



MicroRNA Regulation in Sexually Transmitted Diseases: Pathogenic Mechanisms and Clinical Implications

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Received: 15 October, 2025; Revised: 10 December, 2025; Accepted: 24 December, 2025

Abstract

Background: Sexually transmitted diseases (STDs), including viral and bacterial infections such as genital warts, syphilis, gonorrhea, and *Chlamydia trachomatis* (CT), present ongoing global health challenges. MicroRNAs (miRNAs) have emerged as critical regulators of host-pathogen interactions, offering novel insights into disease mechanisms and potential clinical applications.

Objectives: This review synthesizes current evidence on the role of miRNAs in STD pathogenesis, with a focus on their regulatory functions in immune response modulation, signaling pathway disruption, and clinical relevance as biomarkers and therapeutic targets.

Methods: We conducted a comprehensive analysis of miRNA studies related to STDs, integrating data from in vitro, in vivo, and clinical research to evaluate their influence on disease progression and outcomes.

Results: Dysregulated miRNAs are central to STD pathogenesis. In HPV-induced genital warts, miR-34a-5p downregulation correlates with PD-L1 upregulation, while miR-26a and miR-143/145 disrupt PTEN and PI3K/AKT signaling. Syphilis exhibits elevated miR-338-5p in latent infections and miR-142-3p-mediated immune evasion. In gonorrhea, miR-146a suppresses NF-κB signaling, aiding bacterial survival, whereas *Chlamydia* infections involve miR-30c-5p and miR-135a in bacterial clearance and T-cell regulation. MicroRNAs modulate key pathways such as PI3K/AKT, TLR, and NF-κB, influencing immune responses and disease progression across STDs. Their diagnostic and therapeutic potential is promising but requires further clinical validation.

Conclusions: MicroRNAs represent valuable biomarkers and therapeutic targets for STDs. Future research should prioritize mechanistic elucidation and translational studies to advance STD management strategies.

Keywords: MicroRNAs, Sexually Transmitted Diseases, Biomarkers, Immune Regulation, Therapeutic Targets, Pathogenesis

1. Introduction

Sexually transmitted diseases (STDs) constitute a major global public health burden, transmitted through sexual contact and associated behaviors (1). These infections, which include viral agents such as human papillomavirus (HPV) and bacterial pathogens like *Treponema pallidum*, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* (CT), contribute significantly to

morbidity, reproductive health complications, and socioeconomic strain (2, 3). Despite ongoing efforts, prevention and treatment strategies remain suboptimal, underscoring the need for novel molecular insights (4).

Recent advances in genomics and bioinformatics have highlighted the regulatory roles of microRNAs (miRNAs) in infectious diseases. MicroRNAs are small,

non-coding RNAs that fine-tune gene expression post-transcriptionally, influencing immune responses, cellular signaling, and pathogen persistence (5-7). In STDs, miRNA dysregulation has been linked to disease progression, immune evasion, and clinical outcomes, presenting opportunities for improved diagnostics and targeted therapies (8, 9). This review aims to consolidate current knowledge on miRNA involvement in both viral and bacterial STDs, with an emphasis on mechanistic pathways and clinical implications, thereby addressing a critical gap in the integrative understanding of miRNA-mediated regulation in STD pathogenesis.

2. Structure and Function of MicroRNAs

MicroRNAs are highly conserved, single-stranded noncoding RNAs, typically 21-25 nucleotides in length, that regulate gene expression post-transcriptionally (10, 11). By binding to the 3'-untranslated region (3'-UTR) of target mRNAs, miRNAs guide the RNA-induced silencing complex (RISC) to degrade transcripts or suppress translation (12, 13). This regulatory capacity allows miRNAs to maintain cellular homeostasis under physiological conditions.

In pathological states, miRNA expression is frequently altered, contributing to diseases such as cancers, inflammatory disorders, and infections (14, 15). Conversely, certain miRNAs may also promote homeostasis, reflecting their dual roles in health and disease. In the context of STDs, miRNAs modulate host immune responses and pathogen-related signaling pathways, influencing infection outcomes (8, 16).

3. Correlation Between MicroRNAs and Sexually Transmitted Diseases

3.1. Role of MicroRNAs in Genital Warts

Genital warts, or condyloma acuminatum (CA), are primarily caused by HPV types 6 and 11 (17). HPV enters basal epithelial cells and replicates during epithelial differentiation, leading to lesion formation (18). Clinically, genital warts are classified into four types: Classic CA, keratotic warts, popular warts, and flat warts, all characterized by high contagiousity and recurrence (19).

MicroRNAs play a pivotal role in CA pathogenesis by regulating cell proliferation, apoptosis, and

differentiation. For example, miR-34a-5p is downregulated in CA tissues, while PD-L1 is upregulated, demonstrating an inverse correlation with diagnostic potential (AUC: 0.954) (20). miR-26a overexpression degrades PTEN mRNA, impairing tumor suppression (21). Loss of miR-143 or miR-145 disrupts NRAS/PI3K/AKT signaling (22), and reduced miR-99b elevates IGF-1R expression, further activating PI3K/AKT and driving proliferation (23). Autophagy-related miRNAs, such as miR-30a-5p and miR-514a-3p, are diminished in CA, while autophagy proteins (Atg5, Atg12, Atg3) are upregulated (24). Additional miRNAs, including miR-22-3p (25), miR-31, miR-9 (26), miR-155, and miR-203 (27), correlate with wart size, HPV subtype, and recurrence, though their precise mechanisms require further study (Table 1).

3.2. Role of MicroRNAs in Syphilis

Syphilis, caused by *Treponema pallidum*, progresses through distinct clinical stages (37). Beyond traditional serological tests (28), miRNAs show promise for early detection and monitoring. miR-338-5p is elevated in latent syphilis and associated with T-cell receptor signaling (38). Differential expression of miR-195-5p, miR-223-3p, and miR-589-3p distinguishes serofast from cured patients (39). Mechanistically, miR-101-3p downregulates TLR2, reducing cytokine production in macrophages (31), while miR-142-3p impairs phagocytosis in dendritic cells and macrophages during secondary syphilis (35) (Table 2).

3.3. Role of MicroRNAs in Gonorrhea

Gonorrhea, caused by *Neisseria gonorrhoeae*, affects millions annually, with rising antimicrobial resistance (33, 41). Bacterial lipo-oligosaccharide (LOS) induces miR-146a overexpression in monocytes, inhibiting NF- κ B via IRAK1/TRAF6 and suppressing TNF- α and IL-1 β production, which may facilitate bacterial persistence (42). Reduced miR-718 in infected macrophages enhances PI3K/AKT signaling via PTEN downregulation, dampening inflammatory responses and increasing host susceptibility (43).

3.4. Role of MicroRNAs in Genital Chlamydia trachomatis Infection

The CT infections are often asymptomatic but can lead to pelvic inflammatory disease and infertility (36,

Table 1. Regulatory Effects of MicroRNAs on Condyloma Acuminatum Through Host Protein Modulation

miRNA	Biological Function	Molecular Target	Ref
miR-9	Influences disease progression, lesion size, and HPV strain specificity	HK2	(28)
miR-22-3p	Determines HPV variant susceptibility	VEGF	(29)
miR-26a	Promotes abnormal cellular proliferation	PTEN	(30)
miR-30a-5p/miR-514a-3p	Mediates autophagy processes in CA pathogenesis	Atg5, Atg12, Atg3	(31)
miR-34a-5p	Affects clinical course, wart dimensions, HPV subtype, and diagnostic potential	PD-L1	(32)
miR-99b	Contributes to disordered cell growth	IGF-1R	(24)
miR-143/miR-145	Drives aberrant proliferative activity	NRAS, PI3K p110α, and phosphorylated AKT	(33)
miR-143/miR-155	Modulates disease characteristics and HPV strain specificity	NRAS, PI3K p110α, and phosphorylated AKT	(34)
miR-149-3p	Impacts disease progression and lesion morphology	HE4	(35)
miR-203	Determines HPV variant specificity	p63 and Survivin	(36)

Abbreviations: HPV, human papillomavirus; CA, condyloma acuminatum; HK2, hexokinase 2; VEGF, vascular endothelial growth factor; PTEN, phosphatase and tensin homolog; Atg, autophagy-related proteins; PD-L1, programmed death-ligand 1; IGF-1R, insulin-like growth factor 1 receptor; HE4, human epididymis protein 4; MicroRNAs, miRNA, microRNA.

Table 2. MicroRNAs Modulate Syphilis Infection by Regulating Host Proteins

miRNA	Biological Function	Molecular Target	Ref
miR-101-3p	Suppresses cytokine production in macrophages	TLR2 3' UTR	(4)
miR-142-3p	Enhances syphilis disease progression	DC	(6)
miR-195-5p/miR223-3p, mir-598-3p	Serves as diagnostic biomarker and treatment response predictor	Multiple gene targets	(40)
miR-338-5p	Identifies serofast patients and aids in latent syphilis diagnosis	RANBP17, XPO1, and XPO6	(2)

Abbreviations: TLR2, toll-like receptor 2; UTR, untranslated region; DC, dendritic cells; RANBP17, RAN binding protein 17; XPO1, Exportin 1; XPO6, Exportin 6; miRNA, microRNA.

44). Dysregulated miRNAs influence susceptibility and outcomes. miR-146a and miR-155 alter vaginal microbiota and T-cell function (45). Symptomatic infections show elevated miR-142 and miR-147, while asymptomatic cases upregulate miR-449c, miR-6779, and miR-519d (46). Experimentally, miR-378b deficiency impairs bacterial clearance but reduces inflammation (47). miR-30c-5p modulates mitochondrial dynamics via Drp1, inhibiting CT replication (48), and miR-135a regulates CD4⁺ T-cell trafficking through the CXCL10/CXCR3/CCR5 axis (30) (Table 3).

4. Discussion

MicroRNAs serve as master regulators of cellular processes, including differentiation, apoptosis, and

signaling, and are increasingly recognized for their roles in STD pathogenesis (5, 49). Their ability to modulate immune responses and pathogen persistence underscores their potential as biomarkers and therapeutic targets (50).

In HPV infection, miRNAs such as miR-34a-5p and miR-26a disrupt PI3K/AKT and MAPK signaling, promoting epithelial proliferation and immune evasion (20, 51). Similarly, in gonorrhea, miR-146a and miR-718 fine-tune NF-κB and PI3K/AKT pathways, influencing bacterial survival and host inflammation (42). Syphilis presents a unique challenge with the serofast state, where miRNAs like miR-338-5p and miR-142-3p modulate TLR pathways and phagocytic functions, impairing clearance of *Treponema pallidum* (35, 38). In *chlamydia*

Table 3. Micro RNAs Modulate Genital *Chlamydia* Infection by Regulating Host Proteins

miRNA	Biological Function	Molecular Target	Ref
miR-30c-5p	Impairs bacterial growth and alters mitochondrial dynamics	Tumor protein p53	(19)
miR-135a	Modulates immune cell trafficking and regulatory functions	CXCL10	(23)
miR-142/miR-147/miR-449c/miR-6779/miR-519d/miR-449a/miR-2467	Potential biomarkers for tracking disease progression	Multiple gene targets	(44)
miR-146a/miR-155	Alters vaginal microbial environment	Not specified	(45)
miR-378b	Regulates CT replication and influences reproductive complications	EMT markers	(46)

Abbreviations: CXCL10, C-X-C motif chemokine ligand 10; EMT, epithelial-mesenchymal transition; miRNA, MicroRNA.

infection, miRNAs coordinate immune cell recruitment and bacterial containment through mitochondrial regulation and chemokine signaling (30, 48).

A unifying theme across these infections is miRNA-mediated regulation of key pathways such as PI3K/AKT, TLR/NF-κB, and autophagy. These interactions highlight conserved mechanisms of host-pathogen interplay and suggest broad therapeutic potential. However, translational applications require deeper mechanistic insights and validation in larger clinical cohorts (52).

5. Conclusion

This review underscores the central role of miRNAs in regulating immune responses and signaling pathways in STDs. While significant progress has been made in identifying dysregulated miRNAs and their targets, challenges remain in translating these findings into clinical practice. Future research should focus on:

- Elucidating precise mechanistic networks through integrated omics approaches

- Validating miRNA biomarkers in diverse, large-scale clinical populations

- Developing targeted miRNA-based therapies for enhanced STD management

By bridging molecular insights with clinical applications, miRNA research holds promise for advancing diagnostic accuracy, therapeutic precision, and preventive strategies in STD care.

Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this

article.

Authors' Contribution: M. K. and A. A.: Conceptualization and design; A. H., R. B., A. H., and A. V.: Initial drafting; A. A.: Final revision.

Conflict of Interests Statement: The authors declare no conflict of interest.

Funding/Support: The present study received no funding/support.

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