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Exposome, Ultrafine Particles, and Glioblastoma: A New Perspective

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Abstract Glioblastomas (GBM) are the most common primary brain tumors in adults, but their causes remain largely unknown. Environmental exposures are suspected to play a role; however, the data is limited due to analytical challenges and the difficulty of obtaining brain samples for cohort studies. This study investigates the chemical exposome in GBM, with a focus on an underexplored source: Ultrafine particles (UFPs), the smallest component of air particulate matter. UFPs are known to penetrate the brain and transport hazardous substances, and previous epidemiological studies suggest a potential link between ambient air UFPs and disease incidence. This study leveraged the Bellvitge Glioma Cohort (BGC) from HUB-IDIBELL, a unique retrospective cohort of 400 patients with high-quality histopathology brain tumor samples collected from 2005 to present. Additionally, non-tumor brain samples from autopsies were analyzed. In this proof-of-concept study, 33 GBM samples and 20 non-tumoral brain samples were examined using a comprehensive HRMS-based wide-scope target and nontarget analysis. We also analyzed 20 UFP samples from the metropolitan area of Barcelona, where cohort patients lived. A total of 49 exogenous chemicals, including various industrial compounds, were identified. While chemical profiles in GBM differed significantly from those in healthy brain tissue, no direct link to disease onset could be established. However, the results underscore the need for thorough assessments of potential chemical contributions to GBM. Notably, several air pollutants linked to road traffic, such as tire additives, were detected, supporting the hypothesis that hazardous chemicals may access the brain via the olfactory pathway. Our UFP analysis from the Barcelona area revealed over 20,000 features, including chemicals previously identified in the brain (e.g., tire additives), further substantiating this hypothesis.
Keywords: Exposure, brain cancer, air pollution, HRMS

1. Introduction

Glioblastomas (GBM) are the most common primary brain tumours in adults whose causes are yet to be established. Although environmental exposures are suspected, available data is limited, mainly due to analytical constraints and the challenges associated with obtaining brain samples for cohort studies. In this regard, the association between chemical exposure and GBM remains an uncharted frontier. This study seeks to investigate the chemical exposome in GBM and explore a potentially underexplored source of exposure: Ultrafine particles (UFPs), the smallest component of air particulate matter. This idea is substantiated by the ability of UFPs to penetrate the brain and transport hazardous substances. Furthermore, previous epidemiological research has hinted at a plausible correlation between UFPs in ambient air and disease incidence Weichenthal et al., 2020; Wu et al., 2021).

2. Methods

A unique retrospective cohort of 500 patients, including brain tumour sample with high-quality histopathology data (Bellvitge Glioma Cohort, BGC HUB-IDIBELL; 2005-present), as well as non-tumour brain tissue samples from autopsies. In this proof-of-concept study, a total of 33 glioblastoma samples (16 methylated and 17 non-methylated tumours) along with 20 non-tumoural samples were examined combining HRMS-based wide-scope target and suspect strategies (Gil-Solsona et al., 2021; Gutierrez-Martín et al., 2023). Additionally, metabolomics workflows were employed to identify variations in endogenous chemical profiles among the different glioma subtypes studied.

3. Preliminary results

In this proof-of-concept study, we provide the first evidence of a wide array of exogenous chemicals present in human brain tissue, offering new insights into the potential role of environmental exposures in glioblastoma (GBM). Using high-resolution mass spectrometry (HRMS) for comprehensive wide-scope target and nontarget screening, we analyzed 33 GBM samples from the Bellvitge Glioma Cohort (BGC), a unique retrospective cohort based at HUB-IDIBELL, along with 20 non-tumoral brain samples obtained from autopsies. Across all samples, we identified 49 distinct exogenous chemicals, including a diverse set of industrial compounds. While chemical profiles in GBM tissue often diverged significantly from those found in non-tumor brain, these

differences do not currently establish a direct causal link to tumor onset. However, the presence of numerous potentially hazardous compounds, particularly those associated with road traffic and industrial processes, highlights the need for in-depth investigation into their possible contribution to brain tumor pathogenesis. Among the most notable findings was the detection of tire additives and other air pollutants, which supports the hypothesis that toxicants may access the brain via the olfactory pathway. To further explore this potential route of exposure, we conducted an extensive chemical analysis of 24 ultrafine particle (UFP) samples collected in the metropolitan area of Barcelona, where the majority of BGC patients lived. The analysis revealed over 20,000 chemical features in UFPs, many of which remain unidentified but include several already detected in brain tissue, such as tire-related compounds. This strengthens the plausibility of airborne UFPs as a delivery mechanism for neurotoxic chemicals. Collectively, these findings represent a novel contribution to environmental oncology, offering an unprecedented characterization of both the brain chemical exposome and the contaminant profile of ambient UFPs. Furthermore, they lay the groundwork for future studies assessing how air pollution and particle-bound chemical mixtures may influence GBM development and progression through direct exposure to the central nervous system.

4. Conclusions

This study reveals the presence of exogenous chemicals, including traffic-related pollutants, in GBM and healthy brain tissue. While differences in chemical profiles were observed, no direct link to tumorigenesis was established. The detection of similar compounds in urban UFPs suggests potential airborne exposure routes. These findings highlight the need for further research on environmental contributors to brain cancer, particularly regarding air pollution's role in chemical transport to the brain.

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