PFOS Impairs Glycogen-Lipid Partitioning and Lipophagy via PPP1R3G Suppression in MASH-like Liver Organoids

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Abstract:

Perfluorooctane sulfonic acid (PFOS), a persistent environmental pollutant that accumulates in the liver, may function as a "hidden" risk factor for metabolic dysfunction-associated steatohepatitis (MASH). Although classical metabolic stressors such as high-fat diet (HFD), excessive sugar intake, and obesity are well characterized, the contribution of PFOS under lipid-overload conditions remains unclear. Here, we combined in vivo, in vitro, and in silico approaches to investigate the effects and molecular mechanisms of PFOS on metabolic homeostasis under lipid-overload conditions. PFOS exacerbated hepatic metabolic dysfunction, aggravating glucose-lipid dysregulation in HFD-fed mice and enhanced steatosis in human MASH-like liver organoids. By integrating human MASH liver transcriptomics with machine learning, experimental functional validation, and molecular docking and dynamics simulations, we identified Protein Phosphatase 1 Regulatory Subunit 3G (PPP1R3G) as a PFOS-responsive metabolic hub. Mechanistically, PFOS-mediated suppression of PPP1R3G impaired glycogen synthesis, redirecting glucose flux toward lipid accumulation. Concurrently, PPP1R3G downregulation disrupted lipophagic flux, limiting lipid turnover and promoting lipid droplet deposition. Pharmacological activation of PPP1R3G by Galangin partially restored metabolic balance and lipophagic function under PFOS-exposed MASH-like conditions. These findings establish a mechanistic link between PFOS exposure and MASH progression and highlight PPP1R3G as a metabolically actionable target for mitigating environmentally driven metabolic liver injury.

Keywords:

Perfluorooctane sulfonic acid, protein phosphatase 1 regulatory subunit 3g, metabolic dysfunction-associated steatohepatitis, glucose-lipid metabolism.