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The International Journal of Biochemistry & Cell Biology 38 (2006) 1441–1449
IJBCB
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Cells in focus

Cells of the anterior pituitary

Chung-Man Yeung [a], Chi-Bun Chan [a], Po-Sing Leung [b], Christopher H.K. Cheng [a,*]

[a] *Department of Biochemistry, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong, China*
[b] *Department of Physiology, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong, China*

Received 10 November 2005; received in revised form 18 February 2006; accepted 24 February 2006
Available online 3 March 2006

Abstract

The anterior pituitary is made up of a number of cell types that are essential for such physiological processes as growth, development, homeostasis, metabolism, and reproduction. These include the hormonal cells corticotropes, thyrotropes, gonadotropes, somatotropes, lactotropes and a small population of mammosomatotropes, together with a non-hormonal cell type called the folliculo-stellate cells. The anterior pituitary hormonal cells are highly differentiated and are committed very early on during embryonic development. Their development is tightly regulated by both extrinsic signals as well as by endogenous gene expression. Many transcription factors that shape the development and functions of the anterior pituitary cells have been identified. Even after differentiation, pituitary cells continue to undergo mitosis and this process could be augmented under certain conditions in adulthood. Some anterior pituitary cells are multifunctional and exhibit mixed phenotypes. Pituitary tumors, which are mostly monoclonal in nature, are rather common. The molecular pathogenesis of pituitary tumorigenesis involves complex and diverse mechanisms. Aberrant intra- and extra-pituitary factors are involved. Mutations of some genes specific to pituitary tumors also play a role.

Keywords: Anterior pituitary; Cell lineage development; Transcription factors; Tumorigenic mechanisms

Cell facts

- The anterior pituitary is composed of five major cell types including corticotropes, thyrotropes, gonadotropes, somatotropes and lactotropes. These cells produce hormones that regulate adrenal function, thyroid function, reproduction, growth and lactation.
- Somatotrope is the major cell type of the anterior pituitary, constituting approximately 50% of the cell population, followed by lactotrope (10–25%), corticotrope (10–20%), thyrotrope (10%), and gonadotrope (10%).
- The lactotropes and somatotropes take up acidophilic stains, and the corticotropes take up basophilic stains, while the thyrotropes and gonadotropes do not stain well with either type of stains. These classical cell-staining techniques are now replaced by modern techniques of immunohistochemistry and in situ hybridization.
- Anterior pituitary cells are highly differentiated and are committed very early on during development to synthesize unique hormone products.
- Anterior pituitary cells respond to complex central and peripheral signals by trophic hormone secretion and by exhibiting reversible changes in cell growth leading to hyperplasia or sometimes adenomas from the functional pituitary cells. Pituitary adenomas are benign neoplasms made up of hormonal adenohypophyseal cells.

* Corresponding author. Tel.: +852 2609 6801; fax: +852 2603 5123.
E-mail address: chkcheng@cuhk.edu.hk (C.H.K. Cheng).

1357-2725/$ – see front matter
doi:10.1016/j.biocel.2006.02.012

1. Introduction

The pituitary, a small but complex gland situated underneath the hypothalamus in the sella turcica, is crucial for the maintenance of various homeostatic functions including growth, metabolism, and reproduction. It is connected to the hypothalamus and the brain by the pituitary stalk and is composed of two lobes, the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis). A third lobe, the intermediate lobe, is rudimentary and ill defined in human. The cells of the anterior pituitary, which are named according to the trophic hormones that they produce, include the following cell types: corticotropes (adrenocorticotropic hormone (ACTH) and related peptides producing cells), thyrotropes (thyroid stimulating hormone (TSH) producing cells), gonadotropes (luteinizing hormone (LH) and follicle stimulating hormone (FSH) producing cells), somatotropes (growth hormone (GH) producing cells), and lactotropes (prolactin (PRL) producing cells). A small population of mammosomatotropes also exists which produces both GH and PRL. These hormonal cells are associated with a non-hormonal cell type in the anterior pituitary called the folliculo-stellate cells.

2. Cell origin and differentiation

The different cell types of the anterior pituitary are distributed within the acini of the adenohypophysis. The process of adenohypophyseal cell differentiation and development follows a particular pattern and temporal sequence (Treier et al., 1998). Pituitary cells are highly differentiated and are committed very early on during development to synthesize unique hormone products. During mammalian pituitary development, distinct cell types emerge from a common primordium (Dasen & Rosenfeld, 1999). In mouse, for example, organogenesis of the anterior pituitary begins at embryonic day 8.5 (E8.5) as certain cells of the oral ectoderm thicken and invaginate to form the nascent pituitary referred to as the Rathke's pouch (RP) (Fig. 1, Panel A) (Gleiberman, Fedtsova, & Rosenfeld, 1999). At E11.5, all RP cells are committed and the first appearance of the various cell types (as indicated by the expression of specific hormone mRNAs) occurs in a specific manner temporally and spatially between E12.5 and E16.5 (Denef, 2003). The positions of the anterior pituitary cell types are initially determined as they emerge from the proliferation zones (Ericson, Norlin, Jessell, & Edlund, 1998; Treier et al., 1998) and induction of specific transcription factors is required for the different cell types to progress beyond initial patterning (Lamolet et al., 2001; Zhao et al., 2001). The induction of transcription factors acting as activators or repressors determine the fate of the cells (Scully & Rosenfeld, 2002). Over the years, many transcription factors that shape the development and functions of the anterior pituitary cells have been identified (Savage, Yaden, Kiratipranon, & Rhodes, 2003), as summarized in Fig. 2. For instance, a novel T box factor called Tpit plays an essential role in the differentiation of the corticotrope lineage (Lamolet et al., 2001), and Pit-1 is required for the terminal differentiation of the somatotropes, lactotropes, gonadotropes, and thyrotropes (Andersen & Rosenfeld, 2001). It was found that Pax6 controls formation of the dorsalventral boundary during pituitary organogenesis. In *Pax6*-mutated mice, an increased number of thyrotropes and a decreased number of somatotropes and lactotropes were observed resulting from uncontrolled cell growth of the ventral lineages along the dorsalventral axis (Kioussi et al., 1999). The dorsalventral patterning of the developing pituitary is also affected by Prop1, which represses growth of the dorsal lineages and activates expansion of the ventral lineages (Raetzman, Ward, & Camper, 2002). In addition, it was reported that *Prop1*-deficient dwarf mice possess a dysmorphic pituitary because of failed differentiation of the pituitary lineages after formation of the RP (Ward et al., 2005). Lhx3 is another critical factor in the differentiation of the pituitary lineages. Although formation of the RP was normal in homozygous *Lhx3*-mutated mice, failure of the RP to proliferate afterwards caused a depletion of the thyrotropes, gonadotropes, somatotropes and lactotropes probably through inactivation of Pit-1 expression (Sheng et al., 1996). In addition to endogenous gene expression, early pituitary development is also regulated by extrinsic signals. The most important initial extrinsic signals include members of three protein families, viz. bone morphogenic protein, fibroblast growth factor (FGF) and Wnt (Ericson et al., 1998; Treier et al., 1998).

Pituitary cell differentiation and growth are dependent on many locally produced and released molecules acting in autocrine or paracrine manners. These include nitric oxide, ATP, acetylcholine and peptide factors such as endothelins, activins, neurotropins, leukemia inhibitory factor and insulin-like growth factors (Scully & Rosenfeld, 2002). Post-differentiation cell proliferation is required for normal pituitary development. Hypothalamic hormones and target organ hormones are implicated in proliferation of the anterior pituitary cells. Growth factors are also required for expansion of the

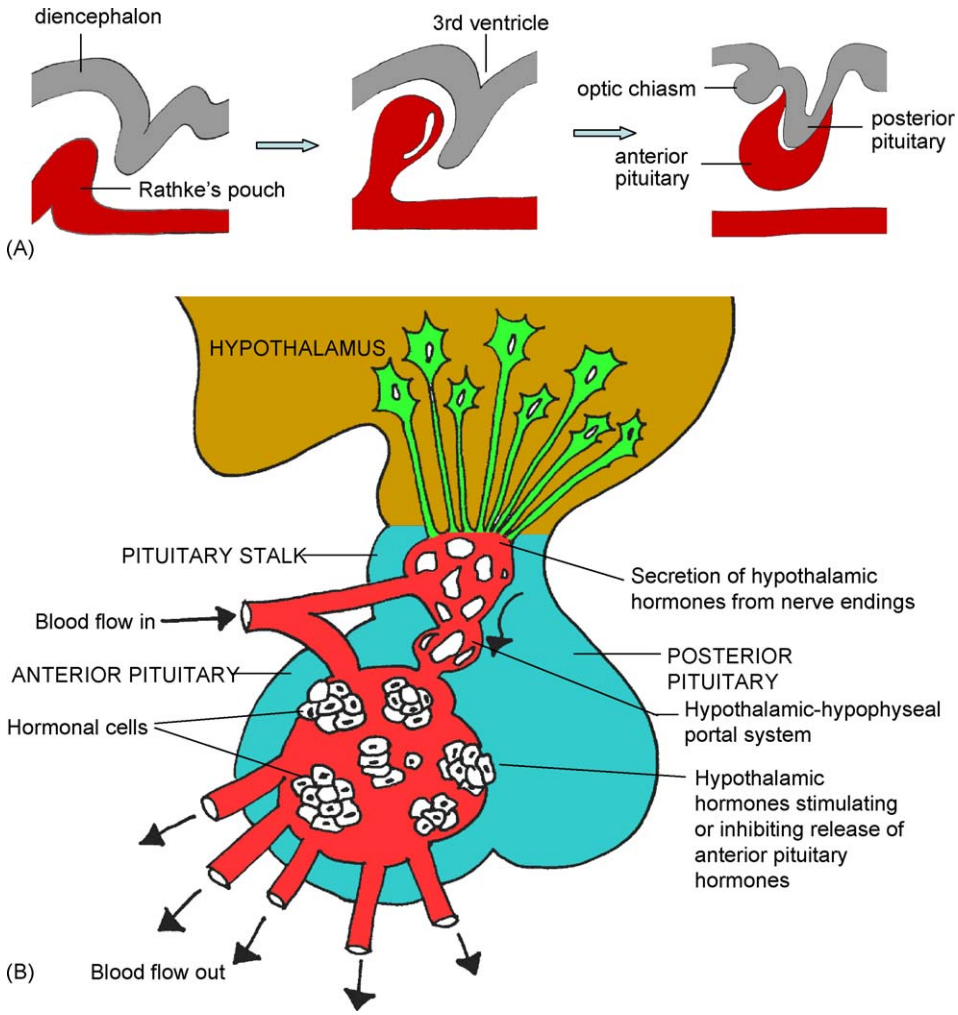

Fig. 1. (A) Development of the pituitary. (B) The hypothalamic–hypophyseal portal system connecting the hypothalamus and the anterior pituitary.

pituitary cell populations in the developing gland. Even after so-called terminal differentiation, pituitary cells continue to undergo mitosis, which could be augmented under certain conditions in adulthood. For instance during pregnancy the pituitary gland enlarges with most of the growth resulted from lactotrope hyperplasia. Pre-existing lactotropes proliferate and somatotropes are recruited to switch from GH to PRL production (Melmed, 2003). Reversible transdifferentiation also occurs in the pituitary whereby cells are recruited from heterologous cell types (Vidal, Horvath, Kovacs, Lloyd, & Smyth, 2001). GH-producing cells also have the capacity to transdifferentiate to gonadotropes (Childs, 2002).

In summary, transcription factors and growth factors regulate the processes of cell migration, proliferation and differentiation in pituitary development. The expression of these factors is highly regulated resulting in correct migration of the RP, proper proliferation of the cells, and eventual cytodifferentiation into the matured cell types. Dysfunction of these processes could result in congenital aberrations and hormone deficiency. The factors that govern cell differentiation in the pituitary also play a part in pituitary tumor development.

3. Functions

The anterior pituitary trophic hormones are secreted in a pulsatile or episodic manner, which is in turn controlled by the synchronized secretion pattern of the hypothalamic hormones. The hypothalamic-anterior

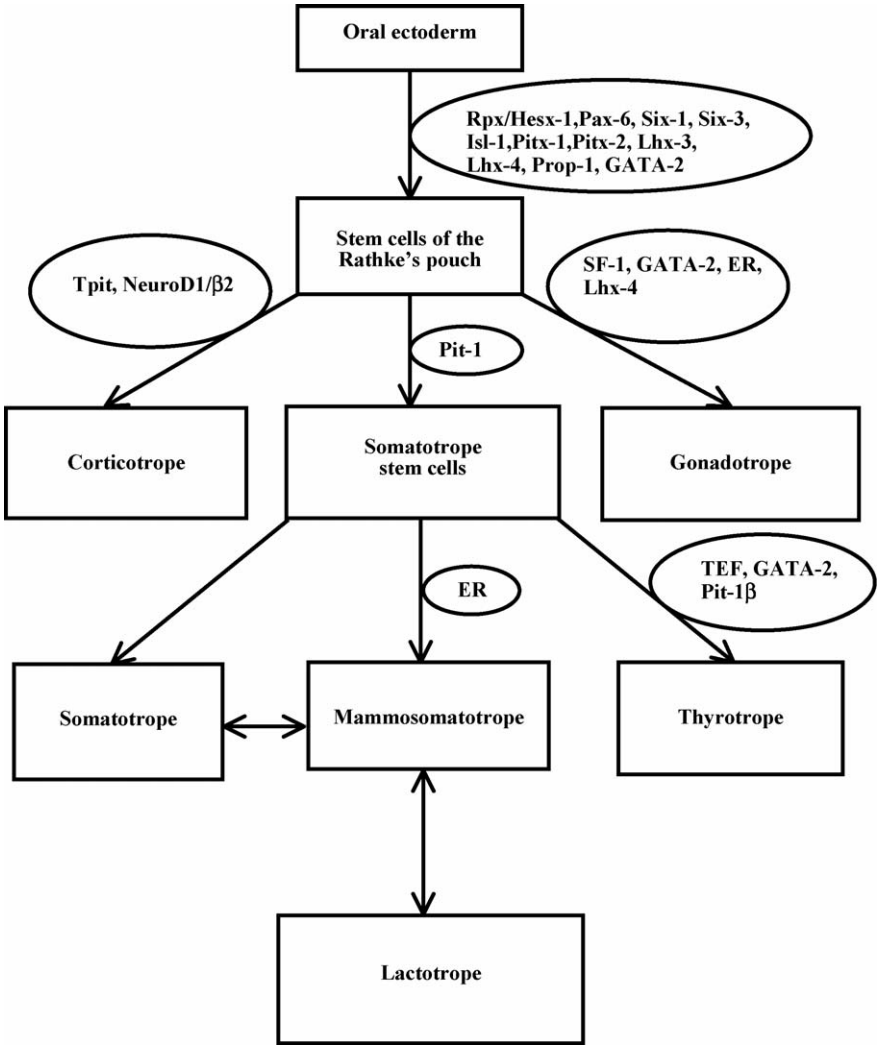

Fig. 2. Anterior pituitary: cell lineage development and transcription factors involved.

pituitary unit integrates both stimulatory and inhibitory central and peripheral signals to synthesize and secrete these trophic hormones by the specific cell types (Melmed, 2003). Each of these cell types expresses unique G protein-coupled receptors, which are specific for the hypothalamic releasing or inhibiting hormones. The production of the various trophic hormones from these cells is under the direct regulation of these hypothalamic hormones brought to the anterior pituitary through the portal circulation system (Fig. 1, Panel B), and their responsiveness can be modified by several other factors including hormone level, negative feedback inhibition, and circadian rhythm. The hypothalamic releasing hormones stimulate hormone biosynthesis in the respective pituitary cell types by enhancement of gene transcription and mRNA stability. These releasing hormones also act rapidly on the cell surface receptors to promote the release of hormones from these cells. The best-known mechanism involves activation of the adenylate cyclase-cyclic AMP–protein kinase A (PKA) pathway. The release of GH, PRL, ACTH and TSH by their respective hypothalamic releasing hormones is mediated by this mechanism. Elevation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) is the prerequisite to hormone exocytosis in all pituitary cells (Tse & Tse, 1999). This $[Ca^{2+}]_i$ elevation is contributed by two possible sources. The release of stored Ca^{2+} from the endoplasmic reticulum (ER) accounts for the intracellular source and the influx of Ca^{2+} via the voltage-gated calcium channel (VGCC) represents the extracellular source. When a specific pitu-

itary cell type is stimulated by a particular ligand such as corticotropin releasing hormone, the cyclic AMP–PKA pathway is triggered leading to an influx of extracellular Ca^{2+} via the VGCC. Alternatively, the phospholipase C (PLC)–protein kinase C (PKC) pathway is activated causing a biphasic response of $[Ca^{2+}]_i$ increase in the pituitary cells: a transient spike due to the Ca^{2+} release from the ER followed by a sustained elevation from the extracellular source. Hormones that activate the PLC–PKC pathway include gonadotropin releasing hormone and thyrotropin releasing hormone (Kwiecien & Hammond, 1998). The hypothalamic inhibitory hormones such as somatostatin and dopamine also employ the cyclic AMP and calcium-dependent pathways to decrease hormone secretion from the respective pituitary cells. They act partly by inhibiting adenylate cyclase and partly by other mechanisms such as decreasing the availability of calcium to the cell.

The traditional view of hypothalamic control of anterior pituitary hormone secretion is that each hypothalamic releasing hormone modulates the release of a single hormone and that each cell type could respond to only one releasing hormone. However, this classical concept needs to be modified in the light of recent studies suggesting that hypothalamic control of pituitary function is probably more complicated than previously thought. Each of the major anterior pituitary cell types contains discrete subpopulations (multiresponsive cells) that are able to respond to several hypothalamic-releasing hormones (Villalobos, Nunez, Frawley, Garcia-Sancho, & Sanchez, 1997). There is increasing evidence indicating that some anterior pituitary cells are multifunctional in nature and could exhibit mixed phenotypes. These cells may be involved in paradoxical secretion (secretion of a hormone evoked by a non-corresponding releasing hormone) and transdifferentiation (phenotypic switch between different mature cell types without cell division) (Nunez, Villalobos, Senovilla, & Garcia-Sancho, 2003; Villalobos, Nunez, & Garcia-Sancho, 2004). Interestingly, multifunctional cells are found to be more abundant in females than in males, indicating that the hormonal changes associated with the cyclical events in females may promote transdifferentiation suggesting that the female pituitary is more plastic than the male counterpart (Nunez et al., 2003).

4. Associated pathologies

Pituitary tumors are common in human causing a number of pathological complications including growth disorders, sexual dysfunction, infertility, obesity, metabolic disturbances, and mood disorders (Asa & Ezzat, 2002). Abnormality in the proliferation of the anterior pituitary resulting in congenital hormone deficiencies is relatively uncommon. But pituitary adenomas are rather commonplace and have been reported to occur in as much as 20–25% of the general population of which one-third is clinically significant (Asa & Ezzat, 1998). Most pituitary adenomas are comprised of non-metastasizing slow growing neoplasms exhibiting a wide range of hormonal and proliferative behavior (Asa & Ezzat, 2002). Pituitary adenomas are derived from clonal expansion of mutated somatic cells (Alexander et al., 1990; Herman, Fagin, Gonsky, Kovacs, & Melmed, 1990). Tumors may arise from any of the anterior pituitary cell types. GH hypersecretion leads to overgrowth and metabolic problems associated with acromegaly or gigantism; PRL hypersecretion leads to gonadal failure, secondary infertility and galactorrhea; TSH hypersecretion leads to hyperthyroxinemia and goiter; ACTH oversecretion results in Cushing's syndrome; and hypersecreted gonadotropins lead to gonadal dysfunction and reproductive disorders (Melmed, 2003). PRL adenoma is the most common, with GH and ACTH adenomas accounting for about one-third of the pituitary adenomas. TSH adenoma is very rare. Another one-third comes from those immunoreactive against the glycoprotein hormone (LH and FSH) subunits, but these are often without clinical symptoms. Table 1 summarizes the functions of the anterior pituitary cells and their associated tumors. Apart from the endocrine symptoms resulting from the hormonal hypersecretion, sometimes the space-occupying tumor itself, particularly those which grow rapidly giving rise to an intracranial mass, can cause other problems such as depressed secretion of other hormones, visual disturbance, headache and sleeping problems.

Besides the functional classification, the different pituitary adenomas could also be classified radiologically into four categories: grade I enclosed microadenoma, grade II enclosed macroadenoma, grade III invasive but localized tumor, and grade IV invasive and diffused tumor. Classification can also be based on histological examination of the tumor cells. The classical categorization into acidophilic, basophilic and chromophobic adenomas is now being replaced by techniques of immunocytochemistry or in situ hybridization which better define the hormonal nature of the adenomas. Cellular ultrastructure, especially the granular content, is also used in conjunction to give a more precise description of the adenoma type. And because of these advents in cell-staining techniques, plurihormonal adenomas have now been identified.

Table 1
Functions of the anterior pituitary cells and their associated tumors

Cell type	Major reaction in routine staining	Hormone(s) produced	Major biological functions	Major symptoms	Incidence of the associated tumor
Somatotrope	Acidophilic	GH	Somatic growth, hepatic IGF-I production	Acromegaly or gigantism	10–15%
Lactotrope	Acidophilic	PRL	Lactation	Hypogonadism, galactorrhea, sexual dysfunction, infertility	35%
Mammosomatotrope	Acidophilic	GH, PRL	Somatic growth, hepatic IGF-I production, lactation	Acromegaly or gigantism with hypogonadism and galactorrhea	5%
Corticotrope	Basophilic	ACTH and other POMC-derived peptides	Glucocorticoid synthesis and secretion	Cushing's syndrome, Nelson's syndrome	10–15%
Thyrotrope	Chromophobic	TSH	Thyroid hormone synthesis and secretion	Thyroid disorders	2%
Gonadotrope	Chromophobic	LH, FSH	Sperm/egg development, production of sex steroids	Hypogonadism, hypopituitarism	35%

The mechanisms of tumorigenesis in endocrine tissues differ greatly from those in non-endocrine tissues. For example, mutations in the classical oncogenes and tumor suppressor genes (e.g. *ras* and *p53*) that are common in other tumors are rarely seen in pituitary tumors. Instead, pituitary tumors appear to be promoted by the same hormones that regulate normal pituitary functions, and by the same growth factors that are involved in normal fetal pituitary development. In addition, mutations of some other genes are also implicated (Table 2).

Most pituitary adenomas are monoclonal in nature, suggesting that pituitary tumors may arise principally from intrinsic cellular defects which could occur in either one of the following two ways: gain-of-function defects or loss-of-function defects.

On the gain-of-function side, mutations of the α subunit of the stimulatory G protein (Gsα) are associated with the GH-secreting adenomas (Spada et al., 1990). The resultant oncogene, termed *gsp*, is constitutively active leading to activation of adenylyl cyclase, increased production of cyclic AMP, and excessive activation of the cell growth pathway culminating eventually to pituitary adenoma development (Spada, Lania, & Ballare, 1998).

Pituitary adenomas have higher PKC activity and protein level than normal pituitary cells (Alvaro et al., 1992). Also, PKC mutations have been linked to the invasiveness of pituitary tumors (Alvaro et al., 1993). Mutations in *PRKAR1*, the gene that encodes for the regulatory R1 subunit of PKA, are associated with predisposition to pituitary tumor development (Kirschner et al., 2000).

Excessive amounts of growth hormone releasing hormone (GHRH) could be tumorigenic. GHRH alone does not seem to be sufficient. However, GHRH upregulation might promote cell proliferation in already transformed somatotropes. Alternatively, GHRH-induced hyperplasia might provide a favorable environment for subsequent cell transformation. Excessive amounts of estrogen have also been suggested in the pathogenesis of lactotrope adenomas (Kovacs, Stefaneanu, Ezzat, & Smyth, 1994). The cell type-specific expression of estrogen receptor (ER) is also involved in the regulation of pituitary tumor growth. Consistent with this, estrogen treatment is associated with increased expression of the vascular endothelial growth factor (*VEGF*) gene and the pituitary tumor-transforming gene (*PTTG*) (Heaney, Fernando, & Melmed, 2002; Lohrer et al., 2001). While *PTTG* can induce *VEGF* expression (McCabe et al., 2002), whether *PTTG* activation itself would be sufficient for pituitary tumorigenesis is not totally resolved.

Transforming growth factor-α (TGFα), epidermal growth factor (EGF) and EGF receptor (EGFR) are all expressed in the pituitary. TGF-α, which binds to EGFR,

Table 2
Some candidate genes involved in pituitary tumorigenesis

Gene	Putative mechanisms involved	Biological effects	Tumorigenic outcome
PTTG	Gene overexpression	Inhibits chromatid separation Induces bFGF Induces bFGF-medicated angiogenesis Facilitates other mutational events	Activates
Gsα	Point mutations leading to constitutive activation (the resultant oncogene is termed *gsp*)	Activates cAMP cascade	Activates
PKA	PKA activation	Activates CREB Phosphorylates Raf-1	Activates
PKC	Point mutation leading to increased PKC protein amount	Enhances c-jun phosphorylation Enhances CREB dimerization leading to AP-1 activation	Activates
CREB	Increased Ser^{133} phosphorylation leading to CREB activation	CREB dimer binds with cAMP-response elements in the promoters of GH, PRL, TSH and ACTH genes	Activates
Cyclin D1	Allelic imbalance	Allelic imbalance observed in 25% of pituitary tumors	Activates
pRb	Methylation leading to gene inactivation	Uninhibited cell cycle progression and tumor growth	Inactivates
p16	Methylation leading to decreased p16 production	Loss of cell cycle checkpoint function	Inactivates

has been implicated as the mediator of the estrogen-induced lactotrope proliferation (Ezzat, 2001). Expression of EGFR in the pituitary is correlated with tumor aggressiveness, particularly for the somatotrope tumors (LeRiche, Asa, & Ezzat, 1996).

Gonadal cells produce inhibins and activins which control the secretion of LH and FSH from the gonadotropes. The effects of activin are regulated by activin receptors and follistatin, which binds and suppresses activin. Activin receptors are expressed by gonadotrope adenomas whereas follistatin expression is reduced, implying that enhanced activin signaling is involved in pituitary tumorigenesis (Penabad et al., 1996).

Basic FGF (bFGF) is normally produced in the folliculo-stellate cells to control the production of pituitary hormones in a paracrine fashion. This growth factor has been reported to be expressed in pituitary adenomas. In addition, the pituitary tumor cells express a specific isoform of the FGF receptor (FGFR) that could cause cellular transformation (Ezzat, Zheng, Zhu, Wu, & Asa, 2002). These results indicate that a defective FGF/FGFR system could lead to pituitary tumor development.

On the loss-of-function side, defects in the hypothalamic dopaminergic inhibitory axis have been associated with lactotrope adenoma pathogenesis (Ezzat, 2001). Some pituitary tumors exhibit dopamine resistance, indicating that a diminished dopamine receptor activity is involved in the tumorigenic process. A similar situation occurs with somatostatin, which inhibits GH secretion. Expression of somatostatin is reduced in certain GH-secreting tumors, as compared to normal pituitary cells (Levy et al., 1993).

Glucocorticoid exerts negative feedback on the pituitary corticotropes. Primary renal failure with prolonged glucocorticoid deficiency leads to corticotrope hyperplasia, which may result in adenoma formation (Scheithauer, Kovacs, & Randall, 1983), and loss of this feedback inhibition might be responsible for the enhanced secretion of ACTH in Cushing's syndrome.

Similar situations are found for thyroid hormones and sex steroids. Thyroid hormones inhibit pituitary thyrotrope proliferation and hormone production. Primary hypothyroidism would give rise to pituitary thyrotrope hyperplasia, which might develop into adenoma. In addition, dominant negative mutants of the thyroid hormone receptors have been reported in some TSH-producing pituitary tumors (Ando et al., 2001). Likewise, the development of pituitary gonadotrope adenomas in primary hypogonadism indicates that the absence of a feedback inhibition would facilitate tumorigenesis (Snyder, 1985).

The tumor suppressor retinoblastoma (*RB*) gene is an important cell cycle regulator. The *RB1* gene promoter region was methylated at a CpG island in tumor cells, resulting in depressed protein expression (Simpson, Hibberts, McNicol, Clayton, & Farrell, 2000). Loss of heterozygosity at the locus of the *RB1* gene has also been identified in human pituitary adenomas.

The cyclin-dependent kinases (CDK) are important enzymes of cell cycle control. Expression of the *CDK1 K1P1* gene was found to be reduced in corticotrope adenomas and other recurrent pituitary ademonas (Lidhar et al., 1999).

The *MEN1* gene encodes for the protein menin which functions as a transcriptional repressor in tumor suppression. Patients who have the MEN1 syndrome inherit an autosomal dominant mutation that is associated with a high incidence of pituitary tumors (Byström et al., 1990).

The molecular pathogenesis of pituitary tumorigenesis involves complex and diverse mechanisms. It is likely that aberrant intra- and extra-pituitary factors are involved. Mutations of some genes specific to pituitary tumors may also play a role.

Acknowledgements

We are grateful to The Chinese University of Hong Kong for the provision of direct grants and for the award of a postdoctoral fellowship (to CMY).

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