cGAS–STING pathway

Neuroinflammation-induced injury is intimately associated with poor prognosis in patients with cerebral venous sinus thrombosis (CVST). The cyclic GMP-AMP synthase-stimulator of the interferon gene (cGAS–STING pathway) axis is a cytoplasmic double-stranded DNA (dsDNA) sensing pathway has recently emerged as a crucial mediator of neuroinflammation in ischemic stroke. However, the role of the cGAS-STING pathway in modulating post-Cerebral Venous Sinus Thrombosis inflammation and the underlying mechanisms involved remain unclear.

A CVST model was induced by ferric chloride in male C57BL/6J mice. The selective cGAS inhibitor RU.521, STING agonist 2'3'-cGAMP, and STING siRNA were delivered by intranasal administration or intraventricular injection. Post-CVST assessments included rotarod test, TUNEL staining, Fluoro-Jade C staining, dihydroethidium staining, western blotting, qPCR, immunofluorescence, immunohistochemistry, ELISA, and flow cytometry.

cGAS, STING, NLRP3, and GSDMD were significantly upregulated after CVST and mostly in the microglia of the mouse brain. CVST triggered the release of dsDNA into the cytoplasm and elicited an inflammatory response via activating the cGAS-STING axis. RU.521 decreased the levels of 2'3'-cGAMP, STING and downstream inflammatory cytokines, and suppressed the expressions of NLRP3 inflammasome and pyroptosis-pertinent components containing cleaved caspase-1, GSDMD, GSDMD-C, pro-and cleaved IL-1β, and cleaved IL-1β/pro-IL-1β. Besides, RU.521 treatment also reduced oxidative stress, lessened the numbers of microglia and neutrophils, and ameliorated neuronal apoptosis, and degeneration along with neurological deficits post-CVST. 2'3'-cGAMP delivery enhanced the expressions of STING and related inflammatory mediators, NLRP3 inflammasome, and pyroptosis-relevant proteins, whereas these alterations were significantly abrogated by the silencing of STING by siRNA.

The data demonstrate that repression of the cGAS-STING pathway diminishes the neuroinflammatory burden of CVST and highlight this approach as a potential therapeutic tactic in CVST-mediated pathologies [1)].

1)
Ding R, Li H, Liu Y, Ou W, Zhang X, Chai H, Huang X, Yang W, Wang Q. Activating cGAS-STING axis contributes to neuroinflammation in CVST mouse model and induces inflammasome activation and microglia pyroptosis. J Neuroinflammation. 2022 Jun 10;19(1):137. doi: 10.1186/s12974-022-02511-0. PMID: 35689216.