Microglial NLRP3-gasdermin D activation impairs blood-brain barrier integrity through interleukin-1β-independent neutrophil chemotaxis upon peripheral inflammation in mice

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Presenter: Hsin-Yu Wu **Date/time:** 2025/10/30, 16:20-17:10

Commentator: Dr. Chun-Hsien Chu **Location:** Room 601, med college building

Background: The blood-brain barrier (BBB) is a crucial structure maintaining brain homeostasis and protecting neural tissue. Recent studies suggest that peripheral inflammation impairs BBB integrity, leading to neuroinflammation and tissue damage. However, the molecular mechanisms by which peripheral inflammation disrupts the BBB and triggers neuroimmune responses remain unclear. This study focuses on the role of the NLRP3–GSDMD axis in this process. **Objective:** To build clinically translatable diagnostic and prognostic models for gastric cancer using large-scale targeted metabolomics data combined with machine learning approaches.

Results: Using a mouse model of repeated intraperitoneal LPS injections to induce peripheral inflammation, we found that repeated stimulation significantly increases proinflammatory cytokines (IL-1β, IL-6) in the brain, causing increased BBB permeability, which is highly dependent on NLRP3 inflammasome activation. NLRP3 activation triggers caspase-1-induced cleavage of GSDMD, forming pores that facilitate neutrophil infiltration across the BBB. Neutrophils secrete matrix metalloproteinases (MMPs) that degrade tight junction proteins, exacerbating BBB damage. Cell-type specific experiments confirm that the microglial NLRP3–GSDMD axis drives CXCL chemokine production and neutrophil brain infiltration.

Conclusion: This study uncovers the molecular pathway linking peripheral inflammation to BBB disruption via the NLRP3–GSDMD–CXCL/neutrophil–MMP axis, highlighting it as a potential therapeutic target for neuroinflammatory diseases and providing insights into how systemic inflammation impacts brain health.