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RESEARCH PROGRESS ON LONG NON-CODING RNA-MEDIATED SEPSIS PROGRESSION

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Abstract: Sepsis represents a severe dysregulation of the host response to infection. In recent years, the involvement of long non-coding RNAs (lncRNAs) in the onset and progression of sepsis has garnered significant attention. This review outlines the expression profiles and regulatory functions of lncRNAs in sepsis, emphasizing their associations with inflammatory processes, immune dysregulation, and organ injury. It highlights the molecular pathways through which lncRNAs influence sepsis by modulating inflammatory signaling, immune cell activities, and programmed cell death. Additionally, the potential utility of lncRNAs as diagnostic markers and therapeutic targets is discussed.
Keywords: Long non-coding RNA; Sepsis; Inflammatory response; Immune regulation; Organ injury; Molecular mechanism

1 INTRODUCTION

Sepsis remains a major contributor to global mortality, characterized by a complex pathophysiology involving uncontrolled inflammation, immune impairment, and multi-organ failure [1]. Although treatment strategies have advanced, mortality rates persist at high levels, underscoring the need for novel diagnostic and therapeutic approaches. Long non-coding RNAs (lncRNAs), which exceed 200 nucleotides and lack protein-coding potential, have emerged as crucial regulators in numerous diseases. Research indicates that lncRNAs participate in gene expression control, chromatin organization, and protein interactions, impacting key processes such as inflammation, immunity, and cell death [2-5]. Advances in high-throughput sequencing have unveiled dysregulated lncRNA expression in sepsis, shedding light on their functional importance. This article synthesizes current knowledge on lncRNA mechanisms in sepsis and explores their clinical potential.

2 OVERVIEW OF LONG NON-CODING RNAS

LncRNAs are RNA molecules longer than 200 nucleotides with limited protein-coding capability. They are categorized based on genomic context into sense, antisense, bidirectional, intronic, and intergenic types. Unlike shorter non-coding RNAs like miRNAs, lncRNAs exhibit complex structures and operate through diverse mechanisms [6-7].
The functional spectrum of lncRNAs includes: (1) serving as scaffolds in ribonucleoprotein complexes; (2) acting as competing endogenous RNAs (ceRNAs) to sequester miRNAs; (3) guiding chromatin-modifying complexes; (4) influencing transcriptional activity; (5) modulating mRNA stability and translation; and (6) facilitating intercellular communication. These roles position lncRNAs as pivotal regulators within gene networks, contributing to both normal physiology and disease [8-10].

3 EXPRESSION PATTERNS OF LONG NON-CODING RNAS IN SEPSIS

High-throughput studies have identified extensive alterations in lncRNA expression in sepsis patients and experimental models [11]. For instance, peripheral blood mononuclear cells from septic individuals show hundreds of differentially expressed lncRNAs, some correlating with disease severity and outcomes [12]. Upregulated lncRNAs such as NEAT1, MALAT1, and HOTAIR, and downregulated ones like MEG3 and GAS5, are frequently reported [13-15].
Organ-specific lncRNA expression changes are also evident. In septic acute lung injury, PFI and Lnc-IL7R are elevated [16-17]; in kidney injury, TUG1 and AK139328 are altered [18]; and in myocardial dysfunction, H19 and KCNQ1OT1 are dysregulated [19-20]. These variations suggest tissue-specific regulatory roles. Moreover, lncRNA expression dynamically shifts with sepsis progression: pro-inflammatory types like THRIL and LincRNA-ERS rise during hyperinflammation, while immunomodulatory lncRNAs such as NR_045064 and uc.48+ dominate during immunosuppression.

4 MECHANISMS OF LNCRNAS IN SEPSIS PATHOGENESIS

4.1 lncRNAs and Inflammatory Response in Sepsis

LncRNAs modulate sepsis-associated inflammation through various avenues. As ceRNAs, they sequester miRNAs to derepress inflammatory mediators. For example, NEAT1 sponges miR-125a-5p, alleviating suppression of TRAF6 and activating NF-κB to enhance cytokine production [21-22]. Similarly, MALAT1 influences the miR-146a/TRAF6 axis, impacting TLR4 signaling [23-24].

Direct involvement in inflammatory pathways is also common. THRIL complexes with hnRNPL to modulate TNF-α transcription [25-26], while LincRNA-EPS interacts with hnRNPL to suppress inflammatory genes [27]. The pseudogene-derived lncRNA Lethe binds NF-κB, curtailing its activity [26, 28-29]. These interactions fine-tune inflammatory responses.

LncRNAs also regulate inflammasomes: MEG3 inhibits NLRP3 assembly [30-31], and GAS5 binds glucocorticoid receptors to boost anti-inflammatory cytokines like IL-10 [32]. Conversely, SNHG1 promotes NLRP3 activation, worsening inflammation [33].

4.2 lncRNAs and Immune Regulation in Sepsis

4.2.1 Immune cell modulation by lncRNAs

Immune cell functions are extensively regulated by lncRNAs. In macrophages, TUG1 upregulation upon LPS stimulation enhances activation and cytokine release; its knockdown mitigates these effects [34]. Mechanistically, TUG1 binds miR-142-3p to elevate NCOA1, influencing polarization and inflammation [35]. In lymphocytes, NRON dysregulation in septic T cells impairs calcineurin-NFAT signaling, leading to immune dysfunction [36-37].

4.2.2 lncRNAs and immune evasion

Pathogens exploit lncRNAs to evade immunity. Viral lncRNAs, like HCMV's β2.7, bind hnRNP A2/B1 to suppress interferon responses, aiding persistence [38-40]. Bacterial infections may similarly alter host lncRNAs to impair immunity, though this area requires further study [41-42].

5 LNCRNAS IN CELL DEATH AND ORGAN DAMAGE IN SEPSIS

5.1 lncRNAs and Apoptosis

Apoptosis of immune and parenchymal cells contributes significantly to sepsis pathology. LncRNA-ATB upregulation in septic T cells promotes apoptosis via miR-200c/ZEB1 signaling [43-47]. In macrophages, MEG3 overexpression accelerates apoptosis through p53 activation [48-49].

In organ cells, HOTTIP upregulation exacerbates cardiomyocyte apoptosis via miR-125a-5p/Bax [50-51], while MIAT sponges miR-205 to increase Caspase-3 expression, worsening renal injury [52-54].

5.2 lncRNAs and Tissue/Organ Injury

LncRNAs are implicated in organ-specific damage: PFI and MALAT1 aggravate lung injury by promoting apoptosis and endothelial permeability [55-56], whereas MEG3 is protective [31]. In the kidney, TUG1 and H19 exacerbate injury through HMGB1 and let-7/STAT3 pathways [57-58]. In the heart, H19 and KCNQ1OT1 affect contractility and apoptosis [59-60].

6 LNCRNAS AND COAGULATION ABNORMALITIES

Coagulopathy is a critical aspect of sepsis. UCA1 upregulation in sepsis enhances coagulation via miR-143-3p/TF signaling [61-62]. LncRNAs may also influence platelet function, though detailed mechanisms remain elusive.

7 DIAGNOSTIC AND THERAPEUTIC POTENTIAL OF LNCRNAS IN SEPSIS

LncRNAs show promise as biomarkers: panels like MALAT1/HOTAIR/GAS5 improve diagnostic accuracy and prognosis prediction [63]. Therapeutically, targeting pro-inflammatory lncRNAs (e.g., NEAT1, THRIL) or supplementing protective ones (e.g., MEG3, GAS5) ameliorates sepsis in models [64]. Nanocarrier systems may enhance delivery, but challenges in specificity and safety remain.

8 CONCLUSIONS AND PERSPECTIVES

This review outlines the expanding roles of lncRNAs in sepsis pathophysiology. Their involvement in inflammation, immunity, and organ injury provides insights into disease mechanisms and highlights translational opportunities.

Outstanding issues include: (1) validating lncRNA biomarkers in larger cohorts; (2) elucidating spatiotemporal regulation; (3) exploring interactions with other epigenetic mechanisms; and (4) improving therapeutic delivery.

Future directions involve standardizing detection methods, integrating multi-omics data, understanding heterogeneity, and advancing precision medicine. LncRNAs hold potential as novel targets for improving sepsis outcomes.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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