

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. The purpose of this study is to develop a novel test method that can assess the DNT of chemicals focusing on neuroinflammation through microglia and the differentiation of neural stem cells into neurons and astrocytes. In 2021, we were able to generate a transgenic zebrafish line selectively expressing fluorescent proteins mVenus, Cerulean, and mCherry in microglia, neurons, and astrocytes. In 2021, we will try to establish a method to assess the DNT of chemicals on the microglial dynamics and the differentiation of neurons and astrocytes, which can be useful to elucidate the adverse outcome pathways related to neuroinflammation.

Timeline:

March 2020 ~

Topics:

JCIA LRI Annual Workshop (2021)

Publications: [1-4]

1. Nishimura Y, Kanda Y, Sone H, Aoyama H: **Oxidative Stress as a Common Key Event in Developmental Neurotoxicity.** *Oxidative Medicine and Cellular Longevity* 2021, **2021**:6685204.
2. Higuchi A, Wakai E, Tada T, Koiwa J, Adachi Y, Shiromizu T, Goto H, Tanaka T, Nishimura Y: **Generation of a Transgenic Zebrafish Line for In Vivo Assessment of Hepatic Apoptosis.** *Pharmaceuticals* 2021, **14**(11):1117.
3. Adachi Y, Higuchi A, Wakai E, Shiromizu T, Koiwa J, Nishimura Y: **Involvement of homeobox transcription factor Mohawk in palatogenesis.** *Congenital Anomalies* 2022, **62**(1):27-37.
4. Nishimura Y, Kurosawa K: **Analysis of gene-environment interactions related to developmental disorders.** *Front Pharmacol* 2022, in press.