Review

Meningiomas – insights into genetics and correlations with histological features

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Abstract

Meningiomas are the most common intracranial tumors. They occur more frequently in women and may be completely asymptomatic. According to the World Health Organization, the ability to invade and to develop recurrences represents the criterion which is used to designate three grades of meningiomas. In the last decade, advanced knowledges in genetics and molecular biology have improved our understanding of the clinical behavior of meningiomas. In addition to mutation or loss of *NF2* gene, recurrent mutations of other genes, such as *TERT, TRAF7, AKT1, AKT3, SMO, KLF4, SMARCE1, POLR2A, SUFU, BAP-1, PIK3CA, TSLC1, CDNK2A, PTCH1, TP73, PTEN, NDRG2, S6K,* and *CDNK2B* have been identified within subsets of meningiomas. This review provides an overview and updates of the current knowledge of the genetics of meningioma in correlation with its histopathology. The insights into genetics and molecular profile of meningiomas may provide a valuable step towards developing new therapeutic approach for this type of intracranial tumor.

Keywords*: meningioma; meningothelial cells; WHO grade; NF2; gene mutations*

Introduction

Meningiomas are tumoral proliferations of meningothelial (arachnoid) cells, their location being as variable as the location of the component cells [1]. Since the first modern description of meningiomas by Cushing, at the beginning of the last century, the aim of numerous studies has been that of elaboration of specific criteria of aggressiveness in order to apply adequate therapeutic protocols [2, 3].

Currently, the scientists' interest regarding meningiomas is focused on defining the genetical profile of the tumor cells which is reflected in biological behavior, histologic type, location, clinical evolution, and prognosis. In this context, monosomy 22 and neurofibromatosis type 2 (NF2) diseases, harbouring inactivating mutations of *NF2* gene, have been the first genetic anomalies correlated to meningiomas development [4]. These initial observations have been later completed by the identification of other genetic alterations, such as *DAL-1, TRAF7, AKT1, KLF4, PTCH1, SMARCE1, BAP1, SMO,* and *PIK3CA* mutations [4, 5]. These mutations have been identified in approximate 80% of sporadic meningiomas [4, 5].

The knowledge of intratumor molecular heterogeneity is also important considering the possible occurrence of tumor subclones, especially in malignant meningiomas [6, 7]. Consequently, tumors would display therapy resistance and this may be addressed by alterative therapeutic tools, i.e. immunotherapy [6, 7].

All these accumulated data are opening new perspectives of targeted therapy and, subsequently, of improved prognosis, continuous research being needed for their clinical validation.

Epidemiology

Meningiomas represent approximate 15% of the total amount of cerebral tumors, being frequently located in the vicinity of venous sinuses, in the supratentorial region, along the medial area of parietal and frontal lobes, and in the sphenoid wing regions [8]. Less frequently, meningiomas may be located in the optic nerve sheath, cerebellopontine angle, choroid plexus, and spinal cord [8, 9]. Although, they are predominantly solitary lesions, multiple locations may be encountered in approximate 9% of patients [10].

Meningiomas represent about 37% of primary cerebral tumors in USA, with the standardised prevalence rate of 97.5/100,000 individuals, as the most frequent primary intracranial adult tumor [11]. It is estimated that 27,100 newly diagnosed patients would be registered in 2017, in USA [12]. The necroptic diagnosis of meningiomas is not unusual, as the annual incidence of these reports is 3.9-5.3/100,000 cases [13].

These tumors are encountered most frequently in adults, with a peak incidence in the 6th and 7th decades. Meningiomas represent just 1.4% to 4% of intracranial tumors in children [14]. However, aggressive meningiomas have been also reported in children, most of them being identified within variable genetic syndromes [14].

Women are more frequently affected, with women: men ratio of approximate 1.7-2:1 [15]. There are some researchers reporting an even greater female-to-male ratio (3.33:1) for the posterior fossa meningiomas [16]. This feature has suggested the hypothesis of estroprogestative hormones involvement in the etiopathogeny of the disease, without reliable evidences to support this assertion up to now [17, 18].

Next to genetic mutations, another contributor currently known to be associated to meningothelial tumor proliferation is represented by radiations to the head which have been demonstrated as facilitating factors of tumorigenesis [18, 19]. Commonly, the patients with a history of head radiation are developing more aggressive, atypical, or multifocal types of meningiomas [20].

Supplementary, studies performed in groups of children which had head radiation as therapeutic protocol for different types of cancer, have shown a direct correlation between high-dose radiotherapy and consequent meningiomas development [21, 22].

Although the hypothesis of dental radiographs involvement as an initiator of meningiomas formation has been launched, no direct correlation could be yet found between these two events [23-25].

Historical perspective and morphology fundamentals

The meningothelial tumors have been described in literature by different authors using variable terms, such as "epithelioma", or "dural endothelioma", or "angioendothelioma", or "fungus of the dura mater", or "fungoid tumors", or "psammoma", or "fibrosarcoma", or "meningeal fibroblastoma", or "meningoblastoma", or "mesothelioma of the meninges" [26-28].

The current term of "meningioma" was firstly used in 1922 by Harvey Cushing, for the characterization of a particular type of tumoral proliferation developed both in cerebral and in spinal cord locations [29].

However, the first documentation of this tumoral lesion had probably occurred several centuries before, in 1614, when Felix Plater, from University of Basel, registered in the autopsy of Sir Caspar Bonecurtius a relatively round tumor, with the size of a medium apple, exhibiting a firm consistence, covered by a membrane, entwined with veins, without a connection to the cerebral substance [28]. This is considered to be the first detailed gross description of a meningioma, in a patient showing progressive physical and mental decline [28, 30].

Although Plater is still considered the first person reporting a meningioma in the history of medicine, in fact this is not the first one registered in humans. This finding is based on the paleonthological studies performed on human fossils discovered in 1933, in a quarry near Steinheim an der Murr, in southern Germany, in which lesions compatible with meningioma had been found, dating for about

365,000 years old [28, 31]. Accordingly, this is the first case of benign leptomeningeal lesion resembling meningioma reported in *Homo erectus* line [28, 31].

Few centuries later from the first gross description, Zanobi Pecchioli, Professor of Surgery at the University of Siena, had performed, in 1835, the first documented surgical intervention in literature that registered the successful resection of a meningioma [32].

Virchow is the first one to describe sand-like granulations in these meningothelial proliferations and had named them "psammoma body", in 1863 [33], while Bailey and Bucy had demonstrated their origin from the arachnoid cap cells [34].

Gross and microscopic features

The meningiomas are well shaped tumors, sometimes showing a lobulated pattern, with an increased up to firm consistency. They often infiltrate dura or dural sinuses and less frequently the cranial bones, overlying skin, or cerebral arteries walls [15]. The subjacent nervous tissue is compressed, generally without a direct cerebral invasion [4]. When meningiomas are developing along the sphenoid wing, they are presenting as flattened tumoral masses, rendering their name of "en plaque meningioma" [15]. The atypical variants of meningiomas are much larger and commonly show areas of necrosis. The microcystic subtype is particular by intratumoral or peritumoral cysts formation [35, 36].

Meningiomas may be also localized in the orbit, rarely having the optic nerves sheath as an origin [15, 37]. They may be also located in the spinal cord (intradural extramedullary), mainly in its cervical thoracic region. Differently from the intracerebral location, spinal meningiomas may seldom infiltrate the adjacent bone tissue [15, 38].

Rare meningiomas locations may be: skin, nasal cavity, lung, or mediastinum, all of these may most probably represent the result of tumor proliferations developed in ectopic cellular areas exhibiting common structural and ultrastructural characteristics within meningothelial cells [39-42].

Although different in origin, meningiomas exhibit a multitude of microscopical features, a feature that has led to the necessity of their classification. In 1900, Engert proposed a first morphological classification into four types, as following: fibromatous, cellular, sarcomatous, and angiomatous [43]. This classification has been repeatedly modified both as number and nomenclature of meningiomas categories. Thus, according to Cushing and Bailey classification, realized in 1928, the meningiomas have been categorized into four types (meningothelial, fibroblastic, angioblastic, and osteoblastic), while Russell and Rubinstein, in 1971, have proposed a five-type classification (syncytial, transitional, fibroblastic, angioblastic, and mixed type) [44].

Currently, according to 2007 WHO classification revised in 2016, meningiomas are classified in 15 morphological types which have been categorized into three groups of variable aggressivity, according to their microscopical characteristics and clinical evolution. Thus, grade I, grade II (atypical), and grade III (malignant) meningiomas have been described (Table 1) [15, 45, 46]. Meningothelial (Figure 1), fibrous (Figure 2), and transitional meningiomas are the most prevalent WHO types registered in medical practice [15].

Nonetheless, the revision of some morphological criteria has been performed in 2016, allowing the classification of benign arachnoid cell proliferations into atypical meningioma type. Subsequently, nowadays, all meningiomas associated with the invasion of the cerebral nervous tissue are categorized as atypical meningiomas. The rationale of the implementation of this criterion of classification has been supported by clinical observations showing that patients diagnosed with grade I meningiomas associated with the infiltration of the subjacent cerebral nervous tissue showed the same risk of local tumor relapse and of mortality as those registered in grade II WHO meningiomas [45, 46].

Another aggressivity criterion for all types of meningiomas is the mitotic count. Accordingly, based on the same WHO classification, 4-19 mitoses/10 microscopic high-power fields (HPF) represents a criterion of increased tumor aggressivity for

meningiomas and, as a consequence, they are currently listed as atypical meningiomas.

Moreover, the diagnosis of atypical meningioma has to be supported by the association of three to five of the following morphological criteria: highly cellular tumors, with groups of small cells, exhibiting high nuclear: cytoplasmic ratio and conspicuous nucleoli, disposition into sheets, by changing the usual whorled pattern, along with tumor necrosis [45, 46]. Accordingly, meningiomas exhibiting less than 4 mitoses/10 HPF or maximum two of the previous morphological traits are categorized as grade I meningiomas [47]. If there is a loss of epithelial membrane antigen (EMA) expression, along with an increase in mitoses number, reaching more than 20 mitoses/10 HPF, meningiomas are regarded as Grade III [45, 46].

The microscopical features of the tumor cells are variable, as they may appear as clusters of cells without evident cell membranes, arranged in tight groups, in meningothelial type, or of elongated cells associated with an important collagen deposition in between them, in fibroblastic type of meningiomas [15]. In transitional meningioma, common features are noticed, exhibiting different proportions, characteristic both for syncytial and fibroblastic meningiomas, while numerous psammoma bodies are seen in psammomatous meningioma (Figure 3) [15, 44]. In secretory meningioma subtype, PAS-positive eosinophilic secretions, known as pseudopsammoma bodies, are identified [15, 44].

Atypical meningiomas show a group of morphological criteria associated to their enhanced aggressivity, expressed by an increased cellularity, high mitotic index and prominent nucleoli. Anaplastic types of meningiomas are the most aggressive categories, showing morphological traits which may mimic a sarcoma or a high grade carcinoma, complementary morphological examinations being necessary for tumor origin confirmation [44].
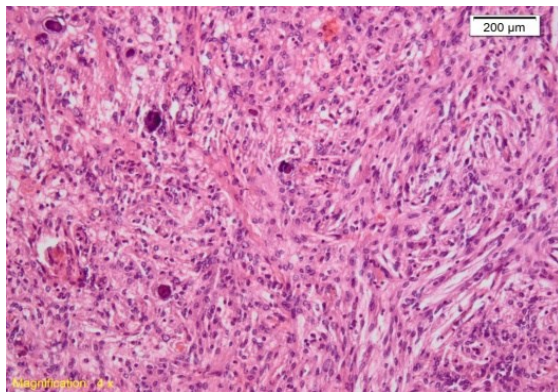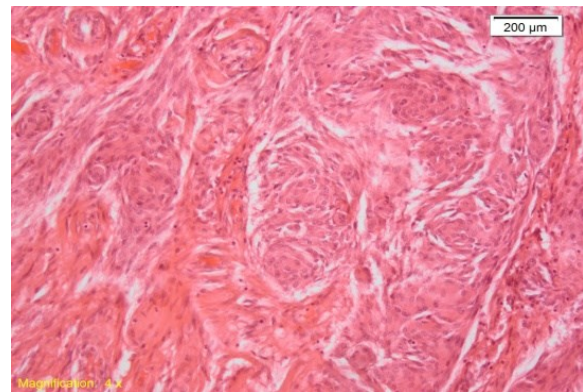

Fig. 1. Meningothelial meningioma (HE, x200)
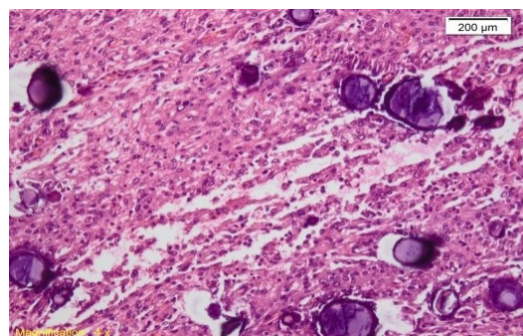

Fig. 2. Fibrous meningioma (HE, x200)

Fig. 3. Psammomatous meningioma (HE, x200)

Table 1. WHO classification of meningiomas (adapted after Louis et al., 2016) [15]

Meningioma WHO grade	Histological type
WHO grade I Meningioma	Meningothelial meningioma
	Fibrous meningioma
	Transitional meningioma
	Psammomatous meningioma
	Angiomatous meningioma
	Microcystic meningioma
	Secretory meningioma
	Lymphoplasmacyte-rich meningioma
	Metaplastic meningioma
WHO grade II Meningioma	Chordoid meningioma
	Clear cell meningioma (intracranial)
	Atypical meningioma
WHO grade III Meningioma	Papillary meningioma
	Rabdoid meningioma
	Anaplastic (malignant) meningioma

There are numerous evidences which support meningiomas origin from meningothelial cells of the arachnoid villi [3, 44]. Usually, in large venous sinuses, arachnoid extensions cross the entire thickness of the dura mater, slightly pushing the sinus endothelium inside the lumen. These prominences are exhibiting a connective tissue core covered by endothelium. They are forming the arachnoid villi which are directly connecting cerebrospinal fluid, from the arachnoid perforating the dura mater, to the sinuses lining endothelium [44]. The arachnoid villi represent the cerebrospinal resorption structures from the subarachnoid space to the venous system. With aging, arachnoid villi are increasing in size and may even become mineralized and, as a consequence, they become visible with naked eye, as granulations, known as Pacchionian granulation [48]. Electron microscopy studies along with molecular analyses have demonstrated that both arachnoid and tumor meningothelial cells have common ultrastructural features and similar matrix distribution of type I, III, and IV collagens, and laminin [49].

Genetic mutations in meningiomas and the signaling pathways targeted

Meningiomas are sporadic or developed within neurofibromatosis type 2 (NF2), an autosomal dominant genetic syndrome characterized by the mutation of *NF2* gene, located on chromosome 22q12.2 [8, 50]. Both *NF2* allele mutations are inducing the loss of merlin (schwannomin), protein which is involved in the regulation of leptomeningeal cells proliferation [8]. Both *NF2* alleles inactivation has been the first genetic defect described in patients diagnosed with this type of cerebral tumor [8]. *NF2* gene is strongly expressed in embryonic stage, while it is mainly expressed in meningeal and Schwann cells, in lens and nerves, in adults [50].

Merlin protein is part of 4.1 protein family, with homologies with other proteins, such as ezrin, radixin, and moesin [8]. Merlin is located underneath the cell membrane and acts in the regulatory mechanism of cell membrane-cytoskeleton interaction, by mediating the cell membrane adherence to Actin filaments, in Sodium ions transport, in motility, and in intercellular contact [51, 52]. Another function is that of tumor suppressor, by prevention of proliferation and uncontrolled growth of arachnoid, by inhibiting CUL4A-RBX1-DDB1-VprBP/DCAF1 E3 ubiquitin-protein ligase complex [53].

Merlin inactivation has been registered in up to 70% of meningiomas, a feature constantly identified in meningothelial rather than in fibroblastic tumor type [54, 55]. Additionally, *NF2* gene mutations along with a

reduced merlin expression are correlated with increased Yes-associated protein (YAP) which is involved in the regulation of the arachnoid cells proliferation rate [50, 52].

Not only *NF2* gene mutations are reported in literature (Table 2), but also other genetic anomalies responsible for different protein expression associated to meningiomas [52]. Specifically, loss of 4.1B (DAL-1) protein expression, as a result of *DAL-1* gene mutation, on chromosome 18p11.32, is inducing the perturbation of the arachnoid control of cellular proliferation [56]. The later finding is supported by studies showing that approximate 50% of benign meningiomas harbor multiple genetic mutations involving *TSC1* or both *NF2* and *DAL-1* gene [52, 56, 57].

Moreover, complex molecular analyses have revealed that an important percentage of meningiomas (30-85%) have intercellular adhesion and motility perturbations associated not to *DAL-1* but to *TSLC-1* gene. The latter is normally codifying a protein that mediates cell membrane adhesion to the cytoskeleton Actin, acting *via* DAL-1 protein [50, 52, 56].

Recent studies have revealed that the meningothelial tumor aggressivity is based on a multitude of genetic mutations registered in a list which has new members continuously added [3]. The analysis of this list reveals that associated mutations of cellular cycle, such as CDKN2A and CDKN2B, with mutations of genes located on chromosome 9, have been rarely detected in atypical type and more constantly in malignant types of meningiomas [15]. Moreover, CDNK2A mutations are associated with low patients' survival rate [2, 15, 58].

Other genetic mutations have been recently registered in about 40% of sporadic non-*NF2*-mutant meningiomas, involving intercellular communication regulators, i.e. *AKT1* or of cellular growth and proliferation, such as *AKT3* and *PIK3CA*, transcriptional regulators, such as *STAT3, POLR2A,* and *GL1,* cellular apoptosis coordinators, including arachnoid location, such as *TRAF7, c-fos,* or *bcl-2,* Hedgehog pathway regulating adult stem cells, involved in maintenance and regeneration of adult tissues, such as *SMO* and *SUFU,* cellular motility coordinators, i.e. *TERT*, and tumor suppressors, such as *KLF4* and *BAP1* (Table 2) [59–66].

These mutations are associated with morphological characteristics and with local aggressiveness, leading to the idea of a correlation between the spectrum of genetic mutations and their association with morphological type, along with therapy and evolution characteristics. In this regard, an almost exclusive association has been noticed between *KLF4* gene mutations with secretory meningioma phenotype, while *TRAF7* mutations are more frequently registered in non-secretory meningioma variants [67]. Moreover, *TRAF7/AKT1* and *SMO* mutations are correlated to particular locations, as corresponding meningiomas have been identified in anterior fossa, median middle fossa, or anterior calvarium [4]. Meningiomas associated to *TRAF7/KLF4* mutations are most constantly formed in certain locations, such as median posterior, anterior, median and lateral middle fossae and comprised by cells exhibiting an evident secretory feature [4].

Table 2. Correlation between genes along with their codified proteins functions and mutations associated to different meningiomas grade

Grade	Gene	Location	Synthesized protein	Protein function	References
Grade I Meningioma	NF2	22q12.2	merlin	tumor suppressor	[8, 50]
	YAP1	11q22.1	YAP / YAP1	transcriptional regulator in the Hippo signaling pathway	[50, 52]
	DAL-1	18p11.32	4.1B (DAL-1)	cell motility and adhesion	[4, 5, 52, 56, 57]
	TSC1	9q34.13	hamartin	cell growth and size regulation	[52, 56, 57]
	TRAF7	16p13.3	E3 ubiquitin ligase TRAF7	apoptosis inducer	[4, 5, 64, 67]
	POLR2A	17p13.1	RPB1 (DNA-directed RNA polymerase II subunit RPB1)	transcriptional regulation	[60]

	TSLC-1	11q23.3	cell adhesion molecule 1	mediates intercellular adhesion in a Ca(2+)-independent manner	[50, 52, 56]
Grade II Meningioma	TP73	1p36.3	p73	apoptosis inducer	[68-70]
	PTEN	10p23.3	phosphatidylinositol-3, 4,5-trisphosphate 3-phosphate	tumor suppressor	[69]
	AKT1	14q32.32	AKT1 kinase	intercellular communication	[4, 5, 63, 64]
	c-fos	14q24.3	c-fos	transcription factor	[59-66]
	bcl-2	18q21.33	Bcl-2	apoptosis regulator	[59-66]
	PTCH1	9q22.3	patched protein	Hedgehog pathway receptor	[4, 5, 70]
	GLI1	12q13.3	Zinc finger proteins	transcription factor	[59-66]
	STAT3	17q21.2	STAT3 protein	transcription factor	[59-66]
	CDNK2A	9p21.3	p16	tumor suppressor, cell cycle progression (G1/S phase)	[2, 15, 58]
	CDNK2B	9p21.3	p15	tumor suppressor, cell cycle progression (G1/S phase)	[15]
	TERT	5p15.33	hTERT	immortalization of cancer cells	[61]
Grade III Meningioma	TP73	1p36.3	p73	apoptosis inducer	[68-70]
	PTEN	10p23.3	phosphatidylinositol-3, 4,5-trisphosphate 3-phosphate	tumor suppressor	[69]
	SUFU	10q24	sufu	negative regulator in Hedgehog pathway	[66, 70]
	CDNK2A	9p21.3	p16	tumor suppressor, cell cycle progression (G1/S phase)	[2, 15, 58]
	CDNK2B	9p21.3	p15	tumor suppressor, cell cycle progression (G1/S phase)	[15]
	AKT1	14q32.32	AKT1 kinase	intercellular communication	[4, 5, 63, 64]
	bcl-2	18q21.33	Bcl-2	apoptosis regulator	[59-66]
	SMO	7q32.1	smoothened GPCR	cell localization (Hedgehog pathway)	[4, 5, 63, 64]
	PTCH1	9q22.3	patched protein	Hedgehog pathway receptor	[4, 5, 70]
	S6K	17q23.1	S6 kinase	cell growth, motility, and adhesion	[71]
	NDRG2	14q11.2	NDRG2	tumor suppressor	[68]
	PIK3CA	3q26.32	p110 alpha (p110α)	cell growth and division (proliferation)	[4, 5, 65]
	TERT	5p15.33	hTERT	immortalization of cancer cells	[61]
	KLF4	9q31.2	Kruppel-like factor 4	tumor suppressor	[4, 5, 62, 64, 67, 74-76]
	SMARCE1	17q21.2	SMARCE1	regulation of growth, division, and maturation (differentiation) of cells	[3, 4, 5, 72, 73]
	BAP1	3p21.1	BAP1	tumor suppressor	[4, 5, 59]
	AKT3	14q43.44	AK3 kinase	proliferation, cell survival, growth, and angiogenesis	[66]

In grade II and III meningiomas other mutations have been registered, such as *TP73,* a regulator of apoptosis, *PTEN* and *NDRG2* gene, as tumor suppressors, including the cerebral location, *PTCH1* genes, Hedgehog pathway receptor [68, 69, 70], and *S6K* gene, located on 17q23.1 chromosome, codifying a protein which coordinates cellular growth, motility, and intercellular adhesion [71].

Clear cell meningiomas are more frequently associated with mutations of *SMARCE1,* a regulator of cellular growth and proliferation, including the arachnoid location,

being different from angiomatous genotype which is characterized by multiple chromosomal polysomies, without *NF2* mutations [3, 72, 73]. Supplementary, *BAP1* mutations have been identified in aggressive meningiomas displaying a rhabdoid histomorphology [59].

However, an important percentage of meningiomas (up to 20% of sporadic types) lack any genetic mutations [5].

The radiation-induced meningiomas are different from spontaneous types, as the former frequently contain multiple chromosomal deletions involving

chromosomes 1p, 6q, 9q, 10q, 14q, 17p, and 18q, being rather multifocal and associated with an aggressive tumor behavior [2, 44]. As *NF2* gene mutations are extremely rare in these tumors, a different molecular mechanism seems to be involved in radiation-induced meningiomas.

Although documentations of genetic profile of meningiomas cells are available, the data are still incomplete, as much as intratumoral cellular heterogeneity is responsible for therapy resistance, along with loco-regional recurrences and metastases development in these tumors. This feature may be possibly related to meningeal cancer stem cells (CSCs) associated to tumor location. The current research focus is the isolation and the characterization of the molecular profile of these CSCs, as much as the arachnoid is made up of a heterogeneous cell population, containing meningothelial, fibroblastic and endothelial cells, but also some cells associated to arachnoid-dura interface. Up to now, results are supporting the possibility of such a CSC occurrence in meningeal tumors, expressing characteristic markers, such as CD133, c-Myc, KLF4, NANOG, nestin, OCT4, SOX2, and vimentin [74-76]. Furthermore, several pathways characteristically involved in stem-cell signaling, belonging to Fibroblast Growth Factor (FGF), Hedgehog, Transforming growth factorβ/Bone Morphogenetic Protein (TGFβ/BMP), or Wnt are responsible for the maintenance of CSCs

and pluripotent stem cells balanced values [77].

Nonetheless, the majority of issues regarding the meningeal stem cells are still waiting for answers, as their accurate characterization and identification might lead to a more efficient control of local tumor proliferation and a consequent prolonged therapeutic response.

Conclusions

The latest years' progresses regarding the genetic profile characterization of the tumor cells have led to the revival of the interest in meningiomas study. The results reported up to present have opened the possibility of a more appropriate correlation between genetic mutations type, microscopical features, and patients' management.

As the current management by chemotherapy and radiotherapy is not providing a complete cure, the discovery of new therapeutic approaches, by targeting CSCs, could open a new era, with the possibility of long term remission of these tumors.

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