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Pituitary adenomas in man and mouse: oncogenic potential of a truncated fibroblast growth factor receptor 4

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Commentary

Despite their prevalence and significant morbidity, the etiology of most pituitary adenomas remains an enigma. Hypotheses that regard the growth factor milieu as a primary cause of pituitary oncogenesis have seesawed with others that maintain the primacy of cell-autonomous transforming events. Like other endocrine glands, the pituitary has a remarkable capacity to respond to physiological demands by either hyperplasia or hypoplasia of specific cell types. These reversible changes, mediated by a diverse set of signaling molecules and their corresponding receptors, could set the stage for pathological overgrowth of clonal cell populations within this tissue. Particular interest has settled on members of the fibroblast growth factor (FGF) family as tumorigenic factors. However, very few bona fide molecular pathogenic mechanisms of pituitary adenoma development and progression have stood the tests of time, causality, and replication in independent clinical populations (Table 1). The first such mechanism was reported in the landmark studies by Vallar and colleagues of activating mutations in the G protein α–stimulating activity polypeptide, which led to the constitutive elevation of adenylyl cyclase activity in pituitary somatotrophs (1, 2). Associated with 4–40% of somatotroph adenomas, identical mosaic mutations are responsible for Leydig cell hypersecretion or tumors and fibrous dysplasia of bone in the McCune-Albright syndrome. Inactivating mutations, on the other hand, produce the endocrine abnormalities of psuedohypoparathyroidism type 1A. A second […]

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Despite their prevalence and significant morbidity, the etiology of most pituitary adenomas remains an enigma. Hypotheses that regard the growth factor milieu as a primary cause of pituitary oncogenesis have seesawed with others that maintain the primacy of cell-autonomous transforming events. Like other endocrine glands, the pituitary has a remarkable capacity to respond to physiological demands by either hyperplasia or hypoplasia of specific cell types. These reversible changes, mediated by a diverse set of signaling molecules and their corresponding receptors, could set the stage for pathological overgrowth of clonal cell populations within this tissue. Particular interest has settled on members of the fibroblast growth factor (FGF) family as tumorigenic factors. However, very few bona fide molecular pathogenic mechanisms of pituitary adenoma development and progression have stood the tests of time, causality, and replication in independent clinical populations (Table 1).

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It is on this background that the report in this issue of the *JCI* by Ezzat, Asa, and their colleagues stands out (7). Previous work from the same laboratory identified the expression in 40% of a random series of human pituitary adenomas of a form of the FGF receptor 4 (FGFR4) mRNA encoding a novel, receptor-related protein (8). Normal pituitary tissue, in contrast, apparently expresses only a smaller, secreted form of FGFR4. Here, these authors demonstrate that the tumor-associated receptor isoform is translated in-frame from an mRNA species and is transcribed from a site in exon 5, apparently under control of some cryptic promoter in intron 4 of the gene (7). Because the N-terminus of this so-called ptd-FGFR4 lacks a signal peptide, the protein is not inserted into the plasma membrane but resides in a cytoplasmic compartment, where it is constitutively phosphorylated on tyrosine residues. Ezzat et al. show here that the expression of a cDNA for the truncated receptor in transgenic mice consistently results in lactotroph pituitary tumors. The authors also developed transgenic mice expressing a wild-type hFGFR4 driven by the same lactotroph-specific *Prolactin* promoter, providing them a particularly

Table 1
Putative pituitary oncogenes and tumor suppressor genes

Gene and locus	Mutation	Pituitary tumor	Nonpituitary	OMIM[A]
GNAS1, 20q13.2	Activating; missense	Somatotroph,corticotroph (rare)	Thyroid, Leydig cells, bone, skin	139320
MEN1, 11q13	Inactivating; nonsense, missense, deletion	Lactotroph, somatotroph, corticotroph	Parathyroid, pancreatic islet	131100
PTTG1, 5q33	High expression; unknown basis	All secretory and nonsecretory types	Multiple carcinomas	604147
FGFR4, 5q35.1-qter	Activating; alternative transcriptional initiation	All secretory and nonsecretory types	Unknown	134935

[A]Online Mendelian Inheritance in Man reference number (12).

well matched control for certain experiments. The full-length receptor, they find, is incapable of inducing pituitary adenomas, despite a comparable pattern of expression.

These experiments demonstrate that targeted expression of a putative oncogene in transgenic mice can recapitulate pituitary adenoma formation. No comparable experiment has been reported for pituitary expression of an activating mutant *GNAS1* allele whose transgenic expression in thyroid follicular cells leads to hyperplasia and adenomas (9). However, in a recently developed mouse model of *Men1* inactivation (10), heterozygous mice are subject to loss of heterozygosity and develop prolactinomas and other endocrine tumors, much like MEN1 patients.

Many additional questions remain to be answered concerning the involvement of ptd-FGFR4 in the pathogenesis of pituitary tumors. Where is the cryptic promoter and what regulates the switch in promoter utilization? Which Tyr residues are phosphorylated and what is the pattern of phosphorylated downstream signaling molecules? Is there an intersection of signaling mechanisms from other tumor models that might reveal a common final pathway in pituitary adenoma development?

One clue may be found in a recent study implicating menin in the growth-inhibitory action of TGF-β by an interaction with the Smad3 transcription factor (11). Accumulating evidence suggests that the control of pituitary cell growth hinges on a balance between FGF-mediated stimulation and TGF-β inhibition. The study by Ezzat et al. (7) now convincingly demonstrates that dysregulation of the stimulatory arm of this balance, based on a novel receptor isoform initially identified in human tumors, is sufficient to induce pituitary adenomas in a mouse model. Future studies will clarify the extent to which this mechanism generalizes to other pituitary adenomas and should reveal whether expression of ptd-FGFR4 is truly the initiating event in adenoma development or is secondary to some other somatic mutation.

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