CHAPTER 7

Activin, TGF-β and Menin in Pituitary Tumorigenesis

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Abstract

Pituitary adenomas are common monoclonal neoplasms accounting for approximately one-fifth of primary intracranial tumors. Prolactin-secreting pituitary adenomas (prolactinomas) are the most common form of pituitary tumors in humans. They are associated with excessive release of the hormone prolactin and increased tumor growth, giving rise to severe endocrine disorders and serious clinical concerns for the patients. Recent studies indicated that the activin/TGF-β family of growth factors plays a prominent role in regulating pituitary tumor growth and prolactin secretion from anterior pituitary lactotrope cells. Furthermore, these studies highlighted the tumor suppressor menin and the protein Smads as central regulators of these biological processes in the pituitary. Alterations in the activin/TGF-β downstream signaling pathways are critical steps towards tumor formation and progression. This chapter will review the role and intracellular molecular mechanisms of action by which activin, TGF-β, Smads and menin act in concert to prevent pituitary tumor cell growth and control hormonal synthesis by the anterior pituitary.

Introduction

The pituitary gland is the primary site of the synthesis, storage and release of hormones that play a predominant role within the entire human body and thus careful regulation of these hormonal levels is essential to maintain homeostasis. Pituitary tumors account for 15% to 20% of clinically diagnosed intracranial tumors. Although considered as histologically benign, pituitary tumors can cause significant morbidity, because of the excessive pituitary hormonal secretion, critical location and expanding size. Despite a critical improvement in recent technologies such as imaging and surgical endoscopy, the removal of pituitary tumors largely depends on the expertise of the surgeon. The most common type of pituitary adenomas are prolactinomas, tumors of the anterior pituitary prolactin-secreting lactotrope cells. Patients with prolactinomas usually present amenorrhea, have infertility issues associated with galactorrhea in females and impotence in males infertility. Prolactinomas often develop sporadically as a monoclonal proliferation but the molecular mechanisms underlying the formation of these tumors remain largely unknown. Besides surgical removal of the tumor, medical therapy for prolactinomas are effective in many cases but usually necessitates long-term treatment with dopamine agonists to normalize prolactin levels. Recent work from our laboratory shed light on the mechanisms by which activin and TGF-β regulate prolactin levels and cell growth arrest in lactotrope cells, through the Smad pathway and the tumor suppressor menin. Such understanding of the signaling pathways that regulate pituitary

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hormonal production and cell growth may prove helpful to open new avenues for future therapies to combat human pituitary adenomas.

**Genetics of Pituitary Adenomas: Role of MEN1 Mutations**

Genetic alterations play an important role in the genesis and progression of pituitary adenomas. These alterations mainly occur in genes coding for tumor suppressors, oncogenes and transcription factors. The initiating event in pituitary adenoma development is primarily due to mutation in the stimulatory guanine nucleotide-binding protein (gsp) and MEN1 genes. The progression event in pituitary adenomas occurs later in the development of the tumors and usually result from mutations in p53, ras, retinoblastoma, metastasis suppressor nm23 and c-myc genes.5

Mutations in the gsp and MEN1 genes are critical to the initiation of pituitary tumors. Gsp is an oncogene that leads to increased cAMP production, GH hypersecretion and cell cycle progression.7,9 The tumor suppressor gene MEN1 is associated with MEN-1 syndrome and characterized by the occurrence of anterior pituitary, parathyroid and pancreatic islet tumors.10 Even though MEN1 gene mutation is usually associated with familial pituitary tumors,10 mutation in the MEN1 gene have also been detected in sporadic pituitary tumors.11,12 These include as 28% of ACTH secreting adenomas,13 20% of the nonfunctional adenomas,13 15-30% of somatotroph adenomas13,14 and 12-14% of prolactinomas.13,15 Loss of heterozygosity (LOH) at the menin locus was also reported in anterior pituitary tumors.16,17 The familial syndrome MEN1 behaves as an autosomal dominant trait with reduced penetrance. Germ-line mutation on chromosome 11q13 that encodes the tumor suppressor menin, is unmasked by a second somatic hit on the remaining allele. The human MEN1 syndrome phenotype is well reflected by the MEN1 heterozygous transgenic mice model which develops tumors with LOH of the wild type chromosome, including 26% of these within the pituitary by the age of 16 months.18 Somatic mutations of the MEN1 gene are not significantly causative in the tumorigenesis of non-MEN1-linked sporadic pituitary adenomas.19,20 Indeed, out of 35 sporadic pituitary adenomas of various secretory phenotypes used in one study, Poncin et al found that only one tumor out of the cohort was homozygote for a mutation in the close proximity of the MEN1 gene promoter.20 A more recent study, performed in a series of tissue samples from 68 sporadic non-MEN1 pituitary tumor patients further confirmed this and found only one case to show detectable menin expression, as measured by immunohistochemistry and immunofluorescence.21 As mentioned above, pituitary disease is significantly more frequent in familial MEN1 cases than in the sporadic form of the disease.12 The prevalence of pituitary adenomas is around 40% in multiple endocrine neoplasia Type I patients, with prolactinomas being the most common type.22,23 In a large study, Verges et al compared the characteristics of pituitary disease developed in 324 MEN1 patients with those of 110 non-MEN1 patients with pituitary adenomas, matched for age, year of diagnosis and clinical follow-up.23 Forty-two percent of the MEN1 patients developed pituitary tumors and interestingly, pituitary disease among the familial MEN1 cases was found to be more frequent than in the sporadic MEN1 cases (59% vs 34% respectively). Furthermore, pituitary adenomas were significantly larger and more aggressive in MEN1 cases compared to patients without MEN1. Indeed, 85% of these MEN1-related prolactinomas developed macro adenomas and one fifth was invasive.23 Therapies based on the use of dopamine agonists for these more aggressive MEN1-related prolactinomas showed little or poor response.23,24 All types of mutation were observed, including frameshifts, nonsenses, missenses, germ-line MEN1 encompassing large deletion, strongly suggesting the absence of any phenotype-genotype correlation.

Together, these studies indicate that the MEN1 gene plays a critical role in the initiation event of familial pituitary adenomas, particularly prolactinomas and potentially in some sporadic ACTH-producing tumors, nonfunctional adenomas, somatotroph adenomas and prolactinomas. Despite the significant recent progress obtained in understanding the genetic basis of the pathogenesis of pituitary adenomas, these studies also highlight the need for further and better understanding of the role of MEN1 mutations in the initiation of pituitary tumors.