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REVIEW

Molecular Mechanisms Underlying Pituitary Pathogenesis

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Abstract During the last years, progress has been made on the identification of mechanisms involved in anterior pituitary cell transformation and tumorigenesis. Oncogene activation, tumor suppressor gene inactivation, epigenetic changes, and microRNAs deregulation contribute to the initiation of pituitary tumors. Despite the high prevalence of pituitary adenomas, they are mostly benign, indicating that intrinsic mechanisms may regulate pituitary cell expansion. Senescence is characterized by an irreversible cell cycle arrest and represents an important protective mechanism against malignancy. Pituitary tumor transforming gene (PTTG) is an oncogene involved in early stages of pituitary tumor development, and also triggers a senescence response by activating DNA-damage signaling pathway. Cytokines, as well as many other factors, play an important role in pituitary physiology, affecting not only cell proliferation but also hormone secretion. Special interest is focused on interleukin-6 (IL-6) because its dual function of stimulating pituitary tumor cell growth but inhibiting normal pituitary cells proliferation. It has been demonstrated that IL-6 has a key role in promoting and maintenance of the senescence program in tumors. Senescence, triggered by PTTG activation and mediated by IL-6, may be a mechanism for explaining the benign nature of pituitary tumors.

Keywords Pituitary tumors · PTTG · OIS · IL-6 · Senescence

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Introduction

Pituitary tumors are mostly benign, nonmetastatic, and monoclonal neoplasms constituted by cells of the adeno-pituitary gland, which generally cause small lesions and present a slow growth (Asa and Ezzat 2009; Dworakowska and Grossman 2009; Melmed 2003; Scheithauer et al. 2006). Each cell type in the pituitary can lead to a particular tumor subtype that can be hormonally active or inactive. Several characteristic hallmarks of pituitary neoplasia point to a unique growth behavior distinct from that of other endocrine and nonendocrine malignancies. Pituitary tumors are invariably benign, and although aggressive local growth may occur, they generally fail to proceed into true malignancy with demonstrable extracranial metastases (Di Ieva et al. 2014). These adenomas are very frequent, constituting up to 15–20 % of intracranial neoplasms, and have an overall population prevalence of ~80 to 90 per 100,000 of the population (Aflorei and Korbonits 2014; Daly et al. 2006; Fernandez et al. 2010; Raappana et al. 2010).

The majority of pituitary adenomas develop sporadically. However, approximately 5 % of the cases arise in the context of familial syndromes and several of the genes involved in these hereditary adenomas have been identified (Alexander 2001; Brandi et al. 2001; Daly et al. 2009; Marx et al. 1999).

The pathophysiological consequences of a pituitary adenoma are related to overproduction of particular pituitary hormones or due to tumor compression and damage to the normal pituitary and vital structures surrounding it (Yu and Melmed 2010).

In recent years, a considerable progress has been made in identifying mechanisms and factors involved in the initiation and progression of pituitary adenomas. Pituitary tumorigenesis appears to be a complex process in which extrinsic and intrinsic factors participate. Oncogene mutations commonly encountered in nonendocrine neoplasms (e.g., ras and p53) are not generally present in pituitary adenomas, yet specific tumor-initiating and tumor-promoting factors have been characterized in animal models, and also in a limited number of human tissue samples. These factors proved to confer an increased proliferative potential to the precursor cell for adenoma formation and enhanced tumor growth, including cell cycle deregulation, overexpression of growth factors, hormonal overstimulation, epigenetically silenced tumor suppressor genes, overexpression of oncogenes, defective signaling pathways, and an altered intrapituitary microenvironment (Asa and Ezzat 2009; Clayton and Farrell 2004; Colao et al. 2010; Dworakowska and Grossman 2009; Elston et al. 2009; Farrell 2006; Melmed 2011; Perez-Castro et al. 2012; Vandeva et al. 2010), all of which contribute to sustained cell proliferation.

In the present review, we focus in the role that miRNAs deregulation, as well as somatic and epigenetic mutations in regulators of the cell cycle, and also specific factors involved in the senescence pathway might be playing in the pathophysiology of the anterior pituitary tumorigenesis, contributing to the current knowledge in key aspects of these mechanisms.

Cell Cycle and miRNAs Deregulation in Pituitary Tumors

In the last years, several mouse models of cell cycle regulators have suggested that some endocrine tissues, such as the pituitary gland, are critical targets for cycle deregulation in cancer and other diseases. Studies have demonstrated that genetic and epigenetic mutations play an important role in the development of human neoplasm (Farrell 2005; Peltomaki 2012). Normal cells contain an intrinsic tumor suppression pathway, which induces permanent arrest, such as cellular senescence, or apoptosis, when cells present excessive damage. For normal cells to become tumors, these tumor suppression barriers have to be circumvented by mutation of one or more pathway components (Hanahan and Weinberg 2011).

Cell cycle deregulation is considered a pathogenic event in the formation of pituitary adenomas. It has been estimated that about 80 % of human pituitary adenomas display alterations at least in one cell cycle regulator (Fedele and Fusco 2010; Quereda and Malumbres 2009). These alterations include overexpression of cyclins (mainly D1, D3, and E), downregulation of the cyclin-dependent kinase inhibitor family (mainly $p15^{Ink4B}$, $p16^{Ink4A}$, $p18^{Ink4C}$, $p21^{Cip1}$, and $p27^{Kip1}$), and pRb expression (Farrell and Clayton 2003).

It is well established that human pituitary adenomas are monoclonal in origin, suggesting that individual tumors are derived from a single cell driven by a somatic gene mutation or mutations (Alexander et al. 1990; Clayton et al. 2000; Herman et al. 1990; Melmed 1994). In recent years, emerging evidence indicates that epigenetic modifications are an 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; Yacqub-Usman et al. 2012). The main cause of gene inactivation in pituitary tumors is DNA methylation (Yacqub-Usman et al. 2012). In fact, reduced levels of $p15^{Ink4b}$, $p16^{Ik4a}$, and $p18^{Ink4c}$ in pituitary adenomas appear to be caused mainly by promoter hypermethylation (Kirsch et al. 2009; Ogino et al. 2005; Yoshino et al. 2007). Over the years, several genes were found to be inactivated in pituitary tumors by genetic or epigenetic mechanisms, and they are functionally linked to the most important tumor suppressors Rb and p53. A recent study (Pease et al. 2013) revealed at least 24 genes found to be epigenetically modified in pituitary adenomas: 16 tumor suppressor genes (like $p16^{INK4A}$, $p21^{CIP1}$, $p27^{Kip1}$, $p14^{ARF}$, SOCS1, RB1/pRb, BMP-4), 2 oncogenes (PTTG and MAGEA3), 3 imprinted genes (GNAs1, NNAT, MEG3), 3 epigenome modifiers (DNMT3b), and 2 transcription regulators (Ik and HMGA2).

The emergence of miRNAs has been one of the defining developments in cancer biology over the past decade. MiRNAs are critical regulators of gene expression. The control of cell proliferation by miRNAs is well established and the alteration of these small, noncoding RNAs may contribute to tumor development by perturbing critical cell cycle regulators. Changes in miRNAs expression in many types of cancer suggest that they may be involved in crucial steps during tumor progression (Croce 2009; Deng et al. 2008). miRNAs are aberrantly expressed or mutated in human cancers, representing a novel class of oncogenes or tumor suppressor genes

(Liu et al. 2012; Nugent et al. 2011; Zhao et al. 2012). miRNAs deregulation has been described in pituitary tumorigenesis, but few studies have described their role in pituitary tumor progression toward aggressiveness and malignancy, like the case of miR-126 and miR-381. PTTG, a protein isolated from pituitary tumor cell line and involved in pituitary tumorigenesis (Abbud et al. 2005; Pei and Melmed 1997), is a target of both miRNAs. MiR-126 and miR-381 were shown to be downregulated in GH-secreting pituitary adenomas (Mao et al. 2010), suggesting that they regulate pituitary adenoma invasion by targeting PTTG. Moreover, each subtype of pituitary adenoma tends to be characterized with specific miRNA profile (Bottoni et al. 2007).

The correlation and function of miRNAs and their target genes in pathogenesis of pituitary adenomas remain largely unknown; however, the altered expression of some miRNA has been associated with tumor diameter, invasiveness, and therapeutic outcomes (Bottoni et al. 2005, 2007; Mao et al. 2010). For example, miR-15a and miR-16-1, located in a region which is frequently deleted in pituitary tumors (Calin et al. 2002), were reported to have lower expression in GH- and PRL-secreting pituitary adenomas than in normal tissue. Their downregulation was correlated with a greater tumor volume and impaired secretion of the anticancer cytokine p43, suggesting that these miRNAs may function as tumor suppressor and their inactivation may contribute to tumor growth (Bottoni et al. 2005).

Oncogene-Induced Senescence in Pituitary Tumors

Cellular senescence, originally related to aging and then defined as a proliferative arrest that occurs in cells after a limited number of cell divisions, is now widely considered as a general biological program of terminal growth arrest (Campisi 2001; Cichowski and Hahn 2008; Collado et al. 2007, 2005; Mooi and Peeper 2006). Senescence consists in a signal transduction program leading to irreversible arrest of cell cycle, followed by different changes in the cellular phenotype. Senescence restrains proliferation, but allows the cell to remain viable and perform its physiological function. Senescent cells appear as a result of the exposure to multiple cellular stress events such as telomere shortening, DNA damage, lysosomal-oxidative stress, or oncogene activation (Campisi 2001; Schmitt et al. 2002; Serrano and Blasco 2001).

While the history of research on cell senescence counts for more than half a century, it is in the last 10 years that the functional relevance of cell senescence in vivo was established. Compelling evidence supporting oncogene-induced senescence (OIS) as a physiologically relevant mechanism limiting tumorigenesis is rapidly emerging. Several lines of evidence have recently implicated OIS, as a vital cause of arrest of benign neoplasms. Senescence markers have been identified in benign human adenomas, like melanocytic nevi (Gray-Schopfer et al. 2006; Michaloglou et al. 2005), murine lung adenomas (Dankort et al. 2007), human dermal neurofibromas (Courtois-Cox et al. 2006), human and murine prostatic adenomas (Chen et al. 2005), murine pancreatic intraductal neoplasias (Collado

et al. 2005), murine lymphomas (Braig et al. 2005), and early murine melanomas (Ha et al. 2007), but not in malignant adenocarcinomas.

Pituitary cells are among the few epithelial cell types that rarely undergo malignant transformation. The precise mechanisms underlying the unique indolent growth of these invariably benign adenomas remain unknown, taking into account that common cancer-associated oncogene mutations rarely take place (Asa and Ezzat 2009). As premature senescence occurs in slow growing benign or early stage tumors but not in late stage or malignant tumors, and pituitary adenomas (especially clinically inactive microadenomas) exhibit stable growth often during decades of observation (Levy and Lightman 2003), senescence could be proposed as a major candidate to explain its benign nature (Arzt et al. 2009). Several lines of research support the observed pituitary adenoma senescent phenotype (Alexandraki et al. 2012; Chesnokova et al. 2007, 2008; Donangelo et al. 2006; Lazzerini Denchi and Helin 2005). Thus, premature pituitary tumor cell senescence appears to bypass pro-proliferative signals, thereby stopping cell proliferation, while preserving vital homeostatic pituitary functions in order to maintain cell viability (Arzt et al. 2009; Melmed 2011).

Normal pituitary cells are under endocrine as well as auto-/paracrine control of numerous growth factors, and disturbances in the expression and/or action of these factors and their receptors contribute to pituitary tumor development and progression. The altered expression of cytokines/growth factors and their receptors was observed in pituitary tumors (Arzt et al. 1999; Asa and Ezzat 2002; Perez Castro et al. 2000; Ray and Melmed 1997; Renner et al. 1996, 1997, 2004), such as TGF-β protein family, TFG-α and EGF, FGF family, nerve growth factor, and D2R and gp130 family. In particular, the putative oncogenic role of the gp130 protein has been demonstrated in lactosomatotroph GH3 tumor cells, which no longer formed tumors in nude mice after gp130 downregulation, indicating that one or more of the gp130 cytokines might play a role in pituitary tumorigenesis (Castro et al. 2003). The expression of almost all of the gp130 cytokines and their corresponding receptors was detected either in normal or tumoral pituitary (Hanisch et al. 2000; Jones et al. 1994; Perez Castro et al. 2001).

IL-6 is produced by tumoral cells themselves but is also delivered to the adenoma cells through IL-6-producing folliculo stellate (FS) cells, which surround or invade the pituitary tumors (Farnoud et al. 1994; Hofler et al. 1984; Renner et al. 1997, 1998; Ueta et al. 1995; Vajtai et al. 2007). IL-6 mRNA was also detected in corticotrophic adenoma cell cultures and other adenoma cell types, such as nonfunctioning, lactotroph, and somatotroph adenomas (Arzt et al. 1999; Borg et al. 2003; Jones et al. 1994).

IL-6 also plays an important role in pituitary tumor progression as it acts as a stimulatory growth factor and enhances the release of vascular endothelial growth factor from FS cells (Gloddek et al. 1999), therefore promoting vessel formation. After mutation and transformation of a normal pituitary cell to a tumoral one, the IL-6 secreted by the surrounding FS cells may act in a paracrine manner to promote the development of an adenoma, by favoring tumor cell number expansion, vessel formation, and perhaps extracellular matrix remodeling through the matrix metalloproteinases that the FS cells produce (Renner et al. 1998). However, this

cytokine also inhibits normal pituitary cells (Arzt et al. 1993). It promotes the DNA synthesis and cell proliferation of GH3 cells, but at the same concentrations it inhibits the growth of normal anterior pituitary cells (Arzt et al. 1993). Furthermore, IL-6 presents opposite effects (inhibitory or stimulatory) in different tumors such as ACTH-, PRL-, GH-secreting and nonfunctioning adenomas, with no apparent association between the kind of response and tumor type or size (Pereda et al. 1996). These different effects in normal and tumoral pituitaries have not yet been elucidated, but might be given by differences in the induction of activating signal pathways or stimulation of cytokine-signaling inhibitor production by the IL-6/gp130 complex (Arzt 2001).

In 2008, Kuilman et al. reported a key role of IL-6 in OIS. His work showed that IL-6 is required for both induction and maintenance of OIS, and acts in a cell-autonomous fashion to enable OIS. This suggests that IL-6 acts in an autocrine manner to regulate OIS. The fact that IL-6 is a cytokine that participates in pituitary tumor development, in addition to the findings of its role in OIS, makes this cytokine an attractive candidate as an autocrine/paracrine stimulator of adenoma progression inducing OIS (Arzt 2001; Arzt et al. 1999, 2009).

It is not clear whether intrinsic pituitary cell IL-6 expression is oncogene regulated. However, endogenous IL-6 may underlie the slow proliferation rate and benign nature of pituitary tumors. It is plausible that paracrine IL-6 effects may allow initial pituitary cell growth (required for senescence bypass), while autocrine IL-6 in the same tumor triggers senescence and restrains aggressive growth and malignant transformation.

An important protein involved in pituitary tumorigenesis is PTTG, which behaves as a mammalian securin homologue controlling separation of sister chromatids during metaphase (Heaney et al. 1999; Pei and Melmed 1997; Zhou et al. 2001), and is also induced by the E2F transcription factor in the pituitary gland (Zhou et al. 2009). PTTG is a proto-oncogene which exhibits oncogene properties and facilitates cell cycle progression (Pei and Melmed 1997; Zhang et al. 1999b). It is overexpressed in a large proportion of pituitary tumors (Filippella et al. 2006; Saez et al. 1999; Salehi et al. 2008; Zhang et al. 1999a), and its expression appears to be correlated with invasiveness, recurrence, poor prognosis, and tumor metastasis (Ramaswamy et al. 2003; Vlotides et al. 2007). PTTG overexpression causes cell transformation in vitro, induces aneuploidy, promotes tumor formation in nude mice, induces basic fibroblast growth factor (which is a potent mitogenic and angiogenic factor), and activates angiogenesis (Heaney et al. 1999; Ishikawa et al. 2001; Yu et al. 2000, 2003). PTTG is required for pituitary tumorigenesis as directed transgenic PTTG overexpression leads to development of focal hormone-secreting pituitary hyperplasia and adenoma formation (Abbud et al. 2005). Either PTTG overexpression or disruption results in dysregulated G2 to M phase cell cycling, activation of DNA-damage signaling pathways, aneuploidy, and chromosomal instability in vitro and in vivo (Kim et al. 2005, 2007; Vlotides et al. 2007). PTTG deletion also results in pituitary-specific senescent features, including upregulation of the CDK inhibitors $p15^{INK4B}$, $p16^{INK4A}$, and $p21^{CIP1}$ (a set of well-known tumor suppressors often inactivated in human cancers), and Rb hypophosphorylation (which is expected since the tumor suppressor signaling pathways

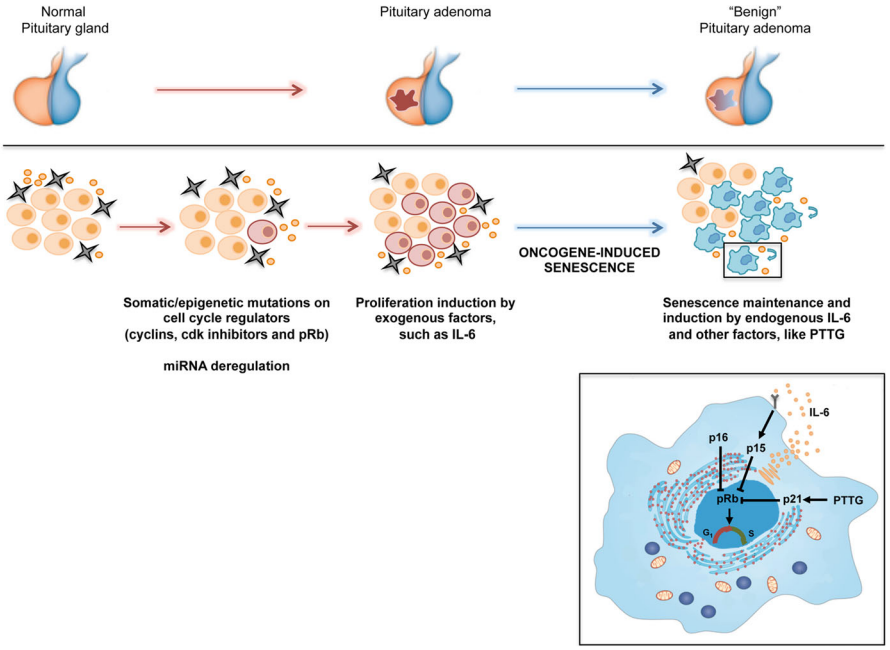

Fig. 1 Pituitary senescence progression model. Pituitary tumor pathogenesis has an initial proliferative phase given by growth factors secreted by the FS and hormone-producing cells, which induce proliferation of the pituitary tumor cells. It is followed by a phase of stopping proliferation via OIS mediated by different factors among which the IL-6 produced by the tumor cells themselves is likely involved, resulting in a benign tumor with stable growth arrest. OIS is also induced and maintained by the overexpression of $p15^{INK4B}$, $p16^{INK4A}$, and $p21^{CIP}$ triggered by the stress signal, such as the activation of PTTG

$p21^{CIP1}$/p53 and $p16^{INK4A}$/pRb are activated in OIS) (Campisi 2005; Dimri et al. 1995), overexpression of cyclin D1, apoptosis block, and elevated senescence-associated β-galactosidase (SA-β-gal) expression (Chesnokova et al. 2005, 2007). While human GH-secreting adenomas, but not carcinomas, abundantly express intra-nuclear $p21^{Cip1}$ (Chesnokova et al. 2007, 2008), gonadotroph adenoma strongly express $p16^{Ink4a}$ and $p15^{Ink4b}$, suggesting that there are tissue-specific pathways involved in senescence activation (Alexandraki et al. 2012; Chesnokova et al. 2011).

Conclusions

Pituitary cell growth regulation by IL-6 reinforce the role of cytokines as factors controlling pituitary cell division, and the findings of the IL-6 role in OIS suggest that endogenous IL-6 might be involved in development of pituitary adenoma senescence, which may explain the benign nature of these frequent tumors (Fig. 1). The presence of senescent cells in the tumor and the relative abundance of different proteins produced by the senescent cells are important biological factors that could

have significant prognostic implications for the disease outcome. Thus, pituitary adenomas could constitute faithful in vivo models of senescence. Several promising lines of research will provide insights into the pathogenesis and treatments of pituitary adenomas. Characterization of specific tumor-associated growth factors, signaling pathways, cell cycle checkpoint disruptions, and miRNA deregulation may be valuable in elucidating novel targeted pituitary tumor therapies (Paez-Pereda et al. 2005).

Pituitary pathogenesis is challenging to study due to its unique biology and behavior. Despite the common occurrence of pituitary adenomas, they are usually not associated with metastasis, and provide an interesting model to further understand the protective role of OIS against malignant transformation. As senescence is considered an important tumor protection barrier, understanding the mechanisms behind the ability of pituitary cells to escape aggressive growth and malignant transformation may provide important insights into cancer-restraining pathways and present new opportunities for subcellular therapeutic approaches.

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