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Topic of Research: "**The role of lncRNA in LPS induced inflammation/acute lung injury and macrophage modulation**".

Findings

This study has unveiled a crucial role for long non-coding RNA SNHG1 in the pathogenesis of sepsis-induced acute lung injury (ALI) and identified it as a key target for therapeutic intervention. Through lncRNA profiling and next-generation sequencing analysis, we discovered significant upregulation of SNHG1 in ALI models. Our research revealed that SNHG1 acts as a central regulator in ALI progression by influencing macrophage polarization, pyroptosis, and oxidative stress. Importantly, we uncovered a novel epigenetic axis involving SNHG1, miR-495, and DNMT1, where SNHG1 promotes DNA methylation of the miR-495 promoter via DNMT1. The natural compound vitexin emerged as a promising therapeutic agent, primarily through its ability to downregulate SNHG1 expression and reverse the epigenetic modifications, thereby mitigating ALI pathogenesis. Modulation of SNHG1 levels through overexpression and knockdown experiments demonstrated its direct impact on inflammatory responses and macrophage phenotypes. These findings not only establish SNHG1 as a critical player in ALI but also highlight the potential of targeting lncRNAs for developing novel therapies. Our study opens new avenues for understanding the complex regulatory networks involving lncRNAs in acute inflammatory diseases and provides a strong foundation for future translational research aimed at exploiting these non-coding RNAs as therapeutic targets in ALI and potentially other inflammatory conditions.

Abstract

Sepsis-induced acute lung injury (ALI) is a life-threatening condition marked by excessive inflammation and tissue damage. Our study investigated the therapeutic potential of vitexin, a natural flavonoid, in mitigating ALI through modulation of long non-coding RNAs (lncRNAs), particularly SNHG1, and microRNA-495 (miR-495).

Using LPS-treated RAW264.7 macrophages, vitexin significantly reduced iNOS and COX-2 expression with minimal cytotoxicity. In a cecal ligation and puncture (CLP) mouse model, vitexin treatment led to reduced lung tissue damage (H&E staining), decreased MPO levels (immunohistochemistry), and improved tight junction integrity via increased occludin expression. Lower LDH activity further confirmed vitexin's protective effect on lung tissue.

Vitexin promoted M2 macrophage polarization, evidenced by increased Arg1, Fizz1, and YM1 expression, and upregulated stem cell markers (cMYC, Nanog, SOX2), suggesting enhanced tissue regeneration. lncRNA profiling and NGS analysis revealed significant upregulation of SNHG1 in ALI models. Functional studies showed that SNHG1 overexpression suppressed M2 markers and increased nitrite levels, while SNHG1 knockdown reversed these effects, indicating its role in inflammatory regulation.

A key finding was the methylation of the miR-495 promoter and elevated DNMT1 expression in ALI, driven by SNHG1. Vitexin reversed this epigenetic modification, reducing DNMT1 levels and restoring miR-495 expression. This established a novel SNHG1/miR-495/DNMT1 axis as a regulatory mechanism in ALI.

Further, vitexin reduced ROS, enhanced mitophagy, and decreased apoptotic cell populations, suggesting it prevents the transition from apoptosis to pyroptosis—a critical step in ALI progression. Transfection studies confirmed that SNHG1 knockdown and miR-495 overexpression suppressed pyroptosis-related proteins (NLRP3, GSDMD, ASC, caspase-1, IL-1β), supporting vitexin's anti-pyroptotic effects.

In conclusion, our study identifies SNHG1 as a central regulator of ALI pathogenesis and highlights vitexin as a promising therapeutic agent. By modulating the SNHG1/miR-495 axis, vitexin attenuates inflammation, promotes tissue repair, and offers a novel lncRNA-targeted strategy for treating ALI and other inflammatory diseases.