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Epigenetic and Posttranscriptional Alterations of Tumor Suppressor Genes in Sporadic Pituitary Adenomas

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1. Introduction

1.1 Epidemiology of pituitary adenomas

Pituitary adenomas are usually benign tumors. Although many of them do not cause clinical symptoms and remain undetected, some leads to hormonal and/or neurological disorders. Because a large proportion of pituitary adenomas are discovered incidentally, the estimation of their prevalence may be difficult. Recently Daly et al. summarized the reported prevalence rate based on *autopsies* and *radiological* series showing a mean prevalence of 14.4 and 22.3% respectively, and a combined analysis yielded a final prevalence rate of 16.7%. Based on three different *population studies* they found that the mean prevalence is 1:1064 (Daly et al., 2009). The most frequent tumors were prolactinomas, followed by non-functioning and growth-hormone (GH) producing tumors (66.2%, 14.7% and 13.2%, respectively). Based on results of an *international, multicentre study* the prevalence of clinically relevant pituitary adenoma is 1:1388 which is 3–5 times higher than that previously reported (Daly et al., 2009).

According to data obtained from 8276 patients the incidence rate of pituitary adenomas is increasing with age, and they occur more frequently in females in early life and in males in later life. Males had larger tumors than females, and a higher incidence was detected in American Blacks compared with other ethnic groups (McDowell et al., 2011).

1.2 Pathogenetic mechanisms leading to pituitary tumorigenesis

Pituitary adenomas usually occur sporadically and most of them have monoclonal origin (Alexander et al., 1990; Herman et al., 1990). Both *hypothalamic* and *hypophyseal mechanisms* including alterations in hypothalamic control of pituitary hormone secretion and somatic mutations in pituitary cells have been considered as possible pathogenetic factors in pituitary tumor development. In experimental models overproduction of GH-releasing hormone may lead to the development of GH-secreting adenoma, while decreased level of dopamine may be associated with prolactinoma development.

Familial pituitary adenomas represent only 5% of all pituitary tumors. Most of these tumors are associated with known genetic defects predisposing to hereditary endocrine tumor syndromes. The most common is multiple endocrine neoplasia type 1 (MEN1), a disorder transmitted in an autosomal dominant manner due to mutations of the *MEN1* tumor suppressor gene. However, in about 20-30% of clinically MEN1 cases mutation analysis failed to reveal mutations of the *MEN1* gene. Mutations in cyclin-dependent kinase inhibitor 1B (*CDKI1B*) gene coding for p27 have been demonstrated in a small subset of patients, and the clinical syndrome has been named MEN4 (Dworakowska & Grossman, 2009).

Another familial disease that includes pituitary adenoma is Carney complex (CNC). This syndrome is caused by mutations of the gene encoding the protein kinase A regulatory subunit-1-alpha (*PRKAR1A*) (Stratakis et al., 2001). *PRKAR1A* is known to be an important effector molecule in many endocrine signaling pathways and its defect leads to various endocrine and nonendocrine tumor formation.

A separate entity among familial pituitary tumors is the familial isolated pituitary adenoma (FIPA) presenting most frequently as familial somatotropinomas or prolactinomas. Patients with FIPA are significantly younger, and their adenoma size is larger compared to sporadic pituitary adenoma counterparts. About 15% of the FIPA patients have mutations of the gene encoding the aryl hydrocarbon receptor-interacting protein (AIP), which indicates that the FIPA may have a diverse genetic pathophysiology (Daly et al., 2009; Dworakowska & Grossman, 2009).

Although McCune-Albright syndrome (MAS) is not a hereditary disorder, it represents a genetic condition related to mosaicism for a mutation of the guanine nucleotide-activating alpha-subunit (*GNAS*) gene. In addition, somatic mutation of the *GNAS* gene is present in 30–40% of GH-secreting pituitary adenomas (Lania et al., 2003; Spada et al., 1990). Mutation of this gene leads to the constitutive activation of the GH receptor and thereby contributes to GH-producing adenoma formation.

Genetic changes of classical tumor suppressor genes (TSGs) such as *TP53*, *PTEN* and *RB1*, or oncogenes (such as *Ras*) rarely contribute to pituitary tumorigenesis. However, overactivation of the *PI3K/Akt/mTOR signaling pathway* has been demonstrated in pituitary adenomas as frequently as in other solid tumors (Rodriguez-Viciano et al., 1997). Both expression and phosphorylation of the Akt was increased in all types of pituitary adenomas with a highest rate in non-functioning pituitary adenomas (NFPA) (Musat et al., 2005). In addition to *PI3K/Akt/mTOR*, the *MAPK cascade* was also found to be involved in cell transformation and proliferation (Ewing et al., 2007; Guan, 1994; Joneson & Bar-Sagi, 1997). Recently, microarray studies indicated that the *WNT and Notch signaling pathways* play a role in the pathogenesis of pituitary adenomas, especially in NFPA (Moreno et al., 2005).

Among *growth factors* the N-terminally truncated isoform of fibroblast growth factor receptor type 4 (pdt-FGFR4) and fibroblast growth factor type 2 (FGF2) were found to be overexpressed in some pituitary tumors, especially in aggressive adenomas while overexpression of bone morphogenic protein type 4 (BMP4) was characteristic for prolactinomas (Ezzat et al., 1995; Ezzat et al., 2002; Morita et al., 2008; Qian et al., 2004).

Cyclin D, a member of cell cycle regulation was shown to be overexpressed in pituitary adenomas, especially in NFPA, while numerous cyclin-dependent kinase inhibitors (CDKIs) were reportedly underexpressed due to promoter hypermethylation. These alterations will be discussed.

Another relatively common alteration in pituitary tumors is overexpression of the oncogene *pituitary tumor-transforming 1 (PTTG1)*, that is indirectly involved in cell cycle through an interaction with p53 and induction of p21 (Salehi et al., 2008). PTTG1 was found to be overexpressed in most pituitary adenomas, particularly in hormone-secreting and aggressively behaving tumors (X. Zhang et al., 1999).

2. Epigenetic mechanisms

Epigenetic mechanisms denote gene expression variability without coding sequence alteration. These mechanisms have important role in development, X chromosome inactivation, and modulation of gene expression in tissue specific manner. Epigenetic machinery includes *DNA methylation, histone modifications* and regulation of gene expression posttranscriptionally by small, *non-coding RNA molecules*.

The compact DNA structure called chromatin is built from nucleosome units. These nucleosomes consist of approximately 150-200 bp of DNA, which is coiled twice around an octamer protein complex composed of core histones (H2A, H2B, H3 and H4). The adjacent nucleosomes are connected by the “linker” H1 histone. From nucleosomes DNA is assembled into a higher structure by covalent modifications of histone proteins. These modifications include methylation, acetylation, phosphorylation and ubiquitination at the N- and C-terminal domains of core histones. DNA and histone modifications influence DNA compaction thereby affect DNA availability for transcription factors and determine transcriptional activity.

2.1 DNA methylation

DNA methylation occurs as a methyl-group on 5' position of cytosine in a CpG dinucleotide (5-methylcytosine). Although CpG dinucleotides are relatively infrequent (~1 per 100 bp) throughout the genome, approximately 7% of them are mapped within CpG islands, which in turn are associated with the promoter regions of approximately 40–50% of all transcribed genes (Baylin & Herman, 2000; Gardiner-Garden & Frommer, 1987; Rollins et al., 2006.) and about 45% of all CpGs can be found in repetitive elements (Ehrlich et al., 1982).

Methylation is accomplished by DNA methyltransferases (DNMT). These enzymes create “de novo” (DNMT type 3a and 3b) or maintain (DNMT1) the methylation pattern, which is a replication-dependent process passing off during S-phase of the cell cycle (Klose & Bird, 2006). Methylation of CpG islands cause gene expression silencing by direct inhibition of transcription factors binding and by recruitment of methyl-binding domain proteins (MBDs) occurring in transcription repressor complexes.

CpG island methylation is correlated with condensed heterochromatin. On the contrary, hypomethylation allows an open chromatin structure and it usually occurs in promoter regions of active genes.

In primary human tumors, methylation patterns are frequently disorganized. Promoter regions of genes are often hypermethylated and, therefore, their expressions are silenced. In general, aberrant CpG island methylation tends to be focal, affecting single genes, but not their neighbours (Zardo et al., 2002). Tumor suppressor genes involved in the regulation of cell cycle, apoptosis or genes participating in DNA repair are often silenced by hypermethylation and they do not have other genetic alterations (eg. mutations) (Brena & Costello, 2007). Beside hypermethylation genome-wide hypomethylation was also implicated in tumor development (Feinberg & Vogelstein, 1983; Gaudet et al., 2003).

2.2 Histone modification

Chemical modification of histones (H) frequently targets lysine residues within their N- and C-terminal tails. Core histone modification is frequently called as ‘histone code’ which determines transcriptional activity by influencing compaction of DNA structure (Jenuwein & Allis, 2001; Turner, 2000). Deacetylated forms of N-tails of H3 and H4 histones have a positive charge that results in a close nucleosome structure because of the negatively charged DNA. Acetylations of lysine residues on histone tails neutralize the positive charge of histones thereby lead to a loose, “opened” chromatin structure (Struhl, 1998) (Fig.1.).

In addition to acetylation, histone modifications may include methylation, phosphorylation, sumoylation, ubiquitination and ADP-ribosylation. Among these mechanisms covalent modifications, such as acetylation of H3 and H4 and methylation pattern on gene expression have been extensively investigated in tumor development. Several enzymes including histone acetyltransferases (HAT), histone deacetylases (HDAC), histone methyltransferases (HMT) and histone demethyltransferases (HDMT) may modify histones. Acetylation of lysine (K) residues associated with H4 and methylation of lysine 9 (K9) in H3 may be present at inactive gene loci. Alternatively, acetylation on K9, K14 and methylation on K4 of H3, or acetylation on K5 of H4 can be found both at active or activating gene loci, reviewed by Tateno et al, 2010 (Tateno et al., 2010; Ezzat, 2008).

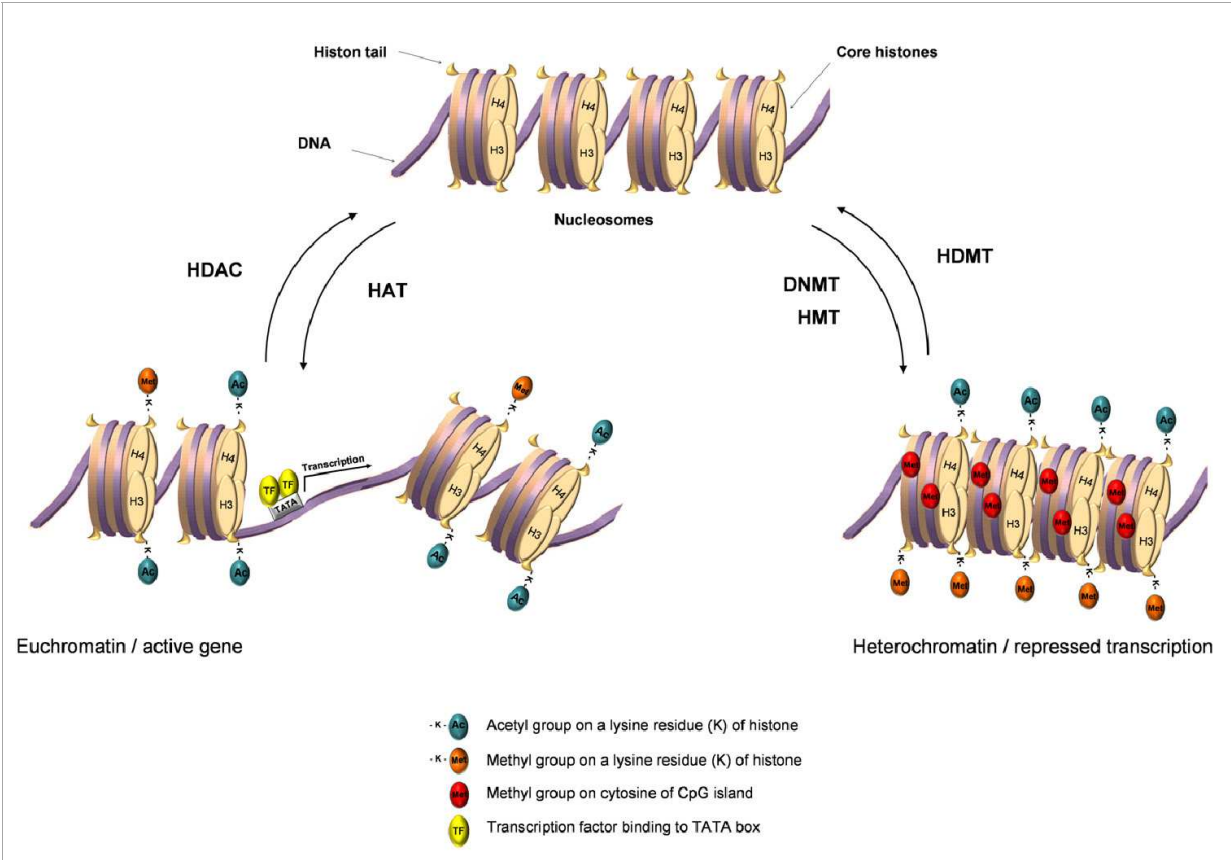


Fig. 1. Histone and DNA modifications.

2.3 Genomic imprinting

Genomic imprinting is related to a special form (or a subgroup) of DNA methylation, which allows monoallelic gene expression in a “parent-of-origin-specific” manner (Wong et al., 2007). Diploid cells have two alleles of each autosomal gene inherited from each parent. Generally both parental alleles are expressed equally, but a subset of genes is expressed by either the maternal or the paternal allele, and this ‘genomic imprinting’ is regulated by epigenetic mechanisms. This process may be also responsible for tissue specific gene expression.

Imprinted expression is restricted to a few hundred genes in the mammalian genome, most of which are found in small clusters. Imprinted clusters have an imprinting control region (ICR) that is usually 1–5 kb. long, differentially methylated and it regulates the imprinting mechanism across the entire domain. Imprinted genes are regulated also by methylation. Many imprinted genes inside of an imprinted cluster are protein-coding genes, however, recently the role of ncRNAs in imprinting regulation was also raised (Zhou et al., 2010).

The most commonly cited example for imprinting mechanism leading to tumorigenesis is the gene encoding insulin-like growth factor type 2 (IGF2). IGF2 is paternally imprinted in most tissues (Ohlsson et al., 1994). It is an embryonic mitogen and it acts as a paracrine and autocrine regulator of cell proliferation (Yu & Rohan, 2000). In cells that express both parental IGF2 alleles, the increased amount of IGF2 may lead to tumor formation. Loss of imprinting (LOI) of *IGF2* has been reported in many tumors including colorectal carcinomas (Cui et al., 2003), Wilm’s tumor (Ogawa et al., 1993), esophageal carcinoma (Zhao et al., 2009), acute lymphoblastic leukemia (Vorwerk et al., 2003) and prostate cancer (Jarrard et al., 1995).

2.4 Regulation by non-coding RNAs (ncRNAs) and microRNAs (miRs)

Thus far small RNAs do not belong tightly to classical epigenetic mechanisms, but based on recent findings we have to classify them into this group as they regulate gene expression without modification of the genetic code. For instance, miRs provide fine tuning of protein expression level, and their role in tumorigenesis has been widely demonstrated.

MicroRNAs belong to non-codingRNAs (ncRNAs) that can regulate gene expression. It was found that about 98% of all transcripts originate from ncRNAs (Mattick, 2001). These arise from exons and introns of protein non-coding genes and from introns of protein-coding genes (Mattick & Makunin, 2005). Non-coding RNAs include transfer-RNAs (tRNAs) involved in mRNA translation, small nucleolar RNAs (snoRNAs) involved in modification of ribosomal RNAs (rRNAs) and small nuclear RNAs (snRNAs) implicated in mRNA splicing (Mattick & Makunin, 2005). Beyond these, several small RNAs (categorized into 13 functional classes) were discovered with diversified biological functions including heterochromatin formation, histone and DNA methylation, mRNA cleavage and transcriptional repression (summarized by Zhou et al., 2010).

MicroRNAs (miRs) are approximately 19-25 nucleotide long, non-coding RNA molecules which posttranscriptionally regulate gene expression via RNA interference by binding 3’ untranslated region (3’UTR) of protein coding mRNA (Lagos-Quintana et al., 2001). This pairing is not a perfect match in the case of mammals but it is in plants. By interacting the target mRNAs miRs repress the target protein expression by three major processes: i) mRNA cleavage, ii) mRNA degradation by deadenylation or iii) inhibition of translation initiation. In addition, miRs regulate expression of other types of ncRNAs (Fig.2.).

It has been proposed that 30-50% of all protein coding genes may be controlled by miRs (Chen & Rajewsky, 2006; Lewis et al., 2005). As miRs may influence numerous mRNA they may participate in the regulation of numerous physiological and pathological cellular processes. Their roles were considered in development (Lee & Ambros, 2001), cell proliferation (O'Donnel et al., 2005), differentiation (Chen & Stallings, 2007), apoptosis (Cimmino et al., 2005) and tumorigenesis (reviewed by Deng et al., 2008) including tumors of endocrine system such as the pituitary gland (Bottoni et al., 2005, 2007; Amaral et al., 2009, Butz et al., 2010, 2011).

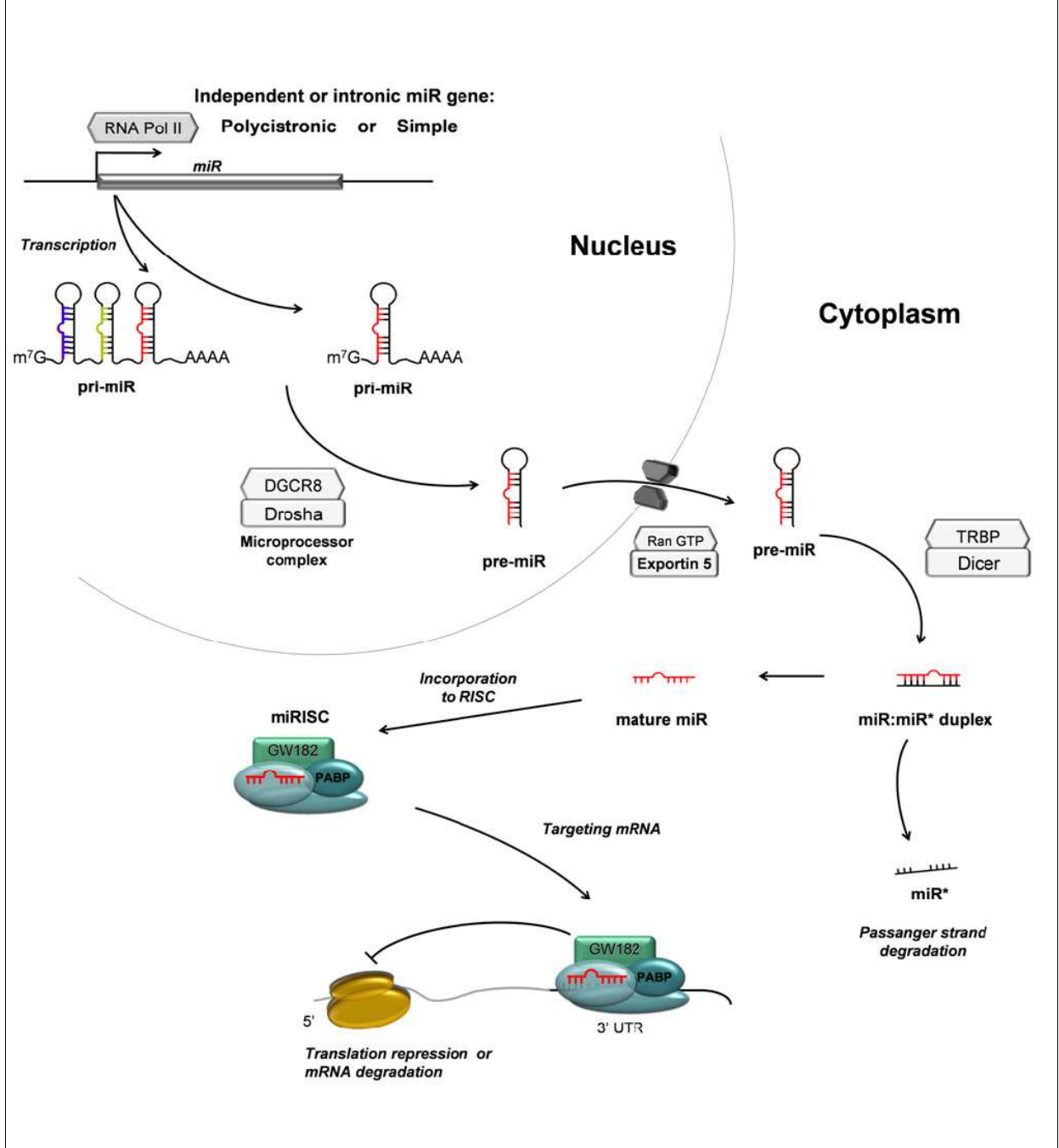


Fig. 2. MicroRNAs' biogenesis and function.

3. Epigenetic alterations involving tumor suppressor genes

3.1 Hypermethylated tumor suppressors

3.1.1 Genes encoding cell cycle regulators

The sensitively balanced cell cycle involves numerous negative and positive regulators. The main proteins involved in this process are the cyclins, cyclin-dependent kinases (CDK) and their inhibitors (CDKI). Alterations of several cell cycle-related genes, especially those involved in the G1/S transition have been associated with pituitary adenomas. Several cell cycle inhibitors (CDKIs) were found to be underexpressed through promoter hypermethylation in pituitary adenomas. CDKIs as members of the INK4 families (p16^{Ink4a}, p15^{Ink4b}, p18^{Ink4c}) and the Cip/Kip (p21^{Cip1}, p27^{Kip1}, p57^{Kip2}) inhibit CDK-cyclin complexes thereby prevent checkpoint transitions (Fig. 3.).

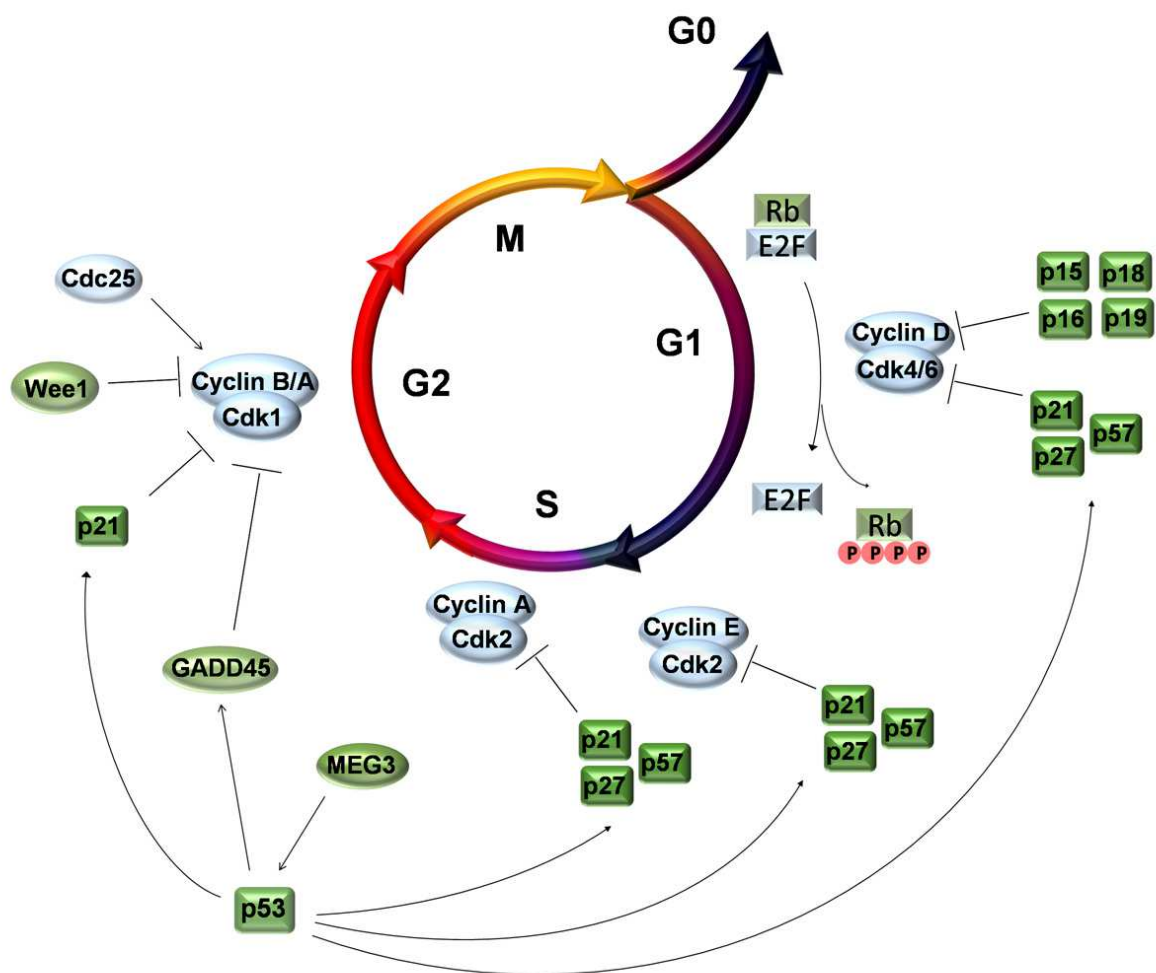


Fig. 3. Regulation of cell cycle.

The restriction point of the G1/S transition requires inactivation of retinoblastoma (Rb) protein via phosphorylation by CDKs. In this process E2F transcription factors are released and transcription of S-phase genes are allowed. The majority of pituitary adenomas express Rb and inactivation of CDKIs (detailed in Table 1) may lead to cell proliferation in pituitary adenomas.

Gene Name	Alterations in pituitary adenomas
pRb (RB1)	<ul style="list-style-type: none">• Promoter hypermethylation in 28.6% (12/42) and 35% (12/34) of adenomas (Ogino et al., 2005; Yoshino et al., 2007)• 90% of adenomas expressed Rb (18/20) and in 60% of Rb-non-expressing adenomas promoter methylation was found (Simpson et al., 2000)• LOH of the RB locus in 100% of invasive and malignant tumors (Pei et al., 1995)
p53	<ul style="list-style-type: none">• Somatic inactivating mutation and increased expression in 33% (2/6) of pituitary carcinomas (Tanizaki et al., 2007)
p14 ^{ARF}	<ul style="list-style-type: none">• Promoter hypermethylation in 6% (2/24) of adenomas (Yoshino et al., 2007)
p15 ^{INK4b} (CDKN2B)	<ul style="list-style-type: none">• Promoter hypermethylation in 32% (11/34) and 35.7% (15/42) of adenomas (Yoshino et al., 2007; Ogino et al., 2005)
p16 ^{INK4a} (CDKN2A)	<ul style="list-style-type: none">• Promoter hypermethylation in 59% (20/34) and 71.4% (30/42) of adenomas (Yoshino et al., 2007; Ogino et al., 2005)
p18 ^{INK4c} (CDKN2C)	<ul style="list-style-type: none">• Promoter hypermethylation in 39.5% (15/38) of adenomas (Kirsch et al., 2009; Morris et al., 2005)
p21 ^{Waf1/Cip1} (CDKN1A)	<ul style="list-style-type: none">• Promoter hypermethylation in 3% (1/34) of adenomas (Yoshino et al., 2007)• Decreased expression in 71% (10/14) of NFPAs (Neto et al., 2005)• Increased expression in 77% (31/40) of hormone producing and 92% (11/12) of GH producing adenomas (Neto et al., 2005)
p27Kip1 (CDKN1B)	<ul style="list-style-type: none">• Absence of promoter hypermethylation in 34 pituitary adenomas (Yoshino et al., 2007)• Decreased expression in adenomas especially in corticotrop adenomas (21/21) (Lidhar et al., 1999; Lloyd et al., 1997; Bamberger et al., 1999)
GADD45 γ	<ul style="list-style-type: none">• Promoter methylation in 58% (19/33) of adenomas (Bahar et al., 2004a; Zhang et al., 2002)
MEG3A	<ul style="list-style-type: none">• Promoter methylation (11/11) of adenomas (Gejman et al., 2008; Zhao et al., 2005)
DAPK	<ul style="list-style-type: none">• Loss of expression in 59% (10/17) of invasive adenomas caused by hypermethylation (45%) or homozygous deletion (36%) (Simpson et al., 2002)
PTAG	<ul style="list-style-type: none">• Loss of expression in 79% (30/38) of adenomas caused by hypermethylation in 20% (Bahar et al., 2004b)
ZAC	<ul style="list-style-type: none">• Loss or decreased expression in (34/34) NFPAs (Pagotto et al., 2000)

Table 1. Hypermethylated tumorsuppressors involved in pituitary tumorigenesis.

GADD45 γ , also known as *cytokine response 6* (CR6) was found to be involved in growth suppression and apoptosis (Zhang et al., 1999). The GADD45 family genes (GADD45 α : GADD45, GADD45 β : MyD118 and GADD45 γ : CR6) are regulated by p53. They influence the expression of p21^{WAF1/CIP1} and proliferating cell nuclear antigen (PCNA) and have a role in DNA damage repair (Fan et al., 1999; Smith et al., 1994; Xiao et al., 2000). They disrupt interaction between CDK1 kinase and cyclin B1 and, therefore, they suppress cell proliferation not only by inhibiting G1/S transition but they also cause G2/M arrest. (Zhan

et al., 1999). They are also involved in apoptosis regulation by activating MAPK and Jun kinase signaling pathways and they cause DNA fragmentation (Takekawa & Saito, 1998). Further studies demonstrated that they are not expressed in the majority of NFPA and GH- or PRL-secreting tumors. Reexpression of GADD45 in human and rodent pituitary-derived cell lines inhibited cell proliferation suggesting that loss of GADD45 may have a role in pituitary tumorigenesis. Methylation of CpG islands of the GADD45 gene was identified in 19/33 (58%) of pituitary adenomas including NFPA, GH- and PRL secreting tumors (Bahar et al., 2004a).

Zhao and coworkers showed that a gene named maternally expressed 3 (MEG3) was strongly expressed in normal pituitary gland while its expression was almost undetectable in pituitary tumors and other cancer cell lines (Zhao et al., 2005). In functional studies methylation inhibitor restored MEG3 expression in human cell lines. MEG3 protein non-coding RNA has multiple splice isoforms and all of them suppress cell growth in vitro by stimulating p53-mediated transactivation (Zhou et al., 2007). All human pituitary cell types express MEG3, while in adenomatous pituitary samples the loss of MEG3 was limited to NFPA of gonadotroph origin (Gejman et al., 2008). It has been shown that inactivation of the MEG3 gene was exclusively due to methylated CpGs in its promoter. (Zhao et al., 2005; Gejman et al., 2008).

3.1.2 Genes encoding regulators of apoptosis

The gene encoding death-associated protein kinase (DAPK) was found to be frequently altered by epigenetic mechanisms in pituitary tumors. Simpson and his colleagues demonstrated that in 34% (11/32) of pituitary tumors expression of the DAPK was undetectable and that almost half of the cases had CpG island methylation in the DAPK promoter region. In addition, loss of DAPK expression was associated with tumor invasiveness. However, only a minority of non-invasive pituitary adenomas (2/35; 5.7%) showed underexpression of the DAPK caused by methylation (Bello et al., 2006). Another protein involved in apoptosis regulation is the pituitary tumor apoptosis gene (PTAG). Its expression was reduced in a significant percent (79%, 30/38) of pituitary adenomas. All corticotropinomas and prolactinomas, 73% of somatotropinomas and 64% of NFPA showed reduced expression of PTAG. Reexpression of PTAG alone failed to influence pituitary cell proliferation or cell viability but significantly augmented the apoptotic response to bromocriptin induction. This „apoptosis sensitization” effect was described also in colon cancer (Bahar et al., 2007). It was also suggested that PTAG loss in pituitary adenomas may be an early step in pituitary tumorigenesis leading to a blunted apoptotic response (Bahar et al., 2004b).

Among other methylated genes involved in the regulation of apoptosis in pituitary cells are ZAC and RASSF1. The ZAC (zinc finger protein which regulates apoptosis and cell cycle arrest, or PLAGL1, pleiomorph adenoma gene like-1) encoding a zinc finger protein was found to be strongly underexpressed in NFPA compared to other types of pituitary adenomas or normal pituitary tissue (Pagotto et al., 2000). ZAC inhibited cell proliferation and colony formation in functional *in vitro* experiments and abolished tumor formation in nude mice. It induced apoptosis and cell cycle arrest independently of pRb, p21^{Waf1/Cip1}, p16^{INK4a}, p27^{KIP2} and p53^{KIP3} (Spengler et al., 1997). Underexpression of ZAC was related either to loss of heterozygosity (LOH) (Pagotto et al., 2000) of the ZAC locus or to hypermethylation. RASSF1A (Ras association domain family 1) was found to exert a tumor

suppressor function in several neoplasms including pituitary tumors. Qian demonstrated that inactivation of the *RASSF1A* was caused by promoter methylation in 38% of all pituitary adenomas and in 83% of higher grade adenomas (Qian et al., 2005). *RASSF1* promoted apoptosis and inhibited cell growth in different cell lines suggesting its general role in apoptosis. This apoptosis promoting effect of *RASSF1* was found to be p53-independent (Vos et al., 2000) while its effect on cell proliferation and cell cycle was connected to the prevention of cyclin D1 accumulation (Shivakumar et al., 2002; Song et al., 2004).

3.2 Histone modifications in pituitary adenomas

As mentioned above the key regulators of histone modifications are DNA methyltransferases. Among these enzymes, DNMT3b, a “de novo” DNA methylation enzyme was found to be overexpressed in functioning pituitary adenomas and NFPAs (Zhu et al., 2008a). Using chromatin immunoprecipitation in AtT20 mouse pituitary cells Zhu et al. demonstrated that histone modifications resulted in a change of DNMT3b expression (Zhu et al., 2008a).

Another protein with reduced expression due to histone methylation was fibroblast growth factor receptor type 2 (FGFR2). The FGFR2 gene transcript has two splice variants. Deletion of the FGFR2-IIIb isoform was associated with inaccurate pituitary development (DeMoorloze et al., 2000). FGFR2 was found to be underexpressed in pituitary tumors compared to normal pituitary tissue (Abbass et al., 1997; Zhu et al., 2007a). Underexpression of the FGFR2 gene was also demonstrated in murine adrenocorticotrophic hormone secreting pituitary tumor cells (Zhu et al., 2007a). FGFR2 has been previously described as tumor suppressor because in functional experiments its enforced expression impeded cell growth and enhanced apoptosis in thyroid cancer cell lines via attenuation of Ras/BRAF/MAPK phosphorylation (Kondo et al., 2007a). In addition, expression of MAGE-A3 (melanoma antigen family A, 3; cancer/testis antigen family 1, member 3), an FGFR2 signaling target molecule showed an inverse correlation with FGFR2 expression (Kondo et al., 2007b; Zhu et al., 2008b). Activation of FGFR2 signaling resulted in methylation of H3 and deacetylation associated to the MAGE-A3/6 promoter down-regulated its expression (Kondo et al., 2007b). Downregulation of FGFR2 signaling caused hypomethylation of MAGE-A3 promoter in pituitary tumors originated from female individuals (Ezzat et al., 2008; Zhu et al., 2008b). MAGE-A3 and its protein family are encoded on X chromosome and normally are expressed in placenta, in testicular germ cells and in several tumors such as melanoma, lung cancer and breast cancer (Hussein et al., 2011; Sigalotti et al., 2004; Yanagawa et al., 2011). MAGE-A3 was found to regulate the expression of p53 and p21 and its downregulation resulted in p21 and p53 accumulation that reportedly occurred occasionally in specific cases of pituitary adenomas (see Table 1.) (Ezzat et al., 2008; Zhu et al., 2008a,b).

There may be several links between processes involved in the mechanism of pituitary development and tumorigenesis. An example of this complex crosstalk is the function of Ikaros (Ik), a zinc-finger DNA binding protein implicated in chromatin remodeling, which has a role in the development of GHRH neurons in hypothalamus and plays an important role in pituitary tumorigenesis via its tumor suppressor function (Ezzat et al., 2005a; Winandy et al., 1995). In pituitary corticotroph cells loss of Ik leads to impaired activation of proopiomelanocortin hormone expression and increased mortality (Ezzat et al., 2005a). Ik-deficient mice have reduced GHRH secretion, a shrunk somatotroph population in pituitary and dwarfism (Ezzat et al., 2006). Ik inhibits access of Pit-1 to GH promoter while it

facilitates Pit-1 binding to prolactin promoter in mammasomatotroph cells by the histone acetylating-deacetylating system (Ezzat et al., 2005a). Ik is also involved in tumorigenesis and was found to be down-regulated by hypermethylation in human pituitary tumors (Zhu et al., 2007b). One negative isoform of Ik, Ik6 was implicated in pituitary tumorigenesis by promoting pituitary cell survival through enhanced antiapoptotic activity through Bcl-XL induction by chromatin histone acetylation (Ezzat et al., 2005b). In addition to apoptosis regulation Ik6 contributes to dysregulated expression of Ik target genes including growth factor receptors such as FGFR4 which are essential for development. In pituitary tumor cells Ik6 interrupts activation of the FGFR4 promoter through its deacetylation, that results in transcription from a cryptic promoter in intron 4 leading to a truncated tumor derived receptor isoform (pituitary derived ptd-FGFR4) with an oncogenic potential (Ezzat et al., 2004; Yu et al., 2003).

3.3 Loss of imprinting

Our knowledge about loss of imprinting (LOI) and its relation to the pituitary tumorigenesis is limited. As imprinting is executed by methylation, altered methylation may lead to LOI. Regarding to the pituitary we already discussed two imprinted tumor suppressor genes, *MEG3A* and *ZAC*, which may be silenced by hypermethylation of both alleles.

In addition, the gene encoding the alpha-subunit of the GTP-binding protein, *Gs* alpha was found to be expressed only from the maternal allele in normal pituitary tissue. However, some GH-secreting pituitary tumors containing *Gsa* mutation express *Gsa* from the non-mutated paternal allele too. This biallelic expression was also present in *Gsa* mutation negative adenomas too (Hayward et al., 2001). In the latter cases relaxation of imprinting occurred.

4. Role of miRs in pituitary adenoma development

Because 30-50% of all protein coding genes may be controlled by miRs (Chen & Rajewsky, 2006; Lewis et al., 2005), it is not surprising that they are implicated in pituitary tumorigenesis. Bottoni et al. described that miR-15a and miR-16-1 may have a pathogenic role in the development GH- and PRL-secreting adenomas (Bottoni et al., 2005). They found that these two miRs were significantly underexpressed in these adenomas. The genes encoding miR-15a and miR-16-1 are located in chromosome 13q14, a region which is frequently deleted in pituitary tumors. These two miRs were found to be negatively correlated with the tumor diameter and miR-16-1 expression showed negative correlation with arginyl-tRNA synthetase (RARS) expression, a putative target in pituitary tumor cells. In addition, RARS associated with the p43 in the aminoacyl-tRNA synthetase complex, and it was suggested that p43 has anti-neoplastic properties in mice. Based on these data it was suggested that in pituitary adenomas miR-16-1 expression may modify RARS level, which associates with p43 in the formation of the ARS complex and that this process may influence tumor growth. Cimmino et al. showed that the antiapoptotic B cell lymphoma 2 (Bcl2) protein is an additional target of miR-16-1. Interaction between miR-16-1 and Bcl-2 may be present in the majority of B-cell lymphoma cases (Calin et al., 2002; Cimmino et al., 2005). The Bcl2 was found to be overexpressed in approximately one-third of pituitary adenomas, while its expression was not detected in normal pituitary tissues (Wang et al., 1996), suggesting that Bcl2 may be implicated in pituitary tumorigenesis through regulation of apoptosis (Bottoni et al., 2007).

The connection between pituitary development and tumorigenesis is further supported by the dual role of a protein, named high-mobility group A2 (HMGA2). HMGA2 is a small nuclear non-histone chromatic protein involved in the regulation of chromatin structure (Fashena et al., 1992) and gene transcription (Grosschedl et al., 1994). In transgenic mice overexpression of HMGA2 leads to initiation of mixed GH/prolactin secreting pituitary adenomas (Fedele et al., 2002). Although the HMGA2 gene was not expressed in normal pituitary, its expression was present in human prolactinomas and NFPA. In prolactinomas its expression was related to amplification and/or rearrangement of its chromosomal loci (Finelli et al., 2002), but in the case of NFPA genetic alteration was absent (Pierantoni et al., 2005). In 2007 two studies using reporter gene experiments showed that expression of HMGA2 was repressed by miR let-7 (Lee & Dutta, 2007; Mayr et al., 2007). In addition, Qian et al. confirmed an inverse correlation between let-7 and HMGA2 expressions in NFPA (Qian et al., 2009).

Our group using whole genome miR expression profiling combined with bioinformatical tools and luciferase reporter systems showed that Wee1 kinase, a kinase involved in the regulation of G2/M transition, was targeted and downregulated by miRs in pituitary tumor samples compared to normal pituitary tissues (Butz et al., 2010). We showed that both the total and phosphorylated forms of Wee1 protein was decreased in NFPA and GH producing adenomas compared to normal pituitary tissues (Fig. 4A.).

After cloning Wee1 3'UTR into a luciferase reporter plasmid we demonstrated that Wee1 downregulation was, at least in part, due to overexpression of miR-128a, miR-516a-3p and miR-155 in NFPA and overexpression of miR-155 in GH producing adenomas. In addition using site directed mutagenesis we validated binding sites (Fig. 4C.) predicted by three different target prediction algorithms in Wee1 3'UTR for miRs: miR-128a, miR-155 and miR-516a-3p, further confirming that downregulation of Wee1 may be related to the overexpression of these miRs in pituitary adenomas. In another study Qi et al experimentally validated two other miRs, miR-195 and miR-372 targeting Wee1 in human embryonic stem cells (hESCs) (Qi et al., 2009). Our group found that miR-195 was moderately overexpressed (1.5 fold) in NFPA and down-regulated in GH-producing adenomas. In pituitary adenomas impairment of cell cycle regulation by Wee1 downregulation may lead to the loss of the G2/M checkpoint, which in turn may allow DNA damage accumulation leading to tumor development (Butz et al., 2010). In addition, multivariate analysis suggested that in non-small-cell lung cancer expression of Wee1 was a prognostic factor: its decreased expression negatively correlated with a higher rate of recurrence and higher Ki-67 proliferation index (Yoshida et al., 2004). Backert et al. reported that Wee1 was underexpressed in colon cancer tissues and cell lines further supporting its tumor suppressor function (Backert et al., 1999).

In addition to cell cycle alterations through Wee1, the TGF β signaling pathway may also play a role in the pathogenesis of pituitary adenomas. This pathway was shown to exert a prominent role in the regulation of pituitary tumor growth and prolactin secretion from pituitary lactotrope cells, and microarray studies indicated that FSH, LH and TSH β -subunit, which are under TGF β regulation, are underexpressed in NFPA (Kulig et al., 1999; Wang et al., 2008). In addition, TGF β administration decreased proliferation and increased apoptosis of HP75 cell line derived from a clinically non-functioning pituitary tumor [Kulig et al., 1999; Danila et al., 2002]. In our study after performing microRNA expression profiling with TaqMan microfluidic card on pituitary adenomas we executed complex bioinformatical procedures including target prediction following pathway analysis using DIANA miR-PathTool software for differentially expressed miRs. Our results suggested involvement of several altered pathways. Of these we selected TGF β signaling and found that

members of TGFβ signaling, Smad3, Smad6 and Smad9 were significantly underexpressed in NFPA compared to normal pituitary tissues using quantitative RT-PCR. In addition, in silico target prediction analysis for Smad3 identified five overexpressed miRs in NFPA compared to normal tissues (miR-135a, miR-140-5p, miR-582-3p, miR-582-5p and miR-938). Our results suggest that these overexpressed miRs may produce downregulation of the TGFβ signaling through Smad3, and these miRs may have a possible role in the complex regulation of the TGFβ signaling pathways involved in the tumorigenesis process of NFPA. (Butz et al., 2011) Also, our miR expression profile analysis suggested that a decrease of TGFβ signaling via Smad3 may result in a shift toward alternative, non-Smad pathways including Ras-MAPK, p38, c-Jun, and PI3K-Akt, which have been already considered as contributing factors in pituitary tumorigenesis (Fig. 5.) (Butz et al., 2011).

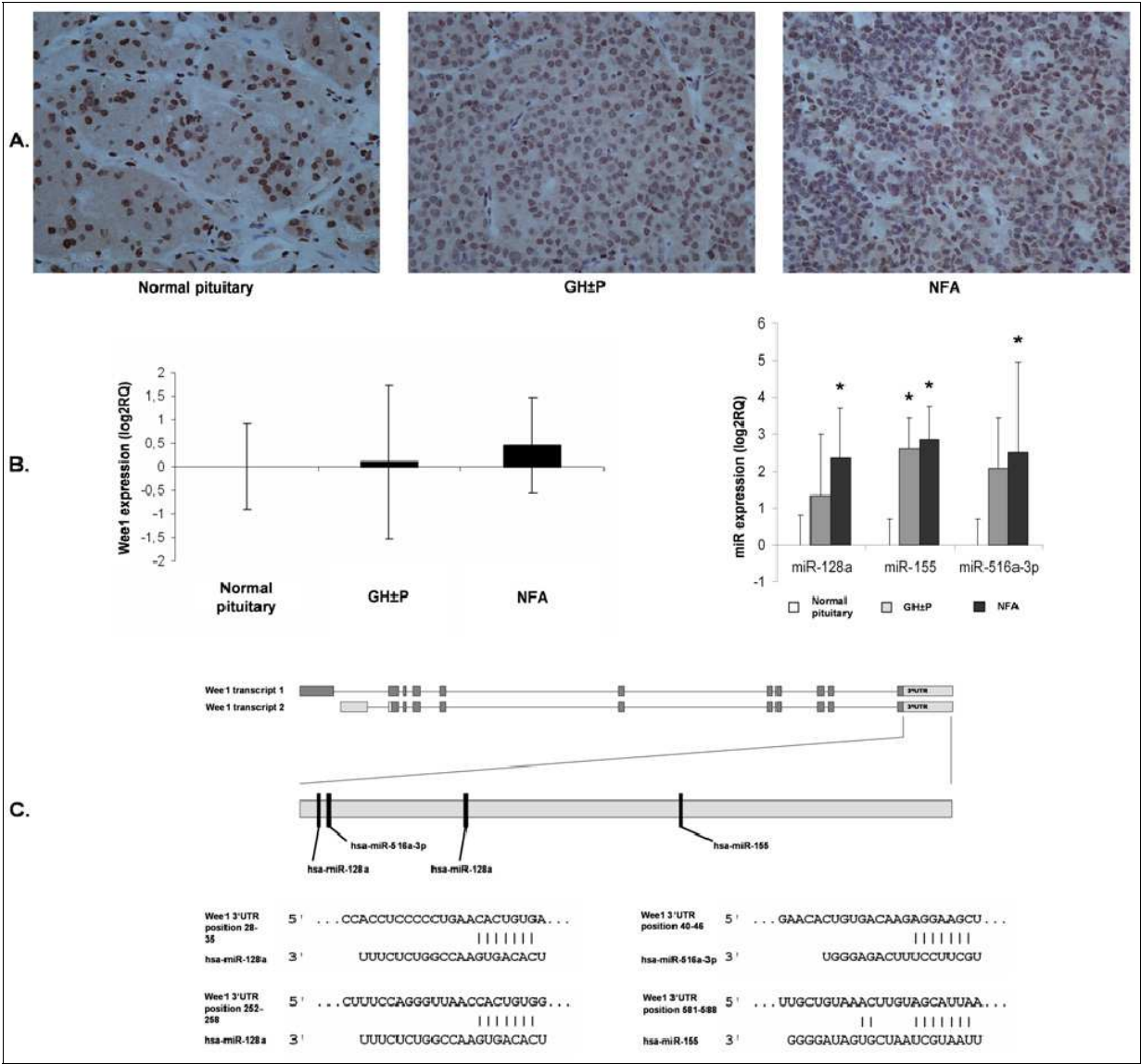


Fig. 4. A: Wee1 immunohistochemistry in normal and adenomatous pituitary. B: Wee1 and its targeting miRs' expression. C: miRs' binding sites at Wee1 3'UTR. (partly presented in paper Journal of Clinical Endocrinology & Metabolism. Vol.95, No.10, (October, 2010), pp. E181-191, ISSN 0021-972X)

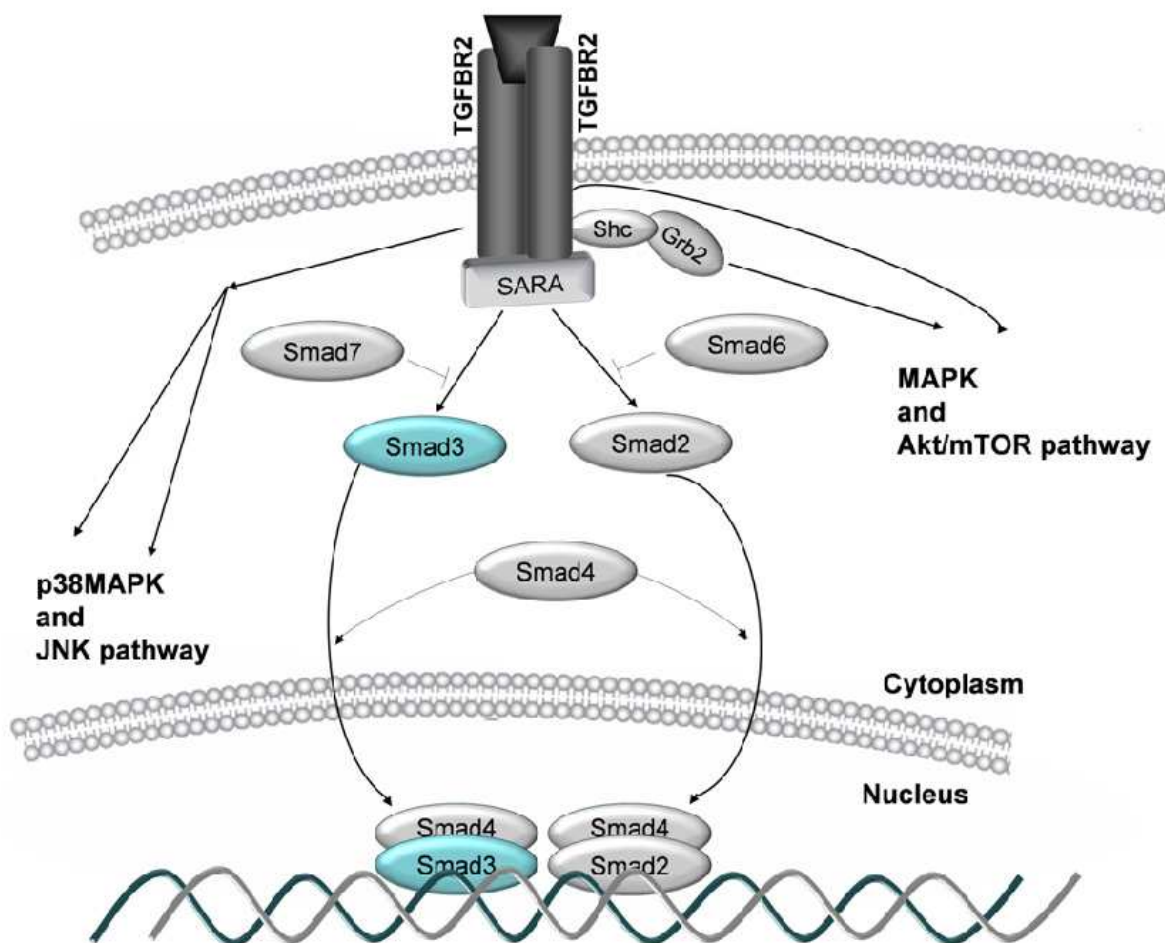


Fig. 5. TGFβ signaling. Smad3 indicated with blue is targeted by several miRs in pituitary.

Another interesting connection between Smad3 and pituitary tumorigenesis arises from a direct interaction of Smad3 with the tumor suppressor menin. Inactivation of menin blocked TGFβ and activin signaling and antagonized their growth-inhibitory properties in anterior pituitary cells (Hendy et al., 2005). It is known that MEN1 gene mutations play a role in MEN1-related pituitary tumorigenesis, but MEN1 gene mutations seem to be very rare in sporadic pituitary adenomas (Prezant et al., 1998; Wenbin et al., 1999). Some reports showed increased menin expression in sporadic pituitary adenomas (Wrocklage et al., 2002). However, there are some conflicting data about menin expression because other reports indicated a significant reduction of menin protein in a high percentage of pituitary adenomas (Theodoropoulou et al., 2004), and studies by several groups using RT-PCR (Asa et al., 1998; Farrel et al., 1999; Satta et al., 1999) showed no differences in MEN1 mRNA levels between pituitary tumors and normal pituitary tissues. All these data may raise the possibility of posttranscriptional mechanisms regulating menin expression via altered expression of miRs. Indeed, in our study we identified 4 miRs (miR-149, miR-570, miR-592, miR-769-5p) potentially targeting MEN1 3'UTR showed a significant overexpression, but further studies are needed to confirm regulation of menin expression by these miRs (Butz et al., 2011).

5. Conclusions and future perspectives

As already shown in several tumor types, the pathogenesis of pituitary adenomas involves epigenetic mechanisms which play a prominent role in the regulation of gene expression. The question is that whether epigenetic alterations, such as DNA and histone modifications are a cause or a consequence in pituitary tumorigenesis. New discoveries and new methodologies in the fields of cell biology, genetics, and genomics open new paths in understanding the complexity of regulatory networks of tumor development. The small RNA systems and their regulatory roles are still uncovered fields in pituitary tumor pathology. To date only miRs of small RNAs have been investigated in pituitary tumorigenesis. It is expected that using novel tools new players and/or new roles for old players will be identified, which may help to develop novel diagnostic and therapeutic approaches.

6. References

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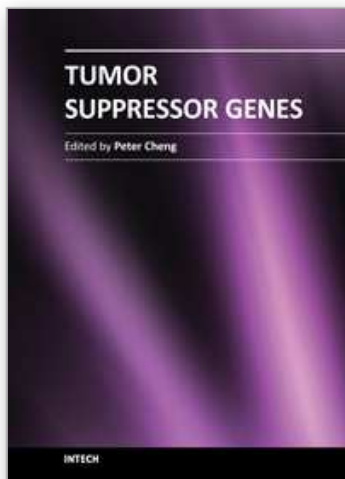
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Functional evidence obtained from somatic cell fusion studies indicated that a group of genes from normal cells might replace or correct a defective function of cancer cells. Tumorigenesis that could be initiated by two mutations was established by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

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