Growth hormone-secreting adenomas: pathology and cell biology

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The majority of patients with acromegaly harbor a functioning growth hormone (GH) pituitary adenoma. Growth hormone-secreting adenomas correspond to about 20% of all pituitary adenomas. From the histopathological point of view, a variety of adenomas may present with clinical signs and symptoms of GH hypersecretion including pure GH cell adenomas (densely and sparsely granulated GH adenomas), mixed GH and prolactin cell adenomas, and monomorphous adenomas with primitive cells able to secrete GH and prolactin including the acidophilic stem cell adenoma and the mammosomatotroph cell adenoma. In this article, the author reviews the main pathological features of the GH-secreting adenomas and some of the molecular genetics mechanisms involved in their pathogenesis. (DOI: 10.3171/2010.7.FOCUS10169)

KEY WORDS • pituitary neoplasm • acromegaly • molecular genetics • animal model

THE great majority of patients with acromegaly have a pituitary GH-secreting adenoma; ectopic GHRH or GH-secreting neuroendocrine tumors producing acromegaly represent less than 5% of the patient population.¹⁰ Growth hormone-secreting adenomas are accompanied by high serum GH and IGF-I levels and signs and symptoms of acromegaly or gigantism.¹⁰ Overall, these adenomas constitute about 20% of all pituitary adenomas.²⁷ Most patients with acromegaly have macroadenomas when first diagnosed, many of them with suprasellar expansion and parasellar invasion.²⁷ Consequently, symptoms due to an expanding tumor mass, including headaches and visual field defects, may also be present in patients with large tumors. In about 30%–50% of the patients, cosecretion of PRL with GH by the tumor results in signs and symptoms of hyperprolactinemia.^{28,47}

Pathological Features of GH-Secreting Tumors

Growth Hormone–Secreting Adenomas

Pure GH-secreting adenomas are histologically classified into the following 2 variants: the DGGH cell ad-

enoma and the SGGH cell adenoma, reflecting the variable amount of secretory granules present in the cellular cytoplasm (Fig. 1).

The DGGH cell adenomas are composed of large cells with eosinophilic cytoplasm showing considerable granularity, reflecting the great numbers of secretory granules seen at the ultrastructural level (Fig. 2). The nucleus tends to be central and oval with prominent nucleoli. Characteristically, immunohistochemical stains show strong GH positivity dispersed diffusely within the entire tumor. At the ultrastructural level, the DGGH adenomas are composed of cells that resemble the normal somatotrophs of the pituitary gland and are characterized by a well-developed rough endoplasmic reticulum network, prominent Golgi complexes, and numerous large (300–600 nm) secretory granules.²⁵

The SGGH cell adenomas contain cells more chromophobic in appearance than DGGH cell adenomas, and they have eccentric nuclei. The most distinctive feature of these adenomas is the presence of paranuclear eosinophilic structures called fibrous bodies. Immunostaining for GH is distributed focally within the tumor, and in the cell it can be in a dotlike appearance, reflecting the small amount of secretory granules seen at ultrastructure. In addition, fibrous bodies are strongly positive for cytokeratin (Fig. 3).³⁷ Fibrous bodies are characterized at the ultrastructural level by an accumulation of intermediate filaments and tubular smooth-surfaced endoplasmic reticulum (Fig. 3).²⁵

Abbreviations used in this paper: CNC = Carney complex; DGGH = densely granulated GH; FIPA = familial isolated pituitary adenoma; GH = growth hormone; GHRH = GH releasing hormone; IGF-I = insulin-like growth factor-I; LOH = loss of heterozygosity; MEN-1 = multiple endocrine neoplasia Type 1; PRL = prolactin; SGGH = sparsely granulated GH.

FIG. 1. Photomicrographs of a GH-secreting adenoma. **A:** A DGGH cell adenoma showing large cells with eosinophilic, granular cytoplasm, and a central nucleus with prominent nucleoli (H & E). **B:** The tumor shows intense and diffuse immunostaining for GH. **C:** An SGGH cell adenoma is characteristically more chromophobic with H & E staining. **D:** Immunohistochemistry for GH is heterogeneous and less prominent for SGGH cell adenomas than for DGGH cell adenomas. Original magnification $\times 200$.

The distinction of these 2 subtypes of GH cell adenomas is important since these tumors appear to have different clinical behavior. The SGGH cell adenomas exhibit more aggressive biological behavior than the DGGH cell adenomas.^{28,38,56} In a review of almost 90 patients with acromegaly who underwent follow-up at our institution, although no significant difference in cure rate and survival was present between these 2 subtypes of GH-secreting adenomas, SGGH cell adenomas were more likely to be locally invasive than DGGH cell tumors.²⁸ Obari et al.³⁸ have reported similar findings with a significantly higher incidence of suprasellar extension and cavernous sinus invasion in SGGH than DGGH cell adenomas (65% vs 38%, respectively; $p < 0.05$). Although no significant differences were seen in clinical presentation and GH or IGF-I levels, these authors reported a lower mean patient age at the diagnosis of an SGGH cell adenoma than that of a DGGH cell adenoma (43.6 ± 11.1 years vs 49.6 ± 13.8 years; $p < 0.05$).³⁸

Additionally, the response of tumors to adjuvant medical treatment appears to differ according to the sub-

FIG. 2. A DGGH cell adenoma. The ultrastructure exhibits well-developed organelles and abundant large secretory granules. Original magnification $\times 2500$ (**A**) and $\times 5000$ (**B**).

FIG. 3. An SGGH cell adenoma. **A:** The ultrastructure of SGGH cells display sparse neurosecretory granules and the typical fibrous bodies (arrow). **B:** Cytokeratin immunostaining highlights fibrous bodies typically seen in these sparsely granulated tumors. Original magnification $\times 2500$ (**A**) and $\times 200$ (**B**).

type of GH cell adenoma.⁷ Tumor subtyping (DGGH) was the strongest predictor of IGF-I normalization in patients with acromegaly receiving postoperative somatostatin analog therapy.

A number of GH-secreting adenomas display secondary immunoreactivity for other pituitary hormones that do not necessarily show clinical or biochemical evidence of hormonal hypersecretion.^{28,46} Secondary immunoreactivity is mostly seen for PRL and for the glycoprotein hormone α -subunit; less frequently, immunoreactivity is seen for β -follicle-stimulating hormone, β -luteinizing hormone, and β -thyroid-stimulating hormone. Apart from the well-characterized mixed GH/PRL-secreting adenomas (see below), plurihormonal differentiation is not clinically symptomatic in the majority of cases.

Mixed GH/PRL-Secreting Adenomas

A large percentage of GH-secreting adenomas also secrete PRL. About half of the patients with surgically removed GH-secreting adenomas in our institution presented with signs and symptoms of acromegaly and hyperprolactinemia.²⁸

Three morphological tumor types that cosecrete GH and PRL can be identified as follows: the mixed GH cell/PRL cell adenoma, the mammosomatotroph cell adenoma, and the acidophilic stem cell adenoma.^{12,24,26,28,31} Mixed GH cell/PRL cell adenomas and mammosomatotroph cell adenomas present clinically with acromegaly and mild hyperprolactinemia; on the other hand, patients with acidophilic stem cell adenoma present with hyperprolactinemia and only rarely with acromegaly. In our experience, these mixed tumors behave more aggressively than any pure GH-secreting adenomas with a lower surgical cure rate.²⁸

Mixed GH Cell/PRL Cell Adenoma. These adenomas morphologically resemble GH-secreting adenomas, but immunohistochemistry is demonstrated for both GH and PRL with varying degrees of staining and distribution. The 2 cell types may form small groups or they may be scattered. At the ultrastructural level, these adenomas are bimorphous tumors, consisting of 2 separate cell populations, DGGH or SGGH cells and PRL cells (Fig. 4).^{12,31}

Mammosomatotroph Cell Adenoma. This rare GH/PRL-producing tumor accounts for less than 2% of all

FIG. 4. Mixed GH/PRL cell adenoma. Ultrastructure of a mixed GH cell/PRL cell-secreting adenoma showing bimorphous cell population with densely granulated GH cells and PRL cells. Original magnification $\times 2500$.

pituitary adenomas and about 8% of tumors associated with acromegaly.²⁴ Histologically, the adenomas are acidophilic on H & E staining, and immunohistochemical analysis demonstrates the presence of GH and PRL in the cytoplasm of the same tumor cells. These findings have been confirmed by double-labeling studies and by immunoelectron microscopy.²⁴ At the ultrastructural level, a monomorphous cell population contains features of GH and PRL cells.²⁵ The cells are mostly similar to DGGH cells, but with irregular secretory granules of variable sizes (200–2000 nm). Granular extrusions and extracellular deposits of secretory material, features consistent with PRL cell differentiation, are characteristically present.

Acidophilic Stem Cell Adenoma. This subtype of mixed adenoma is very rare and represents only the minority of GH/PRL-producing tumors.^{28,44} Unlike the 2 subtypes previously discussed, most of the patients present with symptoms of hyperprolactinemia; acromegaly is uncommon.²⁶ The majority of the tumors are rapidly growing macroadenomas with invasive features, a distinct behavior pattern of ordinary prolactinomas; therefore, the diagnosis of such adenomas is of clinical relevance. Histologically, acidophilic stem cell adenomas are chromophobic with focal oncocyctic changes of the cytoplasm. Immunoreactivity for PRL and, to a lesser extent, GH is present in the cytoplasm of the same tumor cells. Electron microscopy is necessary for precise identification of this adenoma.^{25,26} They are composed of a single population of immature cells exhibiting features reminiscent of both SGGH cells and PRL cells. Oncocyctic change with the presence giant mitochondria is characteristic of these adenomas.

Growth Hormone–Secreting Pituitary Carcinomas

Pituitary carcinomas are very rare, comprising less than 1% of all pituitary neoplasms.^{32,41,45} By definition, pituitary carcinomas are characterized by the presence of either craniospinal dissemination or systemic metastases.⁴⁵

The great majority of reported pituitary carcinomas are hormonally active tumors with endocrine manifestations indistinguishable from those of pituitary adenomas. The most common endocrine syndromes are adrenocorticotrophic hormone–secreting tumors with Cushing disease (42%) and PRL-secreting tumors presenting with hyperprolactinemia (33%).⁴⁵ Carcinomas associated with acromegaly or gigantism represent only about 6% of the reported cases.⁴²

The diagnosis of pituitary carcinoma is dependent on the demonstration of metastatic spread.⁴⁵ There are no morphological criteria to distinguish locally aggressive or even markedly atypical adenomas from carcinomas when the tumor is confined to the sella. However, all reported GH carcinomas have presented as highly invasive tumors at the initial presentation.⁴¹

Medical Treatment and GH-Secreting Adenomas

Medical therapy is part of the multistep treatment of acromegaly.³⁵ Three classes of drugs are mostly available for the treatment of acromegaly including dopamine agonists, somatostatin receptor ligands, and a GH receptor antagonist.³⁵ These drugs may change the morphology of GH-secreting adenomas. Unlike the dramatic effects of dopamine agonists seen in prolactinomas, significant reduction in cell size is uncommonly seen in the GH tumors treated with dopamine agonists and somatostatin receptor ligands. Most frequent changes are characterized by variable degree of perivascular and interstitial fibrosis.^{21,50} An increase in size of the secretory granules and the presence of larger and heterogeneous lysosomes with take-up of secretory granules (crinophagy) are seen at the ultrastructural level and are believed to be due inhibition of hormone release.

Pathological effects of the GH receptor antagonist in GH-secreting adenomas are not very well known. This drug does not have a direct antitumor effect. One case report of a GH-secreting adenoma with comparison of pre- and post-treatment effects reported insignificant changes in morphological features.¹⁶ However, these authors have shown that proliferative markers (Ki 67 and topoisomerase- α) were markedly greater in the pegvisomant-exposed tumor than in the earlier specimen. However, there has not been substantiated confirmation of these findings.

Molecular Genetics of GH-secreting Tumors

Pituitary adenomas appear to result from a multistep and multicausal process in which hereditary genetic disposition, endocrine factors, and specific somatic mutations may serve as contributing factors. Adenomas are mostly monoclonal expansions as demonstrated by X-chromosomal inactivation analysis.¹¹ The great majority of adenomas arise in a sporadic manner, and only a minority of adenomas are part of hereditary or familial syndromes.¹⁴

Familial syndromes in which GH-secreting adenomas arise include the following: 1) MEN-1, linked to somatic mutations of the tumor suppressor gene *MEN-1* located at the 11q13 locus;⁸ 2) CNC, linked to mutations of the tumor suppressor gene *PRKARIA* located at 17q22-24,⁴⁹ and less commonly 3) McCune-Albright syndrome,

linked to activating mutation of the *gsp* oncogene located at 20q13⁵⁵ (see below). Growth hormone–secreting adenomas linked to either MEN-1 or CNC are believed to correspond to about 3% of all GH-secreting tumors.⁹

In addition, a small number of familial pituitary GH-secreting adenomas have been described in the absence of either MEN-1 or CNC. The so-called isolated familial somatotropinoma or FIPA is defined as a clinical syndrome characterized by more than 2 cases of acromegaly or gigantism in a family in the absence of MEN-1 or CNC.⁵³ FIPAs are believed to correspond to about 1% of all GH-secreting adenomas.⁹ In several groups of the FIPAs, an association with LOH at the 11q13 locus unrelated to the *MEN-1* gene has been demonstrated.⁵ Recently, a germline mutation of the aryl hydrocarbon receptor–interacting protein (*AIP*) gene has been reported in a set of Finnish and Italian families with pituitary adenoma predisposition.⁵⁴ The *AIP* gene is located at 11q13, the same region as the *MEN1* gene. Tumor samples from affected individuals showed LOH at the *AIP* locus, suggesting that *AIP* acts as a tumor suppressor gene. In the remaining FIPAs there has not been yet characterization of a single genetic alteration. In the overall group, however, there is a description of mutations of the *AIP* gene in about 15% of families.¹³ Thus far, 3 sites of mutations of the *AIP* gene have been identified in this group of familial somatotrofinomas.³⁹ Mutations of the *AIP* gene were also found in a small number of patients with sporadic pituitary adenomas, mostly GH-secreting tumors.³⁹

The majority of GH-secreting adenomas are, how-

ever, sporadic tumors in which the primary genetic defect remains unknown. A number of oncogenes and tumor suppressor genes have been recognized as potential participants in tumorigenesis of pituitary adenomas including GH-secreting adenomas.¹⁷ As previously discussed, in patients with MEN-1, LOH of 11q13 is present in pituitary adenomas and in other lesions commonly seen in the syndrome, including parathyroid hyperplasia and tumors of the endocrine pancreas.⁸ However, the *MEN-1* gene has not been proven to be a major player in sporadic GH-secreting adenomas.⁴

The most commonly found genetic alteration in sporadic GH-secreting adenomas is the activating mutation of the *gsp* gene.^{29,30,52} The *gsp* oncogene mutation corresponds to a point mutation of the α -subunit of the stimulatory G-protein (GNAS), a stimulatory protein of adenylyl cyclase at the membrane level.^{29,30,33} The GNAS protein is coupled to the GHRH receptor, a G protein–coupled receptor located at the cell membrane of somatotrophs, that mediates GH transcription by inducing cyclic adenosine monophosphate via a cyclic adenosine monophosphate response element-binding protein (CREB). The mutated GNAS protein inhibits GTPase activity, maintaining the adenylyl cyclase system in a continuously turned-on state, therefore mimicking the effects of GHRH on hormone signaling. The *gsp* gene mutation has been identified in about 40% of GH-secreting adenomas in Caucasians and in lower frequency in Asians.^{33,48} Recently, *gsp* gene mutation has been reported in about 10% of tumors of patients with sporadic acromegaly in Brazil.⁵¹

TABLE 1: Genetic alterations implicated in GH-secreting adenomas

Alteration	Associated Disorder
Gene	Inherited or Familial Tumor
<i>Menin</i> (11q13)	MEN-1
<i>PRKR1A</i> (17q22-24)	CNC
<i>gsp</i> (20q13.3)	McCune-Albright syndrome
<i>AIP</i> (11q13)	FIPA
	Sporadic Tumor
<i>gsp</i> (20q13.3)	mostly in DGGH cell adenomas (10%–40% of cases)
<i>CREB</i> (2q32.3-q34)	cAMP response element-binding protein, transcription factor, constitutive phosphorylation†
Oncogene/Tumor Suppressor Gene	Result
<i>PTTG</i> (5q22)*	pituitary tumor–transforming protein, securin protein, overexpression‡
<i>GADD45G</i> (9q22.1-q22.2)*	growth arrest & DNA damage–inducible 45y, proapoptotic factor, epigenetic silencing§
<i>ODC1</i> (2p25)*	ornithine decarboxylase-1, overexpression¶
<i>BAG1</i> (9p12)*	Bcl-2-associated athanogene, overexpression**
<i>CDKN2C</i> (1p32)*	cyclin-dependent kinase inhibitor 2C (p18), underexpression**
<i>WIF1</i> (12)*	Wnt inhibitory factor-1, underexpression††

* Genetic alterations not specific to GH-secreting adenomas.

† According to Bertherat et al.

‡ According to Pei and Melmed.

§ According to Zhang et al.

¶ According to Evans et al.

** According to Morris et al.

†† According to Elston et al.

TABLE 2: Animal models for GH-secreting adenomas in the literature*

Authors & Year	Gene	Model	Pituitary Lesion
Asa et al., 1992, & Mayo et al., 1988	<i>GHRH</i>	transgenic	mammotroph hyperplasia & adenoma
Fedele et al., 2002	<i>HMGA2</i>	transgenic	mixed GH/PRL adenoma
Fedele et al., 2005	<i>HMGA1</i>	transgenic	mixed GH/PRL adenoma
Abbud et al., 2005	<i>αGSU.PTTG</i>	transgenic	plurihormonal hyperplasia & occasional microadenoma (including GH)
Donangelo et al., 2006	<i>αGSU.PTTGxRb +/-</i>	bitransgenic	plurihormonal hyperplasia, higher incidence of adenomas (including GH), & intermediate lobe ACTH tumors
Egashira et al., 2008	<i>Prop1</i>	transgenic	GH, PRL, TSH, &/or gonadotrophin-adenomas

* ACTH = adrenocorticotrophic hormone; TSH = thyroid stimulating hormone.

The presence of *gsp* mutation in a GH cell adenoma does not appear to correlate with patient's age, sex, tumor size, or circulating GH levels.⁴⁸ However, patients appear to have higher circulating levels of α -subunit of glycoproteins. Moreover, *gsp*-mutated adenomas have better response to somatostatin analogs drugs. Growth hormone-secreting tumors with *gsp* mutations, although indistinct from tumors without *gsp* mutations from a morphological point of view, are typically DGGH cell adenomas.⁴⁸

Unlike DGGH cell adenomas that most likely exhibit the *gsp* gene mutation as mentioned previously, SGGH cell adenomas have been demonstrated by some as having preferentially a somatic histidine-to-leucine substitution in codon 49 of the extracellular domain of the GH receptor.² This genetic dissimilarity may explain the low response of SGGH cell adenomas to somatostatin analog drugs.²

The *gsp* oncogene mutation is very rare in other pituitary tumor subtypes, occurring in only 10% of clinically nonfunctioning pituitary adenomas and in 5% of corticotroph adenomas.⁴⁸ As mentioned previously, activating mutation of *gsp* represents the basis of the McCune-Albright syndrome, which is characterized by somatotroph hyperplasia and polyostotic fibrous dysplasia of the bones.⁵⁵

Since mutational events are rare in GH-secreting adenomas, the identification of other candidate genes of significance in the adenoma tumorigenesis has been intensively explored. Several studies have used microarray-based, high-throughput gene profiling for identification of candidate genes and pituitary-specific signaling pathways that may be participate in pituitary tumorigenesis, including studies analyzing GH-secreting adenomas.^{19,20,36,43} Except for genes linked to adenoma subtype, including *GH* and *GHRH-R*,^{36,43} the majority of identified genes with potential tumorigenic effect are not unique to GH-secreting adenomas and seem to contribute to the pathogenesis of most adenomas (Table 1).

Animal Models for GH-Secreting Pituitary Tumorigenesis

Several animal models have been developed for the understanding of pituitary tumorigenesis by overexpressing oncogenes or knocking out tumor suppressor genes known to play a role in human disease. However, these animal models do not completely recapitulate pituitary human tumorigenesis because animal tumor formation is frequently preceded by hyperplasia, an unlikely event in

human pituitary tumor formation. Animal models resulting in GH-secreting adenomas have been well characterized since the late 1980s, particularly with the description of the transgenic mouse for human GHRH³⁴ that, under extended exposure to GHRH, leads to mammotroph hyperplasia and adenoma formation.³ Table 2 shows some of the current animal models that develop GH hyperplasia and/or tumors.

Disclosure

The author reports no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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