Pituitary tumour pathogenesis

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Pituitary adenomas are the most common tumours in the central nervous system, make up approximately 10% of all primary intracerebral tumours [1] and are found incidentally in 3–27% of autopsies [2]. The predisposition to tumour formation of the highly specialized cellular phenotypes that characterize the anterior pituitary is unexplained, but it is tempting to speculate that the same hormones, growth factors and cytokines derived from intra- and extra-pituitary sites that maintain tight hypothalamic pituitary control may also contribute to pituicyte transformation. The interplay between genetic and humoural factors to promote cellular transformation is exemplified in pituitary tumorigenesis and is discussed in this review.

Keywords: pituitary tumors, oncogenes, tumor suppressor genes, angiogenesis

Pituitary tumour initiation

Most pituitary adenomas are discrete, well-demarcated lesions, amenable to surgical resection, but careful microscopic studies demonstrate that significant dural invasion occurs in approximately 25% portending incomplete surgical resection [3]. Some years ago, X-chromosomal inactivation analysis indicated that the primary event heralding the first pituitary cell clonal expansion was an intrinsic pituitary cellular mutation [4]. More recently, this concept has been extended based on the finding of independent monoclonal expansions in tumour tissue from recurrent pituitary tumours derived from the same patient [5]. These latter observations suggest that individual monoclonal expansions develop during the lifetime of the patient and become the dominant tumour mass depending on growth advantage characteristics. The notion that molecular events leading to increased transforming gene expression or silencing of tumour-suppressor genes (TSGs), pituitary and hypothalamic hormonal dysregulation, growth factor excess, environmental or iatrogenic mutagenic stimuli such as external radiation or pharmacological hormone administration may act in concert to promote pituitary tumour development is a useful paradigm that has particular relevance.
to endocrine tumorigenesis [6]. For example, mutational activation of a mitogenic or an angiogenic pathway will place specific growth factors in a key position to drive tumour growth. However, subsequent mutations may then switch the tumour to dependency on an alternate proliferative pathway. This has obvious therapeutic implications with increasing availability of ‘pathway-based’ tumour therapies, and as the nature of the tumorigenic process is to find ways to bypass pharmacological blockade of required growth pathways, we can anticipate development of resistance to many of these components. Furthermore, it proposes that although certain ‘markers’ of the transformed phenotype may be identifiable in pituitary tumours, the same single determining ‘genetic’ event is unlikely in every patient, as combinations and cascades of multiple events may all result in similar pituitary tumour phenotypes. By and large, oncogene activation or TSG inactivation constitutes the two main mechanisms by which genes can promote pituitary tumorigenesis. TSGs act to prevent uncontrolled cell growth and can be inactivated by heterozygous deletion of one of the two alleles encoding the TSG [so-called loss of heterozygosity (LOH)] or by homozygous loss of both the alleles. Epigenetic events such as promoter cytosine preceding guanine (CpG)-island methylation constitute a third mechanism reducing TSG protein expression, including protein-16/cyclin-dependent kinase nuclear 2A protein (p16/CDKN2A) and retinoblastoma 1 (Rb1) [7]. This review discusses some of the factors that have been implicated in pituitary tumorigenesis, and to provide a broader perspective on the field, they have been grouped on a functional basis.

**Cell-cycle regulators**

**Cyclin D1**

As a key regulator of cell growth, the cyclin D proteins (cyclins 1, 2 and 3) have been of extreme interest in pituitary and other tumours. Although one study described allelic imbalance of the cell-cycle nuclear D1 (CCND1) gene in 25% of pituitary tumours [8], suggesting cyclin D gene amplification, immunocytochemistry for cyclin D1 protein expression failed to demonstrate increased cyclin D1 protein expression, and hence, the significance of this finding is unclear.

**Retinoblastoma**

The phosphorylation of the retinoblastoma protein (pRb) is a key downstream effector that signals a cell-cycle transit from G1 to S phase.
Intermediate lobe pituitary tumours occur with an almost 100% penetrance in the heterozygous Rb1 knockout mouse [9], but early studies reported infrequent LOH of Rb1 intragenic markers in human pituitary tumours [10, 11]. LOH in the 13q14 region was observed in some pituitary tumours, but the exact site of loss was not clear and may not involve the Rb gene (Table 1). Additionally, no reduction in Rb1 protein (pRb1) was observed in many of these studies. Additional mechanisms of Rb loss such as Rb-promoter methylation provide an attractive mechanism for Rb inactivation, but despite apparent methylation of the Rb1 promoter or protein-binding pocket regions, some (2/30) tumours still expressed pRb1, but this epigenetic mechanism for Rb inactivation may still play an important role in pituitary tumorigenesis [12].

Cyclin-dependent kinase inhibitors

Protein-16/cyclin-dependent kinase nuclear 2A protein

Phosphorylation of Rb1 is governed by the cyclin proteins, and a family of enzymes, called the cyclin-dependent kinases (CDKs) [13], which are themselves regulated by CDK inhibitors (CDKIs). The CDKI, p16 is encoded by the CDKN2A gene located on chromosome 9p.

As for other TSGs, LOH or homozygous deletion of the CDKN2A gene in pituitary tumours is uncommon, although in one study, 31% of non-functioning (NF) tumours [14] displayed LOH at two other regions telomeric and centromeric to the CDKN2A gene, suggesting an alternate TSG may exist on chromosome 9p. Using methylation-sensitive restriction digestion followed by polymerase chain reaction (PCR) amplification, two additional studies examined methylation of the p16/CDKN2A gene. Methylation in exon 1 in 18 of 20 pituitary tumours which was associated with low pituitary tumour p16 expression by Western blot analysis was reported, and a subsequent study demonstrated p16/CDKN2A gene methylation in 70% (32/46) of NF tumours and 9.5% (2/21) of somatotrophinomas, findings confirmed by Southern blot in some cases [15]. Interestingly, although 78% of p16-methylated NF tumours also failed to express p16, almost one-quarter of tumours exhibited absent p16 expression without evidence of p16/CDKN2A methylation or gene mutation, pointing to additional post-translational mechanisms for p16 inactivation. Furthermore, mice lacking p16, while developing spontaneous tumours at multiple sites and at an early age, do not display a pituitary abnormality.
### Table 1 Candidate factors in pituitary tumorigenesis

<table>
<thead>
<tr>
<th>Name/gene chromosome</th>
<th>Mechanism/action</th>
<th>Outcome</th>
<th>Evidence (caveats)</th>
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<tbody>
<tr>
<td><strong>Cell-cycle factors</strong></td>
<td></td>
<td></td>
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<tr>
<td>pRb/Rb/13q [10–12]</td>
<td>Possibly methylation → inactivation</td>
<td>↓ pRb leading to inhibited cell-cycle progression and tumour growth</td>
<td>Three studies, different approaches and markers, slightly conflicting results. Pei suggests Rb site, Bates site centromeric to Rb, Simpson site telomeric to Rb. One study showed no loss of Rb protein and two showed loss of pRb but no correlation with the LOH pattern.</td>
</tr>
<tr>
<td>P16/CDKN2A/9p [14, 15]</td>
<td>Possibly methylation → decreased p16</td>
<td>Loss of cell-cycle checkpoint function</td>
<td>Loss of one or more microsatellite markers in 31% of NF tumours. In majority of cases, deletions were in regions flanking but excluding p16/CDKN2A.</td>
</tr>
<tr>
<td>Cyclin D1/CCND1 [8]</td>
<td>Allelic imbalance</td>
<td>Allelic imbalance observed in 25% pituitary tumours (all types)</td>
<td>ICC showed no correlation between increased protein expression and CCND1 amplification.</td>
</tr>
<tr>
<td>PTTG1/PTTG1/5q33 [22]</td>
<td>Mechanism of overexpression unclear (no evidence for amplification or mutation)</td>
<td>Inhibits chromatin separation, induces bFGF-mediated angiogenesis</td>
<td>Elevated mRNA in 90% pituitary tumours of all types.</td>
</tr>
<tr>
<td><strong>Signal transduction pathways</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gsα [24, 25]</td>
<td>Point mutation, Arg → Valine</td>
<td>Constitutive activation cAMP cascade</td>
<td>Observed in 40% somatotroph tumours, uncommon in Asian GH-tumours and in other tumour types (5% NF tumours). Normal cAMP levels in GH-secreting.</td>
</tr>
<tr>
<td>CREB [26]</td>
<td>Increased Ser133 phosphorylated (activated) CREB</td>
<td>Binds a dimer with cAMP-response elements in the GH, PRL, TSH and ACTH promoters</td>
<td></td>
</tr>
<tr>
<td>PKA and PKC [27, 29]</td>
<td>Point mutated PKC → increased PKC protein → fibroblast transformation PKC inhibitors abrogate pituitary tumour growth</td>
<td>PKA: activated PKA activates CREB, phosphorylates Raf1 PKC: activation enhances c-jun phosphorylation, enhances CREB dimerization → AP-1 activation</td>
<td>PKC mutations uncommon in pituitary tumours.</td>
</tr>
<tr>
<td>H-ras [32]</td>
<td>Point mutation (codons 12, 13 and 61), amplification</td>
<td>Signal transduction/stimulates tyrosine kinase pathway</td>
<td>Metastatic pituitary carcinoma only.</td>
</tr>
<tr>
<td><strong>Growth and angiogenic factors</strong></td>
<td></td>
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<tr>
<td>FGF-2 and FGF-4 [35–37]</td>
<td>Unknown</td>
<td>Angiogenesis, induces PRL secretion</td>
<td>bFGF Tg mice develop hyperplasia only.</td>
</tr>
<tr>
<td>VEGF [39]</td>
<td>Unknown</td>
<td>Angiogenesis</td>
<td></td>
</tr>
<tr>
<td>HIF-1α [41]</td>
<td>Unknown</td>
<td>Transcriptional activator of VEGF, bFGF</td>
<td>Possible correlation with invasiveness.</td>
</tr>
<tr>
<td>TGFα and TGFβ [43, 44]</td>
<td>Unknown</td>
<td>Promotes lactotroph growth, E2 responsive</td>
<td>Lactotroph tumours in female TGF Tg mice only.</td>
</tr>
<tr>
<td>TGFβ receptor: one mutation of unknown significance</td>
<td></td>
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ACTH, adrenocorticotrophin; AP-1, activating protein-1; bFGF, basic fibroblast growth factor; CCND1, cell-cycle nuclear D1; CDKN2A, cyclin-dependent kinase nuclear 2A; CREB, cAMP response element-binding protein; CRH, corticotrophin-releasing hormone; E₂, oestrogen; GH, growth hormone; GHRH, GH-releasing hormone; GnRH, gonadotrophin-releasing hormone; HIF, hypoxia inducible factor; ICC, immunocytochemistry; LOH, loss of heterozygosity; MMP, matrix metalloproteinase; NF, non-functioning; PI3-K, phosphoinositol-3 kinase; PKA, protein kinase A; PKC, protein kinase C; pRb, retinoblastoma protein; PRL, prolactin; PTTG, pituitary tumour-transforming gene; TGF, transforming growth factor; TRH, thyrotrophin-releasing hormone; TSH, thyroid-stimulating hormone; VEGF, vascular endothelial growth factor.
Protein 27

Protein 27 (p27) regulates G1 cell-cycle progression, and low p27 expression has been reported in pituitary adenomas in comparison with normal pituitary tissue. Additionally, transforming growth factor-β1 (TGFβ1) directly downregulates p27 in rat pituitary cells to induce G1 arrest [16]. Lowest TGFβ1 has been reported in adrenocorticotrophin (ACTH)-secreting adenomas [17], but germline mutation of p27Kip1 gene does not result in a human phenotype, raising some questions regarding the importance of p27 as an initiator of pituitary tumours.

Pituitary tumour-transforming gene/securin

Pituitary tumour-transforming gene (PTTG), a securin that inhibits chromatid separation during mitosis, isolated from rat pituitary tumour cells [18]. Increased or sustained expression of PTTG/securin may disrupt chromatid separation, leading to chromosomal aneuploidy [19], potentially facilitating proto-oncogene activation or TSG loss, and securin overexpression results in in vitro transformation and in vivo tumour growth. Additionally, PTTG exhibits transactivational ability and stimulates basic fibroblast growth factor (bFGF)-mediated angiogenesis, actions that require a proline-rich region near the C-terminus of the PTTG protein [20]. A role for securin in tumorigenesis is also supported by transgenic models where PTTG knockout appeared to slow tumour development in the tumour susceptible Rb+/- mouse [21].

PTTG abundance has been described in various tumour types and correlated with an invasion of colorectal, breast and pituitary tumours [22]. However, studies thus far have not detected tumour securin DNA amplification or mutation, although epigenetic post-translational mechanisms to increase PTTG cannot be ruled out.

Signal transduction pathways

Activating G-stimulatory protein mutations

The heterotrimeric G proteins (guanine nucleotide-binding proteins) comprise of three polypeptide chains (α, β and γ) that either stimulate (Gs) or inhibit (Gi) transduction signals from membrane-associated G-protein-coupled receptors [23]. Stimulatory Gs action reduces its GTPase activity, resulting in increased cAMP formation. Gsα point mutations, particularly of residue 201 (Arg→Cys or His) or 227 (Gln→Arg or Leu), have been demonstrated in approximately 40% of growth hormone
(GH)-secreting pituitary tumours in Caucasians [24], with significantly lower mutation frequency (approximately 5%) in Japanese subjects. These mutations inhibit Gsα GTPase activity, resulting in GH-releasing hormone (GHRH) ligand-independent constitutive activation of cAMP, which results in GH-transcriptional activation, and somatotroph proliferation via a cAMP response element-binding protein (CREB) in the GH promoter. Contrary to expectation, Gsα mutation-positive somatotroph adenomas are smaller, have slightly lower GH-levels and do not respond rapidly to GHRH stimulation, and so Gsp mutations do not provide a unifying mechanism of oncogenesis in pituitary tumours [25].

**Activated cAMP-response element-binding proteins**

As noted above, a CREB binds as a dimer to cAMP-response elements (CRE) in the promoters of several pituitary genes including GH, prolactin (PRL), thyroid-stimulating hormone (TSH) and ACTH genes, and inactive mutant CREB transgenic mice exhibit dwarfism and somatotroph hypoplasia [26]. Significantly, higher amounts of Ser133-phosphorylated and, hence, activated CREB have been reported in some GH-secreting pituitary tumours compared with levels in NF tumours, but this augmented CREB activity was evident even in tumours that did not manifest a Gsα mutation. This would suggest that CREB activation may occur via other mechanisms independent of Gs.

**Protein kinase A and C**

Two other factors function to modify CREB-mediated actions on pituitary gene promoters and, hence, have been studied in pituitary tumours. Downstream of cAMP is a signal transduction protein, called protein kinase A (PKA, cAMP-dependent protein kinase), which when activated in turn activates CREB [27].

A second protein, called protein kinase C (PKC), is a serine/threonine kinase that is activated by diacylglycerol following growth factor/cytokine signalling. Final targets of PKC include c-fos activation and enhancement of c-jun phosphorylation that together result in activating protein-1 (AP-1) activation [28], but additionally, PKC enhances CREB dimerization. Therefore, the PKC and PKA pathways converge and crosstalk at several sights to enhance CREB-mediated actions. High-PKC expression in association with a PKC point mutation has been reported in some invasive pituitary tumours, and PKC inhibitors abrogate pituitary tumour growth and induce apoptosis, but such mutations appear uncommon in pituitary tumours [29].
**Phosphoinositol-3 kinase**

Signalling through the phosphoinositol-3 kinase (PI3-K) family of enzymes phosphorylates inositol phosphate to promote cell proliferation and survival. PI3-K expression is strongly associated with transformation and metastases, and increased PI3-K mRNA expression has recently been reported in pituitary tumours [30].

**Ras oncogenes**

The Ras protein transduces signals from growth factor receptors via GTP-Raf mitogen-activated phosphor-kinase (MAPK) cascade through to final targets, which include c-myc, c-fos and c-jun, in addition to other signal transduction pathways [31]. Three related ras proto-oncogenes (H-ras, K-ras and N-ras) encode monomeric 21 kDa proteins that are structurally similar to the membrane-anchored G proteins. Mutations in the ras GTP-binding or hydrolysis domains, corresponding to codons 12, 13 and 61, which result in continuous ras activation are a common early event in many solid tumours, including colorectal and thyroid cancer, but ras activation is rare in pituitary tumours, and H-ras mutations have only been identified in a single aggressive prolactinoma or metastases from pituitary carcinomas but not in the respective primary tumour [32].

**Growth and angiogenic factors**

Several proteins act to promote tumour growth and angiogenesis, and there is significant overlap in these two aspects of tumour promotion. Like hypothalamic and steroid hormones, much evidence supports a permissive role for growth factors and, to a lesser extent, cytokines in pituitary tumour pathogenesis. Of the growth factors implicated in pituitary tumorigenesis, FGFs have been most studied, particularly FGF-2 (bFGF) and FGF-4. As tumours expand, they require increased blood supply, and angiogenesis has emerged as a key component of the tumour phenotype, although the role of angiogenesis in pituitary tumour formation is unresolved. Some studies have reported higher vascularity in para-adenomatous normal pituitary tissue than pituitary tumours [33], but this contrasts with previous studies [34] in which careful light and electron microscopic analysis of prolactinomas revealed well-formed arteries in 13/16 pituitary tumours, findings absent in eight normal anterior pituitaries. One possible explanation for the discordance is the finding of highly atypical terminal arterioles, in proximity to the pituitary adenoma, indicating perhaps that profound alterations in pituitary
vasculature may precede or accompany pituitary tumour formation, emphasizing that vascular changes in para-adenomatous pituitary tissue need to be interpreted with caution.

**Fibroblast growth factor-2 and fibroblast growth factor-4**

Highest FGF-2 concentrations are found in the pituitary, and FGF-2 is a key regulator of pituicyte growth and differentiation, particularly for lactotrophs [35]. FGF-2 induces PRL secretion from rat anterior pituitary cells and human pituitary adenoma cultures, and elevated immunoreactive FGF-2 that normalized after pituitary tumour resection has been described in serum derived from patients with sporadic and multiple endocrine neoplasia type-1 (MEN1)-associated pituitary tumours [36]. Pituitary FGF-2 overexpression regulated by an α-subunit or a GH promoter resulted in pituicyte hyperplasia but did not induce frank adenomatous transformation, confirming FGF-2 promotes pituitary cell growth but raising some question as to whether FGF-2 of itself can transform pituitary cells. FGF-4 also induces PRL secretion in rat GH4 cells, transforms fibroblasts *in vitro* and causes *in vivo* tumour formation in rats [37]. Additionally, transforming FGF-4 sequences have been isolated from human PRL-secreting pituitary tumours, suggesting a role for FGF-2 and FGF-4 in pituitary tumour progression.

**Vascular endothelial-derived growth factor**

The pituitary also contains abundant vascular endothelial growth factor (VEGF) [38], arguably the most important angiogenic factor in tumorigenesis and a highly sought therapeutic target. Elevated serum VEGF levels have been reported in patients with all types of pituitary tumours [39], although as for bFGF studies, it has not been conclusively demonstrated that the immunoreactive peptides are indeed of pituitary origin. Both bFGF and VEGF expressions have been reported to correlate with pituitary tumour size and aggression, most notably in macroprolactinoma, but additionally bFGF-receptor expression also contributes to pituitary tumour invasion [40].

**Hypoxia inducible factor-1α**

Hypoxia inducible factor (HIF)-1α is a crucial transcription factor involved in the adaptive response to hypoxia and several angiogenic factors, including VEGF, harbour HIF-responsive elements on their promoters. A recent report demonstrated nuclear HIF immunoreactivity in 58 pituitary tumours and their surrounding vascular endothelial cells, but no correlation with tumour vascularity and HIF expression was
observed [41]. Interestingly, highest HIF expression was noted in prolactinomas, which previous studies have suggested are more vascular tumours.

**Transforming growth factor-α and transforming growth factor-β**

TGFα is one of several growth factors that bind the epidermal growth factor receptor (EGFR), which is overexpressed in pituitary tumours. Both bFGF and TGFα are expressed in normal human pituitary tissue in all cell types in the case of TGFα and predominantly in folliculostellate cells and select endocrine cells in the case of bFGF [42]. In pituitary adenomas, both are expressed in all cell types. In rats, oestrogen-induced pituitary enlargement is accompanied by increased bFGF and TGFα expression, and in the case of TGFα, this is possibly mediated by TGFα promoter oestrogen-response elements, and both bFGF and TGFα are downregulated by TGFβ. Furthermore, targeted overexpression of bFGF and TGFα to lactotrophs caused lactotroph hyperplasia, the intriguing difference being that the adenoma development occurred in TGFα-expressing females only [43].

TGFβ-related growth factors include activin, inhibin, bone morphogenetic factor and mullerian inhibitory substance and enhance cell growth and differentiation. In the pituitary, activin stimulates follicle-stimulating hormone (FSH) secretion in some gonadotroph tumours, but many tumours are unresponsive to activin suggesting a role for functional TGFβ receptor in pituitary tumours. However, although several TGFβ receptor isoforms have been detected in human pituitary tumours and TGFβ-receptor type-1 gene knockout mice demonstrate increased susceptibility to pituitary adenoma after chronic oestrogen exposure, only one mutation of uncertain pathogenetic significance was detected in 64 pituitary tumours [44].

**Matrix metalloproteinases**

Matrix metalloproteinases (MMP) comprise a family of proteins involved in angiogenesis and tissue breakdown as part of invasion and metastases. Two recent studies reported increased immunocytochemical and mRNA MMP-2 and MMP-9 expression in pituitary tumours, which correlated with angiogenesis and pituitary tumour invasiveness in one report [45, 46].

**Hormonal factors and their receptors**

Pituitary gene expression and hormone secretion are regulated by several stimulatory and inhibitory polypeptides and steroid hormones released from the hypothalamus or peripheral endocrine organs that may promote pituitary tumour development.
GHRH and somatostatin

Rare GHRH-secreting hypothalamic, bronchial or pancreatic neuroendocrine tumours that induce somatotroph hyperplasia and acromegaly have been reported, and somatotroph adenoma cells are responsive to GHRH in vitro. However, although some pituitary tumours express a truncated GHRH receptor, no abnormalities leading to constitutive GHRH-receptor activation have been identified [47].

Pituitary tumours heterogeneously express five somatostatin receptor subtypes (SSTR1–5) [48], and a heterozygote mutation in the third intracellular loop of SSTR5 was identified in a Gsp-positive GH-secreting tumour [49]. While this finding provides a potential mechanism for somatostatin resistance, which is observed clinically in 10–15% of GH-secreting pituitary tumours, somatostatin receptor mutations appear extremely rare events in pituitary tumours.

Corticotrophin-releasing hormone

Cushing’s disease is caused by an ACTH-secreting pituitary microadrenaoma in 80% of cases. Ectopic corticotrophin-releasing hormone (CRH) production from prostate carcinoma or intrasellar gangliocytoma, or continuous CRH infusion, did not lead to the development of corticotroph adenoma, suggesting that additional intrinsic corticotroph cell mutation may be necessary for the complete corticotroph adenoma phenotype [50].

Thyrotrophin-releasing hormone

Long-standing primary untreated hypothyroidism may ultimately lead to thyrotroph hyperplasia, is most common in young females and is usually reversible with thyroid hormone replacement. In some cases, the gross pituitary enlargement with chiasmal compression or associated hyperprolactinaemia may result in unnecessary pituitary surgery.

Both the α (α₁ and α₂) and the β (β₁ and β₂) thyroid hormone receptor isoforms are ubiquitously expressed in the normal pituitary [51], and alternatively spliced variants of the thyrotrophin-releasing hormone (TRH) receptor have been described, but no activating mutations have been identified in pituitary tumours.

Gonadotrophin-releasing hormone

The occurrence of gonadotroph adenomas in patients with long-standing hypogonadism is well documented, and pituitary adenomas express both
gonadotrophin-releasing hormone (GnRH) and GnRH receptors, although as in the case of the GHRH and TRH receptors, no activating GnRH receptor mutations have thus far been described in pituitary tumours [52].

**Hereditary syndromes**

Several hereditary syndromes are associated with pituitary tumours, although with the exception of Gsα mutations in McCune–Albright syndrome, the molecular events in the hereditary syndromes appear distinct from those implicated in sporadic pituitary tumours.

**Multiple endocrine neoplasia**

The autosomal dominant MEN1 syndrome, characterized by parathyroid adenomas, pancreatic islet cell tumours, is associated with pituitary adenomas in approximately 50% of patients, the majority of which are prolactinomas [90%], with GH-secreting adenomas occurring in a minority of subjects [53]. The menin protein acts as a TSG by interacting with the AP-1 transcriptional factor JunD to repress AP-1-mediated transcription [54], and germline MEN gene mutations have been detected in parathyroid tumours from almost all members of 50 MEN1 families [55] and 25% of sporadic parathyroid tumours. In contrast, although LOH in the MEN1 region is observed in sporadic pituitary tumours, menin function is preserved indicating another genetic abnormality may exist in this region [56].

**Carney complex**

Approximately 10% of patients with Carney’s syndrome, an autosomal dominant disorder associated with cutaneous pigmentation, atrial and other myxomas and male isosexual precocious puberty because of testicular tumour, develop GH-secreting pituitary tumours. ACTH-independent Cushing’s syndrome because of pigmented nodular adrenal hyperplasia also occurs. Recently, the precise molecular defect has been characterized, and mutations in the PK-A regulatory subunit (PKAR) gene located on chromosome 2p16 have been demonstrated [57].

**Mc Cune–Albright syndrome**

Endocrine overactivity (precocious puberty, Cushing’s syndrome, thyrotoxicosis or gigantism) in conjunction with polyostotic fibrous dysplasia and cutaneous hyperpigmentation characterizes the Mc Cune–Albright
syndrome. These patients harbour a germline activating mutation in codon 201 of the Gsα gene, and GH hypersecretion and PRL hypersecretion occur in 27 and 15% of patients, respectively, in association with somatotroph and/or mammosomatotroph hyperplasia or somatotroph adenoma [58].

**Familial acromegaly**

Two brothers with familial acromegaly not associated with MEN1 syndrome have been described, but as these patients were found to harbour LOH on chromosome 11q13, it has been suggested that familial acromegaly may be a phenotypic variant of the MEN1 syndrome, although MEN1 mRNA was expressed and sequencing of the coding regions of the MEN1 gene was normal in these patients.

**Nuclear receptors**

**Sex steroid receptors**

Oestrogen is a powerful stimulator of pituitary lactotroph cellular proliferation, and diffuse PRL cell hyperplasia is a ubiquitous response in the physiological setting of pregnancy and lactation, where 60–70% of adenohypophyseal cells may become immunopositive for PRL. Furthermore, high-dose unopposed oestrogen treatment has been implicated in the growth of prolactinoma in male–female trans-sexuals [59].

It appears that oestrogen replacement therapy does not initiate prolactinoma formation, but oestrogen-induced transcriptional targets include the growth factors [bFGF, VEGF, insulin-like growth factors (IGF’s), epidermal growth factor (EGF) and TGF] and oncogenic proteins (c-myc, c-fos, erb, c-myb, pttg). In addition, oestrogen receptor (ER) expression has been demonstrated in all pituitary tumour types, and as predicted, the highest ER expression is observed in the oestrogen-responsive prolactinomas, although mixed GH/PRL and gonadotroph (FSH and/or luteinizing hormone) pituitary tumours also exhibit significant ER expression. Macroadenomas, particularly prolactinomas in men, exhibit higher ER expression in comparison with microadenomas (size <1 cm), which may explain why macroprolactinomas in males tend to be more invasive, providing a rationale for ER-based therapy in some instances [60].

**Peroxisome proliferator activating and retinoic acid receptor**

There has been some recent interest in the nuclear receptors peroxisome proliferator-activating receptor-γ (PPAR-γ) and the retinoic acid receptor
(RAR) as potential therapeutic targets in pituitary ACTH-secreting and other pituitary tumour subtypes [61, 62]. While preliminary studies indicate PPAR-γ overexpression and absence of the RAR-transcriptional regulator COUP-TF1 in pituitary tumours compared with normal pituitary tissue, no role for these transcription factors in pituitary tumour pathogenesis has yet been demonstrated. It is likely that similar to other growth factors such as FGF, VEGF and steroid receptors such as ER, they primarily have a permissive role in pituitary tumour pathogenesis.

Transcription factors

Adenohypophyseal differentiation is a series of highly specific and temporally regulated events [63], governed by an increasing number of transcription factors such as pituitary homeobox factor (Ptx1), initially described as an activator of propio-melanocortin gene expression, plays a key role in brain and facial development, has been demonstrated in all normal anterior pituitary cell types and the majority of pituitary adenoma subtypes [64], with one recent study reporting reduced Ptx1 and prophet of Pit1 (Prop-1) mRNA expression in corticotroph tumours compared with other pituitary tumours.

A single study has described absent Ptx2 mRNA expression in corticotroph adenomas, with high Ptx2 expression in gonadotroph tumours. Interestingly, although Ptx2 expression was observed in pure lactotroph tumours, no expression was observed in somatotroph adenomas, suggesting a role for Ptx2 in the terminal differentiation of the somatotroph and lactotroph cell phenotype. Another factor implicated in early pituitary development is the Prop-1. Prop-1 protein is required for Pit1 gene expression, and inactivating Prop-1 mutations occur in subjects with combined pituitary hormone deficiency and in Ames dwarf mice. Similar to Ptx1 and Pit1, RT–PCR analyses have demonstrated appropriate Prop-1 expression in normal pituitary tissue and in all pituitary adenomas examined [65]. Therefore, to date, it appears that no clear specific role has emerged for transcription factors in pituitary tumour pathogenesis, and their tissue-specific pituitary expression appears to be universal and independent of hormonal regulation and tumour phenotype.

Other factors implicated in pituitary tumorigenesis

Other factors involved in proliferation, angiogenesis or metastases that have been recently studied in pituitary tumours include galectin-3, bone morphogenic protein-4 and cyclo-oxygenase-2, which have all been
demonstrated to be heterogeneously overexpressed in pituitary adenomas of different subtypes. Additionally, the expression of the growth arrest and DNA-damage inducible gene-45 (GADD-45) has been noted to be significantly lower in pituitary tumours compared with normal pituitary tissue, because of GADD-45 promoter methylation as proposed for several other TSGs [66].

References


