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Topic: Investigating the role of miRNAs and PARP1 inhibition in Sepsis-induced Acute Lung Injury

FINDINGS

Sepsis-induced acute lung injury (ALI) is a life-threatening syndrome characterized by a dysregulated systemic inflammatory response leading to severe pulmonary dysfunction, high morbidity, and mortality. Current management is largely supportive, highlighting a critical need for targeted therapeutic interventions that address both the overwhelming inflammatory cascade and the subsequent failure of tissue repair. The study is grounded in a robust investigation of the molecular mechanisms underlying sepsis-induced ALI, focusing on three key pathways: the TXNIP/NLRP3 inflammasome axis, the SMAD5/NANOG regenerative axis, and the PARP1-mediated inflammatory loop. Our initial findings established the pivotal pathological role of miR-135a-5p downregulation in sepsis-induced ALI. We observed a significant decrease in miR-135a-5p expression in the lung tissue of septic mice, correlating with increased inflammation. By overexpressing miR-135a-5p, we demonstrated its potent anti-inflammatory effects. Mechanistically, we found that miR-135a-5p directly targets and negatively regulates TXNIP, a key activator of the NLRP3 inflammasome. This suppression of the inflammasome, a central driver of pyroptosis and inflammatory signaling, led to a marked reduction in downstream inflammatory mediators, including IL-1β and cleaved Caspase-1. The anti-inflammatory benefits were further evidenced by a significant restoration of the alveolar-capillary barrier, as indicated by increased expression of the tight junction protein Occludin, and a dramatic reduction in neutrophil infiltration (Myeloperoxidase-positive cells). These results collectively underscore miR-135a-5p's critical role in mitigating the acute inflammatory phase of lung injury.

Beyond its anti-inflammatory functions, we discovered a previously uncharacterized pro-regenerative role for miR-135a-5p. We elucidated a precise molecular cascade where miR-135a-5p directly targets and inhibits SMAD5, a key transcriptional regulator in the bone morphogenetic protein (BMP) signaling pathway. By suppressing SMAD5, miR-135a-5p effectively releases the inhibitory control over pluripotency, leading to the upregulation of NANOG, a master regulator of stem cell identity. This single molecular event initiates a broader regenerative program, enhancing the expression of other pluripotency and stemness-associated factors, including OCT4, SOX2, and c-MYC. This activation of the OCT4-SOX2-NANOG network in lung epithelial progenitor cells (AEC2s) creates a pro-regenerative microenvironment, supporting tissue repair and regeneration. This finding is particularly significant as it demonstrates that miR-135a-5p not only dampens the inflammatory response but also actively promotes the lung's intrinsic repair mechanisms.

Parallel to the miR-135a-5p investigation, we validated the therapeutic potential of PARP1 inhibition in the context of sepsis-induced ALI. We confirmed that PARP1 is excessively activated in septic conditions, leading to NAD+ depletion and subsequent cellular energy failure, a critical component of organ dysfunction. Treatment with a PARP1 inhibitor effectively mitigated this vicious cycle. Our data revealed that PARP1 inhibition led to a broad anti-inflammatory effect, evidenced by a significant downregulation of key inflammatory mediators such as iNOS, COX2, and TNF-α. Functionally, this resulted in the preservation of lung architectural integrity, reduced oxidative stress, and decreased inflammatory cell infiltration. Furthermore, PARP1 inhibition was shown to promote cellular proliferation and reduce apoptosis, complementing the pro-regenerative effects of miR-135a-5p. In conclusion, this study provides a strong mechanistic and preclinical foundation for a novel therapeutic paradigm in the management of sepsis-induced ALI. By combining PARP1 inhibition with miR-135a-5p-mediated modulation of the TXNIP/NLRP3 and SMAD5/NANOG axes, we have developed a comprehensive strategy that not only mitigates overwhelming inflammation but also harnesses the lung's own regenerative potential. This work paves the way for a more effective and holistic approach to treating this devastating condition and holds significant promise for translation into future clinical applications.