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Mini Review

The Role of Folate Metabolism-related Gene Polymorphisms in the Development of Meningiomas

STEFANOS S. DRAKOS, FOTEINI ANIFANTAKI, APOSTOLOS ZARROS and CHARIS LIAPI

Department of Pharmacology, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Abstract. *Meningiomas are (usually) slow-growing benign tumors, and several factors have been implicated in their development. Increasing age, previous exposure to ionizing radiation, endogenous hormone status and history, hormone replacement therapy, genetic variants and polymorphisms are the main factors that have been proven or assumed to be involved in meningioma formation. The complex genetic background supporting the pathogenesis of meningiomas includes a large number of mutations and polymorphisms that might be actively involved in tumor development, progression and recurrence. The aim of this mini-review is to summarize the current data concerning the role of folate metabolism-related gene polymorphisms in the development of meningiomas.*

Meningiomas are (usually) slow-growing benign tumors, deriving from arachnoidal (meningothelial) cells and represent the most common type of intracranial tumor (1, 2). Meningiomas more frequently occur in women (with a female:male ratio of 2:1) (3), and are classified by the World Health Organization (WHO) into three main grades: (a) I, benign, over 90% of meningiomas; (b) II, atypical, 4.7-7.2% of meningiomas; and (c) III, malignant/anaplastic, 1-2.8% of meningiomas (4, 5).

Factors that have been proven or are believed to contribute to the development of meningiomas are: (a) increasing age (1), (b) exposure to ionizing radiation (6-8), (c) endogenous hormone status and history (9-12), (d) hormone replacement therapy (9, 10, 13), (e) genetic variants and polymorphisms (14-17), as well as other potential factors (1). A synopsis of these factors is provided in Table I.

Folate (folic acid) is a micronutrient molecule that participates in DNA synthesis, methylation and repair mechanisms (Figure 1) (18). Folate deficiency leads to catastrophic DNA repair, DNA strand breakage and chromosomic damage (19). Folate metabolism-related enzyme-encoding genes display several single nucleotide polymorphisms (SNPs) and/or variable number tandem repeats, which may alter the activities of the encoded enzymes and contribute to the development of several malignancies (*e.g.* acute lymphoblastic leukemia, colon cancer, glioblastoma multiforme and pancreatic cancer) (20-23).

The aim of this mini-review is to summarize the current data concerning the role of folate metabolism-related gene polymorphisms in the development of meningioma.

Molecular Genetics in the Pathogenesis of Meningiomas

Abnormalities in the 22q locus have been identified as being relevant to the pathogenesis of meningiomas (in 40-70% of cases) (17). The majority of sporadic meningiomas that carry a loss on 22q are also characterized by the existence of mutations within the neurofibromatosis type 2 (*NF2*) gene, located on 22q12 (24). The *NF2* gene encodes a protein called swannomin or merlin that links the cytoskeleton to membrane proteins, regulating cell growth and motility (25). Cytogenetic differences in tumorigenesis of the various meningioma subtypes are suggested by the fact that *NF2* gene mutations are detected at different frequencies among these subtypes (24). However, *NF2* gene mutations are probably involved in tumorigenesis, but not in tumor progression, since their frequency in atypical and anaplastic meningioma is close to that noted in fibroblastic ones (26).

Mutations or deletions of the *NF2* gene constitute an early event in almost 50% of all sporadic meningioma cases (27, 28), while the fact that partial 22q loss with no involvement

Correspondence to: Charis Liapi, MD, Ph.D., Associate Professor, Department of Pharmacology, Medical School, National & Kapodistrian University of Athens, 75 Mikras Asias str, GR-11527, Athens, Greece. Tel: +30 2107462531, Fax: +30 2107462554, e-mail: cliapi@med.uoa.gr

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of the *NF2* locus, as well as no loss on 22q, are both frequently observed in meningioma (5), leads to the conclusion that *NF2* gene deactivation is an important – but not a critical – step in meningioma development. Hence, there must be other genes on chromosome 22 or elsewhere that are associated with meningioma development. All of these chromosome gains and losses, as well as candidate genes that are thought to be involved in the development and progression of this type of tumor, are summarized in Table II (2, 5, 25, 29, 30).

The Role of Folate Metabolism-related Gene Polymorphisms

At least 30 different enzymes are involved in folate metabolism (31). Polymorphisms affecting the genes encoding these enzymes lead to lower folate levels compared to those noted in the normal genotype. The most important polymorphisms affect the genes encoding enzymes crucial for folate metabolism: (a) methylenetetrahydrofolate reductase (*MTHFR*), (b) methionine synthase (*MTR*), (c) thymidylate synthase (*TS*), as well as (d) reduced folate carrier (*RFC*). The role of each of the above enzymes is summarized in Figure 1.

Polymorphisms of the MTHFR gene. MTHFR converts 5,10-methyltetrahydrofolate to 5-methyltetrahydrofolate (Figure 1) and polymorphisms of the gene encoding this enzyme, such as the C→T substitution at nucleotide 677 (*MTHFR* 677C→T) and the A→C substitution at nucleotide 1298 (*MTHFR* 1298A→C), lead to lower folate levels (32, 33). These *MTHFR* diplotypes have been recently associated with high risk for meningioma development (p=0.002) (34). The study of Bethke *et al*. (34) was conducted on 631 meningioma cases compared to 1,101 controls. In fact, the highest risk for meningioma development was associated with heterozygosity for both *MTHFR* variants (odds ratio: 2.11, 95% confidence interval: 1.42-3.12) (34). However, this is not in compliance with the findings of Kafadar *et al*. (35), who did not find any association between *MTHFR* 677C→T genotype and meningioma development. The study of Kafadar *et al*. (35) was, however, conducted on a total of 74 patients with histologically-verified primary brain tumors (both meningiomas and high-grade gliomas) compared to 98 tumor-free patients, which is a significantly smaller sample compared to that of Bethke *et al*. (34).

Polymorphisms of the MTR gene. MTR catalyzes the remethylation of homocysteine to methionine in order to maintain adequate intracellular folate levels (Figure 1). The A→G substitution at nucleotide 2756 (*MTR* 2756A→G) of the *MTR* gene, is relatively common and leads to a lower enzyme activity. The study of Semmler *et al*. (36) on 290 patients of Caucasian origin who underwent surgical resection for intracranial meningioma, recently revealed an association between the *MTR* 2756A→G variant and WHO grade III meningioma (p=0.001).

Table I. *Factors considered to contribute to the development of meningiomas*.

Contributing factor	References
Increasing age	1
Exposure to ionizing radiation	
Tinea capitis cohort studies	
Atomic bomb survivors	
Patients receiving diagnostic or therapeutic radiation	6-8
Endogenous hormone status and history	
Menopausal status	
Parity	
Pregnancy history	
Age at menarche	9-12
Hormone replacement therapy	9, 10, 13
Genetic variants and polymorphisms (For more details see text and Table II)	14-17
Other potential causes	1

Other folate metabolism-related gene polymorphisms. Homozygosity of the A→G substitution at nucleotide 66 of the *MTR* reductase gene (*MTRR* 66A→G) has been significantly associated with high risk of meningioma development (odds ratio: 1.41, 95% confidence interval: 1.02-1.94) (34). However, *TS* gene polymorphisms (*TS* 28 base-pair tandem repeats), although being associated with lower TS enzymatic activity (18, 37), have not yet been tested in a sufficient number of meningioma patients (32). On the other hand, the G→A substitution at nucleotide 80 of the *RFC* gene (*RFC* 80G→A) that is associated with higher affinity to folate leading to higher plasma folate levels (38), has not been associated with increased risk of meningioma development (36). Moreover, meningioma patients have been also reported to significantly more frequently carry the c.844_855ins86 variant of *cystathione-β-synthase* (*CBS*), implicated in methionine metabolism, which is related to folate metabolism (36).

Conclusion

The complex genetic background that supports the pathogenesis of meningioma might include a large number of mutations and polymorphisms that might be actively involved in tumor development, progression and recurrence.

Table II. *Synopsis of the genetic background proved or assumed to contribute to the development of meningiomas*.

Genetic abnormalities	Note(s)
A. Chromosomal gains and losses:	
Loss on 1p	The only independent predictor of recurrence in totally resected grade I meningiomas, observed in malignant meningiomas.
Gain on 1q	Found in sporadic meningiomas.
Loss on 6q	Found in sporadic and malignant meningiomas.
Loss on 9p	Anaplastic meningioma patients that bear 9p21 deletion have a shorter survival.
Gain on 9q	Found in sporadic meningiomas.
Loss on 10q	Associated with meningioma progression.
Gain on 12q	Found in sporadic meningiomas.
Loss on 14q	Associated with meningioma progression and recurrent meningiomas.
Gain on 15q	Found in sporadic meningiomas.
Gain on 17q23	Found in sporadic and malignant meningiomas.
Loss on 18q	Found in sporadic and malignant meningiomas.
Gain on 20q	Found in sporadic meningiomas.
Loss on 22q	Relevant to the pathogenesis of meningiomas, in 40-70% of all meningiomas.
Loss on 22q12	Frequently observed in meningiomas.
B. Specific gene abnormalities:	
Deactivation of *NF2*	Probably involved in tumorigenesis, but not in tumor progression; constitutes an early event in almost 50% of all sporadic meningiomas; an important (but not a critical) step in meningioma development.
ATM	Specific combinations of variants are associated with increased risk of meningioma development.
BCR	Down-regulated in high-grade meningiomas.
DAL1	May play an important role in meningioma tumorigenesis.
ERCC2	Variants are associated with increased risk of meningioma development.
GSTM3 *B/*B genotype	Associated with increased risk of meningioma development.
GSTT1 null genotype	Associated with increased risk of meningioma development.
junB	Down-regulated in high-grade meningiomas.
Ki-RAS	Variants are associated with increased risk of meningioma development.
Rad	Down-regulated in high-grade meningiomas.
Progesterone receptor expression	Loss of which is found in atypical meningiomas.
Activation of telomerase	Prominent feature of meningioma progression and present in all anaplastic meningioma cases.

Table III. *Folate metabolism-related gene polymorphisms and their relation to the development of meningioma*.

Polymorphism	Note(s)	References
MTHFR 677C→T	*MTHFR* diplotypes have been associated with high risk for meningioma development. Has not been associated with meningioma patients.	34 35
MTHFR 1298A→C	*MTHFR* diplotypes have been associated with high risk for meningioma development.	34
MTR 2756A→G	Explorative analyses have revealed an association with WHO grade III meningioma.	36
MTRR 66A→G	Homozygosity has been significantly associated with high risk of meningioma development.	34
TS 28bp tandem repeats	Has not been tested in a sufficient number of meningioma patients.	32
RFC 80G→A	Has not been associated with increased risk of meningioma development.	36
CBS c.844_855ins86 variant	Has been reported to be significantly over-represented in meningioma patients.	36

MTHFR: Methylenetetrahydrofolate reductase; *MTR*: methionine synthase; *MTRR*: methionine synthase reductase; *TS*: thymidylate synthase; *RFC*: reduced folate carrier; *CBS*: cystathione-β-synthase.

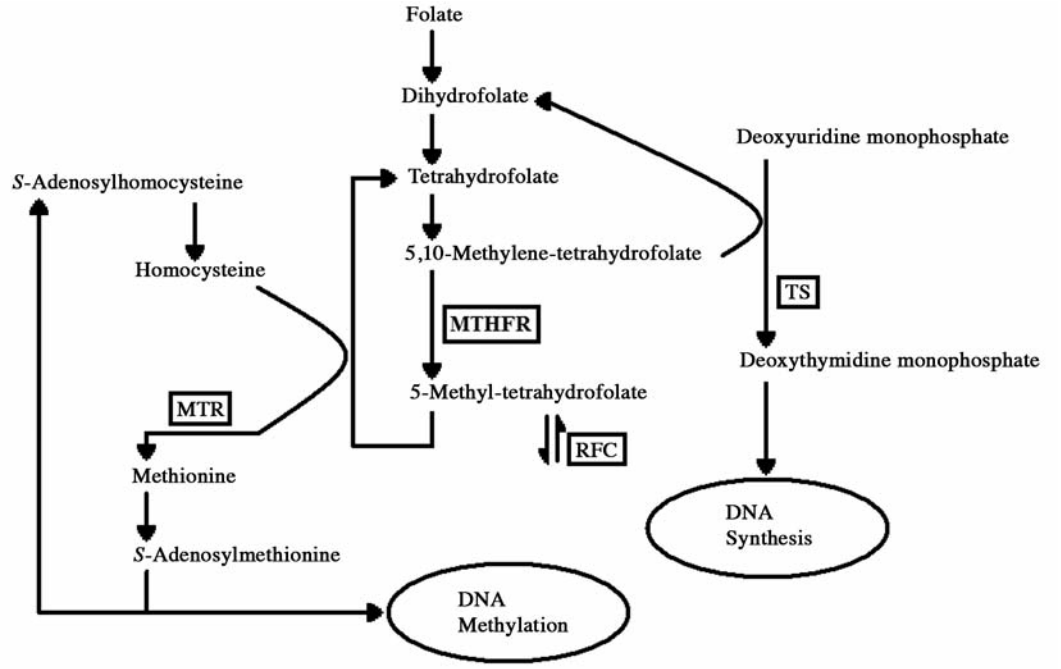

Figure 1. *Synopsis of the main folate metabolism pathways and their role in DNA methylation and synthesis. MTHFR: Methylenetetrahydrofolate reductase; MTR: methionine synthase; TS: thymidylate synthase; RFC: reduced folate carrier.*

The current data indicate that folate metabolism-related gene polymorphisms may play a significant role in meningioma development (Table III). The most significant polymorphisms to date seem to be *MTHFR* 677C→T and 1298A→C, associated with increased risk for meningioma development, and *MTR* 2756A→G variant, which seems to be associated with WHO grade III meningioma. Other folate metabolism-related polymorphisms have also been linked to meningiomas, and further studies should be conducted in order to: (a) establish these (recent) findings, (b) explore the mechanisms behind the involvement of folate metabolism in meningioma tumorigenesis, as well as (c) provide new data concerning the significance of these polymorphisms in a possible chemotherapeutic approach towards the treatment of meningiomas and/or the inhibition of their recurrence.

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