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Review

# Interaction of brain fatty acid-binding protein with the polyunsaturated fatty acid environment as a potential determinant of poor prognosis in malignant glioma

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ABSTRACT

Malignant gliomas are the most common adult brain cancers. In spite of aggressive treatment, recurrence occurs in the great majority of patients and is invariably fatal. Polyunsaturated fatty acids are abundant in brain, particularly ω-6 arachidonic acid (AA) and ω-3 docosahexaenoic acid (DHA). Although the levels of ω-6 and ω-3 polyunsaturated fatty acids are tightly regulated in brain, the ω-6:ω-3 ratio is dramatically increased in malignant glioma, suggesting deregulation of fundamental lipid homeostasis in brain tumor tissue. The migratory properties of malignant glioma cells can be modified by altering the ratio of AA:DHA in growth medium, with increased migration observed in AA-rich medium. This fatty acid-dependent effect on cell migration is dependent on expression of the brain fatty acid binding protein (FABP7) previously shown to bind DHA and AA. Increased levels of enzymes involved in eicosanoid production in FABP7-positive malignant glioma cells suggest that FABP7 is an important modulator of AA metabolism. We provide evidence that increased production of eicosanoids in FABP7-positive malignant glioma growing in an AA-rich environment contributes to tumor infiltration in the brain. We discuss pathways and molecules that may underlie FABP7/AA-mediated promotion of cell migration and FABP7/DHA-mediated inhibition of cell migration in malignant glioma.

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**Contents**



*Abbreviations:* AA, arachidonic acid; ALA, α-linolenic acid; AP, Activator Protein; COX, cyclooxygenases; CYP, cytochrome P450; DHA, docosahexaenoic acid; DGLA, dihomo-gammalinolenic acid; EPA, eicosapentaenoic acid; FABP7 (B-FABP), brain fatty acid binding protein; GFAP, glial fibrillary acidic protein; GLA, gamma-linolenic acid; LA, cis-linoleic acid; LDL, low density lipoprotein; LOX, lipoxygenase; MAPK, mitogen-activated protein kinase; NFI, Nuclear Factor I; PG, prostaglandin; $PLA_2$, phospholipase $A_2$; PPAR, peroxisome proliferator-activated receptor; PPRE, PPAR response element; PUFA, polyunsaturated fatty acid; VLDL, very low density lipoprotein.

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## 1. Introduction

Gliomas are tumors that arise from glial or glial progenitor cells in the central nervous system. These tumors most commonly occur in the brain. A subtype of glioma, called astrocytoma, is characterized by expression of glial fibrillary acidic protein (GFAP), normally found in astrocytes. Anaplastic astrocytoma (grade III astrocytoma) and glioblastoma multiforme (grade IV astrocytoma) are collectively called high-grade astrocytomas or malignant gliomas. Malignant gliomas are the most common cancers of the central nervous system, accounting for ~70% of malignant primary brain tumors [1]. The prognosis of patients with malignant glioma is dismal with median survival times of 3 years and 15 months for patients with anaplastic astrocytoma and glioblastoma multiforme, respectively [2]. Although patients with grade II astrocytomas have a better prognosis, >35% of these tumors recur as high grade astrocytomas, further compounding the challenges associated with the treatment of astrocytoma tumors [3]. Surgical resection and adjuvant radiotherapy followed by chemotherapeutic agents such as temozolomide or nitrosourea is the standard treatment for malignant gliomas. In spite of this aggressive treatment, almost all (>90%) malignant gliomas recur, most commonly within 3 cm from the margin of the original tumor, suggesting that recurrence is due to infiltrative rather than invasive properties of the tumor cells [4–5]. Survival time is very short once recurrence has been diagnosed, usually 3–6 months [4].

Treatment options for recurring malignant glioma are limited because of toxicity and detrimental effects on brain function. For example, radical resection often cannot be considered for the treatment of recurrent tumors because of the associated decline in brain function, as measured by Karnofsky Performance Status, and/or surgery-related morbidity and infection [4,6–7]. A combination of chemotherapy or stereotactic radiosurgery with repeated surgery was shown to improve survival of patients with recurrent glioblastoma compared to surgery alone, although none of the patients in this study survived beyond 44 weeks after treatment [8]. Furthermore, the use of radiotherapy is limited in recurrent tumors because of associated irreversible brain tissue damage and radiation-induced necrosis of normal brain [9]. The recommendation to wait at least 6 months before initiating a second round of radiation treatment further limits this treatment option [4]. Despite the above limitations, the standard treatment for recurrent malignant glioma is still a combination of radiotherapy and chemotherapy [10], highlighting the need of finding new therapeutic strategies that will limit or prevent tumor infiltration and recurrence.

There are reports indicating that lipid metabolism is deregulated in malignant glioma and that altered lipid metabolism is associated with a worse prognosis in these tumors [11–12]. Brain fatty acid-binding protein (B-FABP or FABP7), involved in the intracellular transport of polyunsaturated fatty acids (PUFA), is up-regulated in glioblastoma compared to normal brain tissue and low grade astrocytomas [13–14]. Furthermore, elevated levels of FABP7 in the nucleus are associated with a worse prognosis in glioblastoma [15–16]. We and others have shown that expression of FABP7 in malignant glioma cell lines increases cell motility and migration [13,17]. Importantly, altering the DHA:AA ratio in the culture medium affects cell migration in a FABP7-specific manner, with an increased DHA:AA ratio associated with reduced cell migration [18]. In this review, we discuss how alterations in the lipid environment together with FABP7 expression may affect malignant glioma tumor growth. We propose that a better understanding of the consequences of lipid alterations in malignant glioma may shed light on the mechanisms driving tumor recurrence thereby revealing new approaches for the treatment of malignant glioma.

## 2. Normal brain lipid composition

Lipids constitute ~2% of the total cell mass in most organs. However, in the brain, lipids are major structural components with fatty acids making up about 50% of the total mass of neural membranes [19–20]. Long chain PUFA such as docosahexaenoic acid (DHA, C22:6, ω-3) and arachidonic acid (AA, C20:4, ω-6) are abundant in brain, constituting close to 20% of the dry weight of the brain, including 6% for AA and 8% for DHA [20]. The fatty acid composition of the three major types of brain cells (neurons, oligodendrocytes and astrocytes) has been reported in rats [21]. In 60-day old rats fed a soya oil diet, ω-3 and ω-6 fatty acids constitute ~30%, ~20% and ~29% of the total neuron, oligodendrocyte, and astrocyte lipid content, respectively, including 8%, 5% and 12% for DHA and 10%, 9% and 10% for AA [21].

Although there is no consensus on how fatty acids are taken up by brain, there is evidence that the unesterified fatty acid (albumin-bound) pool in plasma is a major contributor to the fatty acid pool in brain, at least in the case of AA and DHA [22]. The importance of low-density lipoproteins (LDL) and very low density lipoproteins (VLDL) in brain PUFA uptake was assessed using mice deficient for the LDL receptor (LDLr) or VLDL receptor (VLDLr); however, no differences in PUFA levels were detected between knockout mice and the wild type controls, suggesting that LDL and VLDL do not play a major role in PUFA uptake in the brain [23–24]. Fatty acids have also been postulated to enter the brain by passive diffusion and protein-mediated transport by membrane-associated proteins, such as fatty acid transport proteins and fatty acid translocases (CD36) [22]. Inside the cell, long chain fatty acids are transported by a group of intracellular lipid binding proteins called fatty acid binding proteins (FABPs) which are expressed in most tissues [25–34] (Table 1).

It is well established that the essential fatty acids, cis-linoleic acid (LA, 18:2, ω-6) and α-linolenic acid (ALA, 18:3, ω-3), the precursors of AA and DHA, respectively, have to be obtained from the diet because our bodies cannot synthesize them [20,35]. In the liver, LA is converted to gamma-linolenic acid (GLA, 18:3, ω-6), dihomo-GLA (DGLA, 20:3, ω-6), and AA by different desaturases and elongases (Fig. 1) [35]. Similarly, ALA is converted to eicosa-

**Table 1**
Names of different fatty acid binding proteins (FABPs) and the tissues from which they were first isolated.

| Fatty acid binding protein | Tissue |
|---|---|
| L-FABP (FABP1) | Liver[26] |
| I-FABP (FABP2) | Intestine[25] |
| H-FABP (FABP3) | Heart[27] |
| A-FABP (FABP4) | Adipocyte[28] |
| E-FABP (FABP5) | Epidermis[29] |
| IL-FABP (FABP6) | Ileum[30] |
| B-FABP (FABP7) | Brain[31] |
| M-FABP (FABP8) | Myelin[32] |
| T-FABP (FABP9) | Testis[34] |
| FABP12 | Testis and retina[33] |

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