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Genetic and epigenetic mutations of tumor suppressive genes in sporadic pituitary adenoma

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Abstract

Human pituitary adenomas are the most common intracranial neoplasms. Approximately 5% of them are familial adenomas. Patients with familial tumors carry germline mutations in predisposition genes, including *AIP*, *MEN1* and *PRKARIA*. These mutations are extremely rare in sporadic pituitary adenomas, which therefore are caused by different mechanisms. Multiple tumor suppressive genes linked to sporadic tumors have been identified. Their inactivation is caused by epigenetic mechanisms, mainly promoter hypermethylation, and can be placed into two groups based on their functional interaction with tumor suppressors RB or p53. The RB group includes *CDKN2A*, *CDKN2B*, *CDKN2C*, *RB1*, *BMP4*, *CDH1*, *CDH13*, *GADD45B* and *GADD45G*; *AIP* and *MEN1* genes also belong to this group. The p53 group includes *MEG3*, *MGMT*, *PLAGL1*, *RASSF1*, *RASSF3* and *SOCS1*. We propose that the tumor suppression function of these genes is mainly mediated by the RB and p53 pathways. We also discuss possible tumor suppression mechanisms for individual genes.

Keywords

Sporadic pituitary adenoma; Tumor suppression; Genetic mutation; Epigenetic; RB; p53

1. Introduction

Human pituitary adenomas are the most common intracranial tumors, typically arising from hormone secreting cells in the anterior pituitary (Ezzat et al., 2004). Tumors secreting excess pituitary hormones and causing characteristic phenotypic syndromes in patients are classified as clinically functioning adenomas, and include growth hormone (GH) secreting, prolactin (PRL) secreting, adrenocorticotropin (ACTH) secreting and thyrotropin (TSH) secreting tumors. Rarely, tumors producing gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), can cause clinical symptoms of gonadotropin excess. Tumors which do not lead to clinical symptoms are known as clinically non-functioning adenomas (NFAs). NFAs are derived from all types of anterior pituitary hormone secreting cells, but most commonly from gonadotroph cells (Chaidarun and Klibanski, 2002). NFAs can grow very large in size and can cause mass effect resulting in hypopituitarism, headache, vision impairment, and neurologic dysfunction in patients. Despite recent advances in understanding the pathogenesis of these tumors, the underlying cause of the majority of pituitary tumors remains elusive.

Studies have demonstrated that genetic and epigenetic mutations play a determining role in the development of human neoplasms (Peltomaki, 2012). Normal cells contain an intrinsic tumor suppression mechanism which consists of multiple pathways maintaining normal cell homeostasis (Lowe et al., 2004). These tumor suppression pathways regulate many checkpoints which dictate the fate of cells in response to genotoxic, metabolic and other stress stimuli. Cells with excessive damage are prevented from further proliferation by induction of permanent arrest, such as cellular senescence, or programmed death, such as apoptosis. Each tumor suppression pathway is composed of multiple components forming a regulatory cascade. For normal cells to become tumorous, these tumor suppression barriers have to be circumvented by mutation of one or more pathway components (Hanahan and Weinberg, 2013).

The first evidence indicating that pituitary tumors may be caused by somatic mutations, genetic or epigenetic, came from early tumor clonality studies. We investigated X-chromosome inactivation patterns in NFAs from female patients by analyzing restriction fragment length polymorphisms and methylation status of the *phosphoglycerate kinase* (*PGK*) and *hypoxanthine phosphoribosyltransferase* (*HPRT*) genes (Alexander et al., 1990). We found that individual NFAs contain only one type of X-inactivation, paternal, or, maternal, never both. This observation was confirmed by other independent studies (Herman et al., 1990; Jacoby et al., 1990). In addition, similar results were also found in ACTH-secreting adenomas (Biller et al., 1992; Gicquel et al., 1992, 1994; Herman et al., 1990; Zahedi et al., 2001), GH-secreting adenomas (Herman et al., 1990; Jacoby et al., 1990), and prolactinomas (Herman et al., 1990; Jacoby et al., 1990; Ma et al., 2002). These data indicate that human pituitary adenomas are monoclonal in origin suggesting that individual tumors are derived from single cells driven by a somatic gene mutation or mutations.

The second line of evidence came from studies of patients with presumed germ-line mutations in familial pituitary adenomas (FPAs), including multiple endocrine neoplasia type I (MEN1), Carney complex (CNC) and familial isolated pituitary adenoma (FIPA). Patients with these conditions carry germline mutations, and pituitary tumors from these patients display loss of heterozygosity (LOH) in the affected locus. For example, genetic linkage analyses indicate that the genetic defect causing MEN1 is located on chromosome 11q13 (Larsson et al., 1988). Subsequently, the germline mutations in the *multiple endocrine neoplasia type I (MEN1)* gene were identified from this region. Similarly the germline mutation in *cAMP-dependent protein kinase type I-alpha regulatory subunit (PRKARIA)* was identified in CNC patients (Kirschner et al., 2000) and *aryl hydrocarbon receptor interacting protein (AIP)* in FIPA patients (Vierimaa et al., 2006). In addition, germline mutations in *cyclin-dependent kinase inhibitor 1B (CDKN1B)* were identified in patients with an MEN1-like syndrome, but without a *MEN1* gene mutation (Pellegata et al., 2006).

Genetic mutations clearly contribute to the development of FPAs. However, FPA accounts for only ~5% of all pituitary tumors. The genetic mutations identified in FPAs do not play a significant role in the pathogenesis of sporadic tumors. Thus far, *GNAS*, encoding the stimulatory guanine nucleotide-binding protein (G_{α_s}) (Landis et al., 1989; Lyons et al., 1990), is the only gene confirmed which is linked to a subset (~40%) of GH-secreting adenomas (Freda et al., 2007), suggesting that novel somatic DNA mutations, if any, have yet to be identified in vast majority of sporadic tumors. Interestingly, no difference has been found in clinical characteristics, hormone levels or response to therapy in patients with tumors with or without G_{α_s} mutations.

In recent years, emerging evidence indicates that epigenetic modifications are the major alternative force altering the expression of genes involved in neoplastic development (Dawson and Kouzarides, 2012; You and Jones, 2012), including pituitary tumorigenesis

(Tateno et al., 2010). Epigenetic changes include aberrant DNA methylation and histone modification (Jaenisch and Bird, 2003; Peltomaki, 2012). Importantly, DNA methylation has been observed to be the main cause for gene inactivation in pituitary tumors (Yacub-Usman et al., 2012b). DNA methylation involves DNA methyltransferases (DNMTs), which transfer a methyl group from *S*-adenosylmethionine to the 5-position of cytosine residues in DNA. Four major DNMTs have been identified so far: DNMT1, DNMT3A, DNMT3B and DNMT3L. DNMT3A and DNMT3B specifically recognize unmethylated DNA and establish *de novo* methylation patterns (Okano et al., 1999, 1998). DNMT3L does not possess enzyme activity, but functions as a co-factor to stimulate activities of DNMT3A and DNMT3B (Suetake et al., 2004). DNMT1 is universally expressed and responsible for methylation maintenance during DNA replication and repair (Leonhardt et al., 1992; Mortusewicz et al., 2005). Among the three enzymatically active DNMTs, only DNMT3B has been shown to be up regulated in human pituitary tumors by a histone modification mechanism (Zhu et al., 2008). Although DNMT3B was suggested as a putative mediator of epigenetic control in pituitary adenomas (Zhu et al., 2008), it remains to be determined whether it is responsible for gene silencing in these tumors. Over the years, a number of genes have been found to be inactivated in pituitary tumors by genetic or epigenetic mechanisms (Table 1). They are functionally linked to the two most important tumor suppressors, RB and p53. In this review we will discuss recent progress on these tumor suppressive genes involved in the development of human pituitary adenomas.

2. The RB connection

The tumor suppressor RB plays a central role in regulating cell cycle progression (Henley and Dick, 2012). The RB pathway is also involved in the regulation of differentiation, apoptosis and maintenance of genome stability (Dick and Rubin, 2013; Indovina et al., 2013). This pathway is composed of the RB family of proteins, E2Fs, cyclins, cyclin-dependent kinases (CDKs) and CDK inhibitors. When active, RB arrests the cell cycle at G1 by interacting with chromosome remodeling factors (CRFs) and transcription factors E2Fs, thereby inhibiting expression of genes required for cell cycle progression (Henley and Dick, 2012). Phosphorylation of RB releases CRFs and frees E2Fs, which activates expression of genes permitting cell cycle progression. RB is mainly phosphorylated by CDK-cyclin complexes, including cyclin D-CDK4/6 and cyclin E/CDK2, which are negatively regulated by the INK4 and CIP/KIP families of inhibitors. The INK4 family of CDK inhibitors, namely p15^{Ink4b}, p16^{Ink4a}, p18^{Ink4c} and p19^{Ink4d}, specifically inhibit cyclin D/CDK4 or 6, whereas the CIP/KIP family of CDK inhibitors, namely p21^{Cip1}, p27^{Kip1} and p57^{Kip2}, inhibit a broader range of CDKs (Sherr and Roberts, 1999). The RB pathway is compromised if a mutation inactivates one or more components of the pathway. Therefore, the vast majority of human malignancies harbor mutations in the RB pathway (Di Fiore et al., 2013; Nevins, 2001). In human pituitary adenomas, genetic mutations of the RB pathway components are very rare. However, abundant evidence indicates that inactivation of the RB pathway is mediated by epigenetic mutations, which play a significant role in pituitary tumorigenesis.

2.1. The RB pathway and sporadic pituitary adenomas

Genetic mutations of genes in the RB pathway are extremely rare in human pituitary adenomas (Cryns et al., 1993; Ikeda et al., 1997; Jaffrain-Rea et al., 1999; Takeuchi et al., 1998). To date, only a small number of genetic mutations of RB1, p15^{Ink4b} and p16^{Ink4a} have been reported in sporadic tumors (Ogino et al., 2005; Simpson et al., 2001). Most studies have focused on epigenetic modifications, mainly promoter methylation. Very few studies include the investigation of cyclins and CDKs. These data are also inconsistent. For example, Saeger et al. (2001) reported that expression of cyclin D1 was detected in 1 out of

60 tumors by immunohistochemical staining. In contrast, a study by Simpson et al. (2001) indicated that 22 out of 45 tumors were positive for cyclin D1. Jordan et al. (2000) reported that over expression of cyclin D1 was detected in NFAs and cyclin E in ACTH-secreting tumors, respectively. CDK4 carrying mutations at codon R24 are resistant to the INK4 family of CDK inhibitors and have been identified as germline mutations in familial melanoma patients (Soufir et al., 1998; Zuo et al., 1996). However, such CDK4 mutations have not been found in pituitary tumors (Honda et al., 2003; Ogino et al., 2005; Simpson et al., 2001; Vax et al., 2003). These data suggest that cyclins and CDKs may not play a significant role in pituitary tumorigenesis.

The most frequently investigated CDK inhibitor of the CIP/KIP family is p27^{Kip1} encoded by the *CDKN1B* gene, which has been identified as a predisposition gene in MEN-1 like patients (Pellegata et al., 2006). No genetic mutations of the *CDKN1B* gene have been found in sporadic pituitary tumors (Dahia et al., 1998; Igreja et al., 2009; Ikeda et al., 1997; Takeuchi et al., 1998). However, the expression of p27^{Kip1} is generally lower in pituitary tumors compared to that in normal pituitaries (Bamberger et al., 1999; Komatsubara et al., 2001; Korbonits et al., 2002; Lidhar et al., 1999). The *CDKN1A* gene, encoding p21^{Cip1}, has also been investigated and no genetic mutations in this gene were found in pituitary tumors (Ikeda et al., 1997; Yoshino et al., 2007). Expression of p21^{Cip1} was down regulated in approximately 47% of tumors compared to normal pituitary tissue (Hiyama et al., 2002; Suliman et al., 2001). It appears that promoter hypermethylation does not play a role in down regulation of p21^{Cip1} and p27^{Kip1} in pituitary tumors (Yoshino et al., 2007). Therefore, the mechanism for their down regulation remains to be determined.

In contrast, promoter hypermethylation is frequently associated with the INK4 family of CDK inhibitors and the *RB1* gene in pituitary tumors. More than 400 pituitary tumors have been examined for p16^{Ink4a} methylation (Abd El-Moneim and Abd El-Rehim, 2009; Bello et al., 2006; Jaffrain-Rea et al., 1999; Ogino et al., 2005; Ruebel et al., 2001; Seemann et al., 2001; Simpson et al., 1999, 2001, 2004; Woloschak et al., 1997; Yoshino et al., 2007). Promoter hypermethylation of the *p16^{Ink4a}* gene are found in 56% of pituitary tumors. It occurs most frequently in NFAs (69%) and least frequently in GH-secreting tumors (29%). Compared to *p16^{Ink4a}*, *p15^{Ink4b}* and *p18^{Ink4c}* promoter methylation occur less frequently, 38% and 20% of pituitary tumors, respectively (Hossain et al., 2009; Kirsch et al., 2009; Ogino et al., 2005; Yoshino et al., 2007). Loss of p16^{Ink4a} expression is found in 65% of pituitary tumors (Abd El-Moneim and Abd El-Rehim, 2009; Seemann et al., 2001; Simpson et al., 1999, 2001, 2004; Woloschak et al., 1996). *RB1* promoter methylation is found in 27% of pituitary tumors (Bello et al., 2006; Ogino et al., 2005; Simpson et al., 2001, 2000; Yoshino et al., 2007), and loss of *RB1* gene expression occurs in 29% of tumors (Ogino et al., 2005; Simpson et al., 2001, 2000). Two observations need to be pointed out. First, promoter methylation correlates closely with the loss of gene expression (Abd El-Moneim and Abd El-Rehim, 2009; Ogino et al., 2005; Simpson et al., 2004), indicating that gene inactivation in pituitary tumors is likely due to promoter methylation. Second, the methylation of *p16^{Ink4a}* and *RB1* promoters is mutually exclusive in pituitary tumors (Bello et al., 2006; Ogino et al., 2005; Yoshino et al., 2007). Data from two studies indicate that the percentage of pituitary tumors with at least one RB pathway gene silenced due to promoter methylation is approximately 90% (Ogino et al., 2005; Yoshino et al., 2007). Because any one gene inactivation is likely to compromise the function of the RB pathway, these studies strongly suggest that inactivation of the RB pathway contributes to the development of pituitary adenomas.

Animal models provide further evidence supporting the hypothesis that the RB pathway plays a causal role in pituitary tumor development. Mice carrying a heterozygous deletion of the *Rb1* gene rapidly grow pituitary tumors with 100% penetrance (Hu et al., 1994; Jacks et

al., 1992; Leung et al., 2004). Mice with mutations of *p27^{Kip1}* or *p18^{Ink4c}* develop pituitary hyperplasia as well as pituitary tumors (Fero et al., 1996; Franklin et al., 1998; Kiyokawa et al., 1996; Nakayama et al., 1996). Furthermore, mice with a double knockout of both *p27^{Kip1}* and *p18^{Ink4c}* grew pituitary tumors at a much younger age compared to mice with individual gene deletions (Franklin et al., 1998), indicating that these two CDK inhibitors function synergistically in tumor suppression. These knockout mice grew melanotroph tumors in the intermediate lobe (Nikitin and Lee, 1996); no tumors grew in the anterior lobe where human hormone secreting cells reside. This is likely due to the genetic background of the animals which were mixed between C57BL/6 and 129/Sv or its derivatives. It has been demonstrated that *Rb1^{+/-}* mice on a 129/Sv background favors the development of tumors in the intermediate lobe of the pituitary. It was later found that the intermediate lobe of the pituitary is inherently abnormal in 129/Sv mice (Leung et al., 2004). Switching to a C57BL/6 background, by backcrossing, increases anterior lobe tumor development in the *Rb1^{+/-}* mice (Leung et al., 2004). In the aggregate, these studies further demonstrate the critical role that the RB pathway plays in suppression of pituitary tumorigenesis.

Not all human pituitary tumors have *p16^{Ink4a}* or *RB* inactivation (Bello et al., 2006; Ogino et al., 2005; Yoshino et al., 2007), suggesting that inactivation of other genes also contributes to pituitary tumor growth in humans. The RB pathway functions as an effector in cell cycle control in response to growth stimulatory or inhibitory signals, such as growth factors, oncogenic stresses, oxidative stresses and DNA damage (Courtois-Cox et al., 2008; Macleod, 2008; Rayess et al., 2012; Sperka et al., 2013). It also regulates its downstream target genes involved in a broad range of cellular activities (Indovina et al., 2013). Therefore, it is likely that inactivation of inhibitory signaling regulating the RB pathway may also contribute to pituitary tumorigenesis.

2.2. Aryl hydrocarbon receptor interacting protein (AIP)

The *AIP* gene was identified in FIPA patients from two families in Northern Finland (Vierimaa et al., 2006). It consists of 6 exons and encodes a protein of 330 amino acids, containing a peptidylprolyl cis-trans isomerase-like (PPIase-like) domain (amino acids 31-121), a tetratricopeptide repeat (TPR) domain with three TPR motifs (aa 179-298) and a c-terminal α -7 helix (Ca-7h) (Trivellin and Korbonits, 2011). Sequencing DNA from the patient's normal tissues uncovered a nonsense mutation at nucleotide position 40 in the coding region of the *AIP* gene where a cytosine was substituted by a thymidine (c.40 C > T) converting a Gln codon to a stop codon (Q14X) (Vierimaa et al., 2006). Importantly, the wild type allele of the *AIP* gene was found to be lost in all patient tumors. Patients with *AIP* mutations are much younger than the *AIP* mutation negative patients (Vierimaa et al., 2006). All these fit well with the classic “two-hit” tumor suppressor model proposed originally by Knudson (Knudson, 1971), suggesting that the *AIP* gene is a tumor suppressor.

Since the first *AIP* mutations in FIPA were reported in 2006, more than 75 different types of mutations in the *AIP* gene have been identified (Beckers et al., 2013; Cazabat et al., 2012; Cuny et al., 2013). Beckers et al. (2013) reported a comprehensive list of *AIP* mutations in 215 patients reported in literature in a 2013 review. The *AIP* mutation occurs in 26% of familial adenomas based on four studies including 341 tumors (Daly et al., 2007; Georgitsi et al., 2008b; Igreja et al., 2010; Leontiou et al., 2008). Most familial adenomas with *AIP* mutations are GH-secreting and GH/PRL-secreting tumors, which account for 41% and 19%, respectively. Prolactinoma and NFA account for 9% and 16%, respectively. The *AIP* mutation occurs much less frequently in sporadic pituitary adenomas; 3.8% based on 13 independent studies which have examined 1875 tumors (Barlier et al., 2007; Buchbinder et al., 2008; Cazabat et al., 2012; Cuny et al., 2013; DiGiovanni et al., 2007; Georgitsi et al., 2008a, 2007; Iwata et al., 2007; Leontiou et al., 2008; Occhi et al., 2010; Raitila et al., 2007;

Tichomirowa et al., 2011; Yu et al., 2006). No sporadic GH/PRL-secreting tumors have been reported in these studies. *AIP* mutations occur in 5.4%, 4.4%, 3.3% and 2.4% of PRL-, GH-, ACTH-secreting tumors and NFAs, respectively. Approximately two thirds of those mutations are germline. The types of mutations in the *AIP* gene are very heterogeneous. They include nonsense mutations, missense mutations, small in-frame deletions, large deletions and the full gene deletion as well as mutations in introns that affect RNA splicing. These data suggest that mutations in the *AIP* gene are likely a random event in sporadic pituitary tumors and *AIP* inactivation plays an equally important role in the development of these tumors.

To investigate the role of the *AIP* gene in tumorigenesis, an *Aip* knockout mouse line was generated by inserting a gene trap cassette in intron 2. The insertion results in a truncated AIP protein without the TPR domain and the c-terminal alpha-7 helix (Raitila et al., 2010). A homozygous *Aip* inactivation was embryonic lethal. This is consistent with the finding in another *Aip* knockout mouse model by Lin et al. (2007) who observed that *Aip*^{-/-} embryos died between E10.5 and E14.5 due to cardiovascular defects. Heterozygous *Aip* mice grew normally but developed multiple pituitary tumors as early as 6 months of age. All mice developed pituitary tumors at 15 months. The vast majority of the tumors (88%) were GH-secreting. Tumors secreting PRL or GH/PRL are also observed. In addition, the wild type *Aip* allele was found to be lost in all GH secreting tumors judged by LOH analysis and immunochemical staining (Raitila et al., 2010). The tumor spectrum in *Aip* mice resembles that found in FIPA patients with *AIP* mutations. Data from *Aip* mice have thus provided further support that mutation of the *AIP* gene predisposes to pituitary tumor development in humans.

The consensus regarding the molecular mechanisms whereby AIP suppresses pituitary tumor development is through its interactions with a large number of partner proteins. AIP interacts with partners at its TPR and Cα-7h domains (Morgan et al., 2012; Trivellin and Korbonits, 2011). Approximately 90% of *AIP* mutations result in loss of AIP protein expression, AIP proteins without TPR and/or Cα-7h domains, or AIP proteins with mutations in both domains (Beckers et al., 2013). At least 16 proteins have been identified and confirmed to interact with AIP as has been reviewed in detail by Trivellin and Korbonits (2011) and Beckers et al. (2013). The centerpiece of the AIP interacting proteins is aryl hydrocarbon receptor (AHR) (Carver and Bradfield, 1997; Ma and Whitlock, 1997). AHR was originally identified as a ligand dependent transcription factor activated by environmental toxins such as 2,3,7,8-tetrachloro-*p*-dioxin (TCDD) and is involved in xenobiotic metabolism (Denison and Nagy, 2003). AHR is a multiple function protein regulating a variety of cellular activities. When in the inactive state, AHR resides in the cytoplasm where it is bound to AIP, heat shock protein 90 (HSP90) and p23. Ligand binding activates AHR by translocation of the AHR complex to the nucleus. There, AHR is freed from its binding proteins and forms a heterodimer with aryl hydrocarbon receptor nuclear translocator (ARNT) to regulate expression of its target genes which are involved in xenobiotic metabolism, cellular homeostasis, cell proliferation and development (Denison et al., 2011).

A likely mechanism whereby AIP suppresses tumor growth is by regulating AHR function. Indeed, AIP interaction has been shown to stabilize AHR by preventing it from ubiquitin mediated degradation (Kazlauskas et al., 2000; LaPres et al., 2000). In addition, AIP interaction retains AHR in the cytoplasm and enhances its ligand binding (Kazlauskas et al., 2000; LaPres et al., 2000; Petrusis et al., 2000). AIP interaction is essential for AHR function. For example, deletion of *Aip* led to a reduction in AHR levels. In addition, AHR mediated hepatotoxicity is abolished in the absence of AIP (Nukaya et al., 2010). Finally, Cai et al. (2011) reported that AIP formed complexes with ERα, which are recruited to the

promoter of the target gene to inhibit gene transcription. Because AHR binds ER α and inhibits its function (Madak-Erdogan and Katzenellenbogen, 2012), it is likely that AIP inhibition of ER α is mediated by AHR. Taken together, these data support the concept that AIP suppresses tumor growth via AHR signaling.

Overwhelming evidence indicates that AHR plays a role in tumor suppression, primarily by activation of the RB pathway. AHR activated by ligands, such as TCDD, 3-methylcholanthrene, or baicalein, inhibits proliferation or induces apoptosis in several human cell lines via a number of mechanisms. For example, it has been shown that ligand activated AHR (1) induces CDK inhibitors p27^{Kip1} and p21^{Cip1} (Kolluri et al., 1999; Pang et al., 2008), (2) inhibits E2F mediated transcription through displacement of or direct interaction with coactivator p300 (Marlowe et al., 2004, 2008), and (3) activates RB by physical interaction (Elferink et al., 2001; Puga et al., 2000) or by induction of RB hypophosphorylation (Barhoover et al., 2010; Cheng et al., 2012). However, AHR promotion of cell proliferation has also been reported. This discrepancy appears to be due to the experimental approaches used. AHR activation by a ligand usually inhibits cell proliferation (Barhoover et al., 2010; Cheng et al., 2012; Elferink et al., 2001; Pang et al., 2008). The conclusion that AHR promotes cell proliferation is usually based on data obtained by ectopic overexpression of AHR (Wong et al., 2009) or knockdown of AHR by RNAi (Dever and Opanashuk, 2012; Kalmes et al., 2011; Yin et al., 2013). One interpretation of these data obtained from experiments not using ligand treatment is that AHR may have a ligand independent function which is important in the maintenance of cellular homeostasis. Therefore, these studies do not necessarily contradict the hypothesis that AHR mediates ligand induced inhibition of cell proliferation.

2.3. Multiple endocrine neoplasia Type I (MEN1)

MEN1 syndrome is manifested by at least two concurrent endocrine related tumors including parathyroid adenomas, entero-pancreatic endocrine tumors, and pituitary adenomas (Brandi et al., 2001). Sporadic MEN1 accounts for approximately 10% of all patients diagnosed with MEN1 (Trump et al., 1996). Pituitary adenomas are common in MEN1 patients; up to 40% of MEN1 patients are diagnosed with pituitary adenomas (O'Brien et al., 1996; Oberg et al., 1989; Trump et al., 1996; Verges et al., 2002). The *MEN1* gene responsible for the MEN1 phenotype is 9 kb long, containing 10 exons which encode a protein of 610-amino acids, named menin (Chandrasekharappa et al., 1997). *MEN1* gene germline mutations are very common in MEN1 patients. Lemos and Thakker (2008) reviewed in detail MEN1 mutations reported for the first 10 years after the *MEN1* gene was identified (Lemos and Thakker, 2008). LOH has been detected in all types of MEN1 tumors ranging from 10% to 100% (Bystrom et al., 1990; Debelenko et al., 1997; Friedman et al., 1989; Lubensky et al., 1996; Thakker et al., 1989). The loss of *MEN1*- both germline and in tumor tissue is consistent with the two hit model articulated by Knudsen (Knudson, 1971), indicating that *MEN1* is a tumor suppressor. *MEN1* mutations in sporadic pituitary tumors are very rare; a total of 15 tumors with *MEN1* mutations have been identified from 535 sporadic adenomas and only one is a germline mutation (Asa et al., 1998; Bergman et al., 2000; Cuny et al., 2013; Farrell et al., 1999; Fukino et al., 1999; Poncin et al., 1999; Prezant et al., 1998; Schmidt et al., 1999; Tanaka et al., 1998; Wenbin et al., 1999; Zhuang et al., 1997). The extremely low mutation rate suggests that *MEN1* mutations do not play a significant role in sporadic pituitary tumors.

Data from *Men1* knockout mouse models further support the hypothesis that *MEN1* is a tumor suppressor. Several *Men1* mouse models have been created by various schemes (Bertolino et al., 2003a, 2003b; Biondi et al., 2002; Crabtree et al., 2001; Harding et al., 2009; Loffler et al., 2007). These *Men1* mice share a similar phenotype. Homozygous mice

died *in utero* at E11.5 to E13.5 (Bertolino et al., 2003b; Crabtree et al., 2001). Heterozygous mice developed normally. They grew tumors in a spectrum resembling that found in human MEN1. The percent of *Men1*^{+/-} mice developing pituitary tumors varies depending on the study, ranging from 31% to 91% (Bertolino et al., 2003b; Harding et al., 2009; Loffler et al., 2007). Genetic analyses indicate that all pituitary tumors in the mice have lost the wild-type allele of the *Men1* gene (Harding et al., 2009). These data provide further evidence that *MEN1* is a *bona fide* tumor suppressor gene.

Menin plays a role in the regulation of cell proliferation both *in vitro* and *in vivo*. Ectopic expression of menin inhibits proliferation of several human and mouse cell lines *in vitro* (Bazzi et al., 2008; Gao et al., 2009; Kim et al., 1999; La et al., 2004; Schnepf et al., 2006; Shi et al., 2013; Stalberg et al., 2004; Wu et al., 2010) and in nude mice (Kim et al., 1999), and pituitary tumor cells in *Men1* knockout mice (Walls et al., 2012). Conversely, inactivation of menin by RNAi knockdown or deletion of the *Men1* gene leads to an increase in cell proliferation in cultured cells and in mice pancreatic islets (Milne et al., 2005b; Ratineau et al., 2004; Schnepf et al., 2006, 2004). Menin has also been shown to mediate growth inhibition induced by activin and TGF β (Canaff et al., 2012; Kaji et al., 2001; Lacerte et al., 2004). Taken together, cell proliferation inhibition by menin contributes, at least in part, to tumor suppression by the *MEN1* gene.

One plausible mechanism whereby menin inhibits cell proliferation and suppresses tumor growth is by activating the RB pathway. Menin up regulates expression of p27^{Kip1} and p18^{Ink4c} by recruiting MLL to their respective promoter regions (Karnik et al., 2005; Milne et al., 2005b). MLL, a menin interacting protein, is a histone H3 lysine 4 specific histone methyltransferase complex, which activates transcription by histone modification (Milne et al., 2002, 2005a; Yokoyama et al., 2004). Transcription activation by MLL also requires the recruitment of LEDGF by menin (Yokoyama and Cleary, 2008). In contrast, menin represses cyclin B2 expression by interfering with promoter binding of several transcription factors including NF-Y, E2F and α CBP (Wu et al., 2010). Menin does so by recruiting histone H3 deacetylase 3 (HDAC3) to the gene, which inhibits transcription by reduction of histone H3 acetylation. Interestingly, methylation of histone H3 lysine 4 is also reduced (Wu et al., 2010). How does menin recruit MLL and HDAC to specific genes? La et al. (2004) found that menin can physically bind to double stranded DNAs and regulate cell proliferation. This could explain how menin may recognize certain sequences in p27^{Kip1}, p18^{Ink4c} and cyclin B2 genes thereby recruiting MLL and HDAC to their respective locations. Furthermore, Ivo et al. (2011) reported that menin increases the cellular concentration of RB protein via unknown mechanisms. Taken together, the RB pathway is likely a direct downstream target of menin signaling.

2.4. Bone morphogenic protein 4 (BMP-4)

BMP-4, a member of the TGF β superfamily of cytokines, regulates diverse biological activities including development, differentiation and homeostasis. BMP-4 signals through its type I and type II serine/threonine kinase receptors. Ligand bound type I receptors are activated by the type II receptor via phosphorylation. Activated type I receptors phosphorylate R-Smads including Smads 1, 5 and 8, which subsequently associate with Smad4 and translocate to the nucleus where they transcriptionally activate their target genes (Miyazono et al., 2005). Evidence indicates that BMP-4 plays a role in tumor suppression via activation of the RB pathway. For example, BMP-4 inhibits growth of colorectal cancer stem cells by induction of terminal differentiation through up regulation of E-cadherin and down regulation of cyclin D1 (Lombardo et al., 2011). Su et al. (2011) reported that BMP-4 inhibits proliferation of lung cancer cells by induction of premature senescence involving stimulating expression of p16^{Ink4a} and p21^{Cip1}. In addition, BMP-4 inhibits growth of

diffuse-type gastric carcinoma cells and prostate cancer cells by RB activation through up regulation of p21^{Cip1} (Brubaker et al., 2004; Shirai et al., 2011). In addition to activation of RB, BMP4 was shown to induce p53 dependent apoptosis by up regulation of PUMA expression and enhancement of Bax endoplasmic reticulum translocation (Fukuda et al., 2006), suggesting that p53 also plays a role in mediating BMP4 tumor suppression.

The pituitary gland is a BMP-4 target, which regulates pituitary cell proliferation and hormone secretion in a cell type specific manner (Labeur et al., 2010). A link between BMP-4 and human pituitary tumorigenesis was first reported by Takeda et al. (2003), who investigated activin/BMP system in pituitary adenomas including 5 NFAs and 3 gonadotropinomas. No BMP-4 was detected in any tumor by RT-PCR. Recently, Yacqub-Usman et al. (2012a) found that down regulation of BMP-4 occurred in the majority of pituitary tumors when BMP-4 mRNA was determined by RT-PCR (overall 75%, $n = 36$). BMP-4 down regulation occurred most frequently in GH-secreting tumors (100%, $n = 4$), followed by NFAs (88%, $n = 16$), ACTH- secreting tumors (72%, $n = 7$), and prolactinomas (44%, $n = 9$). There are two CpG clusters in the BMP-4 gene. Bisulfite sequencing did not detect any differences in methylation of these CpGs between normal pituitary and pituitary tumors, indicating that DNA methylation does not play a significant role in BMP-4 down regulation. Instead, the level of histone H3 lysine 27 trimethylation (H3K27Me3), which is associated with gene repression (Bernstein et al., 2006; Cao et al., 2002), is significantly elevated in NFAs and GH- secreting tumors. In contrast, H3 lysine 9 acetylation (H3K9Ac), which is associated with gene activation (Karmodiya et al., 2012), is significantly reduced (Yacqub-Usman et al., 2012a), suggesting that the BMP-4 down regulation in pituitary tumors is due to histone modification.

Conflicting data have been obtained when BMP-4 expression is measured at the protein level. In Yacqub-Usman's study, the BMP-4 protein levels, measured by ELISA, were only down regulated in NFA and GH-secreting tumors compared to normal controls (Yacqub-Usman et al., 2012a). Paez-Pereda et al. (2003) reported that BMP-4 protein levels, measured by western blotting, were not down regulated in any pituitary tumor type compared to normal pituitary tissue. Interestingly, both studies showed that among tumor types, BMP-4 protein levels were the highest in prolactinomas. This high BMP-4 expression was believed to promote prolactinoma growth in mice (Paez-Pereda et al., 2003). Giacomini et al. (2006) reported that BMP-4 expression, measured by immunostaining, was significantly down regulated in 13 out of 15 human ACTH-secreting tumors. They demonstrated that BMP-4 inhibited proliferation of AtT20, a murine corticotroph tumor cell line, in culture and tumor growth in nude mice. The cause of these discrepancies is not known. However, it raises the possibility that BMP-4 function is cell type dependent and may promote prolactinoma growth, but suppress ACTH-secreting adenoma development.

2.5. Cadherin 1 (CDH1)

The CDH1 gene encodes E-cadherin, a member of the cadherin family of proteins, which play a major role in maintaining cell–cell adhesion and communication in normal tissues (Angst et al., 2001; Meng and Takeichi, 2009). There are several studies investigating E-cadherin expression in human pituitary adenomas. Immunohistochemical staining is the most common method used to detect E-cadherin. Because the antibodies and staining scoring system used in individual studies vary significantly, it is difficult to compare data between studies. However, the consensus is that E-cadherin expression is lost or significantly reduced in pituitary adenomas compared to normal pituitary tissue regardless of tumor type. For example, Elston et al. (2009) reported that E-cadherin is lost or significantly reduced in 96% of pituitary tumors. A similar result was also reported by Kawamoto et al. (1997). Studies by Qian et al. (2007) found a somewhat lower percentage of tumors with

reduced E-cadherin expression, 62% of 69 tumors. Evang et al. (2011) investigated 48 ACTH-secreting tumors and found that 77% of them had lost or had significantly reduced E-cadherin. Fougner et al. (2010) found that the percentage was 47% in GH-tumors ($n = 83$). However, data from Xu et al. (2002) who studied 127 pituitary adenomas including all tumor types showed that the reduced expression is found only in GH tumors with prominent fibrous bodies. In general, data from most studies do not show any significant differences in E-cadherin expression between tumor types (Elston et al., 2009; Kawamoto et al., 1997; Qian et al., 2007). However, E-cadherin expression is usually significantly lower in invasive tumors compared to non-invasive tumors (Elston et al., 2009; Qian et al., 2007). E-cadherin expression also negatively correlates with tumor size (Fougner et al., 2010). These results indicate that loss of E-cadherin may play an important role in promoting pituitary tumor growth.

The methylation status of the *CDH1* promoter was investigated by methylation specific PCR (MSP). Qian et al. (2007) found that approximately 36% of pituitary tumors had *CDH1* promoter methylation. Interestingly, the number of tumors with *CDH1* methylation increases with tumor grade: 11% of grade I tumors contained *CDH1* methylation, while 63% of grade IV tumors contained *CDH1* methylation. Therefore, the percentage of tumors with promoter methylation is much lower than those with E-cadherin down regulation. This may be due to the limitation of MSP which may not be able to detect all methylation sites in the promoter. Another possibility is that additional mechanisms may be responsible for down regulation of E-cadherin in tumors without *CDH1* methylation. In 16 GH-secreting tumors with prominent fibrous bodies which were negative for E-cadherin expression, Xu et al. (2002) found that 6 had promoter methylation. In contrast, none of the 10 GH-secreting tumors without prominent fibrous bodies, which expressed E-cadherin, showed promoter methylation. These studies indicate that promoter methylation plays a significant role in silencing the *CDH1* gene in pituitary adenomas.

Classical cadherins, which are transmembrane proteins, are key structural components of the adherens junction (Meng and Takeichi, 2009). E-cadherin is a classical type I cadherin found in epithelial tissues. It consists of a calcium binding extracellular domain, which is responsible for calcium-dependent homophilic and heterophilic cell interactions, and a cytoplasmic domain, which binds to catenins regulating intracellular signaling (van Roy and Berx, 2008). E-cadherin plays an important role in tumor suppression (Berox and van Roy, 2009; Jeanes et al., 2008). It is one of the major factors inhibiting epithelial–mesenchymal transition (EMT), which converts epithelial cells to migratory and invasive cells (De Craene and Berx, 2013). Down-regulation of E-cadherin has been shown to increase EMT, promoting invasiveness and metastasis (Osada et al., 1996; Perl et al., 1998; Tiwari et al., 2012; Tryndyak et al., 2010; Vleminckx et al., 1991). Lekva et al. (2012) reported that down regulation of E-cadherin is associated with increases in tumor size and invasiveness of GH-secreting tumors. There are several possible mechanisms whereby E-cadherin suppresses tumor growth. E-cadherin inhibits metastatic spreading of tumor cells by promoting cell–cell adhesion and development of normal epithelial architecture (Jeanes et al., 2008); E-cadherin inhibits mitogenic signaling by sequestering catenins with its cytoplasmic tail (Jeanes et al., 2008; Soto et al., 2008); and finally, E-cadherin inhibits cell proliferation by activation of RB via up regulation of the CDK inhibitor p27^{Kip1} (St Croix et al., 1998).

E-cadherin plays a crucial role in mediating the function of several tumor suppressors, including p53, RB and ESRP1. Wang et al. (2009) found that p53 up regulates E-cadherin expression by promoting degradation of transcription factor Slug, which is known to repress E-cadherin expression (Bolos et al., 2003; Hajra et al., 2002). Conversely, inhibition of p53 results in repression of E-cadherin expression by increasing DNMT1 expression, which epigenetically silences the *CDH1* gene (Cheng et al., 2011). RB inhibits the EMT phenotype

by regulation of E-cadherin expression (Arima et al., 2008). RB interacts with transcription factor AP-2 α and binds to the *CDH1* promoter to activate its transcription (Arima et al., 2008; Batsche et al., 1998). Conversely, RB inactivation down-regulates E-cadherin expression (Arima et al., 2008). ESRP1, the epithelial splicing regulatory protein 1, was identified as one of the two RNA binding proteins regulating splicing of the *FGFR2* gene (Warzecha et al., 2009). Thought to function as a tumor suppressor in colorectal cancer (Leontieva and Ionov, 2009), ESRP1 is a key regulator of EMT, coordinating a complex epithelial alternative splicing network (Dittmar et al., 2012; Warzecha et al., 2010). Down-regulation of ESRP1 induces EMT phenotypes (Reinke et al., 2012; Warzecha et al., 2009). Very recently, ESRP1 was identified as a master regulator of EMT in human GH-secreting adenomas (Lekva et al., 2012, 2013). ESRP1 is positively correlated with E-cadherin expression in GH-secreting adenomas and its depletion by RNAi results in down regulation of E-cadherin in a GH-adenoma cell line (Lekva et al., 2012). Taken together, these studies suggest that down-regulation of E-cadherin plays a significant role in promoting pituitary tumorigenesis.

2.6. Cadherin 13 (CDH13)

The *CDH13* gene encodes H-cadherin, also known as T-cadherin. Qian et al. (2007) found that more than half of pituitary tumors (54%) have lost or significantly reduced expression of H-cadherin. Similar to patterns seen with E-cadherin, H-cadherin down regulation was found more frequently in invasive tumors (74%) than that in non-invasive tumors (38%). Approximately 30% of all pituitary tumors contain hypermethylation in the *CDH13* gene. There is no significant difference in promoter methylation between tumor types. However, *CDH13* methylation is found more frequently in invasive tumors (42%) than in non-invasive tumors (19%) (Qian et al., 2007), consistent with H-cadherin expression. As is the case seen with the E-cadherin study, the number of tumors with *CDH13* promoter methylation is less frequent compared to those with H-cadherin down regulation. Again, this may be due to the technical limitation of MSP or suggests that other, yet to be determined mechanisms, are responsible for the down regulation of H-cadherin in human pituitary tumors.

H-cadherin is a non-classical adherin, as it does not contain transmembrane and cytoplasmic domains but has a glycosylphosphatidylinositol anchor. H-cadherin functions as an adiponectin receptor and may not be involved in cell–cell adhesion (Philippova et al., 2009). Nevertheless, down regulation of H-cadherin by epigenetic silencing has been found in many types of human cancers and H-cadherin inhibits tumor cell proliferation (Andreeva and Kutuzov, 2010). Re-expression of H-cadherin induces G2/M arrest in human cancer cell lines including those derived from gliomas and hepatocellular carcinomas (Chan et al., 2008; Huang et al., 2003). This may be attributed to the induction of p21^{Cip1} expression by H-cadherin (Huang et al., 2003). In addition, H-cadherin has been shown to inhibit angiogenesis by inhibiting endothelial cell migration (Rubina et al., 2007) or insulin-dependent activation of PI3K/Akt/mTOR signaling (Philippova et al., 2012). These studies indicate that tumor suppression is a function of H-cadherin and that epigenetic down-regulation of the *CDH13* gene may contribute to pituitary tumorigenesis.

2.7. Growth arrest and DNA-damage-inducible, beta (GADD45B) and gamma (GADD45G)

The *GADD45* gene family consists of three members, *GADD45A*, *GADD45B*, and *GADD45G*, encoding GADD45 α , GADD45 β , and GADD45 γ , respectively. They are stress response genes. GADD45 expression is normally low, and rapidly increases in response to a wide range of stress signals such as UV and ionizing radiation, inflammatory and pro-apoptotic cytokines, mitogenic stimuli and xenobiotics (Moskalev et al., 2012). Loss of GADD45 expression has been observed in human cancers from a variety of tissue origins (Tamura et al., 2012). Interestingly, the large majority of human cancers do not contain

GADD45 gene mutations. Instead, promoter methylation is the major cause of *GADD45* down regulation (Guo et al., 2013a,b; Tamura et al., 2012). Among the three *GADD45* genes, *GADD45G* is the most frequently inactivated, followed by *GADD45B* and *GADD45A*, in human cancers (Tamura et al., 2012).

To search for genes involved in pituitary tumorigenesis, we compared gene expression profiles between normal pituitary tissue and NFAs using cDNA-representational difference analysis (cDNA-RDA) (Zhang et al., 2002). *GADD45G* was identified as the most frequently detected gene by RDA. Using RT-PCR, we examined *GADD45γ* expression in four normal pituitaries and 36 pituitary tumors. *GADD45γ* was detected in all the normal pituitaries. In contrast, it was only detected in four out of 36 tumors (Zhang et al., 2002), indicating that the vast majority of pituitary tumors have lost expression of *GADD45γ*. This finding was subsequently confirmed by three independent studies (Bahar et al., 2004; Mezzomo et al., 2011; Michaelis et al., 2011). So far a total of 121 sporadic pituitary adenomas including 62 NFA and 59 functioning adenomas have been reported. Loss of or significantly reduced *GADD45γ* expression is found in 74% of all pituitary tumors. Down regulation of *GADD45γ* is more frequently found in NFAs than in functioning tumors (90% and 58%, respectively) (Bahar et al., 2004; Mezzomo et al., 2011; Michaelis et al., 2011; Zhang et al., 2002). To investigate the mechanism of *GADD45γ* down regulation, Bahar et al. (2004) analyzed the methylation status in the *GADD45G* promoter region using MSP. They showed that methylation of the *GADD45G* promoter was detected in 58% of tumors. Among *GADD45γ* negative tumors, 82% had promoter methylation. Conversely, among *GADD45γ* positive tumors, 91% did not have promoter methylation (Bahar et al., 2004). These data strongly indicate that promoter methylation is the major cause for the loss of *GADD45γ* expression in human pituitary tumors. Michaelis et al. (2011) also evaluated *GADD45α* and *GADD45β* expression in pituitary tumors. Expression of *GADD45α* was similar between normal pituitary tissue and pituitary tumors. In contrast, *GADD45β* was down regulated in pituitary tumors by 68-fold judged by microarray data analyzed with the Ingenuity Pathway Analysis program. The *GADD45β* down regulation in tumors was subsequently confirmed by qPCR and immunoblotting. Surprisingly, hypermethylation in the *GADD45B* promoter was not detected in those tumors using bisulfite sequencing (Michaelis et al., 2011). The cause for *GADD45B* down-regulation in pituitary tumors remains to be determined.

The three *GADD45* members share a high degree of protein homology. However, they are not functionally identical, differ in tissue distribution and may respond to different stress signals (Liebermann et al., 2011; Tamura et al., 2012). Nevertheless, evidence supports the concept that *GADD45β* and *GADD45γ* have tumor suppression functions (Liebermann et al., 2011; Tamura et al., 2012). Re-expression of *GADD45β* and *GADD45γ* inhibits proliferation of both human and rodent pituitary cell lines. We introduced *GADD45γ* into PDFS cells, derived from a human NFA, and observed a significant inhibition in cell proliferation (Zhang et al., 2002). Similar results were also observed in rat pituitary GH4 and mouse pituitary AtT20 cells (Zhang et al., 2002). Michaelis et al. (2011) re-expressed *GADD45β* in LβT2, which is a mouse gonadotroph tumor cell line, and repressed LβT2 xenograft tumor growth in nude mice. One mechanism whereby *GADD45β* and *GADD45γ* inhibit cell proliferation is by arresting the cell cycle at the G1/S or G2/M phase (Fan et al., 1999). G2/M arrest is due to inhibition of CDK1/cyclin B1 (Chung et al., 2003; Fan et al., 1999; Vairapandi et al., 2002). G1 arrest is likely mediated by up regulation of p21^{Cip1}, inhibition of CDK2/cyclin E and induction of RB hypophosphorylation (Fan et al., 1999). Interaction with PCNA may also play a role in *GADD45β* and *GADD45γ* induced cell cycle arrest (Azam et al., 2001; Vairapandi et al., 1996). Therefore, these data indicate that *GADD45B* and *GADD45G* genes may suppress pituitary tumor growth by activation of the RB pathway.

3. The p53 connection

Tumor suppressor *TP53* is a stress response gene which plays a central role in maintaining cellular homeostasis and tumor suppression (Vousden and Prives, 2009). Normally, p53 is maintained at a low level by MDM2 and MDM4. MDM2 functions as an E3 ubiquitin ligase and initiates ubiquitination of p53, thereby mediating its degradation. MDM4 does not possess enzyme activity, but assists MDM2 binding to p53. A variety of stress signals activate p53 by posttranslational modification and stabilization via blocking MDM2/4 mediated degradation (Kruse and Gu, 2009; Perry, 2010; Wade et al., 2010). P53 is a potent transcription factor, regulating expression of genes which mediate its tumor suppression function, such as cell cycle arrest, DNA repair, senescence, and apoptosis (Vousden and Prives, 2009). *TP53* is one of the most commonly inactivated genes in human cancers (Olivier et al., 2010; Soussi, 2011). However, it is very rarely mutated in human pituitary adenomas (Herman et al., 1993; Levy et al., 1994; Tanizaki et al., 2007). To date, only one case of a confirmed *TP53* somatic mutation has been identified in an atypical corticotroph adenoma (Kawashima et al., 2009). This raises the question of whether p53 is involved in human pituitary tumorigenesis. In mice, deletion of both *Trp53* (the mouse p53 gene) alleles leads to development of a wide spectrum of tumors, which do not include pituitary tumors. However, *Trp53* deletion dramatically accelerates pituitary tumor growth in *Rb*^{+/-} mice. For example, Harvey et al. (1995) observed that the earliest age when pituitary tumors were observed in *Rb*^{+/-} mice was 38 weeks and some tumors were not detected until week 71. In contrast, all *p53*^{-/-}*Rb*^{+/-} mice died of tumors by 25 weeks of age and 33% of them had pituitary tumors. Williams et al. (1994) reported that the mean age of survival for *Rb*^{+/-} mice was 47 weeks and 100% of mice grew pituitary tumors. The mean age of survival for *p53*^{-/-}*Rb*^{+/-} mice was 17 weeks and 94% of them grew pituitary tumors. These results indicate that p53 indeed plays a role in tumor suppression in the pituitary. However, loss of p53 does not initiate pituitary tumor development. Instead, p53 plays a role in promoting pituitary tumorigenesis. It must be emphasized that p53 is regulated by and responds to a variety of stress signaling pathways, and that p53 function is mediated by its target genes. Therefore, p53 is as “functionally effective” as its regulators and target genes. Thus, for example, promoter methylation of p14^{ARF}, which is well known to activate p53 by inhibition of MDM2, has been found in a small percentage (12%) of pituitary tumors in several studies (Bello et al., 2006; Kirsch et al., 2009; Yoshino et al., 2007). Significant down regulation of p14^{ARF} expression was also observed in pituitary tumors by Western blotting (Michaelis et al., 2011). This indicates that the signaling to p53 mediated by p14^{ARF} is interrupted in some pituitary tumors and suggests that inactivation of p53 signaling indeed contributes to human pituitary tumorigenesis. In addition to p14^{ARF}, several genes whose expression are lost or significantly reduced have been identified in human pituitary adenomas (Table 1). We will discuss how they may contribute to tumor suppression via p53.

3.1. Maternally expressed gene 3 (MEG3)

The association between the *MEG3* gene and human pituitary tumors was first established by comparing gene expression profiles between normal pituitary and NFAs using cDNA-RDA (Zhang et al., 2002). We identified *MEG3* as one of the most under expressed genes in NFAs. In contrast, the level of *MEG3* expression is very high in the normal human pituitary. No *MEG3* RNA was detected in 11 human pituitary adenomas, including 9 NFAs and 3 GH-secreting adenomas by RT-PCR (Zhang et al., 2002). To confirm this finding, we and others have examined additional tumor samples for *MEG3* expression. A total of 147 sporadic pituitary adenomas including 79 NFAs have been investigated (Cheunsuchon et al., 2011; Gejman et al., 2008; Mezzomo et al., 2011; Zhang et al., 2003; Zhao et al., 2005). Using conventional RT-PCR, only three out of 54 NFAs contained detectable *MEG3* (Mezzomo et al., 2011). In contrast, *MEG3* was detected in 35 out of 49 functioning tumors.

These data were confirmed by qRT-PCR. The overall *MEG3* expression in NFA (0.02 ± 0.02 , $n = 25$, $p = 0.006$, t -test) is significantly lower compared to that in normal pituitary (1.0 ± 0.88 , $n = 10$). In contrast, there is no significant difference in *MEG3* expression between functioning adenomas (0.55 ± 0.47 , $n = 19$, $p = 0.16$) and normal human pituitary tissue (Cheunsuchon et al., 2011). These data indicate that *MEG3* is specifically lost in NFAs and its inactivation may play a significant role in the development of NFAs but not functioning adenomas.

MEG3, an imprinted gene, belongs to the *DLK1-MEG3* imprinting locus located on 14q32 and consists of 10 exons. We first determined whether gene deletions are responsible for loss of *MEG3* expression in NFAs (Zhao et al., 2005). Two micro satellite markers flanking exons 4 to 9 of the *MEG3* gene were quantified using qPCR. No differences in both markers were found between NFAs and normal pituitary tissues, indicating that these tumors do not contain genomic deletions of the *MEG3* gene. We next sequenced each individual exon of the *MEG3* gene and did not find any small deletions or point mutations in these tumors (Zhao et al., 2005). These data exclude genetic mutations as a mechanism for *MEG3* loss in NFAs. Expression of the *MEG3* gene is regulated by two differentially methylated regions, IG-DMR and *MEG3*-DMR, which are methylated in the paternal but not the maternal allele (da Rocha et al., 2008). The IG-DMR is approximately 13 kb upstream of the *MEG3* gene. The *MEG3*-DMR is ~2 kb long overlapping with the *MEG3* promoter and extends into intron 1. We determined the methylation status in both the IG-DMR and *MEG3*-DMR by bisulfite sequencing. We found that methylation was significantly increased in both the IG-DMR and *MEG3*-DMR in NFAs compared to normal pituitary tissue (Gejman et al., 2008; Zhao et al., 2005), suggesting that epigenetic changes in these two regulatory region are responsible for silencing of the *MEG3* gene in NFAs. This mechanism is also supported by another finding. The *MEG3* promoter contains a cAMP response element (CRE), which is required for expression of the *MEG3* gene (Zhao et al., 2006). CRE sequences contain a CpG dinucleotide. Its methylation status directly determines CRE mediated transcription. For example, the *CD86* gene promoter contains two CREs. No *CD86* expression was detected in cells with methylated CREs. In contrast, *CD86* was readily detected in cells with unmethylated CREs (Romero-Tlalolini et al., 2013). The mouse insulin promoter also contains a CRE. Kuroda et al. (2009) found that CRE methylation alone reduced promoter activity by 50%. In addition, chromatin immunoprecipitation analysis indicates that CpG methylation blocks binding of transcription factors to endogenous CREs (Kuroda et al., 2009; Romero-Tlalolini et al., 2013). These data suggest that CRE methylation likely plays a role in *MEG3* gene down regulation.

Strong evidence suggests that *MEG3* is novel tumor suppressor gene (Zhou et al., 2012). It encodes a long non-coding RNA (lncRNA) (Zhang et al., 2010; Zhou et al., 2007). In addition to NFAs, *MEG3* expression is lost or significantly down regulated in a number of human cancers. Re-expression of *MEG3* inhibits proliferation of several human cancer cell lines (Zhou et al., 2012). It is particularly interesting to note that p53 is the only known *MEG3* target. *MEG3* induces p53 accumulation, which is in part mediated by down regulation of MDM2, and activates expression of p53 target genes (Zhou et al., 2007). In mice, maternal deletion of the *Meg3* gene results in perinatal death (Zhou et al., 2010). Furthermore, we reported that *Meg3* inactivation stimulates expression of angiogenesis promoting genes and increases angiogenesis activity (Gordon et al., 2010), suggesting that *MEG3* inhibits angiogenesis. Because p53 is a well known angiogenesis inhibitor (Teodoro et al., 2007), it is possible that *MEG3* inhibits angiogenesis via activation of p53. Whitson et al. (2013) recently demonstrated that GDF15, a *MEG3* activated p53 target gene (Zhou et al., 2007), suppresses angiogenesis (Whitson et al., 2013). *MEG3* plays an important role in suppression of human NFAs, likely through activation of p53.

3.2. O-6-methylguanine-DNA methyltransferase (MGMT)

Genomic DNA can be alkylated by chemotherapeutic and environmental compounds at the O6-position of the DNA base guanine, which results in O6-alkylguanines (O6G), including O6-methylguanine (O6MeG), O(6)-[4-oxo-4-(3-pyridyl)butyl]guanine (O6pobG), and O6-chloroethylguanine (O6ClG) (Christmann et al., 2011). MGMT is the main repair enzyme and transfers the alkyl group to a cysteine residue in its active site (Pegg et al., 1995). In the absence of MGMT, the base pair O6G:C would become O6G:T after one round of replication, which causes a transition from G:C to A:T and results in a point mutation after further replication. Therefore, MGMT is the main defense mechanism against mutation driven carcinogenesis caused by O6-alkylating agents. Conversely, MGMT activity may be needed for tumor cell survival. In the absence of MGMT, O6-alkylguanine caused O6G:T mismatch activates DNA mismatch repair (MMR), leading to DNA double strand breaks, which in turn triggers apoptosis leading to cell death (Kaina et al., 2007). Therefore, it is not surprising to note the inconsistency of reported MGMT expression in human cancers. MGMT expression is high in some reports but inactivated in others (Christmann et al., 2011; Sharma et al., 2009). MGMT status may be tissue type and tumor stage specific.

There are very few studies reporting MGMT status in human pituitary tumors. McCormack et al. first reported MGMT was down regulated in a small percentage of pituitary tumors; only 13% of tumors ($n = 88$) had low MGMT expression. The tumor samples include all types of pituitary adenomas. No difference in MGMT expression levels was found among tumor types and degree of invasiveness (McCormack et al., 2009). In contrast, Fealey et al. (2010) reported that 78% of silent subtype 3 (SS3) pituitary adenomas ($n = 23$) have lost MGMT expression judged by immunohistochemical staining. Lau et al. (2010) examined MGMT immunoexpression of 30 pituitary carcinomas and 30 pituitary adenomas. Low MGMT expression was found in 57% of carcinomas and 50% of adenomas. Salehi et al. (2011) examined MGMT expression in 12 SS3 tumors and 10 pituitary carcinomas. They found that 11 of SS3 tumors stained negative or low (less than 10% cells positive) for MGMT protein. Five carcinomas exhibited low MGMT staining. Although the number of reports is small, inactivation of MGMT in pituitary adenomas, especially in aggressive tumors, appears to be a frequent event.

Promoter methylation was investigated in three studies. McCormack et al. (2009) reported that 9% of pituitary tumors had *MGMT* promoter methylation ($n = 46$). Bello et al. (2006) found the promoter methylation in 23% of tumors ($n = 35$). Salehi et al. (2011) reported that *MGMT* methylation was detected in 5 out of 12 aggressive SS3 pituitary adenomas. These results indicate that promoter methylation is not a major mechanism responsible for MGMT down regulation in human pituitary adenomas. There is strong evidence indicating that p53 positively regulates MGMT expression. Ionizing radiation up-regulates MGMT expression in mouse fibroblasts and rat hepatoma cell lines expressing wt p53, but fails to do so in those cells lacking wt p53 (Grombacher et al., 1998). In addition, inactivation of p53 by knockout techniques reduces MGMT expression by more than 90% in neonatal murine astrocytes (Blough et al., 2007). Knockdown of p53 expression by RNAi also reduces MGMT expression in SF767 human astrocytic glioma cells (Blough et al., 2007). These data indicate that p53 plays a crucial role in regulation of MGMT expression. Lost or low MGMT expression levels could be explained by the possibility that p53 signaling may have been compromised in human pituitary tumors.

In mouse models, high MGMT expression levels protect mice from alkylating agent induced cancers (Becker et al., 1997; Dumenco et al., 1993). Conversely, MGMT deficient mice are prone to alkylating agent induced tumor growth (Iwakuma et al., 1997). These studies suggest that MGMT is critical in suppressing tumor development caused by alkylating agent induced DNA mutations. Considering the fact that the loss of MGMT expression encourages

DNA point mutations, it is likely that *MGMT* plays an important role in suppression of pituitary tumors.

3.3. Pleiomorphic adenoma gene-like 1 (PLAGL1)

PLAGL1, also known as *ZAC*, is an imprinted gene expressed only from the paternal allele (Kamiya et al., 2000). *PLAGL1* is highly expressed in the normal anterior pituitary. However, its expression was either lost or significantly reduced in 59% of 41 tumors investigated by Pagotto et al. (1999). *PLAGL1* down regulation was found in all NFAs (including null adenomas and gonadotropinomas, $n = 22$). In contrast, its down regulation was observed in only 11% of functioning tumors ($n = 19$) (Pagotto et al., 2000). Using RT-PCR, Michaelis et al. (2011) found *PLAGL1* was readily detectable in normal pituitary tissue. In contrast, *PLAGL1* was not detected in four of the six gonadotropinomas tested and the remaining two tumors had barely detectable *PLAGL1*. No LOH was detected in pituitary tumor tissues (Pagotto et al., 2000), indicating that a genetic mutation does not play a role in the loss of expression. It has been demonstrated that DNA methylation and histone deacetylation cause the loss of *PLAGL1* expression in breast and ovarian cancers (Abdollahi et al., 1997, 2003; Kamikihara et al., 2005). Thus, epigenetic changes are most likely the mechanism responsible for the reduced expression of *PLAGL1* in human NFAs.

There is evidence indicating that the *PLAGL1* gene is a tumor suppressor. In addition to pituitary adenomas, *PLAGL1* expression has been found to be lost or significantly reduced in tumors from many other tissues, such as ovary (Kamikihara et al., 2005), breast (Bilanges et al., 1999), adrenal gland (Jarmalaite et al., 2011), blood (Valleley et al., 2010), central nervous system (Lemeta et al., 2007), and skin (Basyuk et al., 2005). Re-expression of *PLAGL1* induces cell cycle arrest and apoptosis and inhibits tumor growth in nude mice (Spengler et al., 1997). Inhibition of *PLAGL1* by anti-sense treatment increase proliferation of pituitary tumor cells (Pagotto et al., 1999). In addition, induction of *PLAGL1* plays a role in mediating growth inhibition by the somatostatin analog octreotide (Theodoropoulou et al., 2006). These studies suggest that *PLAGL1* suppresses tumor growth by inhibition of cell proliferation.

PLAGL1 is a zinc-finger transcription factor with an affinity to GC rich DNA (Hoffmann et al., 2003). The GC-rich region was later identified to contain an Sp1 responsive element (Liu et al., 2011). *PLAGL1* functions as a cofactor physically binding to several transcription factors and co-factors, including p53 (Huang et al., 2001), AP1 (Wang et al., 2011), Sp1 (Liu et al., 2011), histone acetyltransferase PCAF (Hoffmann and Spengler, 2008) and histone deacetylase 1 (HDAC1) (Liu et al., 2008). A likely mechanism by which *PLAGL1* activates transcription of its target genes is through binding to GC rich or Sp1 responsive elements in the promoter where *PLAGL1* interacts with p53, Sp1 or AP1 and recruits PCAF and p300 to the sites (Hoffmann and Spengler, 2008; Liu et al., 2011; Wang et al., 2011). *PLAGL1* also interacts with HDAC1 to inhibit its histone deacetylation activity (Liu et al., 2008). Two target genes have been identified to mediate *PLAGL1* induced growth inhibition: p21^{Cip1} (Hoffmann and Spengler, 2008; Huang et al., 2007; Liu et al., 2008, 2011; Wang et al., 2011) and PPAR γ (Barz et al., 2006). As a p53 target gene, CDK inhibitor p21^{Cip1} is known to induce cell cycle arrest (Warfel and El-Deiry, 2013). Interestingly, p21^{Cip1} is also a target gene of PPAR γ and has been shown to mediate PPAR γ growth inhibition (Bonofiglio et al., 2008). These data indicate that p21^{Cip1} is a direct or indirect target of *PLAGL1*. In sum, *PLAGL1* is lost or significantly reduced in NFAs. *PLAGL1* inhibits cell proliferation which is likely mediated by up regulation of p21^{Cip1}. Taken together, therefore, inactivation of *PLAGL1* may be one of the mechanisms leading to pituitary tumor growth.

3.4. Ras association (RalGDS/AF-6) domain family member 1 (RASSF1)

RASSF1, also known as RASSF1A, belongs to a family of Ras effectors, which consist of a conserved motif, the RalGDS/AF6 Ras association (RA) domain (van der Weyden and Adams, 2007). There is strong evidence indicating that *RASSF1* is a tumor suppressor (Donninger et al., 2007) and it is inactivated in many human cancers, mainly through promoter hypermethylation. It is involved in maintenance of genomic stability, and regulates cell cycle progression and apoptosis (Donninger et al., 2007). To determine RASSF1 status in human pituitary tumors, Qian et al. (2005) examined 52 pituitary adenomas for promoter methylation using MSP and RASSF1 expression using RT-PCR. They found *RASSF1* promoter hypermethylation in 20 tumors (38%). RASSF1 expression was lost or significantly reduced in 22 tumors (42%), 18 of which have promoter hypermethylation (82%). There are no differences in promoter hypermethylation and RASSF1 expression between NFA and functioning adenomas (Qian et al., 2005). These data indicate that down regulation of RASSF1 is common in human pituitary tumors and that promoter hypermethylation plays a major role in silencing the RASSF1 gene.

There are several possible mechanisms whereby *RASSF1* contributes to tumor suppression in the pituitary. RASSF1 controls mitosis progression by inhibition of APC-CDC20. Loss of RASSF1 causes cell division defects manifested by centrosome abnormalities and multipolar spindles (Song et al., 2004). RASSF1 also arrests cell cycle at G1 by inhibition of cyclin D1 accumulation (Shivakumar et al., 2002). Another possibility is that RASSF1 activates p53 by promoting MDM2 degradation, which results in cell cycle arrest (Song et al., 2008). In addition, RASSF1 induces cell cycle arrest by induction of p21^{Cip1} independent of p53 (Thaler et al., 2009). Finally, RASSF1 represses expression of ER α , inhibiting estrogen independent signaling (Thaler et al., 2012). These data indicate that RASSF1 may suppress tumor growth via multiple pathways.

3.5. Ras association (RalGDS/AF-6) domain family member 3 (RASSF3)

RASSF3, also known as *RASSF5*, *NORE1*, *NORE1A* and *NORE1B*, is another member of the RASSF family of Ras effectors. As with *RASSF1*, *RASSF3* is inactivated in many human tumors (Djos et al., 2012; Geli et al., 2007, 2008; Lee et al., 2010; Macheiner et al., 2006). Recently, Peng et al. (2013) investigated DNA methylation in GH-secreting adenomas using HG18 CpG plus promoter microarray and found *RASSF3* gene promoter methylation in all tumors examined ($n = 27$). In addition, RASSF3 expression was significantly reduced in all tumors compared to normal controls, suggesting that an epigenetic change is responsible for the gene silencing (Peng et al., 2013). There are several ways by which RASSF3 may suppress tumor growth. Similar to RASSF1, RASSF3 activates p53 by direct interaction with MDM2 and promotes its degradation via ubiquitination. Activation of p53 by RASSF3 induces cell cycle arrest and apoptosis (Kudo et al., 2012). RASSF3 also stimulates p21^{Cip1} expression by promoting p53 nuclear localization (Calvisi et al., 2009) and suppresses cell growth by ERK pathway inhibition (Moshnikova et al., 2006). Finally, RASSF3 mediates TNF- α induced apoptosis (Park et al., 2010). Therefore, RASSF3 may function as a tumor suppressor in the pituitary.

3.6. Suppressor of cytokine signaling 1 (SOCS1)

Buslei et al. (2006) reported that expression of SOCS1 is down regulated in the majority of pituitary adenomas due to promoter methylation, which was found in over 86% of NFAs. It occurred less frequently in ACTH- and GH-secreting tumors, 33% and 18%, respectively. Methylation was not found in prolactinomas. SOCS1 is a negative regulator of cytokine signaling. Cytokines regulate cell proliferation, survival and differentiation by phosphorylation of Janus kinases (JAK), which in turn phosphorylate signal transduction and activation of transcription (STAT) proteins. Phosphorylated STAT proteins dimerize

and translocate to the nucleus to activate the target genes. SOCS1 negatively regulates the JAK/STAT signaling by binding to JAK and blocking STAT phosphorylation and is also a part of a ubiquitin ligase E3 complex, which targets proteins involved in cellular signaling, such as JAK and FAK, for ubiquitin mediated degradation (Mallette et al., 2010; Zhang et al., 2012). Therefore, *SOCS1* is thought to function as a tumor suppressor due to its ability to blocking STAT activation (Zhang et al., 2012). Its down regulation in pituitary adenomas suggests that SOCS1 plays a role in pituitary tumor suppression by inhibition of JAK/STAT signaling.

In addition to JAK/STAT inhibition, SOCS1 may suppress tumor growth by activation of p53. Calabrese et al. (2009) showed that STAT5-induced senescence in normal cells is mediated by SOCS1 activation of p53. SOCS1 directly interacts and forms a complex with both p53 and DNA damage regulated kinases ATM/ATR, where p53 is stabilized by phosphorylation at serine 15 (Calabrese et al., 2009). These data indicate that activation of p53 by SOCS1 plays an important role in senescence induction, which is a well known tumor suppression mechanism.

4. Conclusion

Multiple genes are involved in the development of sporadic pituitary adenomas. Although this may reflect the heterogeneity of these tumors, it may also indicate that inactivation of multiple genes is necessary to transform pituitary cells. We have included the 20 genes in this review we felt were most pertinent to understanding pituitary tumorigenesis, particularly in sporadic tumors. However, we have not included several other genes whose expression is also down regulated in human pituitary adenomas, including *cAMP-dependent protein kinase type I-alpha regulatory subunit (PRKARIA)* (Kirschner et al., 2000), *fibroblast growth factor receptor 2 (FGFR2)* (Zhu et al., 2007b), *IKAROS family zinc finger 1 (Ikaros)* (Zhu et al., 2007a), and *lectin, galactoside-binding, soluble, 3 (LGALS3)* (Ruebel et al., 2005). The *PRKARIA* gene has been linked to CNC only. No mutation in this gene has been found in sporadic tumors. We did not discuss *FGFR2*, *Ikaros* and *LGALS3* because they were reported in one study, respectively, with a limited number of tumors examined. More tumors need to be investigated before a link between these genes and sporadic pituitary adenomas can be established.

Overall, pathways leading to sporadic pituitary development can be generally grouped into two categories: one category is functionally connected to the RB pathway and the other to p53, although this categorization is not absolute (see Fig. 1). Data from studies with animal models, human pituitary tumors and *in vitro* cell line models suggest that inactivation of the RB pathway may play an initiation role in the development of sporadic pituitary adenomas; while inactivation of genes which function via the p53 pathway may play a promoting role. Pituitary adenomas are benign tumors. They very rarely develop into carcinomas. When dispersed into primary culture, pituitary tumor cells typically only can survive a few passages before they stop growing and die. All these observations indicate that certain components of the stress response system are still functional in benign pituitary tumors. Because p53 is the major stress response gene, these data suggest that the p53 pathway has been compromised but not completely abolished, consistent with the fact that p53 is rarely mutated in pituitary tumors. What signals cause down regulation of these tumor suppressive genes? What are the exact downstream target genes affected by inactivation of these genes? How do these genes cooperate to suppress pituitary tumors? Clearly there are many questions that need to be addressed before our understanding of the underlying pathogenesis of pituitary tumors may be used as the foundation to develop new therapies for patients with these tumors.

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Abbreviations

AHR	aryl hydrocarbon receptor
AIP	aryl hydrocarbon receptor interacting protein
BMP-4	bone morphogenetic protein 4
CDK	cyclin-dependent kinases
CDKN1A	cyclin-dependent kinase inhibitor 1A
CDKN1B	cyclin-dependent kinase inhibitor 1B
CDKN2A	cyclin-dependent kinase inhibitor 2A
CDKN2B	cyclin-dependent kinase inhibitor 2B
CDKN2C	cyclin-dependent kinase inhibitor 2C
CDH1	cadherin 1, type 1, E-cadherin (epithelial)
CDH13	cadherin 13, H-cadherin (heart)
CNC	Carney complex
DNMT1	DNA methyltransferase 1
DNMT3A	DNA (cytosine-5-)-methyltransferase 3 alpha
DNMT3B	DNA (cytosine-5-)-methyltransferase 3 beta

DNMT3L	DNA (cytosine-5-)-methyltransferase 3-like
EMT	epithelial–mesenchymal transition
ESRP1	epithelial splicing regulatory protein 1
FPA	familial pituitary adenoma
FIPA	familial isolated pituitary adenoma
GADD45B	growth arrest and DNA-damage-inducible, beta
GADD45G	growth arrest and DNA-damage-inducible, gamma
GNAS	guanine nucleotide-binding protein G(s) subunit alpha
HDAC3	histone deacetylase 3
MEG3	maternal expression gene 3
MEN1	multiple endocrine neoplasia type I
MGMT	O-6-methylguanine-DNA methyltransferase
MLL	myeloid/lymphoid or mixed-lineage leukemia protein 1
NFA	clinically non-functioning pituitary adenoma
PLAGL1	pleiomorphic adenoma gene-like 1
PRKAR1A	protein kinase, cAMP-dependent, regulatory, type I, alpha
RASSF1	Ras association (RalGDS/AF-6) domain family member 1
RASSF3	Ras association (RalGDS/AF-6) domain family member 3
SOCS1	suppressor of cytokine signaling 1
TCDD	2,3,7,8-tetrachloro- <i>p</i> -dioxin

Fig. 1. Schematic illustration of RB and p53 connections with tumor suppressive genes which are genetically or epigenetically inactivated in human sporadic pituitary adenomas. The upper panel includes genes functionally connected to the RB pathway. The lower panel includes genes functionally connected to p53. The cross talk between p53 and the RB pathway is mediated by p21^{Cip1}. Several genes, including *BMP-4*, *E-Cadherin*, *PLAGL1*, *RASSF1*, and *RASSF3* are functionally connected to both p53 and RB. Circles on pink background are components of the RB pathway. Circles on yellow background are components of the classic p53 pathway. Blue with names in red are genes down regulated in pituitary tumors. Green arrows, positively regulation; Red "T" lines, negatively regulation.

Table 1 List of tumor suppressive genes inactivated in sporadic pituitary adenomas.^a

Gene	Description
<i>AIP</i>	Aryl hydrocarbon receptor interacting protein, predisposition gene for FIPA, inactivated in 3.8% sporadic pituitary tumors by genetic mutations (number of tumors examined, <i>n</i> = 1875)
<i>BMP-4</i>	Bone morphogenetic protein 4, cytokine of the TGFβ superfamily, down regulated in 45% of pituitary tumors (<i>n</i> = 107)
<i>CDKN2A</i>	Cyclin-dependent kinase inhibitor 2A, p16 ^{Ink4a} , inhibits CDK4/6 and activates RB, silenced by promoter methylation in 56% of pituitary tumors (<i>n</i> = 426)
<i>CDKN2A</i>	Alternative open reading frame of <i>CDKN2A</i> transcripts, p14 ^{Arf} , inhibits MDM2 and activates p53, silenced by promoter methylation in 12% of pituitary tumors (<i>n</i> = 69)
<i>CDKN2B</i>	Cyclin-dependent kinase inhibitor 2B, p15 ^{Ink4b} , inhibits CDK4/6 and activates RB, silenced by promoter methylation in 38% of pituitary tumors (<i>n</i> = 76)
<i>CDKN2C</i>	Cyclin-dependent kinase inhibitor 2C, p18 ^{Ink4c} , inhibits CDK4/6 and activates RB, silenced by promoter methylation in 20% of pituitary tumors (<i>n</i> = 83)
<i>CDKN1A</i>	Cyclin-dependent kinase inhibitor 1A, p21 ^{Cip1} , a p53 target gene, inhibits CDK2, CDK4 and activates RB, component of the RB pathway, down regulated in 47% of pituitary tumors (<i>n</i> = 111)
<i>CDKN1B</i>	Cyclin-dependent kinase inhibitor 1B, p27 ^{Kip1} , a predisposition gene for MEN4, inhibits CDK2, CDK4 and activates RB, down regulated in 45% of sporadic pituitary adenomas (<i>n</i> = 404)
<i>CDH1</i>	E-cadherin, classical epithelial cadherin, cell adhesion protein, inhibitor of epithelial–mesenchymal transition, silenced by promoter methylation in 36% of pituitary tumors (<i>n</i> = 85)
<i>CDH13</i>	H-cadherin, a nonclassical cadherin, silenced by promoter methylation in 30% of tumors (<i>n</i> = 69)
<i>GADD45B</i>	Growth arrest and DNA-damage-inducible protein GADD45β, inhibits CDK1/cyclin B1 and interacts with PCNA, down regulated in pituitary tumors (<i>n</i> = 14)
<i>GADD45G</i>	Growth arrest and DNA-damage-inducible protein GADD45γ, inhibits CDK1/cyclin B1, interacts with p21 ^{Cip1} and PCNA, silenced by promoter methylation in 58% of tumors (<i>n</i> = 33)
<i>MEG3</i>	Maternally expressed gene 3, a long non-coding RNA, a p53 activator, silenced in 96% of NFAs (<i>n</i> = 79), down regulated in 30% of functioning adenomas (<i>n</i> = 68)
<i>MEN1</i>	Predisposition gene for multiple endocrine neoplasia type I syndrome, encodes menin, inactivated in 3% of sporadic pituitary tumors by genetic mutations (<i>n</i> = 535)
<i>MGMT</i>	O-6-methylguanine–DNA methyltransferase, involved in DNA repair, silenced by promoter methylation in 18% of tumors (<i>n</i> = 93)
<i>PLAGL1</i>	Pleiomorphic adenoma gene-like 1, also known as ZAC (zinc finger protein which regulates apoptosis and cell cycle arrest), down regulated in 64% of pituitary tumors by RT-PCR (<i>n</i> = 47)
<i>RASSF1</i>	Ras association (RalGDS/AF-6) domain family member 1, a p53 activator, silenced by promoter methylation in 38% of pituitary tumors (<i>n</i> = 52)
<i>RASSF3</i>	Ras association (RalGDS/AF-6) domain family member 3, also known as RASSF5, a p53 activator, silenced by promoter methylation in all pituitary tumors (<i>n</i> = 27)
<i>RB1</i>	Retinoblastoma 1, the core member of the RB pathway, a negative cell cycle regulator, silenced by promoter methylation in 27% of pituitary tumors (<i>n</i> = 158)
<i>SOCS1</i>	Suppressor of cytokine signaling 1, inhibitor of JAK/STAT pathways, a p53 activator, silenced by promoter methylation in 51% of pituitary tumors (<i>n</i> = 57)

^aPercentages of tumors with genetic or epigenetic mutations for each individual gene are calculated based on data obtained from references cited in the main text.