Molecular Pathology of Sporadic Pituitary Tumors

Pituitary tumors are mostly benign monoclonal adenomas that are either hormonally functional or nonfunctional. They are usually sporadic, but some families with an autosomal dominant mode of inheritance have been identified [7,12]. Activating mutations have been described in a subset of growth hormone (GH)–secreting adenomas, which harbor mutations in the α-subunit of the Gs protein. Amino acid substitutions at either Arg-201 or Gln-227 result in constitutive activation of the Gs α-subunit by inhibition of intrinsic GTPase activity. These findings led to the proposal that the α gene is converted into an oncogene, gsp, in cells which proliferate in response to cAMP [11,17].

In contrast to other tissues, an interesting feature of pituitary tumors is the rare occurrence of pathologically confirmed carcinoma. The lack of progression from adenoma to carcinoma is intriguing and may possibly help elucidate mechanisms of pituitary neoplasia. The definition of pituitary carcinoma depends on the demonstration of cerebrospinal or extracranial metastases, and not on histological criteria. The majority of reported pituitary carcinomas are nonsecretory, and less than 5% are prolactin-secreting [14]. Tumors exhibiting cerebrospinal metastases due to invasion and dissemination via the subarachnoid space are most often nonfunctional. In contrast, tumors associated with extracranial metastases usually produce ACTH, and the liver appears to be the preferred site of metastatic spread [15]. There are currently no reliable histological or biochemical markers for pituitary carcinoma. Although pituitary carcinomas may represent a component of the biological spectrum of pituitary tumors arising from the transformation of a benign tumor, it is possible that they may arise de novo.

Although transgenic models of pituitary adenoma formation secondary to overexpression of hypothalamic hormones exist, several additional lines of evidence suggest that hypothalamic factors alone are unlikely to be sufficient to initiate the multistep process of tumor formation but may be permissive for tumorigenesis [1]. Evidence for intrinsic somatic genetic mutations in pituitary adenomas, invasive adenomas, or carcinomas are presented in an attempt to dissect the mechanisms of pituitary tumorigenesis and to determine whether carcinomas represent a distinct entity or one end of a biological spectrum.

Genetic changes that contribute to tumor formation include altered gene function, altered gene expression, or loss of genes. Utilizing the candidate gene approach, many investigators have randomly screened pituitary adenomas for mutations of dominantly acting oncogenes, including *H-ras*, *N-ras*, *c-fos*, *c-myc*, *SEA*, *PDGFβ*, *HSTF1*, and *BCL1* [2]. A single point mutation in codon 12 of *H-ras* in one highly invasive prolactinoma was identified, suggesting that *ras* mutations are not prevalent in pituitary adenomas [9]. Twenty-five years ago, De Mars proposed that gene carriers for familial cancers were heterozygous for a recessive mutation and that reduction to the homozygous state resulted in cancer. Subsequently, Knudson's 2-hit tumorigenesis hypothesis emerged resulting from his analysis of the age-specific incidence of familial and sporadic retinoblastomas. These predictions were confirmed at the molecular level for the development of retinoblastoma. The retinoblastoma gene is a prototype of a class of genes termed *tumor suppressors*, the presence of which is required in normal cells to prevent the emergence of a tumor [10,18]. The gene for MEN-1, an inherited predisposition to pancreatic, parathyroid, and pituitary neoplasms, was mapped to chromosome 11q13. Deletions on chromosome 11q13 were observed in 5 of 13 sporadic GH cell pituitary adenoma tissues, suggesting that inactivation of a tumor suppressor gene, possibly at the MEN1 locus at 11q13, is an important event in the formation of pituitary adenomas [16]. Loss of 11p as well as loss of heterozygosity (LOH) at the PGYM

locus in 1 of 7 sporadic prolactinomas and LOH at 11q13 in 2 of 3 sporadic prolactinomas has also been reported [3,6].

Recent studies [8] showed the development of pituitary tumors in 5 of 20 mice heterozygous for an Rb mutation, as well as in 4 chimeric animals derived from heterozygous embryonic stem cells. Because these tumors occurred in the adenohypophyseal pars intermedia and also stained for POMC, we decided to target the Rb gene in human pituitary tumors, which, however, do not contain a well-defined intermediate pituitary lobe. Rb heterozygosity also predisposes to osteosarcoma, lung, breast, prostate, and bladder carcinomas [4,19].

Mutation of one of the Rb alleles was detected in 1 invasive silent corticotroph adenoma and in 4 pituitary carcinomas, compared with intact Rb alleles present in benign pituitary adenomas and in normal lymphocytes [13]. The Rb gene product functions to constrain growth of normal cells, and mutation of an Rb allele appears to be associated with a loss of function mutation, allowing unrestrained neoplastic cell growth [5].

Although the p53 gene is the most frequently mutated tumor suppressor gene in human cancer, no mutations were observed in 22 nonsecretory and 22 GH adenomas, 1 invasive adenoma, or in 4 carcinomas [6,13]. Mutations in p53 are usually closely linked to exogenous tumorigenic factors. Lack of p53 mutations may be explained by the fact that mutations fail to provide a growth advantage or the presence of an active multidrug resistance gene in the pituitary, which clears toxins.

Examination of pituitary metastatic tissue from 3 ACTH and 1 prolactin-cell carcinoma revealed the presence of mutations in codons 12, 13, and 18 of *H-ras* in 3 of 4 extrapituitary metastatic deposits. Mutations at codons 12 and 13 are known to convert *ras* into an active oncogene, although the significance of the codon 18 mutation is currently unclear [13]. *Ras* mutations may not be essential in primary pituitary tumor formation but may have a role in initiating or sustaining their metastases, or both. In vivo, *ras* activation is an early event, suggesting that other factors are required for pituitary metastasis. Mutation of 1 allele of Rb was also detected in all the pituitary carcinoma metastases utilizing a sensitive polymerase chain reaction technique [20]. In summary, these data indicate that allelic loss of Rb represents a genetic mutation occurring in invasive adenomas and carcinomas, whereas *ras* mutations appear to occur as a late event in the pituitary tumor and are associated with pituitary metastases.

Although survival varies, the average survival time for pituitary carcinoma from onset of symptoms is 4 years. Several lines of evidence suggest that sporadic pituitary tumors (adenomas versus invasive adenomas/carcinomas) may encompass 2 distinct biological entities, each arising de novo. In the majority of reported cases, metastatic disease and therefore the diagnosis of pituitary carcinoma was only established post mortem. Thus, patients with invasive pituitary adenomas may harbor clinically silent metastases, and because treatment of metastatic disease does not appear to alter their prognosis, the presence of nonfunctioning metastases in invasive adenomas is probably under-reported. Therefore, pituitary carcinoma may be more prevalent than appreciated. In contrast, control of hypersecretion by hormonally active invasive adenomas is warranted for treatment of metastatic disease. The long and relatively benign natural history of adenomas and the relative paucity of identified oncogenic mutations in adenomas further suggest distinct mechanisms for these 2 tumor types. Availability of serial operative samples from aggressive tumors will allow the sequence of mutational events to be determined, which should help elucidate the pathogenesis of pituitary tumors. These insights will facilitate diagnosis, prognosis, and management of patients with pituitary tumors, and suggest that hormonal manipulation of patients with aggressive tumors may not be sufficient to produce a cure.

Diane Prager
Shlomo Melmed

References

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