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# Clinical transcriptomics-guided development of mRNA-LNP for immunotherapy in sepsis-induced ARDS

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Sepsis remains a leading cause of mortality in intensive care units and frequently progresses to sepsis-induced acute respiratory distress syndrome (ARDS), which carries mortality rates of up to 50%. Current treatments are largely supportive, and no therapies exist to directly restore immune homeostasis. Through clinical transcriptomic profiling of peripheral blood mononuclear cells from patients with sepsis and sepsis-induced ARDS, we identified a novel immune regulator associated with poor prognosis and enriched in megakaryocytes and CD14 monocytes. Mechanistic studies revealed that this regulator modulates megakaryocyte activation and monocyte inflammatory responses, while cell–cell communication analysis indicated that highly expressing megakaryocytes drive monocyte infiltration into the lung. Silencing of this regulator altered cytokine secretion and immune trafficking, thereby contributing to parenchymal injury. To translate these findings into therapy, we developed an inflammatory monocyte–targeted mRNA lipid nanoparticle (LNP) that serves as an immunotherapeutic platform to enhance regulator expression. In murine models of sepsis, systemic delivery of the mRNA-LNP reduced immune infiltration, reduced inflammation, and attenuated lung injury. Collectively, our data establish a clinical transcriptomics–driven framework for developing mRNA-LNP immunotherapies in sepsis and sepsis-induced ARDS.