A Proposed Mechanistic Link Between PFAS Contamination and Cancer: An Integrated Molecular Dynamics and NMR Study

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PFOA (Perfluorooctanoic acid), a type of PFAS (per- and polyfluoroalkyl substances), is a chemical used in the manufacturing of many products. PFOA is classified as an IARC Group 1 carcinogen (same ranking as asbestos and tobacco smoke) and is a ubiquitous environmental contaminant. Yet the mechanism through which PFOA causes cancer is unknown. This study investigates whether PFOA directly binds and inhibits human thymidylate synthase (hTS), the enzyme solely responsible for thymidylate synthesis and an established anticancer drug target. Binding was characterized using Differential Scanning Fluorimetry (DSF), MicroScale Thermophoresis (MST), and ^{1}H-^{15}N HSQC NMR spectroscopy. The inhibitory mechanism was investigated using all-atom explicit-solvent molecular dynamics (MD) simulations across four systems (apo, PFOA-bound, PFOA replica, and ternary PFOA+dUMP). DSF and MST data confirmed PFOA's destabilizing effects and affinity for hTS. NMR profiles for PFOA and dUMP (hTS' substrate) were completely uncorrelated, indicating different mechanisms of action. Although the NMR profile for PFOA was weak, the data still support global conformational change. MD simulations revealed that PFOA occupies a site near the active site, and that PFOA's carboxylate head captures His256 and breaks the His256–Thr55 hydrogen bond, leading to the catalytic Cys195–Asp218 distance increasing by +1.47 Å, and reducing the approximate active-site competence from 76% (apo) to ~33% (PFOA system). These results propose that PFOA allosterically disrupts hTS' catalytic geometry, providing the first plausible atomic-resolution mechanism linking PFOA exposure to cancer.

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