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Comment on "Elucidating the molecular mechanisms of perfluorodecanoic acid and perfluorooctane sulfonic acid on glioblastoma through network toxicology and bioinformatics"

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To the Editor,

We read with great interest the recent study by Chen *et al*[1] titled "Elucidating the molecular mechanisms of perfluorodecanoic acid and perfluorooctane sulfonic acid on glioblastoma through network toxicology and bioinformatics". The authors successfully constructed a "PFASs–Targets–GBM" network and experimentally validated that perfluorodecanoic acid (PFDA) and perfluorooctane sulfonic acid (PFOS) exposure can enhance the proliferation and migration of glioblastoma (GBM) cells via the MMP2/MMP9 axis. We commend the authors for their innovative approach in bridging environmental toxicology with neuro-oncology, highlighting a potential, yet overlooked, environmental risk factor for GBM progression. However, to translate these in vitro findings into a valid clinical or epidemiological warning, two pivotal pharmacokinetic factors warrant further discussion.

Physiological relevance of exposure dosages

A critical challenge in toxicological studies is the "dose-response" discrepancy between laboratory models and environmental reality. The study demonstrated the oncogenic effects of PFDA/PFOS at specific experimental concentrations[1]. However, human environmental exposure is typically chronic and low-dose. The serum concentrations of PFASs in the general population are often in the nanomolar (nM) range, whereas in vitro assays often employ micromolar (μM) concentrations to elicit observable phenotypes. It is crucial to clarify whether the concentrations used in the validation experiments align with clinically relevant cumulative levels found in human brain tissue. If the oncogenic phenotype is only observable at supraphysiological doses, the actual risk to GBM patients from standard environmental exposure might be overestimated. We suggest that future validation should involve chronic low-dose exposure assays, which better mimic real-world scenarios.

The blood–brain barrier permeability factor

Unlike peripheral tumors, GBM resides behind the blood–brain barrier (BBB). For systemic pollutants like PFDA/PFOS to directly modulate MMP2/MMP9 expression in glioblastoma cells, they must effectively cross the neurovascular unit. While some perfluoroalkyl substances have been detected in brain tissue, their transport efficiency varies significantly by chain length and functional group. The current study's mechanism relies on direct interaction between the chemicals and GBM cells[1]. Without accounting for BBB permeability, the "network" links may remain theoretical. We recommend that future studies incorporate BBB in vitro models (e.g. transwell co-culture with endothelial cells) to verify that PFDA/PFOS can indeed reach the tumor site in sufficient quantities to trigger the observed molecular changes.

Conclusion

In summary, Chen *et al*[1] provide a pioneering framework linking PFASs to GBM. Addressing the issues of dosage relevance and BBB penetration would significantly strengthen the causal link proposed in this study and guide future epidemiological investigations.

Ethical approval

Not applicable.

Consent

Not applicable.

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