The Molecular Pathogenesis of Pituitary Adenomas: An Update

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<td>doi:10.3803/EnM.2013.28.4.245</td>
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The Molecular Pathogenesis of Pituitary Adenomas: An Update

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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 cannot 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 mechanism 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...
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 domain disorder, Carney complex (CNC), is mainly caused by the mutation of cAMP-dependent protein kinase A type 1 alpha regulatory subunit (PRKAR1A) [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 DEREGULATED 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-Albright 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 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 as 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 90% of familial and about 30% of sporadic pituitary adenomas. When the p16 expression is silenced, the phosphorylation of 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 adrenocorticotropic 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 phrase 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.
increased 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 HMGAA2 gene located, accounts for the HMGAA2 overexpression restricted in human prolactinomas [69]. The mechanism responsible for the deregulation of HMGAA proteins in other subtype pituitary adenomas remains elusive. A recent study presented by D’Angelo et al. [70] suggested a miRNA-dependent impairment of HMGAA/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 HMGAA2; miR-34b and miR-548c-3p target on both the HMGAA1 and HMGAA2; 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, HMGAA 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 oncogenes, and 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 as 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, onco-
genesis, as well as cell cycle abnormalities in pituitary tumorigen-
esis. 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 satisfac-
tory human pituitary adenoma cell lines and animal models.
Therefore, future work is expected in generating workable hu-
man functional and nonfunctional pituitary tumor cell lines, and
establishing satisfactory animal models, which will be of great
importance in understanding the molecular events governing pi-
tuitary 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.

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