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Integrated Role of TNF-α and MicroRNAs in the Pathogenesis, Progression, and Clinical Outcomes of Urinary Tract Infection: A Review

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Abstract

Urinary tract infections (UTIs) are among the most prevalent bacterial infections worldwide, representing a major healthcare burden due to their high recurrence rate and increasing antimicrobial resistance. Although bacterial virulence factors play a central role in infection establishment, host immune responses are equally critical in determining disease progression and clinical outcomes. Tumor necrosis factor-alpha (TNF-α) is a key pro-inflammatory cytokine involved in early immune activation; however, its dysregulation contributes to excessive inflammation and tissue damage. Recently, microRNAs (miRNAs), particularly miR-155 and miR-125, have emerged as crucial regulators of inflammatory signaling pathways. This review aims to provide a comprehensive analysis of the interplay between TNF-α and miRNA regulatory networks in UTIs. Evidence indicates that miR-155 enhances inflammatory responses through NF-κB activation, whereas miR-125 acts as a negative regulator to maintain immune balance. Disruption of this regulatory axis contributes to disease severity, recurrence, and renal complications. Furthermore, circulating miRNAs have shown promising potential as non-invasive biomarkers for diagnosis and prognosis. Despite significant advances, the precise molecular mechanisms underlying cytokine–miRNA interactions remain incompletely understood. Future research should focus on targeted therapeutic strategies aimed to modulating this axis and improve patient outcomes.

Keywords: UTI, TNF-α, miR-155, miR-125, inflammation, biomarkers, immune response

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Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections worldwide and represent a major public health concern due to their high recurrence rate and increasing antimicrobial resistance. Women are particularly susceptible to UTIs because of anatomical and physiological factors, and recurrent infections often require repeated medical intervention [1]. In addition, the widespread use of antibiotics has contributed to the emergence of multidrug-resistant uropathogens, complicating disease management [2].

The UTIs are commonly caused by uropathogenic *Escherichia coli* (UPEC), which possesses several virulence factors that facilitate bacterial adhesion, colonization, biofilm formation, and persistence within the urinary tract [3]. Although bacterial virulence is essential for infection establishment, host immune responses also play a critical role in determining disease severity and progression.

Among the inflammatory mediators involved in UTIs, tumor necrosis factor-alpha (TNF-α) is considered a key regulator of immune activation. TNF-α promotes leukocyte recruitment and pathogen clearance; however, excessive or prolonged inflammatory signaling may contribute to tissue damage and renal complications [4]. Recently, increasing attention has been directed toward microRNAs (miRNAs) as important post-transcriptional regulators of immune and inflammatory responses [5].

Particularly, miR-155 and miR-125 have emerged as major regulators of TNF-α-mediated inflammatory pathways. While miR-155 enhances inflammatory signaling, miR-125 functions as a negative regulator that helps maintain immune balance. Therefore, this review aims to summarize the interplay between TNF-α and miRNA regulatory networks in UTIs and highlight their potential roles as diagnostic biomarkers and therapeutic targets [6].

Overview and Epidemiology

The UTIs are among the most common bacterial infections worldwide and remain a major healthcare concern because of their high recurrence rate and increasing antimicrobial resistance. UPEC is the predominant causative pathogen and possesses several virulence factors that facilitate bacterial adhesion, colonization, and persistence within the urinary tract [7].

Recently, microRNAs (miRNAs) have emerged as important post-transcriptional regulators of immune and inflammatory responses during infectious diseases. Among these, miR-155 and miR-125 are considered key regulators of inflammatory signaling pathways in UTIs due to their opposing biological functions [8]. miR-155 primarily enhances inflammatory responses through activation of pathways associated with NF-κB signaling and cytokine production, whereas miR-125 acts as a negative regulator that suppresses excessive inflammation and promotes immune homeostasis [9–11].

The balance between miR-155 and miR-125 plays a crucial role in controlling the intensity and duration of immune responses during UTIs. Dysregulation of this regulatory axis may contribute to

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persistent inflammation, epithelial damage, recurrent infections, and disease progression [12–15]. In addition, altered expression patterns of these miRNAs have shown promising potential as diagnostic and prognostic biomarkers, particularly because of their stability in biological fluids such as serum and urine [16,17].

Mechanistic roles of miR-155 and miR-125 in inflammatory regulation during urinary tract infections

MicroRNA-155 (miR-155) is recognized as one of the major regulators of inflammatory signaling during UTIs. Its expression is rapidly induced following activation of pattern recognition receptors (PRRs), particularly Toll-like receptors (TLRs), by bacterial components such as lipopolysaccharides (LPS) from uropathogenic Escherichia coli (UPEC) [18,19]. Activation of these receptors stimulates downstream signaling pathways involving MyD88, NF-κB, and AP-1, leading to increased transcription of miR-155 [20].

Once expressed, miR-155 amplifies inflammatory responses by suppressing negative regulators such as suppressor of cytokine signaling 1 (SOCS1) and SHIP1, thereby enhancing cytokine-mediated signaling pathways [21,22]. Consequently, the production of pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β becomes intensified, promoting leukocyte recruitment, immune cell activation, and pathogen clearance during UTIs [22-25]. In addition, miR-155 contributes to adaptive immunity by promoting T helper 1 (Th1) and T helper 17 (Th17) differentiation, further strengthening antibacterial immune responses [26].

Despite its protective role, excessive or prolonged expression of miR-155 may result in pathological inflammation. Sustained cytokine production can cause epithelial injury, urothelial barrier disruption, recurrent infections, and bacterial persistence through biofilm formation and intracellular survival [27–29]. Furthermore, elevated miR-155 activity has been associated with renal involvement and progression to pyelonephritis due to increased inflammatory infiltration and tissue damage [30]. Clinically, circulating miR-155 has been proposed as a potential biomarker for disease severity and a promising therapeutic target, although complete inhibition may impair host defense mechanisms [31–35].

In contrast, microRNA-125 (miR-125), including miR-125a and miR-125b, functions as a key anti-inflammatory regulator that maintains immune homeostasis during UTIs [36,37]. miR-125 directly targets TNF-α mRNA, reducing cytokine production and attenuating inflammatory pathways such as NF-κB and MAPK signaling [38,39]. During the resolution phase of infection, miR-125 acts as a molecular brake that limits immune activation, reduces tissue damage, and promotes restoration of epithelial integrity [40,41].

Additionally, miR-125 participates in feedback inhibition mechanisms that suppress excessive inflammatory responses by counteracting TNF-α and IL-6 signaling [42]. It also regulates immune cell behavior by promoting the transition of macrophages from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype and modulating adaptive immune responses [43]. Reduced expression of miR-125 has been associated with persistent inflammation, epithelial damage, recurrent UTIs, and progression to upper urinary tract complications [44]. Conversely, balanced upregulation of miR-125

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contributes to tissue protection and recovery, although excessive suppression may impair bacterial clearance [45,46].

From a clinical perspective, miR-125 has significant potential as both a biomarker and therapeutic target due to its stability in serum and urine [47]. Therapeutic strategies based on miR-125 mimics may help restore immune balance and reduce excessive inflammation, although challenges related to delivery and specificity remain unresolved [48,49]. Overall, the balance between miR-155 and miR-125 represents a critical regulatory axis controlling inflammation during UTIs, where dysregulation of this equilibrium contributes to chronic inflammation and disease progression [50], table (1) and fig. (1).

Table (1): Comparative roles of miR-155 and miR-125 in inflammatory regulation and clinical outcomes of urinary tract infections

Aspect	miR-155	miR-125
Function	Pro-inflammatory regulator that amplifies immune activation	Anti-inflammatory regulator that maintains immune homeostasis
Main targets	SOCS1, SHIP1	TNF-α mRNA and inflammatory signaling mediators
Associated cytokines	Increases TNF-α, IL-6, IL-1β	Suppresses TNF-α and reduces inflammatory cytokine production
Biological effect	Enhances NF-κB signaling, leukocyte recruitment, and inflammatory amplification	Limits excessive inflammation and promotes resolution of immune responses
Role in UTIs	Supports pathogen clearance but may contribute to tissue damage and recurrent inflammation when overexpressed	Protects urothelial integrity and reduces inflammatory injury during infection resolution
Clinical role	Associated with severe inflammation, recurrent UTIs, and pyelonephritis	Associated with immune regulation, tissue recovery, and reduced inflammatory complications
Biomarker significance	Elevated circulating levels may indicate disease severity and active inflammation	Reduced expression may reflect impaired immune regulation and chronic inflammatory status
Therapeutic potential	Targeted inhibition using antagomiRs may reduce hyperinflammation	miRNA mimics may restore immune balance and suppress excessive cytokine signaling

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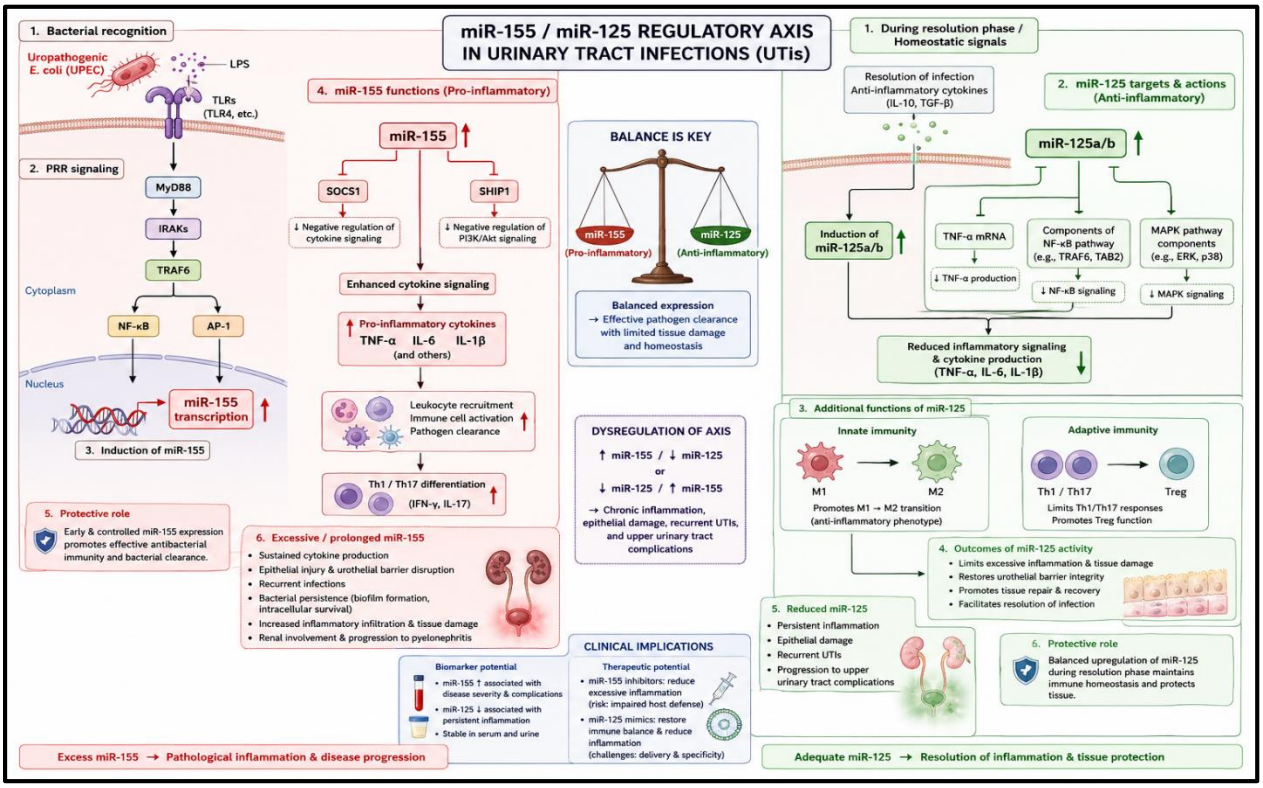

Figure (1): Schematic representation of miR-155/miR-125 immune regulation in urinary tract infection (Thakur *et al.*, 2026)

The regulatory axis in inflammation microRNA-155 / microRNA-125

The miR-155/miR-125 regulatory axis represents one of the most sophisticated molecular systems governing inflammatory balance in UTIs. Rather than acting as isolated regulators, these two microRNAs function within a tightly coordinated network that integrates innate immune activation with feedback inhibition. This dualistic system provides a dynamic framework that not only determines the intensity and duration of inflammatory responses but also offers substantial potential for diagnostic and therapeutic applications. In recent years, increasing evidence has positioned this axis at the forefront of translational research, particularly in the context of precision medicine and non-invasive biomarker discovery [52].

From a diagnostic perspective, the miR-155/miR-125 axis offers a unique advantage due to its ability to reflect real-time immune status. Unlike conventional biomarkers that often provide static or indirect measurements of inflammation, microRNAs directly represent regulatory activity at the molecular level [53]. miR-155 serves as a sensitive indicator of immune activation, with elevated levels correlating strongly with the upregulation of pro-inflammatory pathways, particularly those mediated by NF-κB signaling. Increased expression of miR-155 has been consistently associated with heightened cytokine

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production, immune cell recruitment, and tissue inflammation, making it a reliable marker of active infection and inflammatory severity [54].

In contrast, miR-125 functions as a marker of regulatory control within the immune system. Its expression reflects the counter-regulatory mechanisms that limit excessive inflammation and promote resolution. Reduced levels of miR-125 are often indicative of impaired immune regulation, leading to sustained cytokine production and increased risk of tissue damage. Therefore, the combined assessment of miR-155 and miR-125 provides a comprehensive molecular snapshot of the inflammatory landscape, capturing both the activation and suppression arms of the immune response [55].

One of the most significant advantages of using miRNAs as biomarkers is their remarkable stability in biological fluids. Unlike proteins or cytokines that may degrade rapidly or fluctuate significantly, miRNAs are protected within extracellular vesicles or bound to protein complexes, allowing them to remain stable in serum, plasma, and urine [56]. This stability enables reliable detection using sensitive techniques such as RT-qPCR, even in low concentrations. In the context of UTIs, where non-invasive diagnostic methods are highly desirable, circulating miR-155 and miR-125 offer a promising alternative to traditional laboratory tests [57].

Furthermore, the diagnostic utility of this axis extends beyond simple detection of infection. The relative expression levels of miR-155 and miR-125 can be used to stratify patients based on disease severity and progression. For example, a profile characterized by high miR-155 and low miR-125 expression is indicative of an exaggerated inflammatory response, often associated with severe or complicated UTIs. Conversely, balanced or normalized expression levels suggest effective immune regulation and a favorable clinical outcome. This dual-marker approach enhances diagnostic accuracy and provides valuable prognostic information that can guide clinical decision-making [58].

In addition to their diagnostic potential, miR-155 and miR-125 have emerged as attractive targets for therapeutic intervention. The concept of targeting microRNAs is based on their central role in regulating multiple genes and pathways simultaneously, offering a more comprehensive approach compared to conventional therapies that focus on single targets. In the case of UTIs, modulation of the miR-155/miR-125 axis provides an opportunity to restore immune balance and reduce pathological inflammation [59].

Therapeutic strategies targeting miR-155 primarily aim to suppress its pro-inflammatory effects. This can be achieved using antisense oligonucleotides, commonly referred to as antagomiRs, which bind specifically to miR-155 and inhibit its activity [60]. By reducing miR-155 expression, these inhibitors can decrease cytokine production, limit immune cell overactivation, and prevent tissue damage. Experimental studies have demonstrated that inhibition of miR-155 leads to attenuation of inflammatory responses, highlighting its potential as a therapeutic target in conditions characterized by hyperinflammation [61], Table (2).

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Table (2): Clinical and therapeutic significance of the miR-155/miR-125 axis in urinary tract infections

Aspect	miR-125-Based Therapeutic Strategies and Clinical Implications
Therapeutic approach	Therapeutic approaches involving miR-125 focus on enhancing its anti-inflammatory function through the use of miRNA mimics that restore or augment miR-125 expression [62].
Mechanism of action	miR-125 mimics suppress cytokine production and regulate immune signaling pathways by targeting TNF-α and other inflammatory mediators, thereby reducing excessive inflammation and promoting tissue recovery [62].
Clinical relevance	This strategy is particularly important in recurrent or chronic UTIs, where persistent inflammation contributes significantly to disease progression [63].
Delivery challenges	One of the major limitations of miRNA-based therapies is the efficient and tissue-specific delivery of miRNA modulators. The urinary tract possesses anatomical and physiological barriers that may limit therapeutic accumulation at target sites [63].
Off-target effects	Due to the pleiotropic nature of miRNAs, they can regulate multiple genes simultaneously, raising concerns regarding off-target effects and unintended biological consequences [64].
Delivery optimization	Advanced delivery systems, particularly nanoparticle-based carriers, are considered essential for improving stability, specificity, and therapeutic efficacy of miRNA modulators [64].
Need for balanced regulation	Therapeutic modulation should aim to restore physiological balance rather than induce complete inhibition or excessive overexpression of miRNAs [65].
Risks of excessive miR-155 inhibition	Excessive suppression of miR-155 may weaken host immune defenses and impair pathogen clearance mechanisms [65].
Risks of excessive miR-125 overexpression	Uncontrolled overexpression of miR-125 may lead to immunosuppression and increased susceptibility to infection [66].
Systems biology perspective	The miR-155/miR-125 axis functions as an integrated regulatory network controlling cytokine production, intracellular signaling pathways, and immune cell behavior [66].
Role in disease outcome	This regulatory axis determines whether UTIs progress toward successful resolution or chronic inflammatory disease by controlling the transition from acute inflammation to immune resolution [66].
Precision medicine potential	Integration of biomarker profiling with targeted miRNA-based intervention may support personalized therapeutic strategies according to the inflammatory profile of individual patients [67].
Clinical advantages	Personalized modulation of the miR-155/miR-125 axis may improve clinical outcomes, minimize unnecessary antibiotic use, and help address antimicrobial resistance [67].

Epidemiology and risk factors:

Urinary tract infections represent one of the most prevalent bacterial infections globally, affecting individuals across all age groups and imposing a significant burden on healthcare systems. Epidemiological data consistently demonstrate a markedly higher incidence among females, which is primarily attributed to

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anatomical and physiological factors [68]. The relatively shorter female urethra, in addition to its close proximity to the anal region, facilitates the ascension of uropathogenic bacteria into the urinary tract. Furthermore, hormonal fluctuations—particularly during pregnancy and menopause—play a critical role in altering the local microenvironment of the urinary tract, including changes in vaginal flora, mucosal immunity, and epithelial integrity, thereby increasing susceptibility to infection [69].

The development of UTIs is multifactorial, involving a complex interplay between host-related and environmental risk factors. Sexual activity remains one of the most prominent contributing factors, as it enhances the mechanical transfer of uropathogens into the urethral opening. In addition, urinary catheterization is strongly associated with infection risk, as it disrupts natural defense mechanisms and provides a direct route for bacterial entry [70]. Catheter surfaces also serve as substrates for biofilm formation, enabling bacteria to adhere, proliferate, and resist both antimicrobial agents and host immune responses. This biofilm-mediated persistence represents a major challenge in clinical management, particularly in hospitalized or immunocompromised patients [71].

Chronic medical conditions further exacerbate the risk of UTIs. Diabetes mellitus, for instance, is associated with impaired immune function, including reduced neutrophil activity and altered cytokine responses, which collectively diminish the host's ability to effectively eliminate pathogens. Elevated glucose levels in urine also create a favorable environment for bacterial growth. Similarly, immunosuppression whether due to underlying disease or therapeutic interventions compromises host defense mechanisms and increases vulnerability to infection. These conditions not only predispose individuals to initial infection but also contribute to recurrence and complications [72].

Recurrent UTIs constitute a significant clinical concern, often reflecting the failure of complete bacterial eradication. One of the key mechanisms underlying recurrence is the ability of uropathogens to persist within biofilms and intracellular reservoirs. Biofilms provide a protective niche that shields bacteria from antibiotic penetration and immune-mediated clearance, while intracellular bacterial communities allow pathogens to evade detection and re-emerge following treatment. This persistence contributes to chronic inflammation and repeated infection episodes, highlighting the need for more effective therapeutic strategies [73].

In recent years, antimicrobial resistance has emerged as a critical global challenge in the management of UTIs. The widespread and often inappropriate use of antibiotics has led to the selection of multidrug-resistant strains, particularly among UPEC, which remains the predominant causative agent [74]. Resistance to commonly prescribed antibiotics not only complicates treatment but also increases the likelihood of treatment failure, prolonged infection, and recurrence. This growing resistance underscores the urgent need for alternative diagnostic and therapeutic approaches, including the identification of novel molecular biomarkers and targeted therapies [75].

Collectively, these factors illustrate that UTIs are not merely simple infections but rather complex conditions influenced by host susceptibility, microbial virulence, and environmental determinants.

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Understanding these multifaceted interactions is essential for improving disease management and developing more effective strategies to prevent recurrence and combat antimicrobial resistance [76].

Role of tumor necrosis factor-alpha in urinary tract infections

Tumor necrosis factor-alpha (TNF-α) is a central pro-inflammatory cytokine that plays a pivotal role in the initiation, amplification, and regulation of immune responses during UTIs. As part of the innate immune system, TNF-α is rapidly produced following the recognition of invading uropathogens, particularly Gram-negative bacteria such as *E. coli*. This early cytokine response represents a crucial first line of defense, orchestrating a cascade of immunological events that contribute to pathogen clearance while simultaneously influencing disease severity and clinical outcomes [77].

The production of TNF-α is primarily triggered through the activation of PRRs, especially TLRs, expressed on uroepithelial cells and resident immune cells such as macrophages and dendritic cells. These receptors detect pathogen-associated molecular patterns (PAMPs), including lipopolysaccharides (LPS), leading to the activation of intracellular signaling pathways [78]. Among these, the nuclear factor kappa B (NF-κB) pathway is particularly important, as it drives the transcription of TNF-α and other pro-inflammatory mediators. This rapid induction of TNF-α ensures an immediate and robust immune response to bacterial invasion [79].

Functionally, TNF-α exerts a wide range of biological effects that are essential for effective host defense. One of its primary roles is the recruitment and activation of immune cells at the site of infection. TNF-α promotes the expression of adhesion molecules on endothelial cells, facilitating the migration of leukocytes, particularly neutrophils, from the bloodstream into infected tissues. These recruited cells play a critical role in bacterial clearance through mechanisms such as phagocytosis, production of reactive oxygen species, and secretion of antimicrobial peptides [80].

In addition to immune cell recruitment, TNF-α enhances vascular permeability, allowing plasma proteins and immune mediators to access the site of infection more efficiently. This contributes to the establishment of an inflammatory microenvironment that supports pathogen elimination. TNF-α also stimulates the production of other cytokines and chemokines, including interleukin-6 (IL-6) and interleukin-1 beta (IL-1β), thereby amplifying the inflammatory response and ensuring a coordinated immune reaction [81].

Despite its essential role in host defense, the activity of TNF-α must be tightly regulated to prevent excessive inflammation and tissue damage. In the context of UTIs, uncontrolled or prolonged TNF-α signaling can lead to detrimental effects, particularly within the delicate epithelial lining of the urinary tract. Excessive cytokine production results in increased epithelial permeability, disruption of the urothelial barrier, and damage to surrounding tissues. This not only exacerbates inflammation but also facilitates bacterial persistence and increases the risk of recurrent infections [82].

The pathological consequences of dysregulated TNF-α signaling are particularly evident in severe or complicated UTIs. Elevated TNF-α levels have been associated with the progression of infection from

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the lower urinary tract to the upper urinary tract, including the kidneys. In such cases, excessive inflammation can contribute to the development of pyelonephritis, characterized by renal tissue damage, impaired kidney function, and potential long-term complications. Furthermore, persistent TNF-α activation may promote fibrosis and structural alterations within renal tissues, highlighting its role in disease progression beyond acute infection [83].

At the molecular level, the regulation of TNF-α is mediated through complex feedback mechanisms involving various signaling pathways and regulatory molecules. Among these, microRNAs have emerged as critical modulators of TNF-α expression. Specifically, miR-155 and miR-125 play opposing roles in controlling TNF-α levels, with miR-155 enhancing its production and miR-125 suppressing it. This interaction forms a tightly regulated axis that ensures a balanced immune response. Disruption of this regulatory network, characterized by increased miR-155 and decreased miR-125 expression, leads to sustained TNF-α signaling and contributes to inflammatory dysregulation in UTIs [84].

Clinically, TNF-α has gained significant attention as a potential biomarker for disease severity and progression. Elevated levels of TNF-α in serum or urine have been correlated with increased inflammatory activity, higher bacterial load, and greater risk of complications. Monitoring TNF-α levels may therefore provide valuable insights into the inflammatory status of patients and assist in guiding therapeutic decisions. However, the use of TNF-α as a standalone biomarker is limited by its dynamic nature and lack of specificity, which has led to increased interest in combining it with molecular markers such as miRNAs for improved diagnostic accuracy [85].

From a therapeutic perspective, targeting TNF-α signaling presents both opportunities and challenges. Inhibition of TNF-α activity has been successfully applied in the treatment of various inflammatory diseases; however, its application in infectious conditions such as UTIs requires careful consideration [86]. While reducing TNF-α levels may alleviate excessive inflammation and tissue damage, it may also impair the host's ability to effectively clear pathogens. Therefore, therapeutic strategies must aim to modulate rather than completely suppress TNF-α activity, maintaining a balance between immune defense and inflammatory control [87].

Recent advances in molecular medicine have highlighted the potential of indirect modulation of TNF-α through regulatory pathways, particularly those involving microRNAs. By targeting miR-155 or enhancing miR-125 expression, it may be possible to fine-tune TNF-α levels without compromising immune function. Such approaches represent a promising direction for the development of more precise and personalized therapeutic strategies in the management of UTIs [88].

MicroRNA regulation in urinary tract infections

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression at the post-transcriptional level and play essential roles in controlling immune and inflammatory responses. In infectious diseases, particularly UTIs, miR-155 and miR-125 are considered key regulators of inflammatory signaling pathways [89].

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The miR-155 is strongly induced during infection through activation of NF-κB signaling pathways. It enhances inflammatory responses by targeting negative regulatory proteins such as suppressor of cytokine signaling 1 (SOCS1), resulting in increased production of pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β. Although this response is important for pathogen clearance, excessive miR-155 expression may contribute to hyperinflammation, tissue damage, and increased disease severity [90].

In contrast, miR-125 functions as a negative regulator of inflammation by suppressing cytokine production, particularly through targeting TNF-α mRNA. This activity limits excessive immune activation and supports immune homeostasis. Reduced miR-125 expression has been associated with uncontrolled inflammatory responses, whereas its upregulation contributes to protection against inflammatory damage [91].

The balance between miR-155 and miR-125 is critical for regulating the intensity and duration of inflammatory responses. Dysregulation of this axis, characterized by increased miR-155 and decreased miR-125 expression, may lead to sustained inflammation, impaired immune regulation, and adverse clinical outcomes in UTIs [92].

Tumor necrosis factor-alpha / microRNA regulatory axis

The interaction between tumor necrosis factor-alpha (TNF-α) and microRNAs constitutes a highly integrated and dynamic regulatory network that plays a pivotal role in the pathogenesis and progression of UTIs [36]. TNF-α, as a central pro-inflammatory cytokine, not only initiates immune responses upon pathogen recognition but also modulates gene expression at the post-transcriptional level through the regulation of specific miRNAs. Notably, TNF-α has been shown to induce the expression of miR-155 via activation of the NF-κB signaling pathway, leading to amplification of inflammatory cascades and enhanced immune cell recruitment [93].

Subsequently, miR-155 reinforces this response by targeting key negative regulators of inflammatory signaling, such as SOCS1 and SHIP1, thereby sustaining cytokine production and establishing a positive feedback loop that prolongs and intensifies inflammation [94]. While this mechanism is essential for effective pathogen clearance, its persistent activation may contribute to excessive inflammatory damage and tissue injury [95].

In contrast, miR-125 functions as a critical counter-regulatory molecule within this network. It directly targets components of the TNF-α signaling pathway, including TNF-α mRNA itself, thereby attenuating cytokine production and limiting the magnitude of the inflammatory response. This negative feedback mechanism is essential for restoring immune homeostasis and preventing uncontrolled inflammation [96].

The balance between miR-155 and miR-125 therefore represents a finely tuned regulatory axis that governs the intensity and duration of immune responses. Disruption of this balance—characterized by

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overexpression of miR-155 and/or downregulation of miR-125 can lead to sustained inflammatory signaling, epithelial cell damage, and increased susceptibility to recurrent infections and renal complications. Such dysregulation has been increasingly recognized as a key factor contributing to disease severity and poor clinical outcomes in UTIs [97].

Collectively, the TNF-α/miRNA regulatory axis emerges as a central determinant of host-pathogen interactions, linking innate immune activation with post-transcriptional gene regulation. Understanding this axis not only provides deeper insight into the molecular mechanisms underlying UTI pathogenesis but also highlights its potential as a diagnostic and therapeutic target for controlling inflammation and improving patient outcomes [98].

Clinical Implications and Biomarkers

Recent advances have underscored the significant potential of circulating microRNAs (miRNAs) as non-invasive biomarkers for both the diagnosis and prognosis of urinary tract infections (UTIs). Owing to their remarkable stability in biological fluids, including serum, plasma, and urine, as well as their resistance to enzymatic degradation, miRNAs provide a reliable reflection of underlying molecular and pathological changes. These characteristics have positioned miRNAs as highly promising tools in translational and clinical research, particularly in the context of inflammatory and infectious diseases [99].

Among these, miR-155 has emerged as a key indicator of inflammatory activation. Elevated circulating levels of miR-155 have been consistently associated with intensified immune responses, increased cytokine production, and greater disease severity. Its upregulation reflects the activation of pro-inflammatory signaling pathways, particularly those mediated by NF-κB, and may serve as a marker of ongoing immune dysregulation [100]. In contrast, miR-125 is more closely associated with the regulatory arm of the immune response. Variations in its expression levels reflect the balance between pro- and anti-inflammatory signaling, with reduced expression often correlating with excessive inflammation and impaired immune control [101].

Importantly, the combined assessment of miR-155 and miR-125 expression profiles offers a more comprehensive understanding of the inflammatory status and disease progression in UTIs. This dual profiling approach may enhance patient stratification, enabling differentiation between mild and severe cases, as well as identifying individuals at higher risk of recurrence or complications. Consequently, miRNA-based signatures hold substantial potential for improving diagnostic accuracy and prognostic evaluation in clinical settings [102].

Beyond their diagnostic value, miRNAs also represent promising therapeutic targets. Modulation of miRNA activity through the use of miRNA mimics or inhibitors (antagomiRs) offers a novel strategy for restoring immune balance and controlling excessive inflammation. For instance, inhibition of miR-155 may attenuate hyperinflammatory responses, whereas supplementation with miR-125 mimics could enhance anti-inflammatory regulation. Despite these promising perspectives, the clinical application of miRNA-based therapies remains in its early stages. Several challenges, including targeted delivery, off-

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target effects, and long-term safety, must be addressed through well-designed clinical trials before their routine implementation can be achieved. [103].

Future perspectives

Future research should focus on elucidating the precise molecular mechanisms underlying the interaction between TNF-α and miRNAs in UTIs. In particular, large-scale clinical studies are needed to validate the role of miRNAs as reliable diagnostic and prognostic biomarkers.

Furthermore, advances in molecular biology and nanotechnology may facilitate the development of targeted therapies aimed at modulating the TNF-α/miRNA regulatory axis. Such approaches may provide more effective and personalized treatment strategies for patients with recurrent or complicated UTIs.

Conclusion

The interplay between TNF-α and microRNA regulatory networks plays a crucial role in the pathogenesis and progression of urinary tract infections. While TNF-α is essential for initiating host immune responses, its dysregulation contributes to excessive inflammation and tissue damage. MicroRNAs, particularly miR-155 and miR-125, serve as key modulators of this process by regulating inflammatory signaling pathways. Understanding this regulatory axis provides important insights into disease mechanisms and highlights its potential as a target for diagnostic and therapeutic applications. Future studies focusing on this interaction may contribute to improved clinical management and better patient outcomes.

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Author's Declaration

The authors confirm that this manuscript is a review article prepared based on the cited literature. The manuscript has not been published or submitted elsewhere for publication.

Conflict of Interest

The authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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