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Genomic and Expression Alterations of Tumor Suppressor Genes in Meningioma Development, Progression and Recurrence

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1. Introduction

Meningiomas are solid tumors of the Central Nervous System arising from arachnoid layer cells, which cover the brain and spinal cord. Meningiomas account for about 34% of primary intracranial tumors, with an annual incidence rate of 6.17 per 100,000 person-year, as reported in a recent population-based study (Yee G. 2009). Many small meningiomas go unnoticed during life and are found incidentally in up to 1.4% of people in autopsy series (Rohringer, Sutherland et al. 1989).

In general, meningiomas display a broad range of histological patterns. The current World Health Organization (WHO) classification lists 16 different variants or subtypes, falling into 3 grade designations. The WHO classification of tumors of the nervous system distinguishes between grade I (benign), grade II (atypical) and grade III (anaplastic or malignant) meningiomas (Table 1, Fig. 1) (Perry, Louis et al. 2007). About 90% of all meningiomas are slowly growing benign tumors of WHO grade I. Atypical meningiomas constitute about 6-8% of cases, although using more current definitions, it has been reported in up to 20%. These WHO grade II meningiomas are histologically defined by increased mitotic activity (four or more mitoses per 10 high-power microscopic fields) and/or at least three of the following criteria: increased cellularity, high nucleus/cytoplasm ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth and necrosis. Approximately 2-3% of all meningiomas show histological features of frank malignancy, including a high level of mitotic activity (20 or more mitosis per 10 high-power microscopic fields) and/or a histological appearance similar to sarcoma, carcinoma or melanoma (Perry, Louis et al. 2007).

Tumor recurrence is the major clinical complication in meningiomas, occurring in 10-15% and 25-37% of patients undergoing curative surgery after 5- and 10-year follow-up periods, respectively (Mirimanoff, Dosoretz et al. 1985; Maillo, Orfao et al. 2007). The most important factors that determine the recurrence of meningiomas are the extension of the tumor resection and the histologic grade (Riemenschneider, Perry et al. 2006; Louis, Ohgaki et al. 2007). Therefore, prediction of relapse occurrence in meningiomas during the first few years following diagnostic surgery still remains a major challenge.

Up to date, none of the common genetic alterations of meningiomas have acquired clinical relevance. However, the analysis of these alterations in relation to histological grade has led to a model in which genetic aberrations are presumably involved in the formation of meningiomas, with subsequent alterations associated with tumor progression (Lomas, Bello et al. 2005; Martinez-Glez, Franco-Hernandez et al. 2008).
Meningiomas were among the first solid tumors recognized as being characterized by a specific cytogenetic alteration, which is monosomy 22. Since then, loss of genetic material from chromosome 22 has been the most consistent aberration, observed in up to 70% of tumors (Perry, Louis et al. 2007; Martinez-Glez, Franco-Hernandez et al. 2009).
Familial occurrence of meningiomas is found in patients with neurofibromatosis type 2 (NF2), usually with multiple meningiomas, as also occurs in other non-NF2 families with predisposition to meningioma. Approximately 50% of NF2 patients suffer from meningiomas, making them the second most frequent neoplasm associated with this tumor syndrome. Sporadic meningiomas were then screened for mutations in the NF2 gene, which was found to be frequently inactivated in up to 60-70% of meningiomas. Therefore, the NF2 gene, located at 22q12.2, is considered the main candidate for the genesis of meningiomas, having a role as a tumor suppressor gene (TSG) (Louis DN and JJ 2000; Martínez-Glez V. 2007).

Meningiomas with low risk of recurrence and aggressive growth	
WHO grade I	Meningothelial meningioma
	Fibrous (fibroblastic) meningioma
	Transitional (mixed) meningioma
	Psammomatous meningioma
	Angiomatous meningioma
	Microcystic meningioma
	Secretory meningioma
	Lymphoplasmacyte-rich meningioma
	Metaplasic meningioma
Meningiomas with greater risk of recurrence and aggressive growth	
WHO grade II	Chordoid meningioma
	Clear cell meningioma
	Atypical meningioma
WHO grade III	Papillary meningioma
	Rhabdoid meningioma
	Anaplastic (malignant) meningioma

Table 1**.** Meningioma grouped by likelihood of recurrence and grade (Perry, Louis et al. 2007).

Other cytogenetic changes secondary to the 22q anomaly, and which are involved in tumor progression to atypical and anaplastic meningiomas, are losses of 1p, 6q, 14q, chr.10, 18q, and gains of 1q, 9q, 12q, 15q, 17q, and 20q (Bello, de Campos et al. 1994; Perry, Gutmann et al. 2004; Perry, Louis et al. 2007; Martinez-Glez, Franco-Hernandez et al. 2009).
Epigenetic alterations seem also to play an important role in the tumorigenesis of meningiomas, as occurs in many other tumor types. These alterations indicate that the silencing by aberrant hypermethylation of gene promoter regions contributes to the genesis and tumor progression of meningiomas (Martinez-Glez, Franco-Hernandez et al. 2008). In

these tumors, aberrant promoter hypermethylation of CpG dinucleotides of several TSG has been described, including *NF2* (26%), *THBS1* (15-30%), *TIMP-3* (24%), *CDKN2A* (10-17%), *MGMT* (6-16%), *p73* (15%), *ER* (15%), *GSTP1* (27%), *RB1* (10%), *DAPK1* (4%), *VHL* (4%) and *CDKN2B* (4-13%) (Bello, Amiñoso et al. 2004; Liu, Pang et al. 2005).

2. Molecular alterations involved in the pathogenesis of meningiomas

2.1 The *NF2* gene

The tumor suppressor gene NF2, located at 22q12.2, is considered the main candidate for the genesis of meningiomas (Martinez-Glez, Franco-Hernandez et al. 2009). Allelic losses of the 22q12.2 chromosomal region encompassing the NF2 gene are found in 40–70% of the sporadic and the vast majority of NF2 associated meningiomas. Additionally, NF2 mutations are found in up to 60-70% of tumors, consistent with a classic two-hit mechanism of tumor suppressor gene inactivation (Ruttledge, Sarrazin et al. 1994). Most of these NF2 mutations are small insertions, deletions, or nonsense mutations affecting splicing sites, with a frequency of NF2 mutations roughly equal among different WHO grades, suggesting that it represents an important initiation rather than progression-associated alteration (Wellenreuther, Kraus et al. 1995).

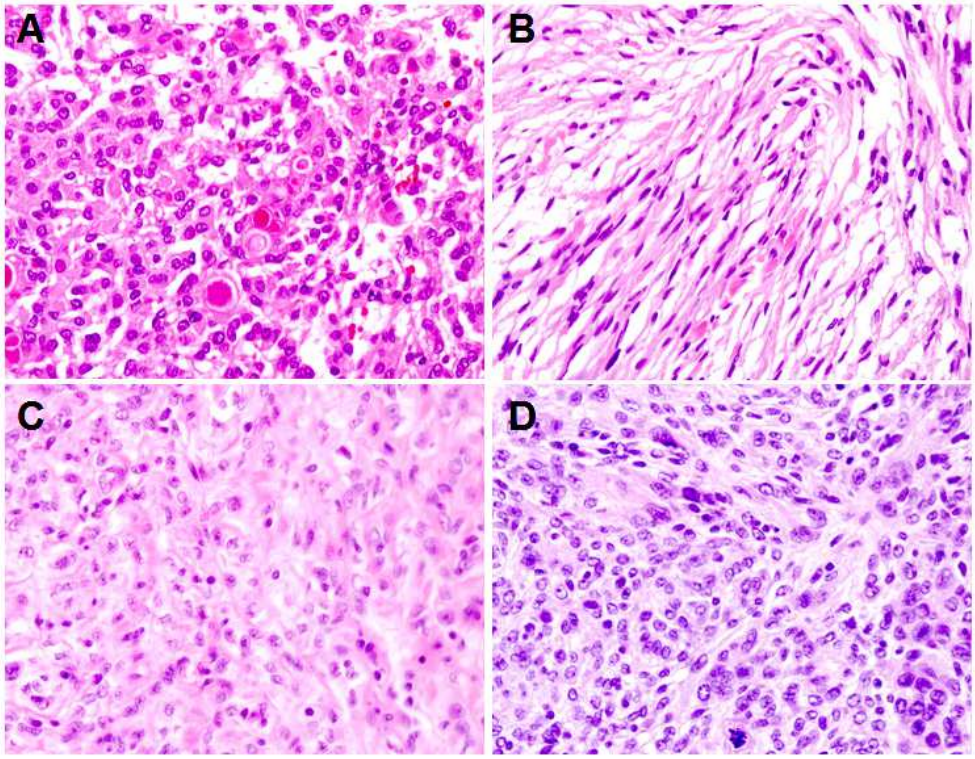

Fig. 1. Histopathological images of a WHO grade I secretory meningioma (A), a WHO grade I fibrous meningioma (B), a WHO grade II atypical meningioma (C), and a WHO grade III anaplastic meningioma (D).

In contrast, differences in the frequency of NF2 alterations have been noted based on variant histology, with higher rates in fibroblastic, transitional and psammomatous than in meningothelial or secretory grade I meningiomas (Wellenreuther, Kraus et al. 1995; Hansson, Buckley et al. 2007; Mawrin and Perry 2010). Thus, NF2 alterations appear to play a preferential role in the mesenchymal like phenotype of meningiomas. Support for this comes from the observation that non-NF2 meningioma families are more likely to develop meningothelial tumors.

Transcriptional silencing by hypermethylation of CpG islands in the promoter region has been accepted as an alternative mechanism to genetic inactivation of tumor-suppressor genes. In fact, site directed mutagenesis demonstrated that a 70-bp region on the *NF2* promoter (-591 to -522 bp from the transcription start site) was essential for the basic expression of the NF2 gene (Kino, Takeshima et al. 2001). At least three CpG sites within this region (at positions -591, -586 and -581) appeared to be of particular importance for silencing of the NF2 gene upon methylation in schwannomas, with the methylation status consistent with the expression/silencing of NF2 mRNA.

In this sense, aberrant methylation of the NF2 gene was detected as the sole alteration in samples of sporadic meningiomas, most of which from grade I tumors (Lomas, Bello et al. 2005). Methylation analysis in two other studies, however, concluded that methylation of the *NF2* promoter is unlikely to play a major role in the silencing of the NF2 gene in meningiomas (van Tilborg, Morolli et al. 2006; Hansson, Buckley et al. 2007).

Alternatively, the NF2 gene may also be inactivated in meningiomas by increased calpain-mediated proteolysis of merlin. Kimura *et al*. demonstrated cleavage of merlin by the ubiquitous protease calpain in meningioma tumors, together with considerable activation of the calpain system resulting in the loss of merlin expression (Kimura, Koga et al. 1998).

The protein product of the *NF2* gene is termed merlin or schwannomin, and meningiomas with associated *NF2* alterations commonly result in a truncated, non-functional merlin protein. Merlin is a member of the 4.1 family of membrane-associated proteins, which also includes proteins ezrin, radixin and moesin. These proteins contribute to the interaction between glycoproteins of the cellular surface and the actin cytoeskeleton, functioning to link cell surface signaling to intracellular pathways (Curto and McClatchey 2008). Thus, alterations in merlin may subtantially affect cell shape and might favor the appearance of a more mesenchymal-like phenotype rather than the epithelioid one, seen more commonly in *NF2* intact meningiomas.

2.2 DAL1/4.1B, a member of the 4.1 protein family

In addition to *NF2*, another gene coding for a member of the 4.1 family of proteins is *DAL1*. This gene encodes for the Protein 4.1B, located on chromosome 18p11.3. *DAL1* gene is generally expressed at high levels in the brain and low levels in the kidney, intestine and testicles (Martinez-Glez, Franco-Hernandez et al. 2008).

DAL1 loss, together with reduced protein expression of its gene product was detected in sporadic meningiomas, affecting more than 70% of tumors regardless of histological grade (Gutmann, Donahoe et al. 2000; Perry, Cai et al. 2000).

This frequency is similar to that of *NF2* absence of protein expression, suggesting that *DAL1*, similarly to *NF2,* could play an important role as an early event in the tumorigenesis of meningiomas.

The similarity between the *DAL1* protein and merlin, with their high levels of expression in the brain and their recurrent loss in meningiomas, led to a mutational study of *DAL1* in a

series of sporadic meningiomas (Martinez-Glez, Bello et al. 2005). The low mutational frequency of this gene discounts sequence variations in *DAL1* as the main mechanism underlying participation of this gene in the neoplastic transformation of meningiomas, and suggests that other inactivating mechanism, such as epigenetic changes, may participate in *DAL1* silencing (Martinez-Glez, Bello et al. 2005).

Additional analyses have shown that *DAL1* suppresses the growth and cellular proliferation in meningiomas by activating, among others, the Rac1-dependent c-Jun-NH(2)-kinase signaling pathway (Martinez-Glez, Franco-Hernandez et al. 2008). However, the fact that transgenic mice lacking *DAL1* do not develop tumors (Yi, McCarty et al. 2005), suggests that DAL1 alterations may represent an early progression associated rather than an initiation event for the development of meningiomas. This suggestion is also supported by the observation of losses of chromosome 18 not preferentially of the 18p11.3 region, but instead associated with clinically aggressive tumors.

The absence of expression of two proteins of the Protein 4.1 family in most of sporadic meningiomas suggests that membrane-associated alterations are important events for the development and/or progression of meningiomas. Future experiments however would be necessary to address the functional role of these proteins in leptomeningeal and meningioma cells which may lead to define membrane- or cytoskeletal-associated pathways in tumorigenesis of meningiomas.

2.3 TSCL1 and 14-3-3 are DAL1/4.1B interacting proteins

A potential interaction with protein 4.1B has been reported for the *Tumor Suppressor in Lung Cancer-1* (*TSLC1*) gene, prompting the study of *TSCL1* in meningiomas. *TSCL1* was originally identified as a transmembrane protein involved in specifying cell adhesion. TSLC1 interacts with the actin filament through DAL-1 at the cell-cell attached site where the complex formation of TSLC1 and DAL-1 is dependent on the integrity of actin cytoskeleton (Yageta, Kuramochi et al. 2002).

Surace *et al.* demonstrated that *TSCL1* is expressed in human leptomeningeal tissues, but is absent in 30% to 50% of benign meningiomas, 70% of atypical, and 85% of anaplastic meningiomas. Atypical meningiomas with high proliferative indices and most of WHO grade III meningiomas showed loss of *TSCL1* expression, while atypical meningiomas with brain invasion but low mitotic index had a similar frequency of loss to that of the benign meningiomas (Surace, Lusis et al. 2004).

Moreover, these authors reported a strong correlation between loss of *TSCL1* expression and decreased patient survival. When WHO grade II were stratified by their *TSCL1* expression status, *TSCL1* loss was correlated with reduced patient survival, irrespective of mitotic index. These findings raise the possibility that *TSCL1* may be an independent predictor of survival for patients with atypical meningioma (Surace, Lusis et al. 2004).

Similarly, other study identified 14-3-3 as a 4.1B–specific interacting protein (Yu, Robb et al. 2002). The 14-3-3 family of proteins are adaptor proteins involved in signal transduction regulation, with a role in cell growth, survival or apoptosis. However, impaired 14-3-3 seems not to affect 4.1B function, suggesting additional proteins involved in 4.1B signaling. The potential importance of 14-3-3 proteins for meningioma growth control is underlined by a recent report showing reduced immunoexpression of certain 14-3-3 protein isoforms in aggressive meningiomas (Mawrin and Perry 2010). Thus, the precise roles of protein 14-3-3 interactions with 4.1B have yet to be determined.

2.4 Other 22q tumor suppresor genes

The close association of *NF2* mutations in meningiomas with allelic loss on chromosome 22 suggests that *NF2* is the major meningioma tumor suppressor gene on that chromosome (Xiao, Gallagher et al. 2005; van Tilborg, Morolli et al. 2006; Simon, Boström et al. 2007; James, Lelke et al. 2008; Striedinger, VandenBerg et al. 2008; Martinez-Glez, Franco-Hernandez et al. 2009; Shen, Nunes et al. 2009). Nonetheless, deletion studies of chromosome 22 have detected losses and translocations of genetic material outside the *NF2* region, thus raising the possibility of other meningioma genes residing on chromosome 22. Candidate genes, among others, include *BAM22, BCR* and *TIMP3* (Fig 2).

BAM22 gene belongs to the human β-adaptin gene family. Adaptins are essential for the formation of clathrin coated vesicles in the course of intracellular transport of receptor-ligand complexes.

The *BAM22* gene has been proposed as a second chromosome 22 locus important in meningioma development, after the neurofibromatosis type 2 gene (Peyrard, Fransson et al. 1994; Guilbaud, Peyrard et al. 1997).

Recently, reduced expression of breakpoint cluster region (BCR) mRNA was found. It has appeared to be downregulated in meningiomas with loss of heterozygosity of 22q. The *BCR* gene is an extremely interesting tumor suppressor candidate, since NF2 and BCR proteins perform similar functions (Wozniak, Piaskowski et al. 2008). BCR contains a serine/threonine kinase that functions as a GTPase-activating protein for p21. The inactivation of *BCR* as well as *NF2* might lead to hyperactivation of RAC pathway, and together with the downregulation of the gene, suggest that *BCR* can be considered as a tumor suppressor candidate (Wozniak, Piaskowski et al. 2008).

Matrix metalloproteinases (MMPs) are proteases capable of degrading extracellular matrix proteins. They are involved in the cleavage of cell surface receptors, the release of apoptotic ligands, and chemokine/cytokine inactivation, playing an important role on cell proliferation, migration (adhesion/dispersion), differentiation, angiogenesis, apoptosis and host defense. The *TIMP3* (tissue inhibitor of metalloproteinase 3) gene on 22q12.3 codes for a protein that can specifically inhibit MMPs by covalent binding to the active site of the enzymes and thus reduces the invasion and the metastatic potential of tumor cells. In addition, overexpression of TIMP3 *in vitro* induces apoptosis and suppresses tumor growth and angiogenesis in different cell line models (Barski, Wolter et al. 2010).

Numerous reports have demonstrated the loss of expression of TIMP3 in meningiomas using diverse approaches, such as microarray expression profiling, real-time reverse transcription PCR analyses or immunohistochemical protein expression studies (Carvalho, Smirnov et al. 2007; Fèvre-Montange, Champier et al. 2009; Barski, Wolter et al. 2010; Pérez-Magán, Rodríguez de Lope et al. 2010). In addition, hypermethylation of the promoter region of *TIMP3* gene has been analyzed showing controversial results (Bello, Amiñoso et al. 2004; Liu, Pang et al. 2005). Recently, *TIMP3* hypermethylation has been associated with meningioma progression, due to 67% of anaplastic meningiomas showed hypermethylation of the *TIMP3* promoter, while this was true for only 22% of atypical and 17% of benign meningiomas. In addition, *TIMP3* hypermethylation and transcriptional downregulation were found exclusively in meningioma with allelic losses on 22q12, in contrast to *NF2* mutation (Barski, Wolter et al. 2010; Pérez-Magán, Rodríguez de Lope et al. 2010). Taken togheter, all these results point out *TIMP3* as an important candidate tumor suppressor gene located in 22q, besides *NF2*.

Other genes located on chromosome 22q have also been proposed as possible TSG candidates: *MN1*, *SMARCB1*, *LARGE*, *RRP22* and *GAR22.* The *MN1* gene (22q12.1) was

found to be disrupted by a balanced translocation in meningioma, although more recent studies suggest a role as a co-activator of the oncogenic transcription than as a TSG (Martínez-Glez V. 2007; Perry, Louis et al. 2007). The protein encoded by the *SMARCB1* gene (22q12.3) is part of a complex that relieves repressive chromatin structures, allowing the transcriptional machinery to access its targets more effectively.

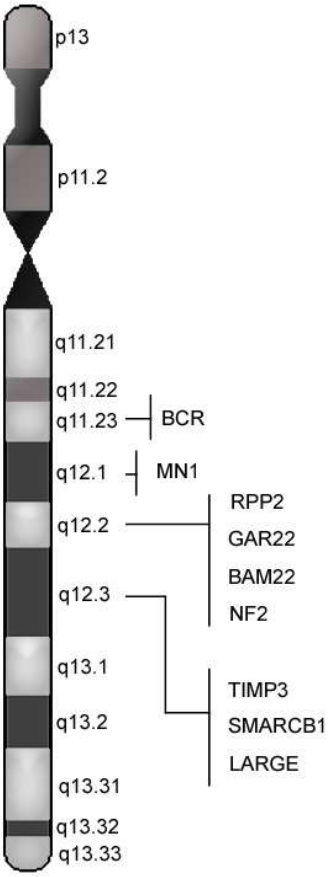

Fig. 2. View of chromosome 22 including candidate TSG involved in meningiomas.

This gene has been found to be a tumor suppressor, and mutations in it have been associated with malignant rhabdoid tumors (Oruetxebarria, Venturini et al. 2004; Martinez-Glez, Franco-Hernandez et al. 2008). In addition, the *LARGE* gene (22q12.3) might be involved in genomic rearrangements associated with tumors (Martinez-Glez, Franco-Hernandez et al. 2008). This gene, which is one of the largest in the human genome, encodes a member of the N-acetylglucosaminyltransferase gene family. Other genes identified in the long arm of chromosome 22 are tumor suppressor genes and are located on 22q12.2, near to NF2: *RRP22* and *GAR22*. The *RRP22* have been identified as a novel, farnesylated member of the Ras superfamily that exhibits the properties of a potential neural-specific tumor

suppressor and is implicated in the regulation of nucleolar transport processes (Elam, Hesson et al. 2005). The protein encoded by the gene *GAR22*, a member of the GAS2 family, is an actin-associated protein expressed at high levels in growth-arrested cells (Goriounov, Leung et al. 2003)

3. Molecular alterations involved in meningioma progression

Meningiomas are generally thought to progress from low-grade to high-grade tumors, although this is not always easy to demonstrate clinically. Indeed, none of the typical genetic aberrations found in meningiomas have acquired clinical relevance. Nevertheless, the analysis of the genetic aberrations in relation to the histologic grade pointed out that malignant progression in meningiomas is associated with the acquisition of additional genetic changes, in a stepwise model for acquisition of chromosomal gains and losses during meningioma progression (Weber, Boström et al. 1997).

As mentioned before, chromosome 22 monosomy or 22q deletions are the most frequent genetic alteration found in meningiomas, and thus are considered as an early event involved in the pathogenesis of meningiomas. Secondary to 22q alterations, genetic changes most frequently associated with meningiomas include 1p and 14q deletions. Moreover, these alterations have been related to tumoral progression in meningiomas (Leone, Bello et al. 1999; Buckley, Jarbo et al. 2005; Espinosa, Tabernero et al. 2006; Maillo, Orfao et al. 2007; Martinez-Glez, Franco-Hernandez et al. 2008).

Genetic alterations in atypical meningiomas include allelic losses of 1p, 6q, 10, 14q and 18q and gains of 1q, 9q, 12q, 15q, 17q and 20q. Anaplastic meningiomas frequently show losses of 6q, 10q and 14q as well as gains and/or amplifications on 17q23 (Weber, Boström et al. 1997; Louis DN and JJ 2000; Martínez-Glez V. 2007; Martinez-Glez, Franco-Hernandez et al. 2008).

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4. Altered regions in meningioma progression

4.1 Loss of 1p

Loss of 1p represent the most frequent genetic alteration secondary to chromosome 22 tumor suppressor gene inactivation (*NF2*/others), which seems to participate in the genesis of the aggressive meningiomas, as this anomaly is found predominantly in atypical (40-76%) and anaplastic forms (70-100%), as opposed to benign meningiomas (13-26%) (Bello, de Campos et al. 1994; Bello, de Campos et al. 2000; Maillo, Orfao et al. 2007; Pérez-Magán, Rodríguez de Lope et al. 2010).

Loss of heterozygosity assays revealed two regions mainly involved in meningioma progression, including 1p36 and 1p32-34, although other regions less frequently lost were also detected at 1p22 and 1p21.1-p13 (Bello, de Campos et al. 2000). Furthermore, a comprehensive study of DNA copy number profiling analysis in meningiomas revealed three 1p and one 1q candidate sites of genomic imbalance on chromosome 1, which may be relevant for meningioma development and progression (Buckley, Jarbo et al. 2005). Therefore, these regions may contain one or more tumor suppressor genes important for meningioma progression. Candidate genes have been pointed out, among others: *ALPL*, *TAp73*, *EPB41*, *RAD54L*, *GADD45A*, *CDKN2C*, and *LMO4*.

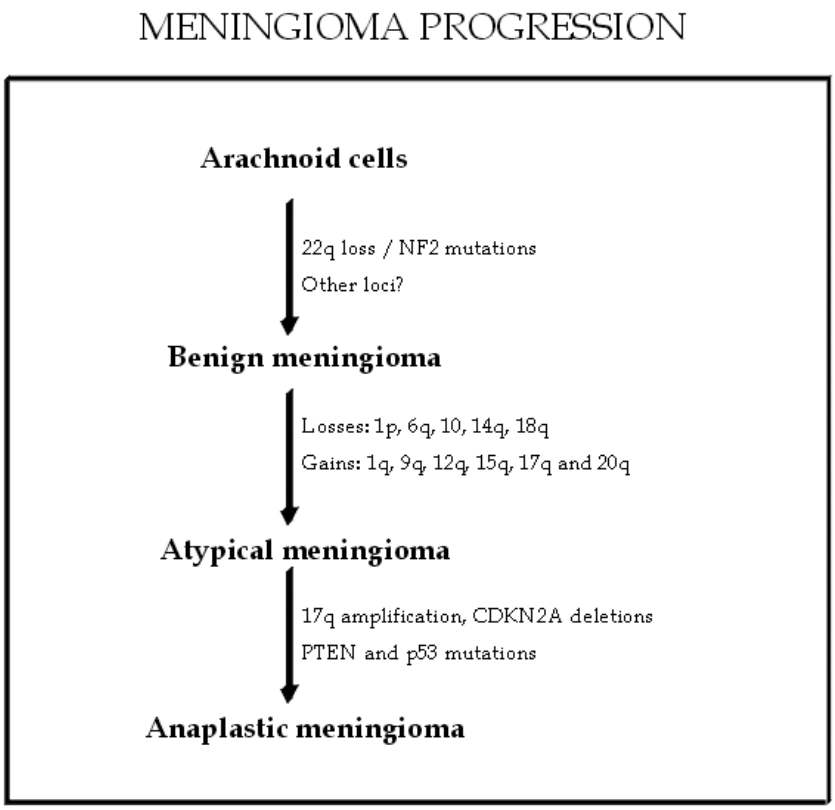

Fig. 3. Molecular alterations associated with tumor progression in meningiomas.

4.1.1 Candidate genes located at 1p36: *ALPL* and *TAp73*

The *ALPL* gene maps to chromosome 1p36.12, and codes for the tissue non-specific form of alkaline phosphatases (APL). In contrast to the brain tissue, the meninges constitutionally exhibit a strong cellular activity of this enzyme, being present in both cytoplasmic membrane and cytosol. Alterations of 1p together with loss of enzyme activity were found in meningiomas, revealing this gene as a good candidate TSG (Müller, Henn et al. 1999). Additionally, the functional expression of the alkaline phosphatase has been related to the mineralization capacity observed in meningiomas, and its loss of expression was associated with increased tumor aggressiveness (Müller, Henn et al. 1999; Sayagués, Tabernero et al. 2007). Further studies of this gene, however, are required.

TAp73 encodes for a protein with significant homology to the p53 tumor suppressor gene throughout its DNA-binding, transactivation, and oligomerization domains. Despite this similarity, animal models showed that p73 is an important player in neurogenesis, sensory pathways and homeostatic control, but its function in tumorigenesis is controversial (Moll and Slade 2004). Mutational analyses of *p73* have been performed in a wide variety of tumor types and, up to date, *p73* is not the target of inactivating mutations in human cancers,

including meningiomas (Lomas, Bello et al. 2001). Aberrant *p73* hypermethylation was also analyzed in meningiomas, showing that although it was more frequent in those tumors with 1p deletion, an independent association of *p73* promoter methylation with the grade of malignancy could not be established (Lomas, Amiñoso et al. 2004). Nevertheless, another study detected 1p LOH and *p73* promoter hypermethylation in the malignantly transformed tumors but not in the lower-grade primary ones (Nakane, Natsume et al. 2007).

4.1.2 Candidate genes located at 1p33-32: *EPB41*, *RAD54L* and *CDKN2C*

The *4.1R* gene (1p33-32), or *EPB41*, belongs to the Protein 4.1 family, which also includes the products of the *NF2* and *DAL1* genes, merlin and Protein 4.1B, respectively. *EPB41* was described to function as a tumor suppressor gene in meningiomas, through the demonstration of both, allelic loss of the *4.1R* gene by FISH, and loss of Protein 4.1R expression in sporadic meningiomas and cell lines by using immunohistochemical assays and western blotting. Moreover, *in vitro* functional experiments in meningioma cell lines supported a tumor suppressor function in these tumors (Robb, Li et al. 2003). Opposite results were obtained by Piaskowski *et al*. (2005) who find no change of mRNA expression between meningionmas with 1p LOH and those without it (Piaskowski, Rieske et al. 2005).

The human homologue of the *Saccharomyces cerevisiae RAD54* DNA repair gene (*hRAD54*) is located at 1p32 (Rasio, Murakumo et al. 1997). The protein encoded by this gene plays a role in homologous recombination related repair of DNA double-strand breaks. The *RAD54L* gene was proposed as a candidate for a tumor-associated gene in neoplasms that display 1p allelic imbalance, such as in meningiomas. However, mutational analysis of this gene in a series of 25 oligodendrogliomas and 18 meningiomas failed to identify any deletions or inactivating mutations of the gene (Mendiola, Bello et al. 1999; Bello, de Campos et al. 2000; Bello, de Campos et al. 2000).

The $p18^{INKC}$ gene (*CDKN2C*, 1p32) is a member of the INK4 family of cycline-dependent kinase (CDK) inhibitors, together with $p16^{INK4a}$, $p15^{INK4b}$, and $p19^{INK4d}$. These inhibitors participate in cell cycle regulation by inhibiting the activity of CDK–cyclin complexes. *CDKN2C* was considered a potential tumor suppressor gene in meningiomas due to its similarities with other members of the INK4 family.

However, absence of genetic and epigenetic alterations of *CDKN2C*, together with no altered protein expression in meningiomas ruled out this gene as the major target of the frequent 1p32 losses in meningiomas (Santarius, Kirsch et al. 2000; Boström, Meyer-Puttlitz et al. 2001).

4.2 Loss of 14q

Another frequent cytogenetic anomaly in meningiomas is the loss of 14q, which shows increasing frequencies paralleling the increase in tumor grade. Therefore, about a third of benign meningiomas show the 14q loss, while 40-57% and 55-100% of atypical and anaplastic tumors, respectively, present this loss (Weber, Boström et al. 1997; Ozaki, Nishizaki et al. 1999; Cai, Banerjee et al. 2001; Simon, Boström et al. 2007; Tabernero, Maillo et al. 2008). Various studies have described different regions ranging from 14q21 to 14q32 (Weber, Boström et al. 1997; Martinez-Glez, Franco-Hernandez et al. 2008). To date, however, the actual targets of this chromosomal lost have been remained large elusive and thus, no 14q tumor suppressor genes have been confirmed in meningiomas. Nevertheless, several 14q tumor suppressor candidate genes have been evaluated, namely *NDRG2* and *MEG3*.

4.2.1 *NDRG2* (14q11.2)

This gene is a member of the N-myc downstream-regulated gene family. The protein encoded by this gene is a cytoplasmic protein that has been found involved in a variety of cancers. It is expressed in low-grade gliomas, but present at low levels or absent in primary glioblastoma. In meningioma tumors, Lusis *et al*. used a differential gene expression approach leading to the identification of *NDRG2* as a potential meningioma associated tumor suppressor gene that is inactivated during meningioma progression. Furthermore, these authors showed that the loss of NDRG2 expression was significantly associated with hypermethylation of the NDRG2 promoter (Liu, Pang et al. 2005; Lusis, Watson et al. 2005).

4.2.2 *MEG3* (14q32)

Recently, it has been reported that the maternally expressed gene 3 (*MEG3*), which encodes a noncoding RNA, could be a tumor suppressor gene at chromosome 14q32 involved in meningioma progression (Zhang, Gejman et al. 2010). Zhang *et al*. showed that *MEG3* is expressed in normal human meningothelial cells, but is low or absent in the majority of meningioma tumors and meningioma cell lines. Moreover, loss of *MEG3* RNA expression as well as loss of MEG3 gene copy number is more common in higher grade meningiomas, and there is an overall increase in CpG methylation in tumors associated with tumor grade. Finally, *MEG3* RNA expression in human meningioma cell lines strongly suppresses tumor cell growth *in vitro,* which is independent of merlin, and activates p53-mediated transactivation. As an imprinted gene encoding a noncoding RNA, *MEG3* seems to suppress tumor development in meningioma via entirely novel mechanisms (Zhang, Gejman et al. 2010).

4.3 Alterations of 9p: *CDKN2A*, $p14^{ARF}$, and *CDKN2B* genes

Losses of chromosome 9p, particularly at the 9p21 region, were frequently found in anaplastic meningiomas but only rarely in atypical and benign meningiomas (Weber, Boström et al. 1997; Boström, Meyer-Puttlitz et al. 2001). Alterations of 9p21 have been found to represent losses of the well-known tumor suppressor genes *CDKN2A* ($p16^{INK4a}$), $p14^{ARF}$, and *CDKN2B* ($p15^{INK4b}$), involved in control of cell-cycle, and inactivated at high frequency in a large variety of human tumors.

Analysis of the alterations (deletions, mutations and promoter hypermethylation) of these tumor suppressor genes in meningiomas revealed that most of anaplastic meningiomas either show homozygous deletions, mutations (mainly in *CDKN2A* and $p14^{ARF}$), or lack of expression of one or more of these genes. Therefore, inactivation of the G1/S-phase cell-cycle checkpoint is an important feature of meningiomas of advanced stage (anaplastic) that likely contributes to the rapid growth and malignant behavior of these tumors, and point it out as a progression associated alteration in meningiomas (Boström, Meyer-Puttlitz et al. 2001). Moreover, by using FISH, other authors reported higher frequencies of 9p or *CDKN2A* alterations in meningiomas, mostly in anaplastic tumors (74% of anaplastic meningiomas, 52% of atypical, and 17% of benign meningiomas). Interestingly, in this study *CDKN2A* deletion was strongly associated with outcome, with 9p deleted anaplastic tumors showing a high risk ratio for death. On the other hand, absence of deletion identified a subset of anaplastic meningioma patients (26%) with prolonged survival (Perry, Banerjee et al. 2002). Therefore, these studies support that chromosome 9p21 deletions are associated with malignant progression of meningiomas, and that it is a poor prognostic factor in anaplastic meningiomas.

4.4 Amplification of 17q region

Amplification of the 17q21-qter region was associated with the mechanism of progression from atypical to anaplastic tumors, due to high-level amplification on 17q was identified in 48-60% of anaplastic meningiomas and in few or none of atypical and benign tumors (Weber, Boström et al. 1997).

The S6 kinase (*S6K*) gene (17q23) was evaluated as the target of the 17q amplification in anaplastic meningiomas, based on its location (Cai, James et al. 2001) and on the observation of increased *S6K* mRNA expression in these tumors compared with benign meningiomas (Surace, Lusis et al. 2004). Experiments performed in meningioma cell lines revealed no effect of S6K overexpression on meningioma cell growth, motility, or adhesion *in vitro*, although S6K overexpression resulted in increased tumor size *in vivo* (Surace, Lusis et al. 2004). Therefore, although previous studies revealed no high-level amplification of the *S6K* candidate gene (Büschges, Ichimura et al. 2002), the study of Surace and coworkers suggests that S6K may be functionally important for meningioma progression (Surace, Lusis et al. 2004). Further studies are needed to map the 17q23 amplicon to determine whether additional genes in this region are amplified in high-grade meningiomas.

5. Molecular pathology of meningioma recurrence

As mentioned before, histological grade and extent of surgical resection are the two most important variables in meningiomas. However, 5% and 40% of benign and atypical tumors, respectively, recur within 5 years even after total gross resection (Riemenschneider, Perry et al. 2006).

The loss of 1p and 14q was suggested as one of the alterations observed in meningioma recurrence (Maillo, Orfao et al. 2007; Tabernero, Espinosa et al. 2007; Pfisterer, Coons et al. 2008). Recently, a higher recurrence rate of meningiomas with 1p36 loss (33%) than that of meningiomas with normal chromosome 1p36 (18%) has been reported (Ruiz, Martínez et al. 2010). In addition, a differential gene expression pattern that distinguishes between original and recurrent meningiomas identified a subset of meningioma recurrence associated genes, and reported novel candidate genes of recurrence. Most of these candidate genes are located at chromosomal regions previously associated with a higher risk of recurrence or malignant progression of meningiomas: 1p, 6q and 14q (Fig 4) (Pérez-Magán, Rodríguez de Lope et al. 2010). Furthermore, an additional comprehensive copy number and gene expression study also identified 6q and 14q loss significantly more common in recurrent tumors and associated with anaplastic histology (Lee, Liu et al. 2010). Finally, an abnormal cDNA gene expression pattern was identified associated with meningiomas displaying genomic deletions at 1p and 14q (Martínez-Glez, Alvarez et al. 2010).

In general, these recurrence-associated genes are underexpressed relative to non-tumoral meningothelial tissue, denoting an overall underexpression of genes in recurrent meningiomas (Lee, Liu et al. 2010; Pérez-Magán, Rodríguez de Lope et al. 2010). Conversely, overexpression of few genes were identified in recurrent meningiomas, remarkably genes of the histone cluster 1 (6p) (Pérez-Magán, Rodríguez de Lope et al. 2010).

Among the 1p candidate genes, the *LMO4* (LIM-only protein 4) gene is one of the candidates consistently reported on several gene expression studies on meningioma recurrence (Carvalho, Smirnov et al. 2007; Fèvre-Montange, Champier et al. 2009; Pérez-Magán,

Rodríguez de Lope et al. 2010) and progression (Carvalho, Smirnov et al. 2007; Fèvre-Montange, Champier et al. 2009). This gene maps to 1p22.3 and belongs to a family of four mammalian LMO proteins which are short transcriptional regulators that play roles in mammalian development; LMO4 is required for the proper closure of the neural tube (Lee, Jurata et al. 2005). Two members of the family, LMO1 and LMO2 act as oncogenes in acute lymphoblastic leukemia and previous studies have defined LMO3 as an oncogene in neuroblastoma (Lu, Lam et al. 2006). Furthermore, overexpression of LMO4 has been reported to induce cell invasion and to be associated with outcome in breast cancer, especially in estrogen receptor negative tumors (Sum, Segara et al. 2005). In pancreatic tumors it was also found overexpressed (Sum, Segara et al. 2005; Yu, Ohuchida et al. 2008), but high LMO4 expression was associated with survival advantage (Murphy, Scarlett et al. 2008).

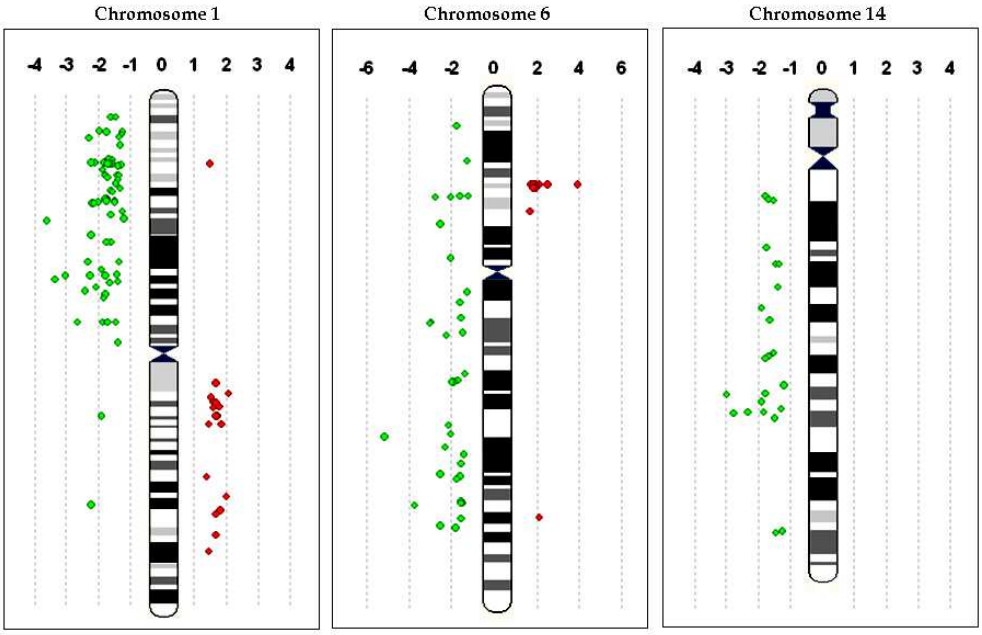

Fig. 4. Location of the genes differentially expressed in original and recurrent meningiomas on chromosomes 1, 6 and 14, plotted according to their map position. Genes with lower (green) and higher (red) levels of expression in recurrences than in original tumors are shown on the left and right, respectively, of the chromosome ideogram.

Surprisingly, underexpression of LMO4 was detected associated with progression and recurrence of meningiomas, as reported on gene expression profiling studies (Carvalho, Smirnov et al. 2007; Fèvre-Montange, Champier et al. 2009); (Pérez-Magán, Rodríguez de Lope et al. 2010). A recent report suggested that LMO4 modulates TGF-β signaling through its interaction with receptor-activated SMADs (Lu, Lam et al. 2006), however its role in meningiomas should be further studied.

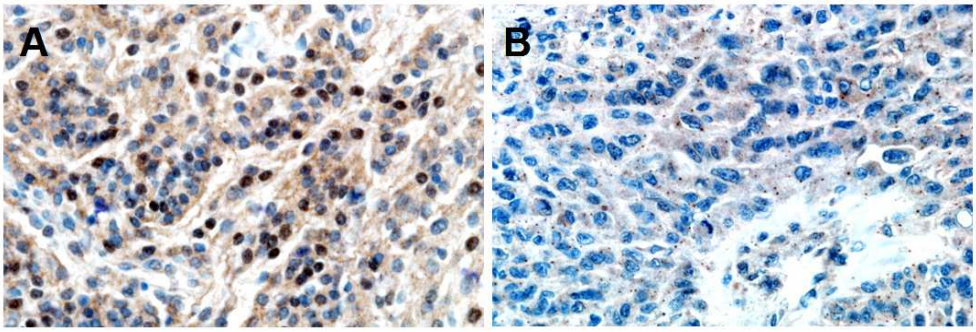

Fig. 5. Immunohistochemistry of meningioma samples with (**A**) positive and (**B**) negative expression of LMO4 (original magnification, ×400).

6. Signal transduction pathways altered in meningiomas

The hallmarks of cancer proposed by Hanahan and Weimberg in a multistep process in which cancer cells acquire the subsequent features that enable them to become tumorigenic and ultimately malignant include: sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis (Hanahan and Weinberg 2011). Abnormalities of these processes involve alteratinos of multiple cell signaling pathways affected in meningioma tumorigenesis, such as the beta-catenin/WNT, NOTCH, TGF-beta or p53 pathways (Ragel and Jensen 2010).

6.1 The beta-catenin/WNT pathway

The Wnt (wingless) signaling pathway involves proteins that regulate the production of Wnt signaling molecules, their interaction with receptors, and the physiological responses that result from the exposure of cells to the extracellular Wnt ligands. The series of events that occur when Wnt proteins bind to cell-surface receptors of the Frizzled family ultimately results in a change of the amount of β-catenin that reaches the nucleus.

Studies using microarray-based gene expression profiling identified altered expression of genes associated with the beta-catenin/WNT signaling pathway in meningiomas with losses of 14q, such as the genes for beta-catenin (*CTNNB1*), the regulatory subunit of cyclin-dependent kinase 5 (*CDK5R1*), ectodermal-neural cortex 1 (*ECN1*) and cyclin D1 (*CCND1*), which were upregulated in atypical and anaplastic meningiomas (Wrobel, Roerig et al. 2005). Increased *CTNNB1* and *CDK5R1* mRNA levels may result in aberrant WNT pathway activity due to increased levels of cytoplasmic β-catenin, which may translocate to the nucleus, where it functions as a transcriptional activator of a number of genes.

The beta-catenin/WNT pathway has also been recently implicated as important in meningioma recurrence, showing loss of expression of *SFRP1* (Wrobel, Roerig et al. 2005; Pérez-Magán, Rodríguez de Lope et al. 2010). This gene belongs to the family of the secreted frizzled-related proteins (SFRP), which are able to downregulate Wnt signaling by forming an inhibitory complex with the Frizzled receptors. The role of *SFRP1* as a tumor suppressor has been proposed in many other cancers (Caldwell, Jones et al. 2004; Chung, Lai et al.

2009). In gliomas, lower expression of *SFPR1* and promoter hypermethylation has recently been reported (Götze, Wolter et al. 2009).

6.2 The Notch signaling pathway

The Notch signaling pathway consists of a family of four cell-spanning proteins that enable extracellular-to-intracellular signaling. Ligand proteins bind to the extracellular portion of the Notch protein, resulting in the proteolytic cleavage and release of the intracellular portion. This cleaved portion translocates to the cell nucleus to alter gene expression. This signaling pathway is important for cell–cell communication and has multiple functions during development as well as adult cellular functions. This signaling pathway is dysregulated in many cancers.

Cuevas *et al*. have identified three components of the Notch signaling pathway: the transcription factor, hairy and enhancer of Split1 (HES1), which is induced in meningiomas of all grades; and two members of the Groucho/transducin-like enhancer of Split family of corepressors, TLE2 and TLE3, altered in high grade meningiomas (Cuevas, Slocum et al. 2005).

Furthermore, it has been reported that activated Notch1 and Notch2 receptors induced endogenous HES1 expression and were associated with tetraploidy in meningiomas. Therefore, a novel function for the Notch signaling pathway in generating tetraploidy and contributing to chromosomal instability in meningiomas was reported. This abnormal Notch signaling pathway may be an initiating genetic mechanism for meningioma tumorigenesis and potentially may promote tumor development (Baia, Stifani et al. 2008).

6.3 p53 signaling pathway

Cell-cycle proteins in human tumors comprise both positive and negative regulators. Negative cell cycle regulators include tumor-suppressor genes, of which p53 has been widely studied in different kinds of human tumors. The *p53* gene is located on chromosome 17p13.1 and composed of 11 exons.

p53 protein is a key player in the cellular response to stress. It is a nuclear phosphoprotein that by binding to DNA in a sequence-specific manner functions as a transcription factor regulating a wide diversity of cellular processes such as cell proliferation, differentiation, apoptosis, senescence, DNA repair, or changes in metabolism.

p53 responds to various forms of cellular stresses by activating the expression of downstream genes that inhibit growth, invasion and/or apoptosis, thus functioning as a tumor suppressor (Vousden and Prives 2009).

The expression of p53 protein is mainly regulated at the post-transcription stage and maintained at a very low level in normal cells. MDM2 is an important regulator of p53; it binds to p53 and inhibits its function by concealing the p53 activation domain and by promoting its degradation. In response to DNA damage, the MDM2 binding site of p53 is phosphorylated and the p53–MDM2 interaction is attenuated inducing the rapid accumulation of p53, relieved from MDM2-mediated suppression. The p14ARF protein, another component of the p53 pathway, binds to the p53/MDM2 complex and inhibits MDM2-mediated degradation of p53, which indicates that $p14^{ARF}$ is an upstream regulator of p53 via MDM2. In addition, p53 downregulates the expression of $p14^{ARF}$ and MDM2, in an autoregulatory feedback loop between p53, MDM2, and $p14^{ARF}$ (Zhang, Xiong et al. 1998).

Analysis of this pathway in meningiomas has shown that deregulations of p14-MDM2-p53 pathway may contribute to the malignant progression of meningioma. Amatya *et al.* found that methylation of *p14^{ARF}* gene is more common to atypical and anaplastic meningioma than in benign meningiomas (Amatya, Takeshima et al. 2004). In addition, high expression of p53 was found in atypical and anaplastic meningiomas (Amatya, Takeshima et al. 2001), although low frequency or absence of mutation of *p53* gene was reported by these and other authors (Weber, Boström et al. 1997). Moreover, frequencies of *p14^{ARF}* hypermethylation of the promoter region increases with the tumoral grade in meningiomas, with higher expression of MDM2 protein the cases with methylation of *p14^{ARF}* gene (Amatya, Takeshima et al. 2004).

6.4 TGF-β signaling pathway

The TGF beta signaling pathway is involved in a wide range of cellular process such as cell growth, differentiation and apoptosis among other cellular functions. Therefore, it is a very heavily regulated pathway. The ligands of the TGF-beta superfamily bind to a type II receptor, recruiting and phosphorylating a type I receptor. As a consequence, the type I receptor activates receptor-regulated SMADs (e.g. SMAD2, SMAD3) which can now bind coSMADs (SMAD4). These complexes accumulate in the nucleus where they act as transcription factors and participate in the regulation of target gene expression.

In vitro studies of this pathway in meningioma cell lines suggest that TGF-β has an inhibitory effect on meningioma proliferation, possibly through Smad 2/3 apoptotic pathways (Johnson, Okediji et al. 2004). However, a recent study of the most relevant molecules of the TGF-beta pathway on meningioma tumors concluded that only attenuated TGF-βRIII expression and TGFB growth inhibition may occur in select higher grade meningiomas (Johnson, Shaw et al. 2011).

7. Conclusions

Meningiomas show a broad range of histopathological patterns that in most of the tumors are featured by similar biological and clinical behaviors. Nevertheless, some difficulties still remain, particularly for designation of atypical WHO grade II meningiomas. In addition, different clinical outcomes and recurrence rates even within the same histopathological grade have been observed. Therefore, it is of relevance the identification of prognostic biomarkers for a proper individualized management of the patients. In these sense, useful genetic models for the mechanisms of tumorigenesis and progression in meningiomas have been described, proposing a number of candidate target genes. However, a big amount of genetic and epigenetic research still has to be done in order to identify patients at risk and to translate this information into effective forms of targeted therapies.

8. Acknowledgments

This work was partially supported by grants G-2009_E/04 and PI-2010/045 from Fundación Sociosanitaria de Castilla-La Mancha and the Consejería de Salud y Bienestar Social, Junta de Comunidades de Castilla-La Mancha; and FIS PI08/1662 from the Fondo de Investigaciones Sanitarias (FIS) of the Instituto de Salud Carlos III (Spain).

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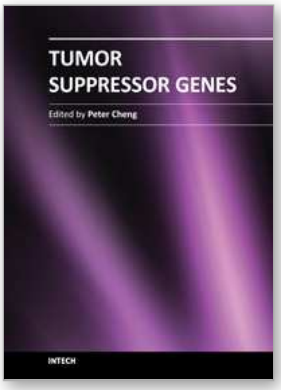

Tumor Suppressor Genes
Edited by Dr. Yue Cheng

ISBN 978-953-307-879-3
Hard cover, 332 pages
Publisher InTech
Published online 03, February, 2012
Published in print edition February, 2012

Functional evidence obtained from somatic cell fusion studies indicated that a group of genes from normal cells might replace or correct a defective function of cancer cells. Tumorigenesis that could be initiated by two mutations was established by the analysis of hereditary retinoblastoma, which led to the eventual cloning of RB1 gene. The two-hit hypothesis helped isolate many tumor suppressor genes (TSG) since then. More recently, the roles of haploinsufficiency, epigenetic control, and gene dosage effects in some TSGs, such as P53, P16 and PTEN, have been studied extensively. It is now widely recognized that deregulation of growth control is one of the major hallmarks of cancer biological capabilities, and TSGs play critical roles in many cellular activities through signaling transduction networks. This book is an excellent review of current understanding of TSGs, and indicates that the accumulated TSG knowledge has opened a new frontier for cancer therapies.

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