NEUROTOXIC MECHANISM OF PFAS AND ITS ASSOCIATED RISKS OF NEURODEGENERATIVE DISEASES

Shichen Wu

Per- and polyfluoroalkyl substances (PFASs) are highly fluorinated compounds noted for environmental persistence and bioaccumulation. Legacy PFAS such as perfluorooctanoic acid (PFOA) can accumulate in the brain, raising concerns about long-term neurotoxic implications. Emerging alternatives such as Hexafluoropropylene Oxide Dimer Acid (HFPO-DA, commercially named as GenX) were introduced due to its reduced persistence, yet evidence suggests they can accumulate at comparable levels and may confer similar risks. The developing central nervous system (CNS) is particularly sensitive to toxicant exposure, and accumulation of PFAS in the CNS has been associated with clinical and biological markers of neurodegenerative diseases (NDs), including Parkinson's Disease (PD) and Alzheimer's disease (AD). Their neurotoxic mechanism conferring elevated ND risk, however, remains poorly understood.

The goal of my thesis is to elucidate the neurotoxic mechanisms of PFOA and its replacement GenX in promoting neurodegenerative disease risk later in life, using human cell culture models. I first evaluated the effects of pre-differentiation GenX exposure in dopaminergic (DA)-like neurons, namely SH-SY5Y cells. I observed that GenX exposure induced persistent nuclear and chromatin alterations, as well as neuronal changes closely related to PD, suggesting its role as a neurotoxicant. To better model CNS development, I investigated the effects of both GenX and PFOA in human induced pluripotent stem cell (hiPSC)-derived cortical neurons. GenX exposure during the neural progenitor cell (NPC) stage decreased chromatin condensation parameter (CCP), enriched differentially expressed genes (DEGs) in AD-related pathways, and induced alterations in AD-related biomarkers specifically manifested with altered Aβ40/Aβ42 ratio, suggesting that developmental GenX exposure may increase ND risk. Developmental exposure of PFOA also induced ND-like neurotoxic features. Neuronal network analysis revealed neurite degeneration – effects not observed with GenX. AD biomarker analysis further confirmed increased phosphorylated tau, lipid droplet accumulation and impaired protein synthesis, indicating AD-like deficits, while no change in Aβ40/Aβ42 ratio was observed. Transcriptomic

analysis using RNA sequencing highlighted ND-related pathways, with tauopathy as a potential mechanism.

Together, these results demonstrate that both legacy and alternative PFASs are neurotoxic but potentially through distinct mechanisms. GenX preferentially disrupts chromatin states and Aβ processing, whereas PFOA induces AD-like phenotypes potentially via tauopathy. This work provides mechanistic insights into PFAS-induced neurotoxicity and underscores the risks posed by both legacy and alternative PFASs.