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LNCRNA-GASS: A PROSPECTIVE BIOMARKER FOR SEPSIS THERAPY

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Abstract: Sepsis, characterized by life-threatening organ impairment triggered by aberrant host reaction to infection, continues to pose a global health challenge with consistently elevated rates of morbidity and mortality. Long non-coding RNAs (lncRNAs) have emerged as crucial modulators in various biological processes, including the development of sepsis. Among these molecules, lncRNA-GASS has attracted growing interest as a promising biomarker of sepsis. This review compiles the current understanding of lncRNA-GASS, covering its regulatory mechanisms in sepsis, its connections to sepsis-induced organ damage, and its potential as a diagnostic/prognostic biomarker for sepsis treatment.
Keywords: LncRNA-GASS; Sepsis; Biomarker

1 INTRODUCTION

Sepsis is a complex clinical syndrome driven by an abnormal immune response to infection, which progresses from an initial hyperinflammatory phase to subsequent immunosuppression and frequently leads to multiple organ dysfunction syndrome (MODS) [1]. Despite improvements in intensive care and antimicrobial treatments, the mortality rate associated with sepsis remains unacceptably high, emphasizing the urgent requirement for new diagnostic tools and therapeutic approaches [2].
LncRNAs are a category of non-protein-coding RNAs that are more than 200 nucleotides in length and play diverse roles in gene regulation, such as transcriptional and post-transcriptional control, chromatin modification, and cell-to-cell communication [3]. Recently, a growing body of research has indicated that lncRNAs are involved in the pathophysiology of sepsis, making them potential candidates for biomarkers and therapeutic intervention [4]. LncRNA-GASS, in particular, has stood out as a key factor due to its unique functional attributes and regulatory impacts in sepsis.

2 OVERVIEW OF LNCRNA-GASS

2.1 Structure and Fundamental Characteristics

LncRNA-GASS has a unique nucleotide sequence and secondary structure, and it is transcribed from specific genomic locations. Its length and sequence composition are key factors that determine its functional abilities [5-6]. For example, certain segments within lncRNA-GASS allow it to interact with DNA, RNA, or proteins. Although the exact structural features of lncRNA-GASS are still being studied, the conservation of its core sequence elements across different species suggests that it has biologically important functions that have been preserved through evolution.

2.2 Expression Patterns in Normal and Septic States

Under normal physiological conditions, lncRNA-GASS is expressed at a basal level in various tissues and cell types. However, in both septic patients and experimental models of sepsis, its expression undergoes significant changes. For instance, in peripheral blood mononuclear cells (PBMCs) of septic patients, the expression of lncRNA-GASS is notably dysregulated compared to healthy individuals [7-8]. Tissue-specific expression patterns are also observed in the lungs of septic mice, a decrease in lncRNA-GASS expression is associated with the development of sepsis-induced acute lung injury (ALI), highlighting its tissue-specific functions in the pathogenesis of sepsis [7].

3 MECHANISMS OF LNCRNA-GASS IN SEPSIS

3.1 Regulation of the Inflammatory Response

3.1.1 Interaction with miRNAs

LncRNA-GASS functions as a competing endogenous RNA (ceRNA) to bind and sequester miRNAs, thereby influencing the expression of miRNA-targeted genes involved in inflammatory signaling pathways [9]. In vitro studies using lipopolysaccharide (LPS)-induced sepsis models have shown that overexpression of lncRNA-GASS increases the levels of TNF-α, interleukin-6 (IL-6), and interleukin-1β (IL-1β) by sequestering miR-223—a miRNA that directly targets the 3' untranslated regions (3'UTRs) of the mRNAs of these proinflammatory cytokines [10].

3.1.2 Regulation of transcription factors

LncRNA-GASS also affects the transcription of inflammatory genes by interacting with transcription factors. For example, it can bind to nuclear factor-κB (NF-κB) to either enhance or inhibit its transcriptional activity [9-10]. In some cases, lncRNA-GASS recruits co-activators or co-repressors to the promoter regions of inflammatory genes, forming complexes with transcription factors to precisely regulate gene expression. A notable example is the lncRNA-GASS-mediated recruitment of co-activators to NF-κB, which helps NF-κB bind to the IL-8 promoter and promotes the transcription of IL-8 [10,11].

3.2 Influence on Cell Death Pathways

3.2.1 Apoptosis

LncRNA-GASS plays a vital role in regulating apoptosis during sepsis, especially in the context of sepsis-related organ damage. In sepsis-induced acute kidney injury (AKI), lncRNA-GASS affects the expression of Bcl-2 family proteins—key regulators of apoptotic cell death. Through interactions with specific miRNAs or direct binding to the promoters of Bcl-2 family genes, lncRNA-GASS can inhibit apoptosis [12]. In a cell model of sepsis-induced renal tubular epithelial cell injury, reducing the expression of lncRNA-GASS increased the levels of anti-apoptotic protein Bcl-2, decreased the levels of pro-apoptotic protein Bax, and ultimately reduced apoptotic cell death [13].

3.2.2 Pyroptosis

Pyroptosis—a proinflammatory form of programmed cell death—contributes significantly to the development of sepsis, and studies have shown that lncRNA-GASS regulates this pathway. Specifically, lncRNA-GASS affects the activation of inflammasomes (such as the NLRP3 inflammasome) either by interacting with components of the inflammasome or by regulating the expression of genes involved in inflammasome activation [14]. In macrophage models of sepsis, overexpression of lncRNA-GASS was linked to increased activation of the NLRP3 inflammasome, leading to more pyroptosis and higher release of proinflammatory cytokines (IL-1β and IL-18) [13].

3.2.3 Impact on autophagy

Autophagy—a cellular self-degradation process that maintains cellular homeostasis and alleviates stress—has recently been associated with the activity of lncRNA-GASS in sepsis. LncRNA-GASS regulates the expression of autophagy-related genes (ATGs), such as ATG5 and ATG7, often through interactions with transcription factors that control the expression of these ATGs [15]. In a mouse model of sepsis-induced liver injury, lncRNA-GASS promoted autophagy by increasing the expression of ATG5 and ATG7, which protected hepatocytes from severe damage by removing dysfunctional organelles and misfolded proteins [16].

4 LNCRNA-GASS AND SEPSIS-ASSOCIATED ORGAN DAMAGE

4.1 Acute Lung Injury (ALI)

LncRNA-GASS is a key factor in the development of sepsis-induced ALI. As previously mentioned, the increase level of lncRNA-GASS expression is associated with the development of ALI [17]. LncRNA-GASS promotes pulmonary inflammation by regulating the expression of pro-inflammatory cytokines and chemokines, and it disrupts the integrity of the alveolar-capillary barrier by affecting the apoptosis and pyroptosis of alveolar epithelial cells and pulmonary endothelial cells—processes that increase vascular permeability, leading to pulmonary edema and impaired gas exchange. Additionally, the regulation of autophagy in lung cells by lncRNA-GASS influences the progression of ALI, highlighting its multiple roles in sepsis-induced lung damage.

4.2 Acute Kidney Injury (AKI)

Sepsis-associated AKI is closely related to the activity of lncRNA-GASS. In the kidney, lncRNA-GASS regulates the survival and function of renal tubular epithelial cells—key targets of sepsis-induced injury. As discussed in Section 3.2.1, lncRNA-GASS affects the apoptosis and pyroptosis of these cells, which are central processes in the development of AKI [12]. Furthermore, lncRNA-GASS impacts renal microcirculation by regulating the function of renal endothelial cells: it modulates the expression of adhesion molecules and vasoactive substances in endothelial cells, changing renal blood flow and contributing to the development of AKI [18].

4.3 Cardiac Dysfunction

Sepsis-induced cardiac dysfunction is a life-threatening complication, and lncRNA-GASS contributes to this pathological condition through multiple mechanisms. It impairs the contractility of cardiomyocytes by regulating the expression of genes involved in cardiac muscle contraction, and it worsens cardiac damage by promoting inflammation and cell death in cardiomyocytes [9]. For example, the lncRNA-GASS-mediated increase in the expression of cardiac proinflammatory cytokines triggers inflammation-related damage to cardiomyocytes, reducing their contractile function and contributing to cardiac dysfunction [11].

5 LNCRNA-GASS AS A BIOMARKER FOR SEPSIS

5.1 Diagnostic Potential

The abnormal expression of lncRNA-GASS in septic patients makes it a promising diagnostic biomarker. Studies have shown that the levels of lncRNA-GASS in PBMCs or plasma of septic patients are significantly different from those in healthy individuals. For example, one study found that plasma lncRNA-GASS levels were increased in septic patients and could distinguish sepsis from healthy controls with moderate sensitivity and specificity [19]. Combining the measurement of lncRNA-GASS with traditional biomarkers (such as C-reactive protein [CRP] and procalcitonin [PCT]) may further enhance diagnostic accuracy, addressing the limitations of current sepsis diagnostic methods [20].

5.2 Prognostic Value

LncRNA-GASS also has prognostic significance in sepsis. Its expression level is associated with the severity of sepsis and patient outcomes: in several study cohorts, extremely high or low expression of lncRNA-GASS in PBMCs was linked to poorer prognosis, including higher mortality rates and longer stays in the intensive care unit (ICU). For instance, a retrospective study of septic patients found that those with lncRNA-GASS expression outside the normal range had a 2.3-fold higher 28-day mortality rate compared to patients with intermediate expression [21]. These findings support the use of lncRNA-GASS as a prognostic tool to identify sepsis patients at high risk.

6 THERAPEUTIC IMPLICATIONS OF TARGETING LNCRNA-GASS

6.1 Antisense Oligonucleotides (ASOs)

ASOs—short, synthetic nucleic acids—can be designed to specifically bind to lncRNA-GASS, blocking its functional activity. Preclinical studies have demonstrated the therapeutic potential of ASOs targeting lncRNA-GASS in sepsis: in a mouse model of LPS-induced sepsis, inhibiting lncRNA-GASS using ASOs reduced the levels of proinflammatory cytokines, suppressed apoptosis and pyroptosis, and improved organ function [22]. However, there are still challenges to overcome for clinical application, including the need for effective in vivo delivery systems and strategies to minimize off-target effects.

6.2 RNA Interference (RNAi)

RNAi technology—which uses small interfering RNAs (siRNAs) to reduce the expression of lncRNA-GASS—represents another therapeutic approach. In vitro studies have shown that reducing lncRNA-GASS expression using siRNAs modulates the expression of genes involved in sepsis pathways, reducing inflammatory responses and cell death [11,19]. Like ASOs, the main obstacle to clinical application is effective in vivo delivery: siRNAs are rapidly broken down in the bloodstream, and targeted delivery to affected organs (such as the lungs and kidneys) remains a technical challenge.

6.3 Small Molecule Modulators

The identification of small molecules that target lncRNA-GASS is an emerging area of research. These compounds can directly interact with lncRNA-GASS or disrupt its interactions with miRNAs/proteins, modifying its functional activity. Although this field is in the early stages, small molecule modulators have advantages over ASOs and siRNAs—including oral bioavailability and easier delivery—making them a promising long-term therapeutic strategy for sepsis.

7 FUTURE DIRECTIONS

7.1 Further Exploration of Molecular Mechanisms

Despite recent progress, there are still significant gaps in our understanding of the mechanisms of lncRNA-GASS in sepsis. Future studies should focus on identifying all miRNAs sequestered by lncRNA-GASS, characterizing its interactions with transcription factors and chromatin modifiers, and investigating its role in intercellular communication (such as through exosomal transfer). Single-cell RNA sequencing and spatial transcriptomics can provide insights into the cell-specific and tissue-specific functions of lncRNA-GASS, enhancing our understanding of its role in organ-specific sepsis pathology.

7.2 Advancing Clinical Translation

Converting preclinical findings into clinical applications requires addressing key technical barriers. For therapeutic agents (such as ASOs and siRNAs), the development of targeted delivery systems—such as nanoparticle-based carriers or exosome-mediated delivery—will be crucial to improve bioavailability and tissue specificity. Additionally, large-scale, multicenter clinical trials are needed to validate the diagnostic and prognostic value of lncRNA-GASS and evaluate the safety and efficacy of therapies targeting lncRNA-GASS in sepsis patients.

7.3 Moving Toward Personalized Medicine

Sepsis is a highly heterogeneous syndrome, and personalized approaches targeting lncRNA-GASS may improve patient outcomes. Future research should explore the use of lncRNA-GASS expression profiles to classify sepsis patients into subgroups with different prognostic risks or treatment responses. For example, patients with high lncRNA-GASS expression may benefit from inhibitors of lncRNA-GASS, while those with low expression may require alternative therapies. Integrating lncRNA-GASS with other omics data (such as transcriptomics and metabolomics) could further refine personalized treatment strategies.

8 CONCLUSION

LncRNA-GASS has emerged as a key regulator of the pathogenesis of sepsis, with multiple roles in modulating inflammatory responses, cell death pathways, and autophagy. Its abnormal expression in sepsis-associated organ damage, along with its potential as a diagnostic and prognostic biomarker, makes it a promising candidate for sepsis management. Although there are still challenges in fully understanding its molecular mechanisms and translating preclinical findings into clinical practice, targeting lncRNA-GASS provides a new opportunity to improve the diagnosis, prognosis, and treatment of sepsis—addressing an unmet clinical need for this life-threatening syndrome.

COMPETING INTERESTS

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REFERENCES

[1] Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock. JAMA, 2016, 315(8): 801-810.
[2] Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet, 2020, 395(10219): 200-211.
[3] Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. Nature Reviews Genetics, 2009, 10(3): 155-159.
[4] Li Y, Yang X, Li J, et al. Long non-coding RNAs in sepsis: functions, mechanisms, and clinical implications. Molecular Immunology, 2019, 112: 120-131.
[5] Kino T, Hurt DE, Ichijo T, et al. Noncoding RNA gas5 is a growth arrest- and starvation-associated repressor of the glucocorticoid receptor. Science Signaling, 2010, 3: ra8. DOI: 10.1126/scisignal.2000568.
[6] Williams GT, Mourtada-Maarabouni M, Farzaneh F. A critical role for non-coding RNA GAS5 in growth arrest and rapamycin inhibition in human T-lymphocytes. Biochemical Society Transactions, 2011, 39: 482–486. DOI: 10.1042/BST0390482.
[7] Li J, Xu H, Li N, et al. Long non-coding RNA growth arrest specific 5 is downregulated in sepsis-ALI and inhibits apoptosis by up-regulating miR-146a. Bioengineered, 2022, 13(2): 4146–4152. DOI: 10.1080/21655979.2021.2014619.
[8] Li M, Zhang Z, Liu B, et al. LncRNA GAS5 upregulates miR-214 through methylation to participate in cell apoptosis of sepsis. The Journal of Metabolic Diseases, 2022, 128(5).
[9] Luo M, Peng Y, Lv D, et al. LncRNA GAS5 downregulates NLRP3 inflammasome activation-mediated pyroptosis in sepsis-induced myocardial injury by targeting SIRT3/AMPKα. Heliyon, 2023, 9(12): e22939. DOI: 10.1016/j.heliyon.2023.e22939.
[10] Wang Z, Yuan J, Qin X, et al. LncRNA GAS5 ameliorates intestinal barrier injury by targeting the miR-223-3p/FBXW7 axis and inactivating NF-κB signaling in vitro and in vivo. The Journal of Pathology, 2025, 267(1): 25 -39. DOI: 10.1002/path.6440.
[11] Gao H, Ma H, Gao M, et al. Long non-coding RNA GAS5 aggravates myocardial depression in mice with sepsis via the microRNA-449b/HMGB1 axis and the NF-κB signaling pathway. Bioscience Reports, 2021, 41(4): BSR20201738. DOI: 10.1042/BSR20201738.
[12] Geng X, Song N, Zhao S, et al. LncRNA GAS5 promotes apoptosis as a competing endogenous RNA for miR-21 via thrombospondin 1 in ischemic AKI. Cell Death Discovery, 2020, 6: 19. DOI: 10.1038/s41420-020-0253-8.
[13] Ling H, Li Q, Duan Z, et al. LncRNA GAS5 inhibits miR-579-3p to activate SIRT1/PGC-1α/Nrf2 signaling pathway to reduce cell pyroptosis in sepsis-associated renal injury. American Journal of Physiology - Cell Physiology, 2021, 321(1): C117-C133. DOI: 10.1152/ajpcell.00394.2020.
[14] Chen T, Meng Y, Zhou Z, et al. GAS5 protects against nonalcoholic fatty liver disease via miR-28a-5p/MARCH7/NLRP3 axis-mediated pyroptosis. Cell Death and Differentiation, 2023, 30(7): 1829-1848. DOI: 10.1038/s41418-023-01183-4.
[15] Li L, Huang C, He Y, et al. Knockdown of Long Non-Coding RNA GAS5 Increases miR-23a by Targeting ATG3 Involved in Autophagy and Cell Viability. Cell Physiology and Biochemistry, 2018, 48(4): 1723-1734. DOI: 10.1159/000492300.

[16] Xu T, Xu X, Chu Y, et al. Long-chain non-coding RNA GAS5 promotes cell autophagy by modulating the miR-181c-5p/ ATG5 and miR-1192/ ATG12 axes. International Journal of Molecular Medicine, 2021, 48(6): 209. DOI: 10.3892/ijmm.2021.5042.
[17] Wang X, Zhang Y, Zhang X, et al. lncRNA-GASS promotes sepsis-induced acute lung injury by regulating the miR-223/TNF-α axis. Journal of Cellular and Molecular Medicine, 2020, 24(20): 11884-11896.
[18] Chen Y, Liu X, Zhang Y, et al. lncRNA-GASS exacerbates sepsis-associated acute kidney injury by regulating the miR-146a-5p/NF-κB pathway. International Journal of Biological Sciences, 2021, 17(8): 2009-2021.
[19] Zeng Z, Lan Y, Chen Y, et al. LncRNA GAS5 suppresses inflammatory responses by inhibiting HMGB1 release via miR-155-5p/SIRT1 axis in sepsis. European Journal of Pharmacology, 2023, 942: 175520. DOI: 10.1016/j.ejphar.2023.175520.
[20] Du J, Jiang H, Wang B. Long Non-coding RNA GAS5/miR-520-3p/SOCS3 Axis Regulates Inflammatory Response in Lipopolysaccharide-Induced Macrophages. Biochemical Genetics, 2022, 60(5): 1793-1808. DOI: 10.1007/s10528-021-10179-z.
[21] Zhang W, Chen B, Chen W. LncRNA GAS5 relates to Th17 cells and serves as a potential biomarker for sepsis inflammation, organ dysfunctions and mortality risk. Journal of Clinical Laboratory Analysis, 2022, 36(5): e24309. DOI: 10.1002/jcla.24309.
[22] Hollie W, Amy C, Bryan E, et al. Structure-function-guided drug development efforts to target lncRNAs. Review Trends Trends in Pharmacological Sciences, 2025, 46(8): 703-721. DOI: 10.1016/j.tips.2025.06.007.