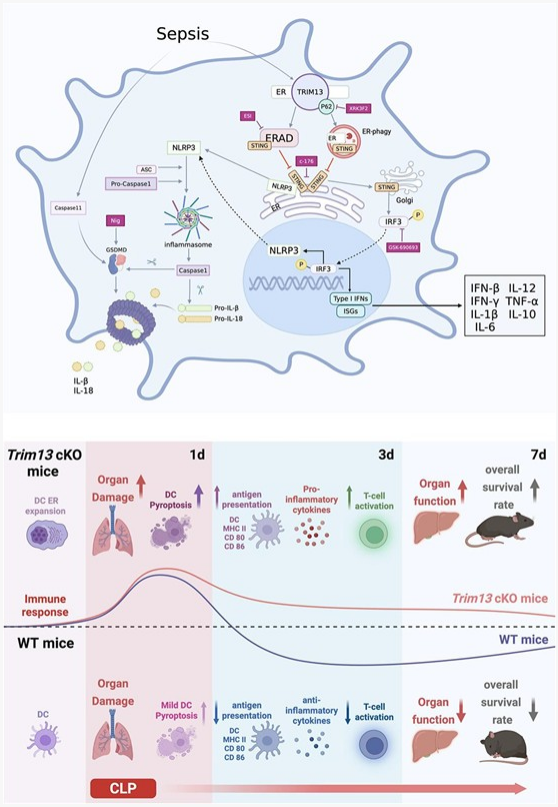
How disabling a single immune regulator helps the body recover from sepsis

GA, UNITED STATES, March 16, 2026 /EINPresswire.com/ -- Sepsis remains a major challenge in modern medicine, claiming millions of lives each year. For decades, clinical management has largely focused on suppressing excessive inflammation. Yet many patients die not from hyperinflammation, but from a prolonged phase of immune paralysis. During this later stage, the immune system fails to control secondary infections, driving progressive organ failure.



Restricting TRIM13 sustains dendritic cell immunity through STING signaling during sepsis.

Dendritic cells (DCs) are increasingly recognized as important contributors to sepsis-associated immune dysfunction. As professional antigen-presenting cells, they bridge innate sensing and durable adaptive immunity, shape effector responses, and determine whether the immune system remains vigilant or falls silent. In sepsis, however, DCs frequently lose their capacity and adopt an immunosuppressive phenotype. Why this shift occurs and whether it can be reversed have remained unclear.

A study published in Burns & Trauma offers a new perspective. Researchers from the Chinese PLA General Hospital report that TRIM13, an endoplasmic reticulum (ER)-resident E3 ligase, functions as a key “brake” on DC activity during sepsis. Importantly, releasing this brake reshapes immune dynamics and improves overall survival in a mouse model.

Tripartite motif 13 (TRIM13) has been implicated in ER quality control. In the study, TRIM13 expression rose rapidly in DCs under septic stress and coordinated two major ER protein clearance systems: ER-associated degradation (ERAD) and ER-selective autophagy (ER-phagy). Through these mechanisms, TRIM13 promoted the ubiquitination and degradation of stimulator of interferon genes (STING), thereby dampening STING signaling and subsequent impaired DC maturation and immune activation.

This observation raised a key question: if TRIM13 suppresses DC activation by driving STING degradation, what happens when TRIM13 is removed from DCs? To test this, the researchers generated DC-specific Trim13 conditional knockout (Trim13 cKO) mice and induced polymicrobial sepsis using the cecal ligation and puncture (CLP) model. The outcome proved time-dependent.

In early sepsis, TRIM13-deficient DCs displayed heightened STING activation. This amplified inflammatory signaling and triggered a transient increase in pyroptosis, modestly worsening early tissue injury. However, the longer-term outcome told a very different story. During the late phase of sepsis, when wild-type (WT) DCs developed an immunosuppressive phenotype, TRIM13-deficient DCs maintained high expression of costimulatory molecules and continued to produce proinflammatory cytokines. Peripheral lymphocyte counts recovered more rapidly, with concomitant improvements in lung, liver, intestinal, and renal function. Most importantly, although early mortality was increased, overall survival was significantly improved in the Trim13 cKO group.

Mechanistically, DC TRIM13 primarily limited STING accumulation via the SEL1L-HRD1 ERAD complex, which promotes STING ubiquitination and proteasomal degradation. When ERAD was compromised, TRIM13 engaged ER-phagy as a compensatory pathway to eliminate ER STING. Silencing TRIM13 in DCs therefore interrupted both quality control processes. As a result, STING persisted within the ER and translocated to the Golgi apparatus, where it activated IRF3 and enhanced type I interferon production. Sustained STING signaling also upregulated NLRP3 expression, promoting inflammasome assembly and pyroptosis. Notably, pharmacological inhibition of STING reversed these changes, supporting sustained STING signaling as the major driver of immune enhancement in TRIM13-deficient DCs.

“Despite tremendous efforts at hyperinflammation control, the consistent failure of anti-inflammatory therapies in clinical trials highlights the importance of restoring immune competence during immunosuppression.” the authors note. “TRIM13 as a negative regulator of persistent DC activation, which dampens the host inflammatory response during sepsis.” By preventing this transition, immune responses can be sustained long enough to support tissue repair and recovery. This work highlights the importance of precise immune modulation, rather than indiscriminate hyperinflammation-targeted therapies, as a strategy for improving sepsis outcomes.

While the current study focuses on polymicrobial sepsis, the implications may extend to other conditions characterized by immune exhaustion, including chronic infections and cancer. Targeting TRIM13 or its associated ER quality control machinery offers a potential strategy for reprogramming immune competence.

References
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