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Molecular alterations in meningiomas: Literature review

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ABSTRACT

Meningiomas, tumors that originate from meningothelial cells, account for approximately 30% of all new diagnoses of central nervous system neoplasms. According to the 2016 WHO classification of central nervous system tumors meningiomas are classified into three grades: I, II, and III.

Past studies have shown that the risk of meningiomas recurrence is strongly correlated with the molecular profile of the tumor. Extensive whole-exome or whole-genome sequencing has provided a large body of information about the mutational landscape of meningiomas. However, such a stratification of meningiomas based on mutational analysis alone has been proven not to satisfy the clinical need for distinction between patients who need (or do not need) an adjuvant treatment.

Combined analysis of exome, transcriptome, methylome and future approaches for epigenetic aspects in meningiomas may allow researchers to unveil a more comprehensive understanding of tumor progression mechanisms and, consequently, a more personalized clinical approach for patients with meningioma.

A better understanding of the genetics and clinical behavior of high-grade meningiomas is mandatory in order to better design future clinical trials. By studying the mechanisms underlying these new tumorigenesis pathways, we should be able to offer personalized chemotherapy to patients with surgery and radiation-refractory meningiomas in the near future. The purpose of this article is to accurately bring the compilation of this information, for a greater understanding of the subject.

1. Introduction

Meningiomas, tumors that originate from meningothelial cells, account for approximately 30% of all new diagnoses of central nervous system neoplasms [1]. According to the 2016 WHO classification of central nervous system tumors [2], meningiomas are classified into three grades: I, II, and III. The grade I meningiomas are typical or benign, stratified into nine histological subtypes including meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lympho-plasmacyte-rich, and metaplastic, and represent 88–94%, of all meningiomas [3]; atypical meningiomas are “intermediate grade” malignancies (grade II) that account for 4.7%–7.2% of meningiomas and that are associated with a 29%–52% post-resection recurrence rate [4]. Moreover, they exhibit a tendency for malignant progression with a significant increase in tumor cell migration and infiltration of surrounding tissues [5]. The anaplastic variant (grade III) is exceedingly rare, accounting for 1%–3% of all meningiomas [6]. The anaplastic histology observed in these tumors associates to poor prognosis with median overall survival of 1.5 years [7], with 5-year survival ranging from 47% to 61% [8–11].

Past studies have shown that the risk of meningiomas recurrence is strongly correlated with the molecular profile of the tumor [12]. Genomic instability is one of the key differentiators between grade I and grade II–III meningiomas [13].

The bi-allelic mutation or loss of the tumor suppressor gene neurofibromatosis 2 (*NF2*) on chromosome 22, is found in approximately 50% of sporadic meningiomas [14–17]. Recent studies employing next generation sequencing methodology have detected new driver mutations in meningiomas, including *TRAF7*, *KLF4*, *AKT1*, SMO, *PIK3CA*, *NOTCH2*, *SMARCB1*, *CHEK2*, *SMARCE1* and *POLR2 A*, particularly in the remaining half of meningiomas with wild-type *NF2* [17–19].

Extensive whole-exome or whole-genome sequencing has provided a large body of information about the mutational landscape of meningiomas [16,17,19–21]. Four distinct meningioma mutational subgroups have been proposed, defined by mutations in *NF2*, *TRAF7*, the hedgehog pathway or *POLR2 A*. However, such a stratification of

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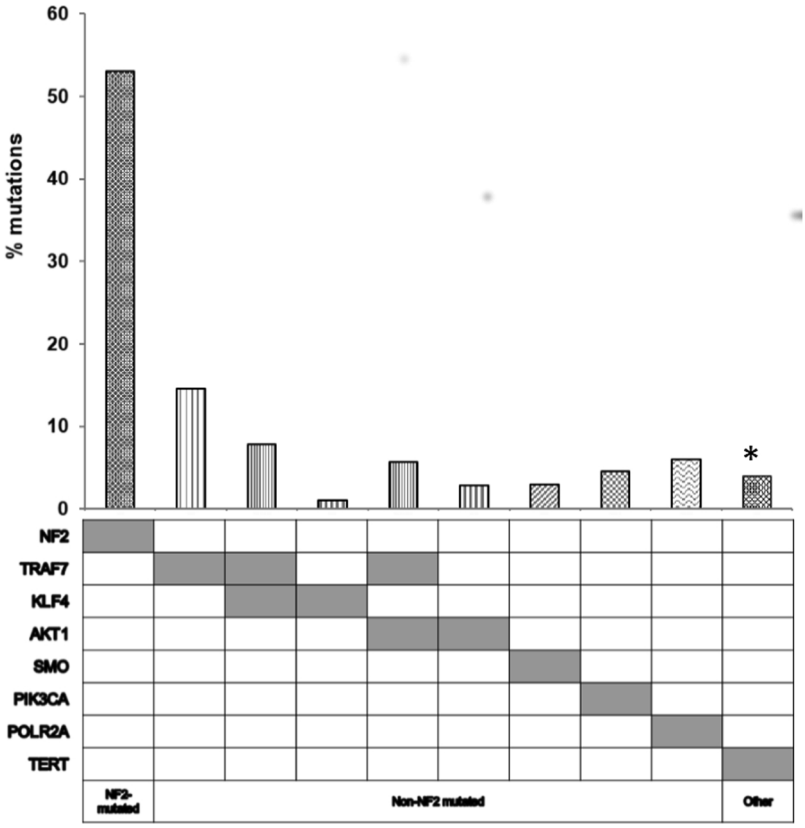

Fig. 1. Frequency of the most common genetic alterations found in meningiomas according to independent studies (17, 18, 20, 39, 41, 51,58, 60, 64, 67). Meningiomas are divided into *NF2*-mutated meningiomas *(NF2* alterations which include *NF2* loss and/or *NF2* mutations) and non-*NF2*-mutated meningiomas. The latter group present *TRAF7* mutations alone or in combination with *KLF4* or *AKT1* mutations, *SMO*, *PI3KCA* and *POLR2 A* (17). Additionally, the occurrence of *TERT* promoter mutations (*) are independent to other mutations, and they are more prevalent in more malignant meningiomas, being, therefore, a prognostic predictor (68, 69).

meningiomas based on mutational analysis alone has been proven not to satisfy the clinical need for distinction between patients who need (or do not need) an adjuvant treatment [17].

2. *NF2*-mutated meningiomas

Abnormalities in the 22q locus have been identified as the most frequent finding in meningiomas, and mutation, allelic inactivation or loss of the tumor suppressor *NF2* [15–17] have been described in approximately half of sporadic meningiomas [22–25] (Fig. 1). Based on this observation, it has been suggested that *NF2* might play a central role in regulating leptomeningeal cell proliferation [26]. Bi-allelic inactivation of the *NF2* gene leads to the loss of its product, merlin, also known as schwannomin [15]. And, *NF2* inactivation is thought to be an early event in sporadic meningiomas pathogenesis, frequently observed in grade I tumors, but also in high-grade tumors [7].

Alterations in the merlin protein have been associated with cell shape, particularly with mesenchymal-like cell phenotypes rather than epithelioid-like ones. Decreased *NF2* expression was observed in up to 80% of transitional or fibroblastic subtypes [27,28], while it was observed in only 28.5% of meningothelial meningiomas, which typically occur at the anterior skull base [29]. Kros et al. [30] analyzed 42 cases of sporadic meningiomas for LOH, karyotyping and fluorescence in situ hybridization, and they have demonstrated a significant correlation between tumor localization at the anterior skull base and an intact chromosome 22q, corroborating the paucity of *NF2* alteration in meningiomas on this site and in megingothelial subtype, the prevalent histological subtype in this site [31].

Although familial meningiomas are uncommon, they are usually associated with *NF2* alteration [32,33].

3. Non-*NF2* mutated meningiomas

Recent genomic analyses have shown that *KLF4*, *TRAF7*, *SMARCE1*, *POLR2 A*, telomerase reverse transcriptase (*TERT*), and *AKT1*, *SMO* are commonly mutated in non-*NF2* mutant meningiomas [16,17,20,34].

3.1. *KLF4* mutations

The *KLF4* gene, located on chromosome 9q31, belongs to a family of 17 members, all containing three C2H2 zinc finger motifs in the C-terminal region [35]. *KLF4* is linked to transcriptional activation and repression, including oncogenic activation and tumor suppression in a context-dependent manner [35,36]. *KLF4*, together with *OCT3/4*, *SOX2* and *c-MYC*, is one of the key genes necessary for the reprogramming of mouse fibroblasts into induced pluripotent stem cells (iPS) [37], indicating its role in stem-cell maintenance (57). *KLF4* mutations in meningiomas are all the same: the missense mutation c.1225 A > c, p.K409D located in the lysine residue at the first of three amino acids of the zinc finger, which makes physical contact with DNA, and is therefore central to DNA binding and highly conserved in evolution [38]. Approximately 9% of meningiomas present with this $KLF4^{K409Q}$ mutation, although it is more prevalent in grade I meningiomas [39]. This mutation was also identified in secretory meningiomas. In contrast, *KLF4* was downregulated in anaplastic meningiomas compared to benign secretory meningiomas, which lead to a decrease of its tumor suppressor role with dysregulation of cell cycle, apoptosis and invasion [40]. Cytokeratins 4 and 19 are clinical hallmarks of secretory meningiomas, and they are regulatory targets of *KLF4* [41]. This interaction may be linked to the presence of cytokeratin-positive globules unique to meningiomas of the secretory variant. In particular, the *KLF4* mutation has also been observed in secretory meningiomas associated with glial tumors, in two different patients with a glioblastoma and an anaplastic astrocytoma [42].

The *KLF4* mutation has also been described in an intraductal papillary mucinous neoplasm of the pancreas [43]. Additionally, in kidney cells, KLF4 co-regulates the bradykinin B2 receptor [44].

3.2. TRAF7 mutations

Tumor necrosis factor receptor associated factors (TRAFs) transduce the cellular effects mediated by TNF family ligands by their ability to couple TNF receptor family proteins to signaling pathways. Functionally, TRAF proteins are involved in innate and adaptive humoral immune responses acting both as cytoplasmic regulatory molecules and as signal transducers for receptors [45]. The RING finger domains of TRAF-2, -6 and -7 activate their downstream pathways by promoting ubiquitination events [46,47]. The function of TRAF7 is still not completely elucidated. However, interaction between TRAF7 and MEKK3 has been described, with enhancement of MEKK3-mediated signaling [46,48]. It was also described that TRAF7 binds to c-Myb and inhibits its transactivation by sumoylation [49]. Finally, it has been shown that TRAF7 is linked Toll-like receptor 2 stimulation which leads to NFκB transcription factor activation [50].

Mutations in *TRAF7*, located on chromosome 16p13.3, are observed in 14.5–20% of meningiomas [39,51]. Serpin2 A [52], matrix metallopeptidase 2 [53], IGFBP4 and IGFBP7 [54,55], which are direct targets of NFκB, are up-regulated in TRAF7-deficient cells. TRAF7 influences signal transduction in several ways. TRAF7 interacts with MEKK3/MAP3K3 through its WD40 domains [56], and NF-κB via its coiled-coil domain, modulating its ubiquitination. The RelA/p65 member of the NF-κB family is also ubiquitinated by TRAF7, and in both cases, TRAF7 promotes Lys-29-linked polyubiquitination [45]. Moreover, down-regulation of stress-related genes ceramide synthase 2, the ubiquitin-binding protein p62 (*SQSMT1*) and the apoptosis-related gene serglycin (*SRGN*), were observed in TRAF7-deficient cells [57].

TRAF7 mutations are highly specific for meningiomas, and they are confined to exons 13–20 coding for the seven WD40 domains in the C-terminal portion (17,51).

Nearly all cases of secretory meningioma (97%) harbor mutations in both *TRAF7* and *KLF4* K^{409Q} but lack mutations in *NF2* [20]. The *TRAF7* mutation is also found in other meningioma subtypes [17]. Interestingly, cumulative observation proved that these *KLF4* and *TRAF7* mutations were both mutually exclusive with the *NF2* alteration [51]

3.3. AKT1 mutations

AKT1, located on chromosome 14q32, is mutated recurrently in meningioma, producing a known oncogenic alteration of glutamic acid to lysine at codon 17 (c.49 G > A, p.E17 K), and has been reported exclusively as not overlapping the *NF2*, *KLF4* and *SMO* mutations [17]. This mutation is commonly observed in meningothelial meningiomas but is rarely reported in meningiomas of higher grades [58]. A majority of meningiomas with *TRAF7* mutations also harbor mutations in *KLF4*, as described above, or in *AKT1* (6.8–9% of meningiomas), but not in both genes [17,20,51]. The $AKT1^{E17K}$ mutation activates constitutively PI3K/AKT/mTOR oncogenic signaling pathway [59]. Moreover, the presence of the $AKT1^{E17K}$ mutation in skull-base meningiomas have been associated with reduced time of recurrence [60].

3.4. POLR2A mutations

RNA polymerase II subunit A gene (*POLR2 A)*, located on chromosome 17p13.1, encodes the largest subunit of RNA polymerase II, the polymerase responsible for synthesizing messenger RNA. The product of this gene contains a carboxy terminal domain composed of heptapeptide repeats that are essential for polymerase activity. Mutations in *POLR2 A* were discovered by searching for somatic mutation in meningiomas that lacked known mutation in classical driver genes described previously (18). Two different mutations at exon 7 (c.1207C > A, p.G403 K or c.1310_1315delACCTTC, p.L438_H439del) were present in 6% of benign meningiomas. *POLR2 A* exon 7encodes the highly conserved catalytic subunit of RNA polymerase II, responsible for interaction with TFIIB during the formation of the pre-initiation complex [61]. These alterations were confirmed as being somatic, exclusive to grade I meningiomas and mutually exclusive with previously established driver genes [17].

3.5. TERT mutations

Telomerase reverse transcriptase gene (*TERT*), located on chromosome 5p15.33, presents reverse transcriptase activity, that maintains telomere ends by adding the TTAGGG telomere repeat. TERT activation has been demonstrated in 10% of grade I, 50% of grade II and 95% of grade III meningiomas. Interestingly, *TERT* promoter mutations (g.228C > T and g.250C > T) are associated with recurrent meningiomas, and the highest frequency of such mutations (28%) are present in recurrent meningiomas with histologic progression [62]. Therefore, *TERT* promoter mutation is predictive of progression [63] and a shorter recurrence-free survival, especially in recurrent higher grade meningiomas [64,65].

4. Epigenetic alterations

4.1. DNA methylation

Patients with WHO grade I meningiomas who were molecularly assigned to an intermediate methylation class (WHO grade I MC int) had a less favorable clinical course than did patients with WHO grade I meningiomas diagnosed solely based on histology. In fact, the outcome of these patients (WHO grade I MC int) was indistinguishable from that of patients with WHO grade II meningiomas. Similarly, patients with WHO grade II meningiomas that were molecularly assigned to a benign methylation class (WHO grade II MC ben) had a better outcome than the average outcome of patients with histologically defined WHO grade II meningiomas. Consequently, the stratification for the methylation class has been demonstrated to be of higher value for the prediction of progression-free survival than WHO grading. The described combinatorial methylation classes have delineated subgroups with distinct prognoses within all WHO grades, showing the benefit of methylation class-based grading and, therefore, potentially reduce under or over-treatment in meningioma patients [51]. In addition, it has been demonstrated that the hypermethylation of the *SFRP1* promoter could be a mechanism of gene inactivation in meningiomas [66]. Moreover hypermethylation of *p73, TIMP3, GSTP1, MEG3, HOXA6, HOXA9, PENK, WNK2* and *UPK3A* have been recently described associated either to tumor progression/malignant transformation or tumor recurrence [67].

4.2. SWI/SNF complex mutations

The switch/sucrose non-fermentable (SWI/SNF) family is an ATP-dependent chromatin-remodeling complex involved in epigenetic regulation in human [68,69]. The catalytic activity of this complex disrupts DNA-nucleosome contacts, moves nucleosomes along DNA and ejects or exchanges nucleosomes, enabling DNA accessibility by opening the chromatin and consequently allowing an active transcription. This complex, also called the Brg-/Brama-associated factor, is a large multimeric assembly of 10–15 subunits. Each SWI/SNF complex contains one of two mutually exclusive catalytic ATPase subunits (either SMARCA2 or SMARCA4), a set of highly conserved core subunits (SMARCB1, SMARCC1 and SMARCC2) and variant subunits, including SMARCE1. Interestingly, heterozygous germline mutations in the *SMARCE1* gene, located on chromosome 17q21.2, were reported in 16 patients from 11 unrelated families with spinal and intracranial clear-cell meningiomas. These mutations were characterized as loss-of-function mutations, including frameshift and nonsense mutations, as well as an inversion and two large deletions. All symptomatic males with a *SMARCE1* mutation developed meningiomas in childhood (age range 2–10 years), while the symptomatic carrier females developed tumors somewhat later in adolescence or early adulthood (age range 14–30 s)

[18,34,70,71]. *SMARCE1* mutations is frequent in spinal cord meningiomas with clear cell histology [18,34,72].Germline mutations in *SMARCB1* have also been reported in three families with both multiple schwannomas and meningiomas [73–77]. Additionally, *SMARCB1* mutations have been reported to cause malignant rhabdoid tumors and schwannomatosis. However, screening for the *SMARCB1* germline mutation on individuals and families with multiple and isolated meningiomas suggested that such mutations are not prevalent in multiple meningiomas [78,79]. Interestingly, *SMARCB1* is located on chromosome 22 in close proximity to *NF2*, and co-occurrence of recurrent *SMARCB1* mutations in NF2-mutated meningiomas has also been described [19].

The importance of the SWI/SNF complex in tumorigenesis has been further reinforced by the detection of somatic mutations in the *ARID1A* and *PBRM1* subunits of SWI/SNF complex, and as major cancer-driving gene mutations in ovarian and renal clear-cell tumor subtypes, respectively [80,81].

4.3. Histone modifications

Another major epigenetic determinant for gene expression and cellular differentiation is the histone modification through methylation and acetylation [82]. Particularly modifications of lysine 27 (K27) of histone H3 play a crucial role in tumorigenesis [83]. Methylation of H3K27 is regulated by the EZH2 subunit of the PRC2 complex [84–86] and trimethylated H3K27 (H3K27me3) is associated to gene silencing [87]. Dysregulation of H3K27 methylation has been identified in several different cancers, including breast, prostate, colon, ovarian cancers, and malignant peripheral nerve sheath tumors [83,88–92]. In meningiomas, H3K27 dysregulation has been described in *AKT1* and *NF2* mutated meningiomas, where complete loss of its trimethylation has been associated to worse outcome, but not an obligatory finding among high-grade meningiomas (17). Immunohistochemical evaluation of H3K27me3 was reported as an useful adjunct tool for determining meningioma grade, particularly for WHO grade II and meningiomas with histological borderline diagnosis of WHO grade I and II.

4.4. Chromosomal copy number variations

Small recurrent regional amplifications on chromosome 6p21-p22, 16p13, 13q33, 17 and 19 have been described (94).

4.5. Micro-RNA

Cumulative evidences suggest miRNAs, a member of the non-coding endogenous RNA region of approximately 22 nucleotides [93] play an important role in a number of biological processes including metastasis, proliferation, apoptosis, stress resistance, tumorigenesis, and cellular differentiation [94–96].miRNA-224 was associated to malignant progression of meningioma (100).

Despite the previously demonstrated association between miRNA expression and a variety of other cancers, Katar, et al [94], examined the association between meningioma and miRNA-21, miRNA-107, miRNA-137 and miRNA-29b expression. Of the four different miRNA types, only miRNA-21 expression showed a significant increase in grade 2 and 3 lesions as compared to grade 1 lesions, and miRNA-107 expression was significantly lower in grade 2 and 3 lesions vs. Grade 1 lesions, while miRNA-137 and miRNA-29 b expression exhibited a statistically nonsignificant decrease in grade 2 and 3 lesions as compared to grade 1 tumors. In this study, despite a decrease in miRNA-137 with increasing disease grade, this difference was not significant, probably due to low sample size.

Saydam et al. [97], examining the association between different types of miRNA and meningioma. They found an increase in miR-335, miR-98, and miR-181a, while miRNA-200a, miRNA-373, and miRNA-575 decreased. Also, in their laboratory study, miRNA-200a inhibited the growth of meningioma in the culture medium. In another study, Wang, [98], et al, identified that, miR-224 expression could predict the overall survival and recurrence free survival of patients with meningioma and it might be a promising therapeutic target for treating malignant meningiomas.

5. Molecular signaling pathways

5.1. WNT

The Wnt pathway is one of the important signaling pathways reported as being dysregulated in meningiomas [99–102]. The activation of Wnt signaling pathway leads to the increase of β-catenin cytosolic levels. This occurs through the binding of Dishevelled (DVL) proteins to AXIN, and translocation to the cell membrane, forming a large molecular complex consisting of Wnt-Fz-LRP5/6-DVL-AXIN. This complex is destroyed when AXIN is pulled out, and then β-catenin can no longer be degraded [103]. The gene that codes for one of the Wnt receptors, Frizzled class receptor 2 (*FZD2*), was reported as differentially expressed in meningiomas compared to non-malignant leptomeningeal cells, being 3.7 fold higher in the tumor [104]. Moreover, genes coding for key molecules of this pathway, namely APC and E-cadherin (*CDH1*), and AXIN, have been reported as having loss of heterozigozity (LOH) and their products as downregulated in meningiomas [105–107], reinforcing the importance of this molecular signaling pathway in these tumors.

5.2. Sonic hedgehog

The smoothened, frizzled class receptor gene (*SMO*) encodes for the smoothened homologue, a member of the Sonic Hedgehog signaling (SHH) pathway, involved in both embryogenesis and several key cellular processes, including proliferation and angiogenesis. *SMO*, located at 7q32.1, interacts with suppressor of fused homologue (SUFU), which translocates the zinc-finger protein GLI1 to the nucleus, subsequently activating target genes [108]. The SMO-mutant is described with a frequency between 3% and 5% of all meningiomas showed 2 recurrent variants, c.1234C > T, p.L412 F (70%) and c.1604 G > T, p.W535 L (15%), and a highly recurrent phenotype of grade I meningothelial lesions arising from the anterior medial skull base [19,39]. The strong association of the *SMO* mutation with meningiomas of the anterior skull base location might be related to the central role of the SHH pathway in the development of the ventral forebrain and median craniofacial skeleton [109,110]. The *SMO* mutations rarely co-occur with mutations of *NF2* or *TRAF7* mutations or with chromosome 22 loss [12]. Germline mutations in *SUFU*, a negative regulator of the SHH signaling pathway, have also been reported in meningiomas (9,10).

5.3. PI3K/AKT/mTOR

The PI3K-AKT-mTOR signaling pathway is another important growth-favoring pathway, particularly associated in a subset of meningiomas harboring PI3K mutations [111]. Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene (*PIK3CA*) is located at 3q26.32 and encodes the phosphoinositide-3-kinase (PI3K) catalytic subunit p110a.Five different well-established oncogenic mutations (E110del, N345 K, E453 K, E545 K and H1047R) in *PIK3CA* have been described (111).

This subset of meningiomas lacked mutations in *NF2*, *AKT1* and *SMO*, but they tended to present *TRAF7* mutations, being meningothelial or transitional subtypes, preferentially localized at the skull-base (64). Another gene in this signaling pathway, *AKT1* is located on chromosome 14q32, and is mutated recurrently in meningioma, producing a known oncogenic alteration of glutamic acid to lysine at codon 17 (c.49 G > A, p.E17 K). And, this mutation has been reported exclusively as not overlapping the *NF2*, *KLF4* and *SMO* mutations [17].

This mutation is commonly observed in meningothelial meningiomas but is rarely reported in meningiomas of higher grades [58]. A majority of meningiomas with *TRAF7* mutations also harbor mutations in *KLF4*, as described above, or in *AKT1* (6.8–9% of meningiomas), but not in both genes [17,20,51]. The $AKT1^{E17K}$ mutation activates constitutively PI3K/AKT/mTOR oncogenic signaling pathway [59]. Moreover, the presence of the $AKT1^{E17K}$ mutation in skull-base meningiomas have been associated with reduced time of recurrence [60]

6. Angiogenesis and anothers ways

Meningiomas are highly vascular tumors, and therefore signaling pathways related to angiogenesis have been studied in these tumors. The cytokine vascular endothelial growth factor (VEGF) was originally described as a vascular permeability factor and as a positive regulator of angiogenesis by promoting the migration, proliferation and tube formation of endothelial cells [112]. VEGF up-regulation was demonstrated in meningiomas, suggesting its role as a pro-angiogenic factor [113–116]. Nonetheless, despite the higher vascularity in higher-grade meningiomas, any parallel increase of VEGF expression was found in atypical or anaplastic meningiomas [117,118]. Additionally, the predictive power of tumor recurrence of the ratio between the pro-angiogenic factor as VEGF and the anti-angiogenic factor as SEMASA, associated with low microvessel density, has been controversial [119]. Remodeling the extracellular matrix (ECM) is relevant for angiogenesis, and metalloproteinases (MMPs) have been widely implicated as mediators of angiogenesis, and also as playing a role in the degradation of the ECM facilitating tumor invasion. Additionally, MMPs regulate cell adhesion, control apoptosis through the release of death or survival factors and regulate the bioavailability and/or activity of growth factors by mediating receptor turnover or by cleaving matrix proteins associated with growth factors [120]. In this scenario, the ability of MMP9 to trigger the release of VEGF, which regulates angiogenesis and vascular permeability, as mentioned [121] is well documented. Upregulation of MMP9 has been related to an increase in intratumoral vascular density, tumor invasion and recurrence and peritumoral edema [122], being pointed out as a predictive factor for tumor recurrences, especially for benign meningiomas [123]. Indeed, for these reasons, associated with controversial results in the literature, we chose to study these markers more thoroughly, in order to find a relationship between these markers and the malignization of these tumors. In our cohort [124,125] we found differential expression of *MMP9* among meningiomas; however its expression was higher among the atypical meningiomas presenting recurrence (Fig. 2B); and no differential expression was observed among distinct grades of meningiomas (Fig. 2A).

Hyaluronic acid is an important component of the brain ECM, known to be a permissive substrate for cell migration in tumor progression [126]. The expression level of CD44, a hyaluronic acid receptor, was found in 71% of benign, 83% of atypical and 100% of anaplastic meningiomas. However, similarly to the MMP9 expression profile, no correlation of its expression level and tumor grade was observed [127]. The loss of the TGF inhibitory effect has also been described in higher-grade meningiomas and in combined alterations of WNT and p53-signaling pathways [128].

The next-generation sequencing approaches have established a somatic mutational profile of meningiomas. However, the mutational status alone or combined to histological subtype and tumor localization have not provided prognostic or therapeutic guidance [129], and additional molecular predictive markers are needed.

7. Discussion

The study of meningioma is undergoing a renaissance due to the application of multiplatform molecular, genomic, and epigenetic profiling. These large-scale, systematic approaches inform a molecular taxonomy that promises to influence diagnosis, disease classification, and, ultimately, clinical management.

Actually, the current WHO classification of the central nervous system (2016), combined histological-molecular classification termed integrated diagnosis is applied for the diagnosis of gliomas [2] because genotype is more significantly associated with prognosis than histology [130]. However, as described above, more detailed investigations about the correlation between genotype and prognosis are required to establish integrated diagnosis for meningioma. In meningioma, few surrogate markers for mutations were reported. Sahm et al. [58] described the strong up-regulation of SFRP1 expression in all meningiomas with AKT1 E17 K. Brastianos et al. [16] demonstrated the strong immunoreactivity for GAB1 in meningiomas harboring SMO mutations, and STMN1 expression was observed in AKT1-mutated and SMO-mutated meningiomas [16]. However, the sensitivity, specificity, and accuracy of the immunohistochemistry for genotyping of meningiomas remain unclear.

As described by Linda, et al, [131] further understanding of the factors that drive meningioma development and progression will lead to the classification of every patient's tumor according to its signature alterations, ushering in an era in which meningiomas will be considered in the same light as other tumors whose molecular underpinnings have fueled the nascent precision medicine age.

8. Conclusion

Combined analysis of exome, transcriptome, methylome and future approaches for epigenetic aspects in meningiomas may allow researchers to unveil a more comprehensive understanding of tumor progression mechanisms and, consequently, a more personalized clinical approach for patients with meningioma.

Disclosure

The authors have no personal financial or institutional interest in

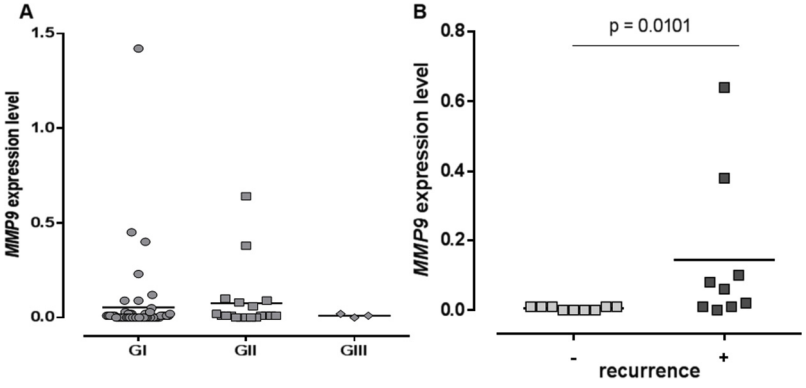

Fig. 2. *MMP9* expression profiles in meningiomas according to WHO grade classification. (A) *MMP9* transcript levels were determined by quantitative real-time PCR in 57 grade I meningiomas (GI), 18 grade II meningiomas (GII) and 3 grade III meningiomas (GIII) according to previous work (105, 106). The relative expression values were calculated according to $2^{-\Delta Ct}$, where ΔCt = Ct specific gene- geometric mean Ct of housekeeping genes the *HPRT* and *GUSB* expression levels for each sample of meningioma. The horizontal bars show the mean *MMP9* expression of each group: GI = 0.050; GII = 0.075; AGII = 0.010. (**A**) The *MMP9* expressions among the groups was not statistically significant ($p > 0.05$, Kruskal Wallis test). However, *MMP9* expression levels according to recurrence (+) or no recurrence (-) in grade II meningiomas were significantly different (p = 0.0101, Kruskal Wallis test), as in (**B**).

any of the drugs, materials, or devices described in this article.

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