Title of Research:

20-3-08

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 the developmental neurotoxicity 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 macrophages resident in the central nervous system, 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 developmental neurotoxicity of chemicals focusing on neuroinflammation through microglia and the differentiation of neural stem cells into neurons and astrocytes. In 2020, we were able to produce a one-color zebrafish that selectively expressed a fluorescent protein mVenus in macrophages/microglia. We also produced two-color zebrafish that expressed fluorescent proteins Cerulean and mCherry in neurons and astrocytes, respectively. In addition, we decided the optimal concentrations of valproic acid, chlorpyriphos, ethinylestradiol, and ethanol, which are positive chemical substances that induce neuroinflammation, to assess the developmental neurotoxicity related to the neuroinflammation in zebrafish. In 2021, we will try to produce a three-color zebrafish that expresses mVenus, Cerulean, and mCherry in macrophages/microglia, neuron, and astrocytes, respectively.

Timeline:

March 1, 2020 - February 28, 2021

Topics:

Oral presentation at JCIA LRI Annual Workshop 2020 “Development of a novel test for the assessment of neuroinflammation useful to elucidate adverse outcome pathways in developmental neurotoxicity” (On-line, August 21st, 2020)

Publications:

Wakai E, Suzumura Y, Ikemura K, Mizuno T, Watanabe M, Takeuchi K, Nishimura Y: An Integrated In Silico and In Vivo Approach to Identify Protective Effects of Palonosetron in Cisplatin-Induced Nephrotoxicity. *Pharmaceuticals* 2020, 13(12):480.