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Review

Receptor Tyrosine Kinases as Candidate Prognostic Biomarkers in Meningioma

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Abstract: Meningioma (MGM) is the most common type of intracranial tumor in adults. The validation of novel prognostic biomarkers to better inform tumor stratification and clinical prognosis is urgently needed. Many molecular and cellular alterations have been described in MGM tumors over the past few years, providing a rational basis for the identification of biomarkers and therapeutic targets. The role of receptor tyrosine kinase (RTKs), including those of the ErbB family of receptors, as oncogenes has been well established in several cancer types. Here, we review histological, molecular, and clinical evidence suggesting that RTKs, including the epidermal growth factor receptor (EGFR, ErbB 1), as well as other members of the ErbB family, may be useful as biomarkers in MGM.

Keywords: epidermal growth factor receptor; ErbB; biomarker; meningioma; intracranial tumor

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1. Introduction

Meningiomas (MGMs) constitute the most common type of primary intracranial tumor in adults, accounting for a little over a third of all intracranial neoplasms. An MGM is defined as a tumor emerging from the meninges, which consist of the dura mater, arachnoid and pia mater that envelope the brain and spinal cord. MGMs occur more commonly in adult females than in males, except for higher grades, and elderly patients, but are rarer in children and adolescents [1]. Currently, MGM is classified into 15 histologic subtypes across 3 grades of malignancy by a World Health Organization (WHO) grading system intended to reflect recurrence rate and prognosis. Thus, grade I benign, grade II atypical, and grade III anaplastic MGMs are further divided into 15 subtypes, among which meningothelial, fibroblastic, and transitional MGM are the most common [2, 3]. In addition to histopathological analysis, positron emission tomography (PET) imaging has contributed with the distinction between low- and high-grade MGMs [4]. Also, other classification methods have been more recently proposed, based on molecular markers such as DNA methylation profiles [5, 6].

Arachnoid cap cells, and, more specifically, prostaglandin D2 synthase (PGDS)-positive arachnoid cells, are the most likely MGM cells of origin [7-9], and the presence of a cancer stem cell compartment has also been proposed [10]. The five-year survival for WHO grade I MGM is over 80%, but patients with anaplastic MGM show greatly reduced survival. The standard treatment in surgically accessible tumors is total surgical resection, which is capable of curing up to 80% of MGM cases. Radiotherapy is used in atypical and anaplastic MGMs, which often show higher recurrence rates, intense invasiveness and poor prognosis, recurrent tumors, and surgically inaccessible MGMs.

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Adjuvant chemotherapy has not been so far shown as effective, and its use is limited to high grade aggressive and relapsing tumors [11-14].

2. Molecular Changes and Novel Molecularly-Targeted Therapeutic Strategies

Several aspects of the genetic and cellular basis underlying MGM have been unraveled and provide novel opportunities for the development of targeted treatments. Next-generation sequencing revealed recurrent somatic mutations in the neurofibromin 2 (*NF2*), TNF receptor associated factor 7 (*TRAF7*), Krüppel-like factor 4 (*KLF4*), AKT serine/threonine kinase 1 (*AKT1*), smoothened (*SMO*), and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) genes, which are collectively found in around 80% of sporadic MGMs and are associated with tumor location, histologic subtype, and clinical outcome [5, 6, 9, 15-17]. The most common chromosomal abnormality in MGM is found in chromosome 22 and occurs 40–70% of grade I tumors. Beyond the loss of chromosome 22, few other chromosomal abnormalities have been observed in benign meningioma [9, 18]. All or part of chromosome 22 is deleted, and the majority of deletions are found in the neurofibromatosis type 2 (NF2) region, suggesting a role for mutated NF2 as an oncogene in MGM pathogenesis [9, 19]. Loss of chromosome 1 is the second most common deletion site in MGM, mostly observed in atypical and anaplastic tumors [20]. Activating mutations in the promoter of the telomerase reverse transcriptase (TERT) gene are associated with higher recurrence, faster progression, and poorer overall survival [21]. Genomic deletion or reduced protein expression of Dystrophin-encoding and Muscular Dystrophy-associated gene (DMD) are

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found in around one third of MGM patients and associated with poorer overall survival. MGMs showing deficient expression of the tumor suppressor gene breast cancer (BRCA)1-associated protein-1 (BAP1) are more aggressive and lead to poor prognosis [9, 22].

Inhibition of receptor tyrosine kinases (RTKs) has been experimentally explored as a basis to reduce tumor growth in in MGM models. Phosphorylated epidermal growth factor receptor (EGFR) mediates aberrant STAT1 activation, and EGFR inhibition impairs cell proliferation and reduces the levels of cyclin D1, phosphorylated AKT, and phosphorylated extracellular signal-regulated kinase (ERK)1/2 [23]. Inhibition of PDGF receptor (PDGFR)-mediated signaling by RTK inhibitors sorafenib and regorafenib inhibits the growth of experimental MGM *in vitro* and *in vivo*, thought PDGFR downregulation and inhibition of p44/42 ERK [24]. A few cases of tumor responses to the multiple RTK inhibitor sunitinib have been reported in patients with grade II and III MGMs [25, 26]. Patients with recurrent MGM tumors refractory to surgery and radiation treated with the oral multi-RTK inhibitor PTK787/ZK 222584 (PTK787) showed that grade II patients had a progression free survival-6 of 64.3 %, a median progression free survival of 6.5 months, and an overall survival of 26.0 months; grade III patients had a progression free survival-6 of 37.5 %, median progression free survival of 3.6 months, and overall survival of 23 months [27]. The PDGFR inhibitor imatinib mesylate may be a well-tolerated therapeutic option capable of stabilize disease in a group of patients preselected on the basis of tumor positivity for PDGR [28].

In terms of intracellular signaling and angiogenesis pathways, increased activity of the phosphoinositide 3-kinase (PI3K)/Akt/ mechanistic target of rapamycin (mTOR) cascade has been reported in MGM, and treatment with mTOR inhibitors reduce experimental MGM growth [29], and mTOR inhibition impairs neuregulin 1-ERBB3

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autocrine signaling in NF2-deficient cellular models of MGM [30]. In addition, a phase 2 clinical study of the mTOR inhibitor everolimus in MGM has provided satisfactory early results [31].

2.1. Potential role for anti-angiogenic, hormone, and immune-based therapeutical modalities in MGM

Expression levels of the vascular endothelial growth factor (VEGF) in atypical and anaplastic MGM are higher than in benign MGM [32]. Small clinical trials have provided early evidence suggesting that treatment with the anti-VEGF monoclonal antibody bevacizumab or the small molecule VEGF and PDGF receptor inhibitor sunitinib may increase progression-free survival in patients with MGM [33-37]. A case study of two radiographically diagnosed intracranial MGM tumors in a patient with concurrent thyroid carcinoma described tumor regression after treatment with cabozantinib, a small molecule RTK inhibitor with potent activity against the VEGF receptor type 2 (VEGFR2) [38]. On the light of increased expression of the programmed death-ligand receptor (PD-L1) in MGM [39], immunotherapy with nivolumab and pembrolizumab is currently under evaluation in phase 2 clinical trials of MGM [9]. MGM cells express progesterone receptor (PR), and the potential of the PR antagonist mifepristone in MGM treatment has been explored, however the currently available clinical results still do not allow the conclusion that any meaningful beneficial effect exists [40-42]. In summary, despite current exploration of cellular components including some RTKs and intracellular signaling pathways, in addition to hormonal modulation, angiogenic processes, and immune responses, as therapeutic targets, to date there is no

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strong evidence supporting the benefit of pharmacological interventions for MGM patients.

3. Current and Candidate Biomarkers in MGM

Many radiological, plasmatic, histological, and molecular prognostic markers have been put forward to help to stratify MGMs. However, to date there are no clinically validated biomarkers to help inform determination of tumor grade and clinical prognosis [20, 43]. Investigation of gene expression features of progressing, recurrent, or grade III MGM tumors revealed that notably aggressive tumor subsets share a substantial group of differentially expressed genes, in addition to identifying genes separating non-recurring from recurrent and malignant grade I or grade II tumors. Moreover, a significant association of a subset of genes with progression-free survival was shown [44].

Proteomic approaches have aided in the effort to validate candidate biomarkers [45]. For example, bioinformatics combined with analysis of protein content profile applied to tumor and blood samples from MGM patients has pointed to proteins including serpin peptidase inhibitor alpha 1, ceruloplasmin, hemopexin, albumin, C3, apolipoprotein, haptoglobin, amyloid-P-component serum and alpha-1-beta-glycoprotein as potential prognostic markers [46]. A small study aimed at identifying MGM-specific proteins in the cerebrospinal fluid (CSF) from 4 MGM patients and 4 patients with a non-brain tumor found increased levels of apolipoprotein E (Apo E), apolipoprotein J precursor (Apo J), and alpha-1-antitrypsin (AAT), and reduced levels of prostaglandin D2 synthase 21 kDa (PTGDS), transthyretin precursor (TTR), and β -2-microglobulin precursor (β2M) [47]. Also using a proteomic strategy, one group has put forward

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retinoblastoma associated protein-1 (RB1) as a critical marker to identify grade I MGM tumors with high risk for recurrence [48].

Other studies quantifying protein content via multiple techniques have aided in the identification of possible protein MGM biomarkers. Semiquantitative analysis of nuclear expression of karyopherin a2 and chromosome region maintenance protein 1, members of the karyopherin protein family that comprises nucleocytoplasmic shuttling receptors importins and exportins, revealed that expression of these proteins correlated significantly with MGM histological grade and predicted tumor recurrence [49]. Expression changes in securin (PTTG1), which prevents sister chromatid separation, and leptin receptor (LEPR) were associated with MGM malignancy [43]. The somatostatin receptor 2A (SST2A) has been proposed as a good immunostain target due to its high sensitivity [50]. Experiments using protein separation by two-dimensional gel electrophoresis and identification of candidate biomarkers by liquid chromatography-mass spectrometry identified seven candidate protein biomarkers, which were capable of differentiate between aggressive and benign WHO grade I MGMs [51]. A study focusing specifically on stem cell-related protein markers revealed differential expression of the G protein-coupled receptor Frizzled 9 (cluster of differentiation 349, CD349) and glial fibrillary acidic protein (GFAP) in grade II/III compared with grade I MGM. GFAP expression correlated with the stem cell markers CD133, stage specific embryo antigen 4 (SSEA4), and vimentin in cell populations enriched in grade II/III tumors [52]. Measurement of protein serum markers has revealed significant increases in amphiregulin (*AREG*), *EGF*, *HB-EGF* and caspase3 in patients with MGM of different grades, helping to establish an MGM protein signature in the blood [53].

Epigenetic changes have been put forward as prognostic markers in MGM [2]. Enhancer of Zeste homolog-2 (EZH2) and trimethyl histone-3 (H3K27me3), which

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mediate histone modifications related to chromatin state, have been examined. Low histological levels of H3K27me3 were found by a systematic review as a marker that may aid the differentiation between grade I and grade II tumors [43]. Immunohistochemical analysis of 149 cases of MGM tumors grade I (n = 102) or grade II (n = 47) has indicated that positivity for EZH2 and negativity for H3K27me3 are associated with higher tumor cell proliferation and significantly more common in grade II MGM compared to grade I tumors. Expression of EZH2 and loss of H3K27me3 were significantly associated with shorter progression-free survival. DNA methyltransferases (DNMT)-1, -3A and -3B, which control DNA methylation, are found in most tumors of either grade, with higher DNMT-1 content in grade II MGMs [54].

Several mutations found in MGM can drive epigenetic alterations, particularly methylation profiles [20]. These include inactivation of genes encoding subunits of the SWI/SNF chromatin-remodeling complexes [55, 56] and loss of the retinoblastoma protein-interacting zinc-finger (*RIZ*) gene [57]. Loss of *RIZ* associates with tumor progression, being inversely correlated with MGM grade [56]. Hypermethylation accompanied by loss of gene expression of WNK lysine deficient protein kinase 2 (*WNK2*), a negative regulator of cell proliferation, is found in 83% of grade II and 71% of grade III tumors [58]. Epigenetic characterization of MGM has also provided unique DNA methylation profiles that allow the segregation of all MGM types, across grades, from other skull tumors, and these classifications can predict progression-free survival with higher accuracy compared to WHO grade alone [20, 59]. The extent of methylation occurring in a set of 5 homeobox genes (*HOXA6*, *HOXA9*, *PENK*, *UPK3A*, and *IGF2bP1*) may predict MGM recurrence [60]. An analysis of microRNA (miRNA) levels in MGM tumors of different grades and in serum found that expression of the miR-497~195 cluster decreases with increased malignancy. Overexpression of cyclin D1 is associated with

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downregulation of the miR-497~195 cluster. The transcription factor GATA binding protein 4 (GATA-4), which is upregulated in malignant MGM, upregulates cyclin D1, thus controlling miR-497~195 cluster expression and stimulating cell viability. Levels of miR-497 are lower in serum exosomes derived from patients with high-grade MGM compared to benign MGM. These data suggest miR-497 as a potential non-invasive biomarker for malignant MGM [61].

Nineteen differentially expressed miRNAs were validated by RT-qPCR using tumor RNA from 15 patients and 5 meninges controls. Tumor suppressor miR-218 and miR-34a were upregulated relative to normal controls, however, miR-143, miR-193b, miR-451 and oncogenic miR-21 were all downregulated. From 10 selected putative mRNA targets tested by RT-qPCR, only four were differentially expressed relative to controls. PTEN and E-cadherin (CDH1) were upregulated, but RUNX1T1 was downregulated. Proliferation biomarker p63 was upregulated with nuclear localization, but not detected in most normal arachnoid tissues. Immunoreactivity of E-cadherin was detected in the outermost layer of normal arachnoids but was expressed throughout the tumors. Nuclear Cyclin D1 expression was positive in all studied meningiomas, while its expression in arachnoid was limited to a few trabecular cells. MGMs of grades I and II appear to share biomarkers with malignant tumors, but with some additional tumor suppressor biomarkers expression. Validation in more patients is of importance [62].

Another study suggested a panel of six serum miRNAs as a potential biomarker. Thus, serum levels of miR-106a-5p, miR-219-5p, miR-375, and miR-409-3p are significantly increased, whereas serum levels of miR-197 and miR-224 are reduced, in MGM patients. Levels of the four increased miRNAs significantly decrease, whereas the two reduced miRNAs increase, after surgical MGM removal. In addition, expression levels of miR-219-5p are positively associated with tumor clinical stage. Moreover, high

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expression of miR-409-3p and low expression of miR-224 associate with recurrence [63]. Together, these findings suggest that combined analyses of genomic, epigenetic, and protein biomarkers may enable the development of new panel to help predict aggressive MGM with high rates of progression and recurrence.

4. RTKs as Candidate Prognostic Biomarkers in MGM

The role of abnormal RTK signaling in oncogenesis and tumor progression is well established. For example, overexpression and activating mutations of genes encoding members of the ErbB receptor family (for example, EGFR or ErbB 1 in non-small cell lung and colorectal cancer, and ErbB 2, also called HER2, in breast cancer) are used to identify subgroups of tumors responsive to small molecule agents (e.g., gefitinib, erlotinib) or monoclonal antibodies (e.g., cetuximab, trastuzumab) that specifically target ErbB receptors [64-66]. Mutations and overexpression of RTKs can also be used as predictive markers of response to targeted therapies [67]. As an illustration in brain tumors, the *EGFR* gene is among the most frequently altered oncogenes in glioblastoma, with 57% of tumors showing amplification, mutation, rearrangement, or altered splicing [68], and EGFR is a prognostic biomarker in GBM [69].

Emerging evidence suggests a potential role for RTKs as biomarkers in MGM. A study using tissue microarrays obtained from a set of 186 MGM tumors analyzed by immunohistochemistry with antibodies targeting intracellular and extracellular domains of EGFR and phosphorylated EGFR revealed that EGFR is overexpressed and activated in most human MGM cases. Remarkably, survival or recurrence was significantly decreased in association with high staining of the EGFR extracellular domain [70].

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Another immunohistochemical study of 113 MGM specimens from 89 patients indicated that EGFR expression may be higher in benign MGM tumors [71]. Examination of 115 MGM tumors via next-generation sequencing, immunohistochemistry, and fluorescent and chromogenic in situ hybridization confirmed expression of EGFR in 93% of samples [72]. Overexpression and constitutive phosphorylation of EGFR-signal transducer and activator of transcription 1 (STAT1) was found in a set of 131 MGMs of different grades and locations by Western blots, qPCR, and immunocytochemistry [23]. A study using high throughput tissue microarray immunohistochemistry (TMA-IHC) with a TMA that included 41 MGMs of various grades as well as two subsets of atypical MGMs found that EGFR is differentially expressed in symptomatic, surgically resected MGMs versus incidental MGMs, and PDGFRβ helps distinguishing anaplastic MGMs from hemangiopericytomas [73]. Northern blot analysis revealed expression of EGFR mRNA in 9 of 11 (82%) primary MGM tumors, and immunocytochemistry confirmed strong positivity at the protein level. In contrast, no EGFR expression was found in samples of non-neoplasical meninges [74]. Another study detected EGFR by immunoblot in six of nine MGMs (67%) and by immunohistochemistry in 13 of 19 meningiomas (68%) MGMs, but not in normal leptomeningeal cells [75]. Importantly, analysis using immunohistochemistry and gene amplification by fluorescence in situ hybridization showed that progression from benign to atypical or anaplastic MGMs associates with an increase in EGFR protein content, so that EGFR immunostaining directly correlates to tumor grade. However, EGFR expression was not associated with overall survival or recurrence-free survival [76].

A study examining 186 primary MGMs found that two members of the ErbB RTK family, HER3 and HER4, were highly expressed in most tumor samples of all grades, both in the cytoplasm and cell membrane, and also in the nucleus for HER4. In contrast,

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non-neoplastic meningeal tissue was not immunoreactive, suggesting a potential diagnostic marker [77]. An immunohistochemical analysis found HER2 expression in 45% of 72 MGM tumors, being 55% grade II/III, and 38.5% of grade I. No significant difference was observed in HER2 expression between grade I and grade II/III meningiomas, primary and recurrent tumors, or males and females [78].

We conducted violin plot analysis of data sets derived from 42 aggressive MGM tumor samples from patients in a previously published patient cohort [79]. Although the analysis revealed an overall similar distribution pattern of genes for different ErbB receptor family members, higher levels of *ErbB2* (HER2) and *ErbB3* (HER3) were observed in a lower density of MGM tumor patients compared to all other members of the ErbB receptor family. High levels of TGFA, *AREG*, *EPGN* (ErbB1 or EGFR receptor ligands) and *NRG3* (ErbB4 or HER4 receptor ligand) were observed in lower density of MGM tumor patients. In contrast, high levels of *HB-EGF*, a ligand of ErbB1 and ErbB4, was observed in a higher density of MGM tumor patients, as well as *NRG4*, a ligand of ErbB4 (Figure 1).

Immunohistochemical analysis of several RTKs (VEGFR1/2/3, PDGFRα/β and c-Kit) in a set of 81 MGMs from 74 patients showed that 29 grade I (45%), 10 grade II (77%), and 4 grade III (100%) tumors were VEGFR-2-positive, and VEGFR-2 expression was significantly correlated with tumor grade [80]. The proto-oncogene *KIT*, which encodes the RTK KIT (cluster of differentiation 117, CD117; mast/stem cell growth factor receptor, SCFR), is robustly expressed in about 20% of MGMs, likely through up-regulation of KIT transcription rather than gene amplification [81]. Another immunohistochemical study of benign MGM tumors with (n = 17) or without (n = 25) recurrence showed that coexpression of the RTK cMET and hepatocyte growth

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factor/scatter factor (HGF/SF) significantly associates with cell proliferation index and recurrence [82].

5. Concluding Remarks

Validating clinically useful prognostic markers remains a major challenge in neuro-oncology. The availability of accurate preoperative biomarkers in MGM patients would improve the pre-surgical assessment of these tumors, their grade and clinical prognosis, and help direct treatment decisions [43]. Advances in the identification of biomarkers in liquid biopsies using samples of cerebrospinal fluid and blood should enable the development of less invasive diagnostic and prognostic methods that will also allow the monitoring of treatment efficacy during disease [83]. Although appropriate biomarkers for routine clinical use in prognostic evaluation of patients with MGM remain to be characterized, the findings reviewed here indicate that RTKs, particularly EGFR and other members of the ErbB family, as well as HB-EGF and NRG4 (ligands of ErbB1 and ErbB4, respectively) should be further investigated as biomarkers potentially capable of aiding in early detection and determination of tumor grade and prediction of clinical outcome upon investigation of surgically removed MGM tumors.

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Legend for Figure

Figure 1. Transcript levels of members of the ErbB RTK family and their ligands in MGM aggressive tumors. Expression levels were examined in previously described transcriptome data sets comprising samples from Vasudevan (GSE101638, n = 42 MGM samples [79]). Expression of genes for ErbB receptors (A) and ligands (B) across all samples is presented in violin format as log2-transformed signal intensity.

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