CONCLUSION

Toxoplasma gondii is a globally distributed parasite with significant clinical relevance. It modulates host immune responses through sophisticated strategies, including downregulation of miR-604 and miR-1303-3p in toxoplasmosis patients. Both miRNAs were found to be negatively correlated with elevated IL-37 levels, suggesting that their reduced expression may contribute to the modified immune environment that promotes parasite survival and tolerance. These findings highlight the importance of studying miRNAs in host-parasite interactions, with potential implications for improving diagnostic, prognostic, and therapeutic approaches for toxoplasmosis.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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