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Glioblastoma and dementia may share a common cause

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SUMMARY

The cause of most glioblastomas is unknown. One cause might lie in the surrounding brain tissue. The interactions between glioblastoma cells and their micro- and macro-environment could create a context that promotes or suppresses tumor growth and protects or exposes the malignant cells to immune attack. Alzheimer's disease has been identified as a protein misfolding disorder (proteopathy), caused by accumulation of abnormally folded A-beta and tau proteins in the brain. These or other changed proteins or as yet unrecognized biochemical brain changes of dementia might promote glioblastoma development. Published data indicate that there is an association between Alzheimer's disease prevalence and malignant brain tumor incidence in 19 US states. Hypothetically, Alzheimer's and glioblastoma may share an as yet unknown peripheral tissue pathway that can promote the progression of both diseases. If this pathway can be identified, new treatments for both conditions may follow.

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Introduction

Gliomas account for more than 70% of all brain tumors. The most frequent (65%) and most malignant histological type is the glioblastoma. Several occupations, environmental carcinogens, and diet (N-nitroso compounds) might be associated with an elevated risk, but the only environmental factor unequivocally associated with an increased risk of brain tumors, including gliomas, is therapeutic X-irradiation. In particular, children treated with X-irradiation for acute lymphoblastic leukemia show a significantly elevated risk of developing gliomas [1]. Recently cytomegalovirus infection has been associated with glioblastoma [2].

Another cause of glioblastoma might lie in the surrounding brain tissue. The interactions between glioblastoma cells and the micro- and macro-environment that surrounds them could create a context that promotes or suppresses tumor growth and protects or exposes the malignant cells to immune attack. Indeed, there is a functional association of cancer cells with their surrounding tissues [3]. Autopsies repeatedly find that most people who die of causes other than cancer have at least some tiny tumors that had gone unnoticed.

Alzheimer's disease has been identified as a protein misfolding disorder (proteopathy), caused by accumulation of abnormally folded A-beta and tau proteins in the brain [4]. Some observations suggest that these or other changed proteins or yet unrecognized biochemical brain changes of dementia might promote glioblastoma development. For example, patients with the most malignant tumors have the worst pre-treatment cognitive function [5].

One study found approximately the same incidence of Alzheimer pathology (senile plaque and neurofibrillary tangles) in brains with or without glioblastoma (42% versus 48%) [6]. Yet senile plaque and neurofibrillary tangle pathology do not consistently differentiate individuals with and without dementia. Some people who are lucid until the end of a very long life have brains that appear riddled with Alzheimer's disease [7]. And in the oldest old, the presence of the APOE epsilon2 allele (APOE2) is associated with a reduced risk of dementia, but paradoxically is associated with increased Alzheimer disease neuropathology [8].

High density lipoprotein is also involved in both glioblastoma and dementia via cholesterol esterase transfer protein (CETP). CETP is a plasma protein that facilitates the transport of cholesteryl esters and triglycerides between the lipoproteins, and modifies levels of high density lipoprotein (HDL). Synthetic and natural human HDL inhibits glioblastoma cell growth in a nontoxic, dose-dependent manner [9]. And there is an association of a functional polymorphism in the CETP gene with memory decline and incidence of dementia [10].

Observations

Data are from the following sources:

Reports of malignant brain tumor incidence 2000–2004 from 19 US states (data from Table 9 of Ref. [11]).

Report of US 2000 Alzheimer's disease prevalence by state from [12].

Linear regression analysis with malignant brain tumors as the dependent variable, Alzheimer's disease prevalence as the independent variable, showed a significant correlation between Alzheimer's disease and malignant brain tumors ($r = 0.934$, $p < 0.001$,

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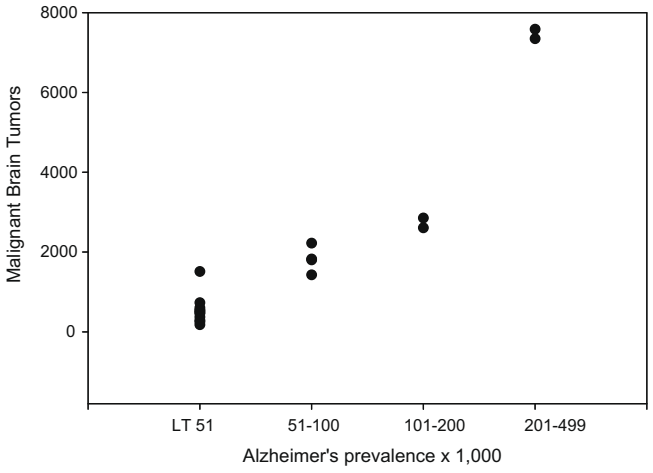

Fig. 1. US 2000 Alzheimer's disease prevalence by state versus reports of malignant brain tumor incidence 2000–2004 from 19 US states. There is a significant correlation ($r = 0.934$, $p < 0.001$). (LT, Less Than).

Fig. 1). Analysis of variance with malignant brain tumor as the dependent variable revealed a significant correlation with Alzheimer's disease prevalence ($p = 0.039$) that was independent of the effects of population ($p < 0.001$) and mean age of the state population ($p = 0.603$).

Hypothesis

There is already interest in treating cancer by inhibiting developmental pathways in surrounding tissues. For example, an experimental Genentech drug inhibiting the hedgehog pathway, which is critical for embryonic and postnatal organ and tissue development, is being used to treat glioblastoma, as well as other cancers [13,14]. However, the hedgehog pathway probably does not play a significant role in Alzheimer's disease. Hypothetically, Alzheimer's and glioblastoma may share an as yet unknown peripheral tissue pathway that can promote the progression of both diseases. If this pathway can be identified, inhibiting it might be a new treatment for both conditions. One pathway might relate to inflammation, since inflammation may play a role in Alzheimer's disease, as well as in many forms of cancer.

Conflicts of interest statement

None declared.

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