



The Molecular Pathogenesis of Pituitary Adenomas: An Update

Citation

Jiang, Xiaobing, and Xun Zhang. 2013. "The Molecular Pathogenesis of Pituitary Adenomas: An Update." *Endocrinology and Metabolism* 28 (4): 245-254. doi:10.3803/EnM.2013.28.4.245. <http://dx.doi.org/10.3803/EnM.2013.28.4.245>.

Published Version

doi:10.3803/EnM.2013.28.4.245

Permanent link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:11879696>

Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA>

Share Your Story

The Harvard community has made this article openly available.
Please share how this access benefits you. [Submit a story](#).

[Accessibility](#)

The Molecular Pathogenesis of Pituitary Adenomas: An Update

Xiaobing Jiang, Xun Zhang

Neuroendocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Pituitary tumors represent the most common intracranial neoplasms accompanying serious morbidity through mass effects and inappropriate secretion of pituitary hormones. Understanding the etiology of pituitary tumorigenesis will facilitate the development of satisfactory treatment for pituitary adenomas. Although the pathogenesis of pituitary adenomas is largely unknown, considerable evidence indicates that the pituitary tumorigenesis is a complex process involving multiple factors, including genetic and epigenetic changes. This review summarized the recent progress in the study of pituitary tumorigenesis, focusing on the role of tumor suppressor genes, oncogenes and microRNAs.

Keywords: Pituitary neoplasms; Oncogenes; Tumor suppressors; Cell cycle; MicroRNAs

INTRODUCTION

Pituitary adenomas are among the most frequent intracranial tumors. Series of radiological and autopsy studies suggest a prevalence as high as up to 22.5% [1]. The cross-sectional studies showed that the prevalence of symptomatic pituitary adenomas ranges from 7.76 in 10,000 to 1 in 1,064 individuals, a rate which is 3 to 5 times higher than that of previously thought [2,3]. Although the majority of pituitary adenomas are benign and rarely transform into malignant types, they usually behave in an aggressive model due to the mass compression and hormone excessive or insufficiency [4]. Surgical resection remains the first line treatment for most of the pituitary tumors except for prolactinomas, with or without adjuvant radiation therapy. However, the invasive pituitary adenomas usually can not be controlled by these treatments. Systemic medical treatment seems to be a potential effective alternative, which is again hampered by the limited understanding of the mecha-

nism underlining the tumorigenesis of pituitary adenomas. Further studies to detail the tumorigenesis will contribute to exploring new targets which will be helpful in development of novel therapeutic approaches for pituitary adenomas.

MONOCLONAL ORIGIN AND PATHOGENIC CHANGES OF PITUITARY ADENOMAS

Pituitary adenomas are considered to be derived either from early progenitor or fully differentiated hormone secreting cells, and have been documented as monoclonal expansion of a genetically mutated cell, demonstrated using X-chromosome inactivation technique [5-8]. However, pituitary adenomas usually exhibit distinct properties from malignancies. They frequently grow slowly and seldom develop into true malignant neoplasms, although they often are accompanied with a range of local invasive behaviors [9]. In addition, the common mutations of oncogenes and tumor suppressor genes, present

Corresponding author: Xun Zhang
Neuroendocrine Research Laboratory, Massachusetts General Hospital and Harvard Medical School, 55 Fruit St, BUL457, Boston, MA 02114, USA
Tel: +1-617-724-7392, **Fax:** +1-617-726-5072, **E-mail:** xzhang5@mg.harvard.edu

Copyright © 2013 Korean Endocrine Society
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

in nonendocrine neoplasms, such as *PKC*, *RAS*, *P53*, and *RB*, are usually absent in pituitary adenomas [9]. However, a number of oncogenes, tumor suppressor genes and cell cycle mediators have been identified to be functionally involved in the initiation and progression of pituitary adenomas [4,5,10]. Furthermore, increasing literature has demonstrated recently a fundamental role of microRNA (miRNAs) and long noncoding RNAs (lncRNAs) in the pathogenesis of pituitary tumorigenesis [11,12].

GENETIC MUTATIONS IN PITUITARY ADENOMAS

The aryl hydrocarbon receptor interacting protein (*AIP*) gene dominant mutations are most frequently implicated in the pathogenesis of familial isolated pituitary adenomas with a prevalence of 15% [13]. In addition, the germline mutation of this gene has been found in all types of sporadic pituitary adenomas, either functioning or nonfunctioning subtypes, with predominance in somatotrophinomas [13-15]. Furthermore, *AIP* mutations seem to be more prominent in patients with young age and large tumors [13,16].

The multiple endocrine neoplasia syndrome type 1 (*MEN1*) gene localizes on the chromosome 11q13, usually acts a tumor suppressor [17]. *MEN1* syndrome is an autosomal dominant familial disorder, about 70% of which bear the *MEN1* gene mutation. However, only 3.5% of the sporadic pituitary adenomas have been found to contain a *MEN1* mutation [17]. Therefore, mutation of *MEN1* may play limited role in sporadic pituitary adenomas. *MEN1* patients without *MEN1* mutations may have mutations in some other gene. Recently, *CDKN1B* (also known as *P27*) inactivating germline mutations have been described in a family presenting a *MEN1* like syndrome (now designed as *MEN4*) [18]. Although one of these mutations was subsequently detected in another *MEN1* family, no mutation was verified in a large cohort of patients with *MEN1* [19]. Therefore, the mutations of *P27* may be less common than initially thought.

The mutation of guanine nucleotide-activating alpha subunit (*GNAS*) gene is the somatic mutation related to the McCune-Albright syndrome [5]. This mutation is also detected in about 30% to 40% of sporadic growth hormone (GH) secreting tumors and might be involved in the transition of an aggressive prolactinoma to a GH adenoma [5,20,21]. Similarly, the autosomal dominant disorder, Carney complex (CNC), is mainly caused by the mutation of cAMP-dependent protein

kinase A type 1 alpha regulatory subunit (*PRKARIA*) [22]. Yet again, this mutation is not detected in human sporadic pituitary adenomas [23].

Oncogene *RAS* mutation is frequent in nonendocrine malignancies, and most associated with the GTPase domain of the protein. However, this mutation is rarely encountered in pituitary adenomas except in some highly aggressive adenomas and pituitary carcinomas [24].

EPIGENETIC MODIFICATION IN PITUITARY TUMORIGENESIS

The term epigenetic modification refers to a process that influences the gene expression without changing the DNA sequence of the gene. DNA methylation is the most common epigenetic modification, which is restricted to the CpG dinucleotides in mammals [25]. The sites with clustered CpG are known as CpG islands, which usually encompass the gene promoter regions. Inappropriate methylation of CpG islands is associated with histone deacetylation and gene silencing. Conversely, it is also suggested that modification of histone tails may lead to CpG island methylation, and therefore reinforce an already established silencing event [25,26]. Many genes silenced by hypermethylation have been found to play a remarkable role in pituitary tumorigenesis, although the exact mechanisms governing site-specific DNA methylation, histone modification, and gene silencing remain unclear.

Cyclin-dependent kinase inhibitor 2A (*CDKN2A*, or *P16*) is the first gene reported to be silenced in sporadic pituitary adenomas, caused by the methylation of *P16* gene CpGs [26]. The frequency of *P16* methylation tends to vary in different pituitary adenoma subtypes: it is most popular in nonfunctional adenomas, but a rare incidence in somatotrophinomas [26]. Death associated protein kinase (DAPK) works as a checkpoint in activating p19/p53 cell cycle, whose expression was found lost in the majority of pituitary adenomas, especially in invasive pituitary tumors. Further studies showed that both methylation and deletion of *DAPK* gene might be responsible for its loss of expression [26]. Fibroblastoma growth factor (FGF) is critical for the development of pituitary. According to the studies from Ezzat group, fibroblastoma growth factor receptor 2 (FGFR2) was significantly down-regulated in half of the human pituitary adenomas, and 45% of the tumors were detected with methylated promoter of FGFR2 gene [10]. Meanwhile, putative target of FGFR2, melanoma associated antigen (MAGE-A), is significantly increased in pituitary ade-

nomas, comparing to that in normal pituitary tissue. In consistent, MAGE-3 promoter is hypermethylated in normal pituitary tissue but hypomethylated pituitary tumors [10]. More interestingly, the mechanism underlying the estrogen induced MAGE-3 expression also involves histone modification. Taken together, these results suggest that epigenetic manipulation plays a significant role in sustaining proper function of FGFR2/MAGE-3 pathway [10]. In addition, the silencing of growth arrest and DNA damage inducible gene *45γ* (*GADD45γ*) and *RB1* gene are also attributed to the hypermethylation of gene CpG island in pituitary tumors [26,27].

Maternally expressed gene 3 (*MEG3*) is highly expressed in normal pituitary and the majority of functioning pituitary tumors, but not detected in nonfunctioning pituitary adenomas (NFAs) [28]. Further studies showed that there is no deletion or mutation in *MEG3* gene, but rather that failure of *MEG3* expression is associated with the epigenetic regulation [29]. There were two differential methylated regions (DMRs) locating in the upstream of *MEG3*, intergenic (IG), and *MEG3*-DMR, which were believed to control the expression of *DLK1-MEG3* imprinting locus [11]. *MEG3*-DMR encompasses the promoter of *MEG3*. Bisulfite sequencing revealed that the methylation of *MEG3* promoter and enhancer was significantly higher in pituitary tumors than that in normal pituitary samples [29]. We also found a cAMP response element (CRE) within the *MEG3* promoter, and deletion of the CRE could significantly reduce the transcription activity. The CRE sequences are CpG dinucleotide rich, which suggests a methylation modification in transcript factor binding [30]. The methylation status *MEG3*-DMR is controlled by IG-DMR, whose hypomethylation is essential for correct imprinting of the *DLK1-MEG3* locus [11]. Recently studies showed the methylated IG-DMR was significantly increased in NFAs, and treatment with demethylating agent resulted in re-expression of *MEG3* in several tumor cell lines, including human breast cancer, meningiomas, neuroblastomas and hepatocellular carcinomas [11,29,31].

ONCOGENES, TUMOR SUPPRESSOR GENES, AND DEREGLATED CELL CYCLES

Oncogenes

The *GNAS* mutation leading to GTPase inactivation can increase the level of cAMP, and therefore enhances GH synthesis and secretion [5]. Postzygotic *GNAS* mutations result in a pattern of organ specificity with the features of McCune-Al-

bright syndrome, but only cause pituitary hyperplasia, rather than focal adenomas [32]. However, in a recent study, Vortmeyer et al. [33] found a spectrum of changes in anterior pituitary gland in acromegalic patients with McCune-Albright syndrome, including hyperplasia and focal adenoma formation, which suggests a developmental role of *GNAS* mutation in pituitary gland. Interestingly, *GNAS* mutation is also suggested to be involved in the transition of an aggressive prolactinoma to a GH adenoma [20]. The relationships between *GNAS* mutation and therapeutic outcomes have been explored in several studies; the results, however, are inconsistent [34,35].

The phosphoinositide 3-kinase (PI3K)/AKT signaling is commonly involved in regulating fundamental cellular process, including cell proliferation, survival and motility, and plays a critical role in human tumorigenesis. Previous studies showed that the PI3K/AKT pathway signaling was activated and enhanced in pituitary adenomas [36]. Subsequently, somatic mutations and amplification of *PIK3CA* gene were observed in pituitary adenomas, and *PIK3CA* mutation tended to be more prevalent in aggressive and recurrent tumors [37].

Pituitary tumor transforming gene (*Pttg*) was originally isolated from rat pituitary tumor cells by differential display, and identified as a securin in regulating sister chromatin separation during mitosis. Recently, increasingly evidence suggests a multifunctional role of *PTTG* in cell physiology and tumorigenesis [38]. Increased expression of *PTTG* is detected in the majority of pituitary adenomas, and its expression is positively correlated with tumor invasiveness and cell proliferation index, ki-67. Furthermore, transgenic mice with overexpression of *Pttg* in pituitary develop focal pituitary hyperplasia and adenoma formation. Abnormality in *PTTG* expression results in aneuploidy and chromosomal instability [38].

Tumor suppressor genes

GADD45γ, a p53-regulated human gene involved in growth suppression and apoptosis, represents the first tumor suppressor involved in pituitary tumorigenesis [39]. Using cDNA representational difference analysis, we have discovered that loss of *GADD45γ* expression is present in the majority of human pituitary adenomas. Transfection of human *GADD45γ* cDNA into pituitary tumor cell lines results in dramatic decreased colony formation, which confirms the tumor suppressing function of *GADD45γ* gene [39]. Another *GADD45* family member, *GADD45β*, is also found to be repressed in pituitary adenoma, and acts as a tumor suppressor [40].

The AIP protein acts as a tumor suppressor by interacting

with the aryl hydrocarbon receptor (AHR), heat shock proteins, surviving, and many other proteins [41]. It plays an important role in modulating cAMP signaling and cellular signaling pathways by modulating the localization of AHR. The structure and function AIP protein have been discussed in detail in a recent review [41]. Most intriguingly, emerging studies discovered that acromegaly patients with *AIP* mutation responded less well to somatostatin analogues (SSAs). In agreement with this finding, there was a relatively higher prevalence of *AIP* mutation in sporadic acromegaly patients who were diagnosed with SSAs resistant GH secreting tumors [16]. All these studies imply a potential role of AIP mutation in the effect of SSAs on GH secreting tumors. Recently, Chahal et al. [42] suggested a mechanism whereby responsiveness to SSAs is via AIP regulation of ZAC1 (zinc finger regulator of apoptosis and cell cycle arrest), which is a putative tumor suppressor and usually diminished in adenomas. Increased AIP mRNA and protein levels are induced with pretreatment of SSAs *in vivo* and *in vitro*. Meanwhile, enforced overexpression of wild-type AIP could upregulate ZAC1 mRNA level; and enhanced cell proliferation and colony formation were observed after decreasing ZAC1 by AIP knockdown [42].

MEN1 gene is located on chromosome 11q13 and encodes menin protein, which acts a scaffold protein in regulating transcription, genome stability, and cell proliferation [9]. Pituitary tumors with *MEN1* mutation tend to be larger and more invasive. Based on the fact that a germline loss of heterozygosity (LOH) involving chromosome 11q13 is observed in almost 90% of familial and about 30% of sporadic pituitary adenomas, this LOH is considered as an initial hit followed by *MEN1* somatic mutation as a second hit that leads to tumor formation, according to the Knudsen's two hit model of tumorigenesis [9,17,43]. Although *MEN1* mutation plays an important role in the etiology of human pituitary tumorigenesis, the involvement of other genes is highly likely. The proposed mechanism whereby *MEN1* mutations lead to tumor formation is by weakening the binding capacity of menin to the other functional proteins, and therefore altering critical events in cell cycle regulation and proliferation [17]. In a *MEN1* gene deletion, leading to absence of menin, reintroduction of *MEN1* gene replacement could generate menin expression in pituitary tumors, and significantly reduce tumor cell proliferation [44].

PRKAR1A is a key component of the cAMP signaling pathway that has been implicated in endocrine tumorigenesis. *PRKAR1A* mutation is predicted to lead to a premature stop codon and nonsense-mediated mRNA decay, thus related to

increased PKA activity and hence tumorigenesis [45]. About 60% of CNC is caused by the mutation of *PRKAR1A* [22]. Up to 75% of CNC cases exhibit hypersecretion of prolactin (PRL) and GH, but clinical manifestations of acromegaly are usually subtle. In the mouse model with tissue specific knockout of *PRKAR1A*, increased prevalence of pituitary adenomas with elevated GH level was observed [46].

Reprimo, a downstream effector of p53, was also shown recently to be down-regulated in the majority of pituitary adenomas, and exhibited capability of increasing tumor cell apoptosis [47]. The potential mechanism responsible for the reprimo repression remains unclear.

Deregulated cell cycle

The pRb/E2F pathway plays a critical role in pituitary tumorigenesis, as it has been clearly shown by experimental mouse models [48]. Progress from G1 to S phase of the cell cycle is restrained by the hypophosphorylated Rb, which is in turn mediated by upstream CDKs and its inhibitors, CDKIs. A number of cell cycle regulators have been supposed to play a role in pituitary tumorigenesis, including Rb1, p16, p21, p27, cyclin D1, and cyclin E [5,26].

CDK4 and its inhibitor p16 play a vital role in cell cycle control by mediating Rb1 pathway. Both p16 and Rb1 are tumor suppressors, and usually silenced by genetic alternation in nonendocrine neoplasms. However, both of their diminished expressions are ascribed to promoter methylation in pituitary adenomas. When the p16 expression is silencing, the phosphorylated Rb1 releases bound E2F transcription factors, which enable cell cycle progress. Specifically, the frequency of p16 methylation tends to be various in different pituitary adenoma subtypes, which is most popular in NFAs, but a rare incidence in somatotrophinomas. It is also suggested that the loss of p16 is an early event of pituitary tumorigenesis [26].

P27 is another cell cycle inhibitor that regulates transition from G1 to S phase of cell cycle. The expression of p27 is reduced in pituitary tumors, and mice with *p27* gene knockout develop organ hyperplasia and pituitary adrenocorticotrophic hormone (ACTH) secreting tumor [18]. More importantly, the loss of p27 expression is consistent with the increased cyclin E in pituitary tumors, which implies that cell proliferation is enhanced by increased cyclin E, when the cell cycle inhibitor p27 is lost. However, the loss of p27 expression has not been associated with *CDKN1B* mutation, which is rarely revealed in pituitary adenomas [49]. The p27 protein levels, but not mRNA levels, are significantly reduced during progression

from normal to neoplastic pituitaries and pituitary carcinomas [49]. One potential mechanism is the translational failure of p27 mRNA, which is controlled by the protein encoded by *DKC1*, whose mutation could affect the translation of p27 mRNAs harboring internal ribosomal entry elements [50].

Similarly, cyclin D1, encoded by *CCND1*, and its assembly with CDK4 plays a crucial role in controlling the cell cycle progress. Previous study showed a higher *CCND1* expression in nonfunctional pituitary adenomas [5]. A recent study suggests that the polymorphism of *CCND1* gene might be an important factor in the early stages of the tumor formation [51].

The high mobility group A (HMGA) protein family members are small nonhistone chromatin proteins, which are abundantly expressed during embryogenesis, but absent in normal adult tissues [52]. Overexpression of HMGA2 has been detected in pituitary adenomas, and mixed GH and PRL secreting pituitary adenomas were observed in transgenic mice with HMGA2 overexpress [53]. Moreover, the level of HMGA2 protein is positively correlated with the invasiveness and Ki-67 index in pituitary adenomas [52]. Subsequent studies discovered that HMGA2 could enhance transcription factor E2F1 activity by up-regulating cyclin B2, and drove cell cycle into S phase thereafter [53-55]. In addition, HMGA1b and HMGA2 can also influence cell cycle by regulating *CCNB2* encoding cyclin B2 and promote pituitary cells proliferation by directly enhancing *PIT1* expression [52,56]. Therefore, cell cycle dysregulation represents the main mechanism by which HMGA proteins induce the development of pituitary adenomas [52].

FGFR2 IIIb, a spliced isoform of FGFR2, is tightly restricted to be expressed in epithelial cell. FGFR2IIIb is considered

as a tumor suppressor, which is silenced in pituitary tumors because of promoter methylation. FGFR2 IIIb activation using its selective ligand FGF7 results in diminished pituitary tumor cell cycle progression. Recent study shows that MAGE-A3 might be a down-stream regulator of FGFR2 IIIb. Downregulation of MAGE-A3 resulted in accumulation of p53 and p21, suggesting that FGFR2 IIIb pathway represent an potential signaling modulating p53 functions in pituitary adenomas [57].

MiRNAs in pituitary adenomas

miRNAs are a class of short noncoding RNAs that posttranscriptionally regulate the target mRNAs translation and degradation, by binding to the sequences at 3' untranslated regions [58]. Increasing evidence indicates that miRNAs are commonly involved in tumor initiation, progression, as well as therapeutic outcomes. Moreover, half of the miRNA genes are located in cancer associated genomic regions, emphasizing a crucial role of miRNAs in tumor pathogenesis [59].

Recently, deregulation of miRNAs is also revealed in pituitary adenomas (Table 1). With microarray analysis, many miRNAs were shown to be differentially expressed in pituitary adenomas comparing to normal pituitary samples, and the altered expression of some miRNAs has been associated with tumor diameter, invasiveness, and therapeutic outcome [60-63]. Moreover, each subtype of the pituitary adenomas tends to be characterized with specific miRNA profile. According to the report by Bottoni et al. [61], 29 differentially expressed miRNAs are used to predict pituitary adenoma types. For example, miR-23a, miR23b, and miR-24-2 expression is in-

Table 1. MicroRNAs with Validated Targets Involved in the Pathogenesis of Pituitary Adenomas

MicroRNA	Pituitary adenomas	Expression	Function	Validated targets
miR-128a, miR-155 and miR-516a-3p	Nonfunctional and GH secreting adenomas	Overexpression	Oncogene	Wee1-like protein kinase
miR-107	Pituitary adenomas	Overexpression	Tumor suppressor	AIP
miR-326, miR-432, and miR-570	Pituitary adenomas	Downexpression	Tumor suppressor	HMGA2
miR-34b and miR-548c-3p	Pituitary adenomas	Downexpression	Tumor suppressor	HMGA1 and HMGA2
miR-326 and miR-603	Pituitary adenomas	Downexpression	Tumor suppressor	E2F1
miR-15, miR-16, miR-26a and miR-196a2	Pituitary adenomas	Downexpression	Tumor suppressor	HMGA2
let-7	Pituitary adenomas	Downexpression	Tumor suppressor	RAS family proteins and HMGA2
miR-26b	GH secreting adenomas	Overexpression	Oncogene	PTEN
miR-128	GH secreting adenomas	Downexpression	Tumor suppressor	BMI1

GH, growth hormone; AIP, aryl hydrocarbon receptor interacting protein; HMGA, high mobility group A; PTEN, phosphatase and tensin homolog; BMI1, B lymphoma Mo-MLV insertion region 1 homolog.

creased in GH and PRL secreting tumors, but decreased in ACTH secreting adenomas and NFAs. Members of miR-30 family were strongly increased in ACTH secreting adenomas, while their level is low in prolactinomas [61].

By targeting mRNA and controlling mRNA translation and degradation, the miRNAs can function with either oncogenic or tumor suppressive activity. In nonfunctioning and in GH secreting pituitary adenomas, Wee1-like protein kinase, which acts as a tumor suppressor protein, was shown to be regulated by the overexpressed miRNAs, miR-128a, miR-155 and miR-516a-3p [64]. In ACTH-secreting adenomas, the expression of miR-145, miR-21, miR-15 and miR-16 is suppressed, while the level of miR-122 and miR-493 is up-regulated in ACTH secreting carcinomas [63,65]. Several contradictory facts remain regarding miRNAs in pituitary tumors. For example, miR-122 is considered as a tumor suppressor in liver tissue; it is however abundantly expressed in ACTH and PRL secreting carcinomas [65]. Some miRNAs seem to act as tumor suppressors, despite they are overexpressed in pituitary tumors. For example, miR-107 is significantly up-regulated in GH secreting and nonfunctional pituitary adenomas, but its overexpression inhibits proliferation of rat pituitary adenoma cells. Furthermore, miR-107 could not silence its target gene AIP, which implies a compensatory regulation mechanism involved [66].

The DLK1-MEG3 genomic region contains a maternally expressed miRNA cluster, which is considered as the largest miRNAs group, among which 53 miRNAs have been identified [67]. Many of them are differentially expressed in variable pathophysiological processes, and found to be involved in the pathogenesis of several malignancies [67]. We detected the level of 18 miRNAs located in this cluster in pituitary adenomas. Intriguingly, 13 of them were lost or significantly diminished, and two of them (miR-431 and miR-770-5p) were slightly higher in NFAs comparing to normal pituitary. In addition, some of them were capable of tumor suppression [68]. The specific roles of these miRNAs in the development of NFAs are to be determined in future studies.

Trisomy of chromosome 12, where *HMG2* gene located, accounts for the *HMG2* overexpression restricted in human prolactinomas [69]. The mechanism responsible for the deregulation of HMGA proteins in other subtype pituitary adenomas remains elusive. A recent study presented by D'Angelo et al. [70] suggested a miRNA-dependent impairment of HMGA/E2F1 pathway, which acts as a pro-oncogene signaling in pituitary adenomas. They identified that a set of miRNAs, including miR-34b, miR-326, miR-432, miR-548c-3p, miR-570, and miR-603, were

apparently down-regulated in pituitary adenomas. Further evidence demonstrated that miR-326, miR-432, and miR-570 target on *HMG2*; miR-34b and miR-548c-3p target on both the *HMG1* and *HMG2*; and miR-326 and miR-603 target on *E2F1*. Finally, overexpression of these miRNAs in pituitary cell lines (HP75, GH3) could inhibit cell growth and retrain the cells in the G1 phase. Similarly, in another study by the same group, HMGA proteins are found as direct targets of miR-15, miR-16, miR-26a, miR-196a2, and *Let-7a* [71]. Additionally, suppressions of *let-7* family members and of miR15a/miR16 are found in most pituitary tumor subtypes [62]. Reduced *let-7* expression possibly causes upregulation of the human RAS family of oncoproteins [61], and low level of miR-15a and miR16-1 inversely correlates with tumor diameter and directly correlates with the secretion of the antineoplastic cytokine p43 [62].

Finally, some miRNAs are of importance for both sustaining normal pituitary development and promoting tumor proliferation. On one hand, miR-26b could up-regulate *Pit-1*, whose loss leads to anterior pituitary retardation, by targeting lymphoid enhancer factor 1 (*lef-1*) [72]. On the other hand, the expression of miR-26b is higher in GH-secreting adenomas than in normal tissues [73]. MiR-26b enhances the ability of pituitary cell lines to form colonies, invade, and formation of pituitary xenograft growth, by directly targeting phosphatase and tensin homolog (*PTEN*) gene. Conversely, miR-128, which is down-regulated in GH-secreting adenomas, behaves an opposite function to miR-26b. More interesting, miR-128 through BMI1 binding on *PTEN* promoter indirectly regulates *PTEN* expression, suggesting an interaction with miR-26b in controlling *PTEN/AKT* pathway [73].

Large noncoding RNAs (lncRNAs): MEG3

lncRNAs are a subgroup of noncoding RNAs that are longer than 200 nucleotides. Multiple studies have unveiled a central role of lncRNAs in human tumorigenesis. MEG3 represents the first and the only recognized lncRNA tumor suppressor in pituitary adenomas. Update about the structure and function of MEG3 in nonfunctioning adenomas and meningiomas has been detailed in recent reviews [11,74,75]. This line of studies will establish novel and unique mechanisms regarding pathogenesis of human NFAs and lncRNA biology in general.

CONCLUSIONS

Pituitary tumorigenesis appears to be a complex process with extrinsic and intrinsic factors involved. Increasing evidence has

demonstrated fundamental roles of tumor suppressors, oncogenes, as well as cell cycle abnormalities in pituitary tumorigenesis. MiRNAs and lncRNAs are considered as new emerging paradigms in pituitary tumorigenesis. However, the question of cause or effect in relation to pituitary adenoma initiation remains unanswered, which is largely constrained by the lack of satisfactory human pituitary adenoma cell lines and animal models. Therefore, future work is expected in generating workable human functional and nonfunctional pituitary tumor cell lines, and establishing satisfactory animal models, which will be of great importance in understanding the molecular events governing pituitary tumor pathogenesis and providing assay and screening models for the development of novel therapeutic approaches.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

- Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, McCutcheon IE. The prevalence of pituitary adenomas: a systematic review. *Cancer* 2004;101:613-9.
- Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. *J Clin Endocrinol Metab* 2006;91:4769-75.
- Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin Endocrinol (Oxf)* 2010;72:377-82.
- Ezzat S, Asa SL. Mechanisms of disease: the pathogenesis of pituitary tumors. *Nat Clin Pract Endocrinol Metab* 2006;2:220-30.
- Melmed S. Pathogenesis of pituitary tumors. *Nat Rev Endocrinol* 2011;7:257-66.
- Alexander JM, Biller BM, Bikkal H, Zervas NT, Arnold A, Klibanski A. Clinically nonfunctioning pituitary tumors are monoclonal in origin. *J Clin Invest* 1990;86:336-40.
- Herman V, Fagin J, Gonsky R, Kovacs K, Melmed S. Clonal origin of pituitary adenomas. *J Clin Endocrinol Metab* 1990;71:1427-33.
- Jacoby LB, Hedley-Whyte ET, Pulaski K, Seizinger BR, Martuza RL. Clonal origin of pituitary adenomas. *J Neurosurg* 1990;73:731-5.
- Melmed S. Mechanisms for pituitary tumorigenesis: the plastic pituitary. *J Clin Invest* 2003;112:1603-18.
- Ezzat S. Epigenetic control in pituitary tumors. *Endocr J* 2008;55:951-7.
- Zhou Y, Zhang X, Klibanski A. MEG3 noncoding RNA: a tumor suppressor. *J Mol Endocrinol* 2012;48:R45-53.
- Shi X, Tao B, He H, Sun Q, Fan C, Bian L, Zhao W, Lu YC. MicroRNAs-based network: a novel therapeutic agent in pituitary adenoma. *Med Hypotheses* 2012;78:380-4.
- Daly AF, Vanbellinthen JF, Khoo SK, Jaffrain-Rea ML, Naves LA, Guitelman MA, Murat A, Emy P, Gimenez-Roqueplo AP, Tamburrano G, Raverot G, Barlier A, De Herder W, Penfornis A, Ciccarelli E, Estour B, Lecomte P, Gatta B, Chabre O, Sabate MI, Bertagna X, Garcia Basavilbaso N, Stalldecker G, Colao A, Ferolla P, Wemeau JL, Caron P, Sadoul JL, Oneto A, Archambeaud F, Calender A, Sinilnikova O, Montanana CF, Cavagnini F, Hana V, Solano A, Delettières D, Luccio-Camelo DC, Basso A, Rohmer V, Brue T, Bours V, Teh BT, Beckers A. Aryl hydrocarbon receptor-interacting protein gene mutations in familial isolated pituitary adenomas: analysis in 73 families. *J Clin Endocrinol Metab* 2007;92:1891-6.
- Marko NF, Weil RJ. Pituitary gland: new pathways in the pathogenesis of pituitary adenomas. *Nat Rev Endocrinol* 2012;8:572-3.
- Oriola J, Lucas T, Halperin I, Mora M, Perales MJ, Alvarez-Escuela C, Paz de MN, Diaz Soto G, Salinas I, Julian MT, Olaizola I, Bernabeu I, Marazuela M, Puig-Domingo M. Germline mutations of AIP gene in somatotropinomas resistant to somatostatin analogues. *Eur J Endocrinol* 2012;168:9-13.
- Tichomirowa MA, Barlier A, Daly AF, Jaffrain-Rea ML, Ronchi C, Yaneva M, Urban JD, Petrossians P, Elenkova A, Tabarin A, Desailoud R, Maiter D, Schürmeyer T, Cozzi R, Theodoropoulou M, Sievers C, Bernabeu I, Naves LA, Chabre O, Montanana CF, Hana V, Halaby G, Delemer B, Aizpun JI, Sonnet E, Longas AF, Hagelstein MT, Caron P, Stalla GK, Bours V, Zacharieva S, Spada A, Brue T, Beckers A. High prevalence of AIP gene mutations following focused screening in young patients with sporadic pituitary macroadenomas. *Eur J Endocrinol* 2011;165:509-15.
- Thakker RV. Multiple endocrine neoplasia type 1 (MEN1). *Best Pract Res Clin Endocrinol Metab* 2010;24:355-70.
- Pellegata NS, Quintanilla-Martinez L, Siggelkow H, Samson E, Bink K, Hofler H, Fend F, Graw J, Atkinson MJ. Germ-line mutations in p27Kip1 cause a multiple endocrine neoplasia syndrome in rats and humans. *Proc Natl*

- Acad Sci U S A 2006;103:15558-63
19. Agarwal SK, Mateo CM, Marx SJ. Rare germline mutations in cyclin-dependent kinase inhibitor genes in multiple endocrine neoplasia type 1 and related states. *J Clin Endocrinol Metab* 2009;94:1826-34.
 20. Lania AG, Ferrero S, Pivonello R, Mantovani G, Peverelli E, Di Sarno A, Beck-Peccoz P, Spada A, Colao A. Evolution of an aggressive prolactinoma into a growth hormone secreting pituitary tumor coincident with GNAS gene mutation. *J Clin Endocrinol Metab* 2010;95:13-7.
 21. Freda PU, Chung WK, Matsuoka N, Walsh JE, Kanibir MN, Kleinman G, Wang Y, Bruce JN, Post KD. Analysis of GNAS mutations in 60 growth hormone secreting pituitary tumors: correlation with clinical and pathological characteristics and surgical outcome based on highly sensitive GH and IGF-I criteria for remission. *Pituitary* 2007;10:275-82.
 22. Kirschner LS, Carney JA, Pack SD, Taymans SE, Giatzakis C, Cho YS, Cho-Chung YS, Stratakis CA. Mutations of the gene encoding the protein kinase A type I-alpha regulatory subunit in patients with the Carney complex. *Nat Genet* 2000;26:89-92.
 23. Kaltsas GA, Kola B, Borboli N, Morris DG, Gueorguiev M, Swords FM, Czirjak S, Kirschner LS, Stratakis CA, Korbonits M, Grossman AB. Sequence analysis of the PRKAR1A gene in sporadic somatotroph and other pituitary tumours. *Clin Endocrinol (Oxf)* 2002;57:443-8.
 24. Karga HJ, Alexander JM, Hedley-Whyte ET, Klibanski A, Jameson JL. Ras mutations in human pituitary tumors. *J Clin Endocrinol Metab* 1992;74:914-9.
 25. Dudley KJ, Revill K, Clayton RN, Farrell WE. Pituitary tumours: all silent on the epigenetics front. *J Mol Endocrinol* 2009;42:461-8.
 26. Farrell WE. Epigenetic mechanisms of tumorigenesis. *Horm Metab Res* 2005;37:361-8.
 27. Bahar A, Bicknell JE, Simpson DJ, Clayton RN, Farrell WE. Loss of expression of the growth inhibitory gene GADD45gamma, in human pituitary adenomas, is associated with CpG island methylation. *Oncogene* 2004;23:936-44.
 28. Zhang X, Zhou Y, Mehta KR, Danila DC, Scolavino S, Johnson SR, Klibanski A. A pituitary-derived MEG3 isoform functions as a growth suppressor in tumor cells. *J Clin Endocrinol Metab* 2003;88:5119-26.
 29. Zhao J, Dahle D, Zhou Y, Zhang X, Klibanski A. Hypermethylation of the promoter region is associated with the loss of MEG3 gene expression in human pituitary tumors. *J Clin Endocrinol Metab* 2005;90:2179-86.
 30. Zhao J, Zhang X, Zhou Y, Ansell PJ, Klibanski A. Cyclic AMP stimulates MEG3 gene expression in cells through a cAMP-response element (CRE) in the MEG3 proximal promoter region. *Int J Biochem Cell Biol* 2006;38:1808-20.
 31. Gejman R, Batista DL, Zhong Y, Zhou Y, Zhang X, Swearingen B, Stratakis CA, Hedley-Whyte ET, Klibanski A. Selective loss of MEG3 expression and intergenic differentially methylated region hypermethylation in the MEG3/DLK1 locus in human clinically nonfunctioning pituitary adenomas. *J Clin Endocrinol Metab* 2008;93:4119-25.
 32. Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. *N Engl J Med* 1991;325:1688-95.
 33. Vortmeyer AO, Glasker S, Mehta GU, Abu-Asab MS, Smith JH, Zhuang Z, Collins MT, Oldfield EH. Somatic GNAS mutation causes widespread and diffuse pituitary disease in acromegalic patients with McCune-Albright syndrome. *J Clin Endocrinol Metab* 2012;97:2404-13.
 34. Fougner SL, Casar-Borota O, Heck A, Berg JP, Bollerslev J. Adenoma granulation pattern correlates with clinical variables and effect of somatostatin analogue treatment in a large series of patients with acromegaly. *Clin Endocrinol (Oxf)* 2012;76:96-102.
 35. Fougner SL, Borota OC, Berg JP, Hald JK, Ramm-Petersen J, Bollerslev J. The clinical response to somatostatin analogues in acromegaly correlates to the somatostatin receptor subtype 2a protein expression of the adenoma. *Clin Endocrinol (Oxf)* 2008;68:458-65.
 36. Musat M, Korbonits M, Kola B, Borboli N, Hanson MR, Nanzer AM, Grigson J, Jordan S, Morris DG, Gueorguiev M, Coculescu M, Basu S, Grossman AB. Enhanced protein kinase B/Akt signalling in pituitary tumours. *Endocr Relat Cancer* 2005;12:423-33.
 37. Lin Y, Jiang X, Shen Y, Li M, Ma H, Xing M, Lu Y. Frequent mutations and amplifications of the PIK3CA gene in pituitary tumors. *Endocr Relat Cancer* 2009;16:301-10.
 38. Yu R, Melmed S. Pituitary tumor transforming gene: an update. *Front Horm Res* 2004;32:175-85.
 39. Zhang X, Sun H, Danila DC, Johnson SR, Zhou Y, Swearingen B, Klibanski A. Loss of expression of GADD45 gamma, a growth inhibitory gene, in human pituitary adenomas: implications for tumorigenesis. *J Clin Endocrinol Metab* 2002;87:1262-7.
 40. Michaelis KA, Knox AJ, Xu M, Kiseljak-Vassiliades K,

- Edwards MG, Geraci M, Kleinschmidt-DeMasters BK, Lillehei KO, Wierman ME. Identification of growth arrest and DNA-damage-inducible gene beta (GADD45beta) as a novel tumor suppressor in pituitary gonadotrope tumors. *Endocrinology* 2011;152:3603-13.
41. Vandeva S, Tichomirowa MA, Zacharieva S, Daly AF, Beckers A. Genetic factors in the development of pituitary adenomas. *Endocr Dev* 2010;17:121-33.
 42. Chahal HS, Trivellin G, Leontiou CA, Alband N, Fowkes RC, Tahir A, Igreja SC, Chapple JP, Jordan S, Lupp A, Schulz S, Ansorge O, Karavitaki N, Carlsen E, Wass JA, Grossman AB, Korbonits M. Somatostatin analogs modulate AIP in somatotroph adenomas: the role of the ZAC1 pathway. *J Clin Endocrinol Metab* 2012;97:E1411-20.
 43. Rostad S. Pituitary adenoma pathogenesis: an update. *Curr Opin Endocrinol Diabetes Obes* 2012;19:322-7.
 44. Walls GV, Lemos MC, Javid M, Bazan-Peregrino M, Jeyabalan J, Reed AA, Harding B, Tyler DJ, Stuckey DJ, Piret S, Christie PT, Ansorge O, Clarke K, Seymour L, Thakker RV. MEN1 gene replacement therapy reduces proliferation rates in a mouse model of pituitary adenomas. *Cancer Res* 2012;72:5060-8.
 45. Bertherat J, Horvath A, Groussin L, Grabar S, Boikos S, Cazabat L, Libe R, Rene-Coraif F, Stergiopoulos S, Bourdeau I, Bei T, Clauser E, Calender A, Kirschner LS, Bertagna X, Carney JA, Stratakis CA. Mutations in regulatory subunit type 1A of cyclic adenosine 5'-monophosphate-dependent protein kinase (PRKAR1A): phenotype analysis in 353 patients and 80 different genotypes. *J Clin Endocrinol Metab* 2009;94:2085-91.
 46. Yin Z, Williams-Simons L, Parlow AF, Asa S, Kirschner LS. Pituitary-specific knockout of the Carney complex gene Prkar1a leads to pituitary tumorigenesis. *Mol Endocrinol* 2008;22:380-7.
 47. Xu M, Knox AJ, Michaelis KA, Kiseljak-Vassiliades K, Kleinschmidt-DeMasters BK, Lillehei KO, Wierman ME. Reprimo (RPRM) is a novel tumor suppressor in pituitary tumors and regulates survival, proliferation, and tumorigenicity. *Endocrinology* 2012;153:2963-73.
 48. Lee EY, Cam H, Ziebold U, Rayman JB, Lees JA, Dynlacht BD. E2F4 loss suppresses tumorigenesis in Rb mutant mice. *Cancer Cell* 2002;2:463-72.
 49. Georgitsi M. MEN-4 and other multiple endocrine neoplasias due to cyclin-dependent kinase inhibitors [p27(Kip1) and p18(INK4C)] mutations. *Best Pract Res Clin Endocrinol Metab* 2010;24:425-37.
 50. Bellodi C, Krasnykh O, Haynes N, Theodoropoulou M, Peng G, Montanaro L, Ruggero D. Loss of function of the tumor suppressor DKC1 perturbs p27 translation control and contributes to pituitary tumorigenesis. *Cancer Res* 2010;70:6026-35.
 51. Cander S, Erturk E, Karkucak M, Oz Gul O, Gorukmez O, Yakut T, Unal OK, Ersoy C, Tuncel E, Imamoglu S. Effect of cyclin D1 (CCND1) gene polymorphism on tumor formation and behavior in patients with prolactinoma. *Gene* 2012;509:158-63.
 52. Fedele M, Palmieri D, Fusco A. HMGA2: a pituitary tumour subtype-specific oncogene? *Mol Cell Endocrinol* 2010;326:19-24.
 53. Fedele M, Battista S, Kenyon L, Baldassarre G, Fidanza V, Klein-Szanto AJ, Parlow AF, Visone R, Pierantoni GM, Outwater E, Santoro M, Croce CM, Fusco A. Overexpression of the HMGA2 gene in transgenic mice leads to the onset of pituitary adenomas. *Oncogene* 2002;21:3190-8.
 54. Fedele M, Visone R, De Martino I, Troncone G, Palmieri D, Battista S, Ciarmiello A, Pallante P, Arra C, Melillo RM, Helin K, Croce CM, Fusco A. HMGA2 induces pituitary tumorigenesis by enhancing E2F1 activity. *Cancer Cell* 2006;9:459-71.
 55. Fedele M, Pentimalli F, Baldassarre G, Battista S, Klein-Szanto AJ, Kenyon L, Visone R, De Martino I, Ciarmiello A, Arra C, Viglietto G, Croce CM, Fusco A. Transgenic mice overexpressing the wild-type form of the HMGA1 gene develop mixed growth hormone/prolactin cell pituitary adenomas and natural killer cell lymphomas. *Oncogene* 2005;24:3427-35.
 56. Palmieri D, Valentino T, De Martino I, Esposito F, Cappabianca P, Wierinckx A, Vitiello M, Lombardi G, Colao A, Trouillas J, Pierantoni GM, Fusco A, Fedele M. PIT1 up-regulation by HMGA proteins has a role in pituitary tumorigenesis. *Endocr Relat Cancer* 2012;19:123-35.
 57. Zhu X, Asa SL, Ezzat S. Fibroblast growth factor 2 and estrogen control the balance of histone 3 modifications targeting MAGE-A3 in pituitary neoplasia. *Clin Cancer Res* 2008;14:1984-96.
 58. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004;116:281-97.
 59. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, Shimizu M, Rattan S, Bullrich F, Negrini M, Croce CM. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. *Proc Natl Acad Sci U S A* 2004;101:2999-3004.

60. Mao ZG, He DS, Zhou J, Yao B, Xiao WW, Chen CH, Zhu YH, Wang HJ. Differential expression of microRNAs in GH-secreting pituitary adenomas. *Diagn Pathol* 2010;5:79.
61. Bottoni A, Zatelli MC, Ferracin M, Tagliati F, Piccin D, Vignali C, Calin GA, Negrini M, Croce CM, Degli Uberti EC. Identification of differentially expressed microRNAs by microarray: a possible role for microRNA genes in pituitary adenomas. *J Cell Physiol* 2007;210:370-7.
62. Bottoni A, Piccin D, Tagliati F, Luchin A, Zatelli MC, degli Uberti EC. miR-15a and miR-16-1 down-regulation in pituitary adenomas. *J Cell Physiol* 2005;204:280-5.
63. Amaral FC, Torres N, Saggioro F, Neder L, Machado HR, Silva WA Jr, Moreira AC, Castro M. MicroRNAs differentially expressed in ACTH-secreting pituitary tumors. *J Clin Endocrinol Metab* 2009;94:320-3.
64. Butz H, Liko I, Czirjak S, Igaz P, Khan MM, Zivkovic V, Balint K, Korbonits M, Racz K, Patocs A. Down-regulation of Wee1 kinase by a specific subset of microRNA in human sporadic pituitary adenomas. *J Clin Endocrinol Metab* 2010;95:E181-91.
65. Stilling G, Sun Z, Zhang S, Jin L, Righi A, Kovacs G, Korbonits M, Scheithauer BW, Kovacs K, Lloyd RV. MicroRNA expression in ACTH-producing pituitary tumors: up-regulation of microRNA-122 and -493 in pituitary carcinomas. *Endocrine* 2010;38:67-75.
66. Trivellin G, Butz H, Delhove J, Igreja S, Chahal HS, Zivkovic V, McKay T, Patocs A, Grossman AB, Korbonits M. MicroRNA miR-107 is overexpressed in pituitary adenomas and inhibits the expression of aryl hydrocarbon receptor-interacting protein in vitro. *Am J Physiol Endocrinol Metab* 2012;303:E708-19.
67. Benetatos L, Hatzimichael E, Londin E, Vartholomatos G, Loher P, Rigoutsos I, Briasoulis E. The microRNAs within the DLK1-DIO3 genomic region: involvement in disease pathogenesis. *Cell Mol Life Sci* 2013;70:795-814.
68. Cheunschon P, Zhou Y, Zhang X, Lee H, Chen W, Nakayama Y, Rice KA, Tessa Hedley-Whyte E, Swearingen B, Klibanski A. Silencing of the imprinted DLK1-MEG3 locus in human clinically nonfunctioning pituitary adenomas. *Am J Pathol* 2011;179:2120-30.
69. Finelli P, Giardino D, Rizzi N, Buiatitot S, Virduci T, Franzin A, Losa M, Larizza L. Non-random trisomies of chromosomes 5, 8 and 12 in the prolactinoma sub-type of pituitary adenomas: conventional cytogenetics and interphase FISH study. *Int J Cancer* 2000;86:344-50.
70. D'Angelo D, Palmieri D, Mussnich P, Roche M, Wierinckx A, Raverot G, Fedele M, Croce CM, Trouillas J, Fusco A. Altered microRNA expression profile in human pituitary GH adenomas: down-regulation of miRNA targeting HMGA1, HMGA2, and E2F1. *J Clin Endocrinol Metab* 2012;97:E1128-38.
71. Palmieri D, D'Angelo D, Valentino T, De Martino I, Ferraro A, Wierinckx A, Fedele M, Trouillas J, Fusco A. Down-regulation of HMGA-targeting microRNAs has a critical role in human pituitary tumorigenesis. *Oncogene* 2012;31:3857-65.
72. Zhang Z, Florez S, Gutierrez-Hartmann A, Martin JF, Amendt BA. MicroRNAs regulate pituitary development, and microRNA 26b specifically targets lymphoid enhancer factor 1 (Lef-1), which modulates pituitary transcription factor 1 (Pit-1) expression. *J Biol Chem* 2010;285:34718-28.
73. Palumbo T, Faucz FR, Azevedo M, Xekouki P, Iliopoulos D, Stratakis CA. Functional screen analysis reveals miR-26b and miR-128 as central regulators of pituitary somatotrophic tumor growth through activation of the PTEN-AKT pathway. *Oncogene* 2013;32:1651-9.
74. Zhang X, Zhou Y, Klibanski A. Isolation and characterization of novel pituitary tumor related genes: a cDNA representational difference approach. *Mol Cell Endocrinol* 2010;326:40-7.
75. Balik V, Srovnal J, Sulla I, Kalita O, Foltanova T, Vaverka M, Hrabalek L, Hajduch M. MEG3: a novel long noncoding potentially tumour-suppressing RNA in meningiomas. *J Neurooncol* 2013;112:1-8.