

Title of Research:

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Development of a novel test for the assessment of neuroinflammation useful to elucidate adverse outcome pathways in developmental neurotoxicity

Principal Investigator:

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Summary of Research:

The incidence of neurodevelopmental disorders such as autism, attention deficit hyperactivity disorder, and learning disabilities is increasing year by year and has become a major social problem. Although chemical exposure during development has been suggested to increase the risk of developing these neurodevelopmental disorders, the detailed mechanisms underlying developmental neurotoxicity (DNT) remain largely unclear. Various molecular initiating events (MIEs) are involved in the developmental neurotoxicity mechanisms of chemical substances, but different MIEs often exert toxicity through a common key event (KE). Developing a test method that can evaluate such a common KE is an effective strategy that will lead to the elucidation of the adverse outcome pathway (AOP) of chemical substances. Impaired differentiation of neural stem cells into neurons and astrocytes, and neuroinflammation mediated by microglia, which are resident immune cells of the brain parenchyma, are attracting attention as the KE common to the developmental neurotoxicity of chemical substances. In this study, we have developed a novel test method that can assess the DNT of chemicals on the morphology of microglia using a transgenic zebrafish line expressing mVenus, Cerulean, and mCherry in microglia, neurons, and astrocytes, respectively. Using the assay, we were able to detect the DNT of ethanol on the formation of microglia. We will apply this method to assess the DNT of other chemicals, such as valproic acid, ethinylestradiol, and chlorpyrifos. We will also analyze the correlation among the morphological change of microglia, neuroinflammation, and neurodifferentiation.

Timeline:

March 2020 ~ February 2023

Topics:

JCIA LRI Annual Workshop (2022)

Publications:

1. Komada M, Nishimura Y: **Epigenetics and Neuroinflammation Associated With Neurodevelopmental Disorders: A Microglial Perspective**. *Front Cell Dev Biol* 2022, **10**:852752.
2. Nishimura Y, Kurosawa K: **Analysis of Gene-Environment Interactions Related to Developmental Disorders**. *Frontiers in pharmacology* 2022, **13**:863664.