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Genomic Characterization of Meningiomas

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Abstract: Meningiomas are common tumours arising from the arachnoidal cap cells of the leptomeninges that can cause significant morbidity by compressing and potentially invading the adjacent brain, vasculature, and cranial nerves. Those tumours arising from the skull base and tumours with more aggressive histopathologic features (World Health Organization grades II and III) are particularly challenging to treat, frequently recurring even after optimal surgical resection and growing despite radiation treatments. Currently, no effective chemotherapeutic options are available for recurrent and aggressive meningiomas. Until recently, the only genetic driver of meningiomas to be identified was

bi-allelic loss of the tumour suppressor gene NF2 on chromosome 22, encoding the protein Merlin. However, several recent efforts have uncovered new driver mutations, particularly in the approximately 40–60 % of tumours that are wild-type for NF2. Such mutations, including those in signalling molecule genes such as AKT1 and SMO, epigenetic modifier genes such as KDM5C and SMARCB1, and additional genes whose function remains unclear, such as TRAF7 and KLF4, predominate in grade-I tumours of the skull base. Patients with these difficult-to-treat tumours may therefore benefit from specific targeted medical therapies based on the mutations present in their individual tumours. Higher-grade tu-

mours are characterized by increased genomic instability, particularly elevated numbers of chromosomal and arm-level losses, though few specific genes involved in their pathogenesis have been identified apart from NF2. Here, we review these recent advances in our understanding of meningiomagenesis through genetic profiling and the potential clinical applications of these findings. **Eur Assoc NeuroOncol Mag 2013; 3 (3): 102–4.**

Key words: meningiomas, genomics, AKT1, SMO

■ Introduction

Meningiomas are the most common primary central nervous system tumour, constituting approximately 1/3 of all primary intracranial tumours [1, 2]. While most meningiomas (80 %) are grade I and do not invade the brain tissue, their growth within the intracranial space often leads to serious and potentially lethal consequences. A significant number of these lesions are located at the skull base, a region that increases both the morbidity of treatment and risk of recurrence after surgery. Overall, 5-year recurrence rates are as high as 18 % for grade-I tumours, leading to significantly reduced long-term survival [3]. Higher-grade meningiomas (grades II and III) are marked by brain invasion, increased mitoses, necrosis, higher nuclear-to-cytoplasmic ratios, or histologic appearance resembling carcinoma, sarcoma, or melanoma [4]. These more aggressive lesions have a worse prognosis, with grade-II and -III recurrence rates as high as 40 % and 80 %, and 5-year overall survival rates of 76 % and 32 %, respectively [2, 5, 6]. While there are case reports and case series of meningiomas progressing from grade I to higher grade [7, 8], the grade-II and -III meningiomas more often are diagnosed on initial resection.

Treatment options for meningiomas of all grades are limited. The primary treatment modality in almost all cases is surgical resection, with recurrence rates primarily related to histological grade and extent of resection [4, 9]. Radiation is often used as an adjunct to surgery in cases of recurrence or growth of residual tumours, with variable response rates [10, 11]. How-

ever, the medical treatment of meningiomas is severely limited, with no effective chemotherapeutic options when surgery and radiation fail to provide durable disease control [12]. Systemic agents that have been investigated in this setting with limited success include hydroxyurea [13], bevacizumab [14], imatinib [15], irinotecan [16], mifepristone [17], and erlotinib [18].

A limited understanding of the causes of these tumours has hampered development of novel medical treatments; however, our understanding of meningiomagenesis has been advanced recently by genomic studies of these tumours that have uncovered a number of genes that may both drive tumour development and offer unique windows for chemotherapeutic interventions.

■ NF2 Syndrome and Gene

The first identification of a genetic cause for meningiomas, nearly 30 years ago, was the discovery of the gene underlying the neurofibromatosis type-2 syndrome on chromosome 22 [19, 20]. The NF2 gene, a tumour suppressor encoding the protein Merlin (also known as Schwannomin), is inactivated by a combination of mutation and deletion in neurofibromatosis-associated meningiomas as well as between 30–70 % of non-syndromic (sporadic) meningiomas [21, 22]. A 2-hit mechanism is commonly seen in these tumours, where a non-sense, splice-site, or frame-shift mutation results in a non-functional product from one allele, while the second allele is knocked out by hemizygous loss, usually by loss of part or all of chromosome 22 [23]. Recently, a radiation-induced meningioma was shown to have a copy-neutral rearrangement (by intrachromosomal inversion), a novel mechanism for disruption of the NF2 gene [24]. Loss of the NF2 gene has also been linked to both neurofibromatosis-associated and sporadic schwannomas [25].

In addition to association with neurofibromatosis and the NF2 gene, predisposition to development of meningiomas has been reported in several other familial syndromes. These in-

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clude syndromes associated with alterations or defects in the NF1, PTCH, CREBBP, VHL, PTEN, and CDKN2A genes [26].

The mechanisms by which Merlin acts as a tumour suppressor are not fully understood. Merlin belongs to the larger 4.1 protein family that interacts with multiple cell surface proteins [27]. Mounting evidence suggests that Merlin is involved in regulation of contact-dependent inhibition of cellular proliferation through a complex network involving cell surface proteins and several intracellular signalling pathways such as the Hippo, Notch, and Patched pathways [28]. There is also evidence that inactivation of Merlin leads to downstream activation of mTOR in meningioma cell lines [29, 30]. Interestingly, allelic losses and decreased expression of DAL1, another member of the 4.1 protein family, have been described in meningioma to varying degrees [23, 31].

While NF2 loss is likely sufficient to drive formation of grade-I meningiomas, other genes may be involved in meningiogenesis and in progression to higher grades [32]. Grade-II and -III meningiomas tend to harbour greater levels of genomic disruption, especially chromosomal losses [33]. Loss of the tumour suppressor CDKN2A/B has been linked to aggressive histology both in human tumours and in mouse models [7, 32], and frame-shift mutation of CDKN2C has also been shown in an NF2-mutant grade-II meningioma [24].

Unfortunately, development of medical therapies targeting NF2 loss in meningiomas has not been successful to date. Furthermore, approximately half of sporadic meningiomas of all grades lack discernible lesions in the NF2 gene [21, 22], leading researchers to re-examine the genetic landscape of sporadic meningiomas in the hopes of discovering additional genes that contribute to meningiogenesis and may be more amenable to targeted therapeutics.

■ Mutations in NF2-Wild-Type Grade-I Meningiomas

Several recent studies profiling the genomic alterations in meningiomas have identified a handful of novel genes as potential drivers of meningiomas, primarily of non-NF2 mutant meningiomas [24, 34, 35]. These genes include AKT1, SMO, TRAF7, and KLF4. Combined, mutations in these genes account for approximately 40 % of grade-I meningiomas, and are almost always mutually exclusive with NF2 loss. Mutations in these genes are found primarily in grade-I meningiomas of the skull base, a region that increases risks of surgical resection and radiation therapies. These mutations also correlated with histological subtype: while NF2 mutations confer a fibrous histology, AKT1 and SMO mutations were present in tumours of meningothelial and transitional histology, and combined TRAF7 and KLF4 mutations were found almost exclusively in the rarer secretory subtype.

Identical mutations in the proto-oncogene AKT1 (E17K substitution) have been found in 27 % of non-NF2 mutant grade-I meningiomas, primarily those of the skull base [24, 34]. This mutation is a known oncogenic alteration frequently encountered in breast, thyroid, lung, and endometrial cancers [36–

38]. The alteration in charge causes constitutively active AKT, leading to activation of downstream mTOR signalling. Meningiomas with the AKT1 E17K mutation show gene expression patterns distinct from NF2 mutant tumours [34] and show immunohistochemical evidence of downstream pathway activation of the mTOR pathway [24]. Interestingly, a novel mutation of MTOR (D1279V) also caused similar downstream activation in an AKT1 wild-type tumour [24]. Targets of the PI3K/AKT/mTOR pathway are already in clinical use in other cancer types [39].

Mutations in the hedgehog signalling member SMO were found in 9 % of non-NF2 mutant grade-I meningiomas, which were mostly located in the anterior midline skull base [24, 34]. Two different mutations in SMO, L412F and W535L, had similar effects on gene expression [34] and downstream pathway activation as measured by GAB1 immunostaining [24]. These mutations have been previously characterized in other tumours such as basal cell carcinoma [40] and desmoplastic medulloblastoma [41]; hedgehog pathway inhibitors are already in use clinically for these tumours [42].

The pro-apoptotic E3 ubiquitin ligase TRAF7 was mutated in 12–25 % of all meningiomas profiled [19, 29] and frequently co-existed with mutations in AKT1 or KLF4, a transcription factor associated with induction of pluripotency in other cell types. Interestingly, the combination of TRAF7/KLF4 mutations was characteristic of all secretory meningiomas profiled [35]. While the mechanisms by which KLF4 and TRAF7 lead to meningioma development are unclear, it is clear from gene expression analyses that distinct differences are observed between these tumours and those driven by NF2 loss [34]. It also remains to be seen whether these mutations, like those in AKT1 and SMO, are amenable to generation of targeted medical therapeutics.

■ Mutations in Epigenetic Modifiers

Mutations in genes categorized as epigenetic modifiers (genes that directly or indirectly modify chromatin structure leading to differential expression of many genes) were identified in 8 % of meningiomas in one recent study [24]. Among these were the histone demethylases KDM5C and KDM6A, as well as the SWI/SNF complex member SMARCB1. The SMARCB1 gene is located 6 Mb from NF2 on chromosome 22, and a “4-hit” model of biallelic inactivation of both genes has been described in familial schwannomas [43]. Interestingly, mutations in SMARCB1 appear to cluster within a small region of the C-terminus, suggesting a gain or alteration of function in these tumours [24, 44]. Germline mutation in the related gene SMARCE1 has also been implicated in familial spinal meningioma [45]. While mutations in epigenetic modifiers are clearly implicated and may be causative in a minority of meningiomas, the mechanisms by which they act remain unknown.

■ Genomic Rearrangements

While most grade-I meningiomas have non-aneuploid genomes or harbour only loss of chromosome 22, a small proportion of these benign tumours show more complex genomic

rearrangements that can affect numerous genes. For example, whole-genome sequencing of a radiation-induced meningioma identified a copy-neutral inversion on chromosome 22 leading to truncation of the NF2 gene in the first intron and fusion with nearby gene TCF-20; this represents a novel mechanism of NF2 disruption, one which would not be detectable with standard exome sequencing or array-based copy number analyses [24]. Another tumour in the same cohort analysed harboured chromothripsis, a simultaneous rearrangement of one or more chromosomes estimated to occur in 2–3 % of aggressive malignancies [46], affecting a large portion of chromosome 1. This rearrangement disrupted the putative tumour suppressor NEGR1, which was also disrupted by rearrangement in a second meningioma [24]. While interchromosomal rearrangements are sufficient to drive several haematologic malignancies and solid tumours, it has yet to be demonstrated whether such alterations are drivers or passengers in meningioma formation.

Conclusions

Recent advances in genetic analysis of tumours through whole-genome and whole-exome sequencing have facilitated the discovery of several new candidate drivers of meningioma genesis, particularly in those tumours that harbour no discernible defects in the tumour suppressor NF2. Several of these recurrent mutations, specifically those in AKT1 and SMO, are promising as treatment targets as there are already drugs in development or use targeting these mutations in other tumour types.

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Conflict of Interest

RB is a shareholder for AstraZeneca and consults for and receives research support from Novartis.

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