CircRNA- a New Bridge Between Gynecological Drug-Resistant Pathogens and Gene Regulation

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Abstract

The emergence of antibiotic-resistant strains, a consequence of the misuse of antibiotics, has rendered drug-resistant bacterial infections an increasingly critical issue in the realm of gynecological infectious diseases. Circular RNAs (circRNAs), a novel class of non-coding RNAs, have been identified as potential stable regulators of gene expression. Evidence suggests that circRNAs can modulate the immune milieu by influencing macrophage polarization and inflammatory pathways, potentially offering a novel therapeutic strategy against drug-resistant infections. This review outlines prevalent drug-resistant pathogens in gynecology and explores the potential and mechanisms by which circRNAs could mitigate gynecological inflammations unresponsive to antibiotic treatments, laying the groundwork for future investigative endeavors.

BACKGROUND

Gynecological infections caused by antibiotic-resistant pathogens such as Staphylococcus aureus, Candida albicans, and Acinetobacter baumannii are notorious for their environmental adaptability, propensity to induce infections, and potential to trigger additional gynecological complications.[1] These infections compromise women's reproductive health and, due to their resistance to a broad spectrum of antibiotics, present escalating therapeutic challenges.[2,3] The threat to women's health is substantial, heightening the complexity of managing related gynecological conditions.

Circular RNAs (circRNAs), a novel category of non-coding RNA, are characterized by their remarkable intracellular stability and diverse biological roles.[4] They can modulate gene expression by interacting with small molecules, participating in numerous physiological processes.[5] This has garnered significant interest in the scientific community. Research indicates that circRNAs can impact macrophage polarization and transformation, thereby influencing the immune environment.[6] This suggests that circ RNAs might serve as an innovative approach to combat common drug-resistant pathogens in gynecology by modulating specific signaling pathways and gene expression.

This review synthesizes recent findings and provides a comprehensive overview of the latest research on circRNA's role in immune regulation and its interaction with gynecological drug-resistant pathogens. The objective is to elucidate the potential link between circRNA and the progression of gynecological inflammations, offering novel therapeutic insights for drug-resistant gynecological pathogens.

The Varieties and Occurrence of CircRNAs

CircRNAs are a group of non-coding RNAs (ncRNAs) ubiquitous in eukaryotes, existing in a closed circular form devoid of a 5' cap and a 3' poly(A) tail.[7,8,9] Their unique structure endows CircRNAs with resistance to exonucleases, such as RNase R, conferring exceptional stability. [10]

CircRNAs are primarily categorized into three types: exon circular RNA (ecircRNA), circular intron RNA (ciRNA), and exon-intron circular

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RNA (EIciRNA), with ecircRNA constituting over 80% of identified CircRNAs.[11]

The biogenesis of CircRNAs involves two pivotal steps. Initially, DNA is transcribed into pre-mRNA of circRNAs by RNA polymerase. Then, spliceosomes align the 5'-splicing site downstream of pre-mRNA with the 3'-splicing site upstream, a process termed reverse splicing due to its reverse direction compared to linear RNA splicing.[12] Various cis-acting elements, trans-acting factors, and regulatory RNA binding proteins influence CircRNA formation during reverse splicing. For instance, the Alu element, a cis-acting factor, has been shown to facilitate reverse splicing.[13]

New Challenges from Gynecological Drug-Resistant Pathogens

In gynecological diseases, highly drug-resistant pathogens pose a grave threat to women's health, potentially leading to conditions such as bacterial vaginosis, endometritis, cervicitis, infertility, and salpingitis.[14] Clinically, common drug-resistant gynecological pathogens include Staphylococcus aureus and Coagulase-negative Staphylococcus, which exhibit significant resistance to penicillin and erythromycin.[15] Additionally, Escherichia coli carrying Extended-Spectrum β-Lactamases (ESBLs) display multi-drug resistance and are almost entirely resistant to penicillins and cephalosporins, making them primary culprits in severe obstetric infections, abortions, premature births, and neonatal sepsis. [16] Candida albicans, the primary cause of vulvovaginal candidiasis (VVC), has demonstrated increasing resistance to fluconazole, the first-line treatment. Luo et al.[17], by analyzing the distribution and drug sensitivity of VVC pathogens, noted a shift from Candida albicans to other species and a rising trend in drug resistance, warranting attention. The increasing infection rates due to bacterial resistance and pathogen shifts present new clinical treatment challenges.

The Dual Nature of CircRNA Immunotherapy

When microorganisms develop resistance, the host's innate immune response becomes crucial. Pattern recognition receptors (PRRs) recognize bacterial. polysaccharides to eliminate pathogens. However, if an inflammatory cytokine storm is triggered, causing severe tissue damage, this defense can be compromised.[18] In such cases, M2 macrophages can mitigate the inflammatory storm. Studies reveal an interaction between circRNA and the host immune system, suggesting potential as diagnostic markers and therapeutic targets for bacterial infections, opening new avenues for drug-resistant pathogen treatment.[19]

While previous studies have shown circRNA expression can influence cellular drug sensitivity,[20] there is no definitive evidence that exogenous circRNA affects bacterial drug sensitivity. Exosomes, vesicles derived from the intracellular body membrane system, are secreted into surrounding fluids with a diameter of 30-150 nm and a double-layer phospholipid membrane structure. They play a pivotal role in intercellular communication, transporting cellular components and status information, including proteins, circRNAs, mRNAs, and miRNAs, with a particular focus on exosomal circRNAs.[21,22]

Exosome circRNAs have been confirmed to regulate macrophage polarization and immune responses.[23] For example, circRNA mSCAR can be delivered to macrophage mitochondria to reverse M1 polarization by reducing mtROS and ameliorate inflammation.[24] CircSAFB2, binding miR-620, can sponge miR-620 in macrophage cytoplasm, reducing JAK1 expression and thereby STAT3 expression, promoting M2 polarization.[25] Similarly, circSAFB2 can enhance SHIP1 expression by sponging miR-155-5p, inhibiting TLR4 signaling and reducing pyroptosis-related proteins and cytokines, thus inhibiting macrophage pyroptosis and inflammation.[26]

However, circRNAs can also exacerbate inflammation. CAPRIN1 inhibits S100A11 translation, while circS100A11 promotes it by binding competitively to CAPRIN1. S100A11 promotes SP3 release from nucleolin and binds to the STAT6 promoter, increasing STAT6 expression, activating M2a macrophages, and aggravating inflammation.[27] CircRNA7, as a miR-7 sponge, prevents miR-7 from binding to PI3K/AKT/mTOR pathway-related genes, activating PI3K and subsequently AKT, regulating mTOR activity, and promoting inflammation progression.[28]

CircRNAs can modulate the inflammatory response through multiple pathways, improving the body's immune environment and indirectly enhancing macrophage phagocytosis of pathogens. Thus, when bacterial resistance leads to suboptimal drug treatment, circRNA-mediated inflammatory responses may offer a novel therapeutic approach for gynecological infectious diseases.

Prospect

This study meticulously analyzes the interplay between circRNA and the immune response. By synthesizing existing research, it is evident that circRNA may alter the immune microenvironment, impacting the body's resistance to drug-resistant bacteria. CircRNA plays a significant role in macrophage polarization, release of inflammatory factors, and signal transduction of the inflammatory response. Importantly, the regulation of the inflammatory response by circRNA is intricate, necessitating a multidimensional evaluation of its impact on the immune microenvironment.

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