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Unveiling The Roles of npcRNA Modulating the Molecular Mechanism of Pathogenic Bacteria Causing Urinary Tract Infections (UTIs)

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Abstract: Urinary tract infections (UTIs) are among the most prevalent and chronic health problems worldwide, impacting millions of individuals annually and posing a substantial financial burden on healthcare systems. UTIs typically initiate when pathogenic bacteria, originating from the gastrointestinal tract, colonize the urethra or periurethral region. Women are more susceptible to UTIs compared to men because of the differences in female lower urinary tract anatomy and its proximity to reproductive organs. The pathogenic bacteria, which are on the World Health Organization (WHO) priority list and cause both uncomplicated and complicated UTIs, are Escherichia coli (UPEC), Klebsiella pneumoniae, Proteus mirabilis, and Staphylococcus aureus. Different therapeutic approaches are necessary to combat UTIs, as seen by the rise in antibiotic resistance in bacteria. Non-protein coding RNAs (npcRNAs) have emerged as promising candidates for regulating genes involved in bacterial pathogenesis and infection, playing a role in modulating gene expression and host-pathogen interactions. By targeting bacterial virulence factors, biofilm formation, and antibiotic resistance mechanisms, npcRNAs provide a novel approach to disrupting infection pathways while minimizing the risk of resistance development.

Keywords: Pathogenic Bacteria, Multidrug resistance, non-protein coding RNAs, Urinary tract Infections (UTIs)

1. Introduction

UTIs represent significant and persistent health problems worldwide, impacting millions of individuals annually and incurring substantial healthcare costs. UTIs are a common pivotal health issue for all genders (Sgarabotto et al., 2025). Unfortunately, because of the lower urinary system and its proximity to reproductive organs, women are more prone to UTIs than males (Finlayson et al., 2025). In simpler terms, the urethra, a tube that leads from the bladder to the point where urine is excreted from the body, is shorter in length in women than in men, which makes it easier for the pathogen that causes UTIs to enter, disseminate, and ascend to internal organs (Czajkowski K et al., 2021). Approximately 50%-65% of women experience UTIs in their lifetime (Deltourbe L et al., 2022). UTIs also occur more frequently in menopausal women due to their oestrogen level depletion, which harms their urogenital lining. Additionally, the urinary system, such as the kidneys (pyelonephritis), bladder (cystitis), and urethra (urethritis), may easily develop UTIs (Lila et al., 2023).

UTI symptoms can be divided into two categories, which are uncomplicated and complicated infections (Bono et al., 2023). The uncomplicated UTIs usually involve the lower urinary tract system, presenting as cystitis (bladder inflammation). A strong host immune response and the emergence of significant inflammation have been shown to worsen mucosal damage during UTIs (Calin et al., 2024). An acute UTI may become chronically inflamed due to this overreaction of the immune system (Calin et al., 2024). According to Zhou Y et al. (2023), acute UTIs are usually caused by bacteria such as E. coli, and the duration of therapy for these infections is often brief, ranging from three to seven days, depending on the antibiotic provided and the severity of the illness. Meanwhile, the treatment of chronic urinary tract infections might be more complicated and require prolonged antibiotic treatments, sometimes lasting seven to fourteen days or more (Zhou Y et al., 2023; Mak et al., 2024).

UTIs can be caused by numerous microorganisms, including bacteria, viruses, fungi, and molds. However, the vast majority of UTIs are caused by bacteria. Uropathogenic Escherichia coli (UPEC), Klebsiella pneumoniae, Proteus mirabilis, and Staphylococcus aureus are frequently found bacterial species

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involved in UTIs (Zhou Y et al., 2023). Among these bacterial pathogens, Escherichia coli is the most common, responsible for nearly 70-80% of uncomplicated UTIs (Al Lawati et al., 2024). These pathogens are substantial contributors to the occurrence of UTIs worldwide and are prioritized by the WHO (WHO, 2023). While viral and fungal UTIs do occur, they are relatively rare and are typically associated with specific clinical settings, such as immunocompromised states or prolonged use of medical devices like catheters (Lila et al., 2023).

Because of their changing multidrug resistance patterns, these microorganisms present an alarming issue that makes treatment more challenging and increases the threat to global health (Klein RD et al., 2020). The ability of the bacteria to produce and sustain infections in the urinary tract of the host cells is supported by several virulence factors, which are adhesins, toxins, and mechanisms that evade host immune defenses (Klein RD et al., 2020). The bacterial adhesion to the host urothelial cells lining usually starts the infection process. This is followed by the production of biofilms, which enhances bacterial survival and antibiotic resistance. Pyelonephritis, a more complex and potentially fatal form of UTI, can result from an infection that has progressed to the kidneys in more severe forms (Belyayeva et al., 2024).

According to WHO (2023), many UTI-causing bacteria have become resistant to antibiotics. This is because the community overuses antibiotics, which has led to genetic changes in pathogens, allowing them to survive exposure to drugs that were once highly effective against multiple infections. Thus, this will potentially lead to millions of deaths annually by 2050 and underscores its criticality as a leading public health concern if there is no proper solution for these infections (Naghavi et al., 2024). Significantly, the "golden era" of antibiotics is approaching its end, which means that developing alternative therapeutic interventions is needed to prevent these infections (Naghavi et al., 2024).

To address the escalating challenge of antibiotic resistance and the limitations of conventional treatment methods, researchers are increasingly investigating molecular therapeutics as a promising and innovative alternative. Among these, RNA-based therapies have emerged as particularly novel and focused approaches (Al-Fadhli et al., 2024). Moreover, non-protein coding RNAs (npcRNAs), once an unexplored area in genomics, are now recognized for their potential to regulate bacterial virulence and counteract antibiotic resistance (Subhadra et al., 2024). By controlling gene expression, npcRNAs offer new opportunities for enhancing treatment strategies, particularly for difficult infections such as UTIs. As research advances, npcRNAs hold promise for developing new methods to combat bacterial pathogenesis and improve UTI management (Subhadra et al., 2024). In this review, we aim to discuss the regulatory roles of npcRNAs in modulating the molecular mechanisms of pathogenic bacteria that cause UTIs.

2. Factors affecting the development and spread of urinary tract infections

UTIs typically initiate when pathogenic bacteria, originating from the gastrointestinal tract, colonize the urethra or periurethral region (Mancuso et al., 2023). Then, they spread into the bladder and ascend to the organs. This process occurs through specific cell adhesion mechanisms (Mancuso et al., 2023). If the inflammatory response of the host is unstable or unable to eradicate the bacteria, they begin to multiply and secrete toxins as well as enzymes that enhance their survival and persistence within the urinary tract of the host cell. Further issues may arise from this, as the bacteria may spread to the kidneys, where their colonization may result in serious infection (Mancuso et al., 2023).

One significant factor is biofilm formation, where bacteria produce a protective layer that shields them from the immune system and antibiotics of the host, making infections more difficult to treat (Smith et al., 2023). Other contributing factors include urinary stasis, where urine flow is blocked, and the use of catheters, which also contribute to the development of UTIs. On the other hand, intrinsic factors include urinary retention, where the bladder does not fully empty, and vesicoureteral reflux, which allows urine to flow backward from the bladder to the kidneys (Smith et al., 2023). Acquired risk factors include frequent sexual activity, prostatic hyperplasia (enlarged prostate) in men, and vulvovaginal atrophy in women (which involves thinning and drying of vaginal walls), which also contribute to UTI risk. Additionally, having a family history of UTIs can increase susceptibility [Smith et al., 2023; Baimakhanova et al., 2025].

To address these challenges, non-protein coding RNAs (npcRNAs) have emerged as key regulators in the pathogenesis of UTIs. These npcRNAs can influence bacterial gene expression, including genes responsible for adhesion, biofilm formation, and urease activity. These factors are essential for bacterial survival and the development of kidney stones. Additionally, npcRNAs may modulate the host's inflammatory and immune responses, potentially contributing to tissue damage and stone formation (Wang et al., 2021). Figure 2.0 shows the anatomy of the human kidneys, highlighting specific areas affected during UTIs that can lead to the formation of kidney stones.

3. Regulatory roles of non-protein coding RNAs in gene expression

NpcRNAs are a diverse class of RNA molecules that do not translate into proteins but perform significant roles in regulating cellular processes (Nemeth et al., 2024). These RNA species vary in size from 50 to 450 nucleotides and are commonly transcribed from non-coding regions of the genome (Kishanraj et al., 2021). NpcRNAs were once considered to be non-functional by-products of transcription and were informally labeled as "junk RNA." This term originated from the early assumption that most of the genome's non-coding regions, which do not encode proteins, were biologically irrelevant. This view largely stemmed from the prevailing central dogma of molecular biology, which concentrated primarily on the translation of genetic information into functional proteins (Haseltine et al., 2024).

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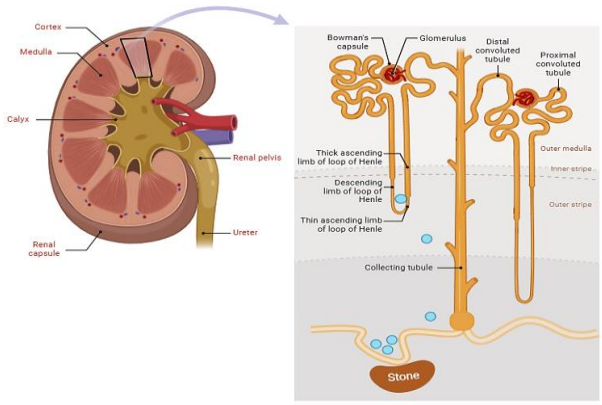

Figure 1. Anatomy of human kidneys, and the specific areas infected and leading to formation of kidney stones (https://www.biorender.com/).

However, this perspective has shifted, and with the emergence of advanced genomic techniques, it has been revealed that npcRNAs play essential roles in cellular regulation, and their functions extend far beyond simple transcriptional noise (Haseltine et al., 2024). NpcRNAs are now acknowledged as key modulators of gene expression and participate in transcriptional and post-transcriptional regulation, as well as in maintaining cellular homeostasis. These molecules typically arise from intergenic regions, which are non-protein coding sequences located between protein-coding genes. The discovery that these intergenic regions serve as a rich source of functional regulatory molecules (Sharma et al., 2024).

Non-coding RNAs generally exert their regulatory effects through sequence-specific interactions with complementary RNA targets, resulting in mRNA degradation or translational repression. The functions of npcRNAs are extensive and multifaceted. They regulate gene expression at various stages, from initiating transcription to modulating mRNA stability and translation. A primary function of npcRNAs is their involvement in post-transcriptional gene regulation. They attach to complementary sequences in the 3' untranslated regions (UTRs) of target mRNAs, causing mRNA degradation or translation inhibition. Besides their role in gene regulation, npcRNAs are crucial for maintaining genome stability (Sharma et al., 2024).

The mechanisms of npcRNAs differ depending on their specific roles. At the post-transcriptional level, cis-encoded npcRNAs can trigger mRNA degradation, inhibit translation, cleave target mRNA (5' UTR overlapping), or induce transcription termination (Chinni et al., 2010). These cis-encoded npcRNAs are transcribed from the same genomic locus as their target mRNA but in antisense orientation, allowing for full complementarity during binding. Conversely, when trans-encoded npcRNA interacts with target mRNA, it can negatively interact with the 5'UTR to prevent the ribosome binding site or promote mRNA degradation with RNase involvement. Both actions suppress translation of the target mRNA. Translation inhibition occurs when a trans-encoded npcRNA binds its target mRNA, forming a structure that blocks the ribosome binding site. Unlike cis-encoded npcRNAs, trans-encoded npcRNAs share only partial complementarity with their target mRNAs. These npcRNAs are encoded at different genomic loci than their targets, enabling them to regulate multiple mRNAs across the genome (Chinni et al., 2010).

Trans-encoded npcRNAs typically require chaperone proteins such as ProQ and Hfq to stabilize their binding to target mRNAs because imperfect base pairing renders the complex susceptible to RNase degradation. ProQ is an RNA chaperone protein primarily present in gram-negative bacteria. It plays an important role in regulating gene expression by binding to RNA molecules, including mRNA and small RNAs (sRNAs). Binding these RNAs stabilizes and protects them from degradation [Mihaita et al., 2025; Singh et al., 2025]. The most studied chaperone is the Hfq protein, which interacts with approximately 40% of npcRNAs in E. coli. According to Schroeder et al. (2016), nearly 50% of bacterial species have trans-encoded npcRNAs that depend on Hfq for stability, with L. monocytogenes being a notable exception, where most trans-encoded npcRNAs function independently of Hfq (Majumder et al., 2022). Unlike trans-encoded npcRNAs, cis-encoded npcRNAs form short, perfectly complementary base pairs with their targets, whereas trans-encoded npcRNAs produce longer imperfect pairings (Chinni et al., 2010).

Similarly, riboswitches are structured elements of npcRNAs classified as cis-encoded RNA elements. They are located in the 5' untranslated region (UTR) of target mRNAs, though they can also occur in the 3' UTR, but less frequently (Olenginski et al., 2024). Riboswitches regulate gene expression by sensing specific metabolite concentrations, making them attractive targets for antibiotic development. Unlike many other regulatory RNAs, riboswitches control transcription and translation without requiring proteins, instead adopting different conformations in response to environmental signals such as temperature changes or the binding of small molecules like ligands or metal ions. Structurally, riboswitches have two main regions: the aptamer region, which binds the ligand, and the expression region, which adopts specific conformations to influence gene expression (Olenginski et al., 2024).

The binding of a ligand to a riboswitch induces structural changes that regulate transcription and translation of the target mRNA. Riboswitches function as molecular "switches," turning gene expression on or off. During transcription, if a ligand binds the aptamer region of the riboswitch, it induces a conformational change that forms a transcription terminator, blocking further transcription and inhibiting gene expression. Conversely, binding a different molecule, known as a linker, can disrupt this terminator, causing anti-termination and allowing transcription to continue. Similarly, in translation, ligand binding can conceal the ribosome binding site (RBS), preventing translation. However, if a linker molecule binds, it can expose the RBS, enabling ribosome attachment and promoting translation (Olenginski et al., 2024).

RNA thermometers/thermosensors (RNATs) also represent a common regulatory mechanism responding to temperature in bacterial pathogens. RNATs are elements typically located in the 5’ untranslated region (UTR) of mRNAs. They function by modifying their secondary structures in response to temperature changes. Alterations in RNA secondary structure significantly

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affect the translation efficiency of the downstream gene due to its proximity to the protein-coding region. RNATs often form stable structures at low temperatures (<30 °C) that block translation of the downstream gene and obscure the ribosome binding site (RBS). Higher temperatures, such as the host body temperature of 37 °C, weaken the RNAT structure due to increased thermodynamic energy. This releases the previously inaccessible RBS and facilitates translation initiation (Loh et al., 2018).

In the urgent effort to combat multidrug-resistant bacteria causing UTIs, innovative therapeutic strategies are critically needed, and molecular biology plays a vital role (Muteeb et al., 2023). Traditionally, molecular biology has focused on elucidating how RNA directs protein production for regulatory functions. However, recent advances in molecular biology, particularly regarding npcRNAs, are transforming this field. NpcRNAs regulate transcription, translation, mRNA stability, and protein interactions. This includes modulating bacterial virulence factors and antibiotic resistance pathways, presenting promising opportunities for developing targeted therapies. Understanding the complex mechanisms of npcRNAs could enable novel treatments that reduce the threat of multidrug-resistant bacteria in UTIs, representing a significant advance in infectious disease management.

4. Bacterial non-protein coding RNA in UTI pathogenesis

4.1 Uropathogen Escherichia coli

Uropathogen Escherichia coli (UPEC), the most common bacterium causing UTIs, attaches to bladder epithelial cells by using type I fimbriae (which promote bacterial adhesion to host tissues) and specifically binds to mannose receptors (Ala-Jaakkola et al., 2022). However, when highly virulent bacteria are present, they can disrupt this balance and weaken the host's defense mechanisms. This disruption can result in urinary tract inflammation, leading to conditions like urethritis, cystitis, and pyelonephritis. Several virulence factors of uropathogenic E. coli (UPEC) contribute to UTIs, including lipopolysaccharides (LPSs), polysaccharide capsules, flagella, outer-membrane vesicles, fimbriae, curli fibers, non-fimbrial adhesins, outer-membrane proteins (OMPs), and iron-acquisition receptors (Zagaglia C et al., 2022).

Based on Zhou (2023), it is highlighted that UPEC involves six phases that lead to UTIs. The process of UPEC infection begins with the bacteria invading and colonizing the periurethral and vaginal areas, using fimbriae and adhesins to attach to host cell surfaces. Additionally, UPEC can ascend into the bladder, where they grow as free-floating cells in the urine. They attach to the bladder lining and interact with host cells. After accumulating, UPEC forms biofilms, which help the bacteria colonize the urinary tract and evade the immune system of the host cell. Biofilms also make the bacteria resistant to certain drugs, leading to chronic and recurring UTIs. When UPEC reaches the kidneys, it releases toxins that kill host tissues, resulting in severe upper UTIs as well as potentially fatal illnesses such as bacteremia, septicaemia, urosepsis, and even death (Zhou et al., 2023).

Based on a clinical report, an elderly 73-year-old woman with type 2 diabetes who had fever, nausea, vomiting, burning, and painful, frequent urination, had evidence of E. coli in UTIs (Ahsan et al., 2024). Her recurring UTI was found to be exacerbated by two strains of E. coli: one that was resistant to several medications and presented treatment difficulties, and another that was responsive to several antibiotics but caused an uncommon infection. Her condition did not improve even after receiving antibiotic treatment with levofloxacin and azithromycin (Ahsan et al., 2024).

From the aforementioned, E. coli stands out as a predominant causative agent of UTIs, being responsible for a significant majority of cases. Its ability to colonize and infect the urinary tract relies on various virulence factors and adaptive mechanisms that enable it to adhere to and invade uroepithelial cells. The genes flhD and flhC in E. coli encode the master regulator of flagellar synthesis (Sun et al., 2022). These genes are co-transcribed by a promoter under the control of multiple transcription factors, each responding to various environmental cues. Sun et al. (2022) highlighted a significant finding involving the npcRNA McaS, which enhances motility and increases the expression of the flhDC operon by binding to the 5' untranslated region (UTR) of its mRNA target. This upregulation results in higher levels of flhDC mRNA and protein production, which are crucial for flagellar synthesis and motility, key factors in the pathogenicity of E. coli in UTIs (Sun et al., 2022).

In contrast, another npcRNA, MicA, also promotes motility but does so independently of flhDC regulation, indicating a different mechanism of motility promotion. This suggests that npcRNAs like McaS and MicA contribute to E. coli's ability to navigate and persist in the urinary tract, potentially influencing the success of infection. The upregulation of motility and flagellar synthesis via these npcRNAs is linked to enhanced virulence, enabling E. coli to better adhere to and invade uroepithelial cells, key steps in UTI development. Through this approach, it is possible to identify the gene and its specific binding regions of the virulence-associated mRNA. Furthermore, gene knockdown studies allow examination of a gene's function by lowering its expression to certain levels and then analyzing the subsequent phenotypic changes. This methodology is an essential tool for validating potential therapeutic targets (Sun et al., 2022).

4.2 Klebsiella pneumoniae

According to Karampatakis (2023), K. pneumoniae is a prevalent pathogen in intensive care unit infections and is the second most common cause of UTIs from both community and hospital sources. Once these bacteria enter the urinary tract, they can adhere to the host epithelial cells lining the urethra and bladder. These bacteria use structures called fimbriae to attach firmly to these cells. Immunocompromised patients can develop serious bloodstream infections from catheter-associated urinary tract infections (CAUTIs), which have high rates of morbidity and mortality (Karampatakis et al., 2023).

Additionally, UTIs are becoming more frequent among residents of long-term care facilities (Karampatakis et al., 2023). The spread of CAUTIs and UTIs caused by K. pneumoniae suggests bacterial factors impair the host immune system. K. pneumoniae

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effectively causes infections by employing numerous virulence factors. Such factors include lipopolysaccharide (LPS), which protects against serum components and aids in survival; capsule prevents host immune cell attacks and modulates immune response; siderophores scavenge iron essential for bacterial growth; urease contributes to catheter encrustation; Type 1 fimbriae form bacterial communities within cells; Type 3 fimbriae assist biofilm development on surfaces; biofilms resist immune responses and antibiotics; and carbapenem resistance restricts treatment options for these infections (Li et al., 2023). According to WHO (2023), carbapenemase-producing K. pneumoniae strains are already present worldwide, with some regions experiencing prevalence rates above 50% (WHO, 2023).

According to another clinical report, it describes a fatal case of septic shock in a 44-year-old patient with compromised immunity, stemming from a UTI caused by multidrug-resistant Klebsiella pneumoniae, specifically extended-spectrum β-lactamase (ESBL)-producing strains. Despite initial negative blood cultures in the ICU, urine tests detected K. pneumoniae. The pathogen was resistant to antibiotics such as amoxicillin and clavulanic acid, which the patient had used prior to hospitalization (Braczkourska et al., 2020).

Based on Kwok (2024), the study explores the posttranscriptional regulation of virulence in hypervirulent Klebsiella pneumoniae (hvKp), a pathogen capable of infecting healthy individuals and posing a significant threat due to its potential to acquire carbapenem resistance, resulting in difficult-to-treat infections. While npcRNA is known to regulate bacterial virulence, its role in K. pneumoniae remains underexplored. Using RIL-seq, the authors investigated the RNA-RNA interaction (RRI) network of hvKp, revealing a prominent role for npcRNAs, including several novel species that were experimentally validated. Among the findings, a stringent subnetwork of RRIs involving virulence-associated genes highlighted the capsule gene loci as a central regulatory hub. The capsule is the primary virulence factor in K. pneumoniae. In UTIs, the capsule is critical for resisting phagocytosis and innate immune responses. One particularly notable npcRNA, OmrB, suppresses capsule production and hypermucoviscosity traits linked to virulence by base-pairing with the kvrA gene (Kwok et al., 2024).

Furthermore, OmrB base pairs within the kvrA coding region, partially suppressing the translation of the capsule regulator KvrA. OmrB, a small RNA, binds to the kvrA gene within its coding sequence (CDS) at positions +81 to +88, disrupting the sequence where the 30S ribosomal subunit binds typically. While it was once believed that npcRNA binding in the CDS region was unlikely due to the ribosome's helicase activity, recent studies suggest such interactions are more common than previously thought. This regulation may depend on features like weak translation initiation signals, such as a non-optimal Shine-Dalgarno sequence or start codon. The kvrA gene in K. pneumoniae shows similar characteristics, with translation initiation possibly occurring at a suboptimal start codon. Although the precise mechanism by which OmrB represses kvrA translation is not fully understood, the findings emphasize growing evidence that npcRNAs can regulate gene expression by binding to CDS regions, affecting virulence-associated phenotypes. Modulation of kvrA expression by OmrB may influence key bacterial factors, such as capsule production and hypermucoviscosity, which are critical for the pathogenicity of K. pneumoniae in the urinary tract [Kwok et al., 2024; Kot et al., 2023].

4.3 Proteus mirabilis

P. mirabilis is a prevalent Gram-negative bacterium that is well-known for causing challenging UTIs, particularly in people who have urinary catheters or urinary tract anomalies. The primary virulence factors linked to various stages of infection, such as flagella, pili or adhesins, urease, hemolysins, and others, are mediated by a catheter into the urethra, bladder, and kidney, resulting in UTIs (Norsworthy et al., 2017). One of the key factors contributing to its prevalence in these infections is its production of diverse types of fimbriae, such as mannose-resistant Proteus fimbriae (MRP). These fimbriae allow the bacteria to attach and colonize in the bladder and kidneys, enhancing their ability to infect uroepithelial cells. P. mirabilis also utilizes two autotransporters, TaaP and AipA, which aid in binding to specific proteins like collagen and laminin found in the urinary tract of host cells. This binding increases the capacity of P. mirabilis to adhere to and invade tissues, leading to the severity of UTIs. Furthermore, P. mirabilis poses a significant challenge in catheter-associated urinary tract infections (CAUTIs) due to its ability to produce urease, which is an enzyme that breaks down urea into ammonia and carbon dioxide (CO_2). According to Wasfi et al. (2020), this process raises the pH of urine, which causes calcium and magnesium phosphate crystals to develop and form a protective biofilm layer on catheters. External antibiotics and the host immune system are unable to penetrate the biofilm, which makes the therapy more difficult to cure (Tian L, et al., 2024).

P. mirabilis urease participates in the formation of urinary stones, which obstruct proper urine flow and can lead to reflux, worsening the infection and potentially causing pyelonephritis (kidney infection) and septicemia (bloodstream infection). This bacterium rapidly attaches to and colonizes the surface of newly inserted urinary catheters, using surface structures like fimbriae and other adhesins (Armbruster et al., 2018). Additionally, P. mirabilis produces toxins such as hemolysin (HpmA) and Proteus toxic agglutinin (Pta), which damage host tissues and promote the spread of the bacteria to the kidneys, leading to acute pyelonephritis. These toxins also facilitate nutrient release from host cells, supporting bacterial growth and survival. P. mirabilis possesses mechanisms to neutralize antibodies, which limit their ability to effectively combat the bacteria (Armbruster et al., 2018).

A clinical report revealed that an 82-year-old woman from Caracas with chronic health issues, including hypertension, diabetes, and recurrent UTIs, was hospitalized after presenting with fever and behavioral changes. She was diagnosed with a UTI caused by P. mirabilis, treated initially with ceftriaxone, but later developed septic shock following femur fracture surgery. The bacteria in her urine were susceptible to several antibiotics, and her blood infection showed specific antibiotic resistance patterns. Further research is needed to discover and explore more about the antibacterial immune responses against P. mirabilis, which

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could potentially lead to new strategies for managing and treating UTIs caused by this bacterium (Maldonado et al., 2022).

Based on Abirami (2022), the author identified and characterized a group of npcRNAs in P. mirabilis that bind to the Hfq protein, a key player in RNA regulation. Thirteen npcRNAs were specifically bound to Hfq using Northern blot analysis, indicating their active expression. These npcRNAs were predicted to target mRNA molecules associated with virulence factors such as fimbriae and flagella proteins. This is necessary for P. mirabilis bacteria to attach to the urothelial cells and initiate infections. This gene has been shown to significantly impact the virulence of P. mirabilis, influencing its ability to cause UTI infections. The npcRNA discussed in these studies is PmiR-137. The removal of the PmiR-137 npcRNA resulted in notable physiological changes in P. mirabilis. These changes included alterations in mobility, biofilm formation, and the ability to respond to environmental stress conditions. This study highlights the regulatory role of npcRNAs in bacterial virulence and provides insight into potential targets for therapeutic interventions against P. mirabilis infections (Abirami et al., 2022).

4.4 Staphylococcus aureus

Staphylococcus aureus is a versatile pathogen causing various infections, from minor infections to severe conditions (Eman et al., 2023). Hospitals frequently have both Staphylococcal infections and UTIs, but S. aureus-induced UTIs are rare, making up only 0.021% to 1.53% of cases. The prevalence of methicillin-resistant S. aureus (MRSA) has increased in hospitals and communities as a result of the increased usage of antibiotics. Therefore, MRSA-induced UTIs that are resistant to common antibiotic treatments have become more frequent, particularly in immunocompromised patients or those with urinary catheters [Yamamoto H, et al., 2022; Gopinath et al., 2022]. S. aureus produces a variety of toxins, such as hemolysins, which can damage host cells and contribute to tissue injury and inflammation. The biofilm matrix formed by S. aureus strains significantly enhances their ability to adhere to host cells and horizontally transfer genetic material through conjugation or transformation (Alshomrani et al., 2023). A resistome and virulome can develop as a result of this process, which promotes the transfer of genes associated with virulence factors and antibiotic resistance. This bacterium is known to build a biofilm and break down urea to produce ammonia, which increases its capacity to form biofilms and adhere to the epithelium, thus promoting its growth and persistence (Xu K, et al., 2023).

According to Delgado (2024), S. aureus can still infect the urinary tract and adapt to the low-iron environment of host tissues. Like other pathogens, S. aureus relies on various mechanisms to acquire iron, an essential nutrient for growth and virulence. The study demonstrates S. aureus uses the ferric uptake regulator (Fur) and npcRNA IsrR to control iron acquisition and metabolism. Specifically, the findings suggest that IsrR plays a significant role in increasing iron uptake, promoting the growth of S. aureus under iron-restricted conditions. This iron acquisition process is important during urinary tract infections, where the host tightly regulates iron levels to limit pathogen growth. During a UTI, the host uses various mechanisms to sequester iron from pathogens in a process known as 'nutritional immunity.' For example, proteins like lactoferrin and transferrin bind iron and prevent bacteria from accessing it. Additionally, the acidic environment and reduced availability of free iron in the urinary tract further limit bacterial proliferation. IsrR's ability to regulate the expression of genes involved in the tricarboxylic acid (TCA) cycle and iron metabolism may play a significant role in the survival and virulence of S. aureus in the urinary tract. In this environment, iron is often limited, making it more difficult for the bacteria to obtain the necessary nutrients for growth. Thus, by controlling genes related to energy production and iron acquisition, npcRNA IsrR helps S. aureus adapt to these nutrient-scarce conditions, improving its ability to persist and cause infection (Delgado et al., 2024).

5. Potential RNA-based targets for treating these urinary tract infections (UTIs)

In contemporary medicine, RNA-based targets have become an innovative approach that is ushering in a new era of personalised and targeted treatment for a wide range of human diseases (Zhu Y, et al., 2022). RNA-based targets have established themselves as an essential tool through groundbreaking discoveries and persistent innovation, providing hope where conventional methods have failed. By specifically targeting disease-related mRNA molecules, RNA-based targets effectively prevent the production of virulence proteins, marking a revolutionary advancement in medicine. To act at the molecular level, this novel therapeutic approach employs a wide variety of RNA molecules, such as oligonucleotides (ASOs), siRNAs, aptamers, mRNAs, ribozymes, and CRISPR/Cas9 (Kim et al., 2022).

Antisense oligonucleotides (ASOs) are short synthetic RNA or DNA molecules. They are designed to bind to particular mRNA sequences and alter their gene expression. The FDA approved the first ASO, Fomivirsen, in 1998 to treat cytomegalovirus retinitis in patients with impaired immune systems (Lauffer et al., 2024). Moreover, Mipomersen is another well-known ASO, authorised in 2013 to treat familial hypercholesterolaemia by inhibiting ApoB-100 mRNA translation (Lauffer et al., 2024). Additionally, FDA-approved siRNA treatments are currently available for acute hepatic porphyria and hereditary transthyretin-mediated amyloidosis. Small interfering RNAs (siRNAs) act by targeting mRNA to reduce protein production (Motamedi et al., 2024).

The application of nucleic acid-based technology has shown promise in combating bacterial infections. Small nucleic acid molecules called aptamers specifically bind to target molecules and show promise in targeting and detecting bacteria such as S. aureus and E. coli (Chen et al., 2022).

When combined with CRISPR technology, aptamers have enhanced bacterial detection techniques, allowing for faster and more accurate diagnosis (Bingshuo Yan et al., 2024). Additionally, messenger RNA (mRNA) therapies offer a promising approach to preventing infectious diseases, such as the COVID-19 vaccines, which use mRNA to instruct cells to produce a particular viral protein that stimulates an immune response [Qin et al., 2022; Deal et al., 2021].

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The potential of ribozymes, RNA molecules that act as enzymes, to cleave mRNA sequences has also been explored. This method targets and silences virulence genes associated with infections (Chen et al., 2024). In conclusion, the capacity of CRISPR/Cas9 gene-editing technology to precisely modify DNA has attracted significant attention due to its promise for genetic repair. Novel strategies to directly target and alter bacterial genomes are currently being evaluated for bacterial infections using CRISPR-Cas9-based methods (Aljabali et al., 2024). This could enable accurate disruption of bacterial pathogens, including antibiotic-resistant strains, providing a promising alternative to conventional antibiotic treatments.

6. Conclusion

UTIs remain a significant public health concern. These bacteria possess complex mechanisms that enable them to colonize and persist within the urinary tract, often leading to recurrent infections and increasing multidrug resistance. As research continues to unravel the potential encoded within npcRNA, the future holds promising advancements that aim to redefine the landscape of healthcare, bringing us closer to effective treatments and cures for previously untreatable conditions. The identification of novel npcRNAs represents a substantial advancement in our understanding of bacterial pathogenesis. These npcRNAs have the potential to fundamentally transform diagnostic and therapeutic strategies for infectious diseases. Integrating npcRNA research into diagnostic methodologies could substantially improve the precision and speed of identifying species-specific pathogens. The development of innovative biomarkers and biosensor technologies based on npcRNAs holds potential for achieving earlier and more reliable infection detection. This approach has the potential to enhance therapeutic interventions and stimulate the emergence of a new market for npcRNA-based drug development. Such progress could yield significant economic benefits, generating revenue and contributing to national economic growth through advanced healthcare solutions and improved public health outcomes.

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