

Yoda1 Ameliorates Meningeal Lymphatic Dysfunction in Murine Models of Cisplatin-Induced Cognitive Impairment

Ethan Cho, BA¹, SangHoon Lee, PhD², Mi-Hyeon Jang, PhD²

¹Rutgers Robert Wood Johnson Medical School, Piscataway, NJ; ²Rutgers Robert Wood Johnson Medical School, Department of Neurosurgery, Piscataway, NJ

Introduction: Chemotherapy-induced cognitive impairment (CICI) is a persistent neurological complication that affects a substantial proportion of cancer survivors, significantly reducing their quality of life. Emerging evidence suggests that dysfunction of the meningeal lymphatic system (MLS), which regulates cerebrospinal fluid drainage and immune surveillance, contributes to impaired brain homeostasis after chemotherapy. However, the role of MLS in CICI remains largely unknown. Accordingly, this study investigates the contribution of MLS dysfunction driving CICI and evaluates strategies to restore lymphatic function. **Methods:** To determine whether MLS dysfunction contributes to CICI, we used Yoda1, a Piezo1 agonist that has been shown to enhance MLS. Mice received Yoda1 or vehicle in combination with cisplatin consisting of 5 treatment days followed by 5 days off, repeated for 3 cycles. One day after completion of treatment, mice underwent a battery of behavioral tests, including the elevated plus maze, the novel object recognition test, and the Morris water maze. Mice were then transcardially perfused with 4% PFA for immunohistochemical analysis of GFAP and IBA1 as markers of astrocyte and microglial activation, respectively. Confocal images were analyzed using Imaris software to quantify astrogliosis and microglial activation, established hallmarks of neuroinflammation. **Results:** We found that cisplatin treatment significantly increased anxiety-like behavior, impaired learning and memory, and exacerbated neuroinflammation. Notably, pretreatment with Yoda1 markedly attenuated these cisplatin-induced neuroinflammation and behavioral abnormalities, suggesting that enhancement of MLS function protects against CICI. **Discussion:** These findings suggest that restoring MLS function may represent a promising therapeutic strategy for preventing or mitigating CICI. **Acknowledgements:** Supported by NJ ACTS CREST Program funded by NIH R25TR004777.

