CHRD 2024: Abstract Submission Form

Presenter Name
Chelsea Lukawy

Presenter Status
Masters Student

Role in the project
Design
Perform Experiments
Analyze Data
Write Abstract

Research Category
Basic Science

Title
Sex-Dependent Immune Modulation: The Impact of Sema3E Deficiency on Macrophages

Background
Sepsis remains a leading cause of mortality worldwide, particularly in pediatric and immunocompromised populations. Characterized by dysregulated immune responses to infection, sepsis leads to widespread inflammation and organ dysfunction. Lipopolysaccharide (LPS), a component of Gram-negative bacterial cell walls, plays a central role in sepsis by activating Toll-like receptor 4 (TLR4) on immune cells, triggering pro-inflammatory cytokine production. Recent research implicates Sema3E and its receptor PlexinD1 in modulating immune responses, with Sema3E deficiency linked to heightened inflammation. However, the mechanism by which Sema3E influences macrophage function remains underexplored, particularly regarding TLR4 activation and sex-specific responses.

Objective
This study aims to investigate how Sema3E deletion impacts cytokine production in LPS-stimulated bone marrow-derived macrophages (BMDMs), focusing on sex differences and receptor dynamics.

Methods
Bone marrow cells were harvested from Sema3E knockout (KO) and wild-type (WT) mice, cultured with M-CSF to generate BMDMs. IL-10, TNF, and IL-1□ levels were measured by ELISA, and TLR4 and CD14 internalization dynamics were analyzed by flow cytometry. A subset of BMDMs were pretreated with Sema3E-Fc before LPS stimulation to assess cytokine regulation.

Results
Sema3E KO BMDMs displayed sex-specific cytokine patterns, with males producing higher IL-10 and females exhibiting elevated TNF. These trends persisted across mouse strains. WT BMDMs also showed distinct temporal cytokine patterns, with males sustaining higher TNF levels and females shifting towards higher IL-10 at later time points. In Sema3E KO BMDMs, TLR4 and CD14 dynamics were disrupted, shifting from an inverse to a positive correlation. Reintroducing Sema3E-Fc reversed cytokine profiles, reducing IL-10 in males and increasing it in females. Sema3E KO BMDMs secreted IL-1β post-LPS stimulation, suggesting NLRP3 inflammasome activation, which was also sex-dependent.

Conclusion
These findings underscore the role of Sema3E in cytokine regulation and highlight sex-specific inflammatory responses relevant to sepsis.

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