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Review

Genetic and epigenetic mutations of tumor suppressive genes in sporadic pituitary adenoma

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ABSTRACT

Human pituitary adenomas are the most common intracranial neoplasms. Approximately 5% of them are familial adenomas. Patients with familial tumors carry germline mutations in predisposition genes, including *AIP*, *MEN1* and *PRKAR1A*. These mutations are extremely rare in sporadic pituitary adenomas, which therefore are caused by different mechanisms. Multiple tumor suppressive genes linked to sporadic tumors have been identified. Their inactivation is caused by epigenetic mechanisms, mainly promoter hypermethylation, and can be placed into two groups based on their functional interaction with tumor suppressors RB or p53. The RB group includes *CDKN2A*, *CDKN2B*, *CDKN2C*, *RB1*, *BMP4*, *CDH1*, *CDH13*, *GADD45B* and *GADD45G*; *AIP* and *MEN1* genes also belong to this group. The p53 group includes *MEG3*, *MGMT*, *PLAGL1*, *RASSF1*, *RASSF3* and *SOCS1*. We propose that the tumor suppression function of these genes is mainly mediated by the RB and p53 pathways. We also discuss possible tumor suppression mechanisms for individual genes.

Contents

Abbreviations: AHR, aryl hydrocarbon receptor; AIP, aryl hydrocarbon receptor interacting protein; BMP-4, bone morphogenetic protein 4; CDK, cyclin-dependent kinases; CDKN1A, cyclin-dependent kinase inhibitor 1A; CDKN1B, cyclin-dependent kinase inhibitor 1B; CDKN2A, cyclin-dependent kinase inhibitor 2A; CDKN2B, cyclin-dependent kinase inhibitor 2B; CDKN2C, cyclin-dependent kinase inhibitor 2C; CDH1, cadherin 1, type 1, E-cadherin (epithelial); CDH13, cadherin 13, H-cadherin (heart); CNC, Carney complex; DNMT1, DNA methlytransferase 1; DNMT3A, DNA (cytosine-5-)-methyltransferase 3 alpha; DNMT3B, DNA (cytosine-5-)-methyltransferase 3 beta; DNMT3L, DNA (cytosine-5-)-methyltransferase 3-like; EMT, epithelial–mesenchymal transition; ESRP1, epithelial splicing regulatory protein 1; FPA, familial pituitary adenoma; FIPA, familial isolated pituitary adenoma; GADD45B, growth arrest and DNA-damage-inducible, beta; GADD45G, growth arrest and DNA-damage-inducible, gamma; GNAS, guanine nucleotide-binding protein G(s) subunit alpha; HDAC3, histone deacetylase 3; MEG3, maternal expression gene 3; MEN1, multiple endocrine neoplasia type I; MGMT, O-6-methylguanine-DNA methyltransferase; MLL, myeloid/lymphoid or mixed-lineage leukemia protein 1; NFA, clinically non-functioning pituitary adenoma; PLAGL1, pleiomorphic adenoma gene-like 1; PRKAR1A, protein kinase, cAMP-dependent, regulatory, type I, alpha; RASSF1, Ras association (RalGDS/AF-6) domain family member 1; RASSF3, Ras association (RalGDS/AF-6) domain family member 3; SOCS1, suppressor of cytokine signaling 1; TCDD, 2,3,7,8-tetrachloro-*p*-dioxin.

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1. Introduction

Human pituitary adenomas are the most common intracranial tumors, typically arising from hormone secreting cells in the anterior pituitary (Ezzat et al., 2004). Tumors secreting excess pituitary hormones and causing characteristic phenotypic syndromes in patients are classified as clinically functioning adenomas, and include growth hormone (GH) secreting, prolactin (PRL) secreting, adrenocorticotropin (ACTH) secreting and thyrotropin (TSH) secreting tumors. Rarely, tumors producing gonadotropins, luteining hormone (LH) and follicle stimulating hormone (FSH), can cause clinical symptoms of gonadotropin excess. Tumors which do not lead to clinical symptoms are known as clinically non-functioning adenomas (NFAs). NFAs are derived from all types of anterior pituitary hormone secreting cells, but most commonly from gonadotroph cells (Chaidarun and Klibanski, 2002). NFAs can grow very large in size and can cause mass effect resulting in hypopituitarism, headache, vision impairment, and neurologic dysfunction in patients. Despite recent advances in understanding the pathogenesis of these tumors, the underlying cause of the majority of pituitary tumors remains elusive.

Studies have demonstrated that genetic and epigenetic mutations play a determining role in the development of human neoplasms (Peltomaki, 2012). Normal cells contain an intrinsic tumor suppression mechanism which consists of multiple pathways maintaining normal cell homeostasis (Lowe et al., 2004). These tumor suppression pathways regulate many checkpoints which dictate the fate of cells in response to genotoxic, metabolic and other stress stimuli. Cells with excessive damage are prevented from further proliferation by induction of permanent arrest, such as cellular senescence, or programmed death, such as apoptosis. Each tumor suppression pathway is composed of multiple components forming a regulatory cascade. For normal cells to become tumorous, these tumor suppression barriers have to be circumvented by mutation of one or more pathway components (Hanahan and Weinberg, 2013).

The first evidence indicating that pituitary tumors may be caused by somatic mutations, genetic or epigenetic, came from early tumor clonality studies. We investigated X-chromosome inactivation patterns in NFAs from female patients by analyzing restriction fragment length polymorphisms and methylation status of the *phosphoglycerate kinase* (*PGK*) and *hypoxanthine phosphoribosyltransferase* (*HPRT*) genes (Alexander et al., 1990). We found that individual NFAs contain only one type of X-inactivation, paternal, or, maternal, never both. This observation was confirmed by other independent studies (Herman et al., 1990; Jacoby et al., 1990). In addition, similar results were also found in ACTH- secreting adenomas (Biller et al., 1992; Gicquel et al., 1992, 1994; Herman et al., 1990; Zahedi et al., 2001), GH-secreting adenomas (Herman et al., 1990; Jacoby et al., 1990), and prolactinomas (Herman et al., 1990; Jacoby et al., 1990; Ma et al., 2002). These data indicate that human pituitary adenomas are monoclonal in origin suggesting that individual tumors are derived from single cells driven by a somatic gene mutation or mutations.

The second line of evidence came from studies of patients with presumed germ-line mutations in familial pituitary adenomas (FPAs), including multiple endocrine neoplasia type I (MEN1), Carney complex (CNC) and familial isolated pituitary adenoma (FIPA). Patients with these conditions carry germline mutations, and pituitary tumors from these patients display loss of heterozygosity (LOH) in the affected locus. For example, genetic linkage analyses indicate that the genetic defect causing MEN1 is located on chromosome 11q13 (Larsson et al., 1988). Subsequently, the germline mutations in the *multiple endocrine neoplasia type I* (*MEN1*) gene were identified from this region. Similarly the germline mutation in *cAMP-dependent protein kinase type I-alpha regulatory subunit* (*PRKAR1A*) was identified in CNC patients (Kirschner et al., 2000) and *aryl hydrocarbon receptor interacting protein* (*AIP*) in FIPA patients (Vierimaa et al., 2006). In addition, germline mutations in *cyclin-dependent kinase inhibitor 1B* (*CDKN1B*) were identified in patients with an MEN1-like syndrome, but without a *MEN1* gene mutation (Pellegata et al., 2006).

Genetic mutations clearly contribute to the development of FPAs. However, FPA accounts for only ~5% of all pituitary tumors. The genetic mutations identified in FPAs do not play a significant role in the pathogenesis of sporadic tumors. Thus far, *GNAS*, encoding the stimulatory guanine nucleotide-binding protein ($G\alpha_s$) (Landis et al., 1989; Lyons et al., 1990), is the only gene confirmed which is linked to a subset (~40%) of GH-secreting adenomas (Freda et al., 2007), suggesting that novel somatic DNA mutations, if any, have yet to be identified in vast majority of sporadic tumors. Interestingly, no difference has been found in clinical characteristics, hormone levels or response to therapy in patients with tumors with or without $G\alpha_s$ mutations.

In recent years, emerging evidence indicates that epigenetic modifications are the major alternative force altering the expression of genes involved in neoplastic development (Dawson and Kouzarides, 2012; You and Jones, 2012), including pituitary tumorigenesis (Tateno et al., 2010). Epigenetic changes include aberrant DNA methylation and histone modification (Jaenisch and Bird, 2003; Peltomaki, 2012). Importantly, DNA methylation has been observed to be the main cause for gene inactivation in pituitary tumors (Yacqub-Usman et al., 2012b). DNA methylation involves DNA methlytransferases (DNMTs), which transfer a methyl group from *S*-adenosylmethionine to the 5-position of cytosine residues in DNA. Four major DNMTs have been identified so far: DNMT1, DNMT3A, DNMT3B and DNMT3L. DNMT3A and DNMT3B specifically recognize unmethylated DNA and establish *de novo* methylation patterns (Okano et al., 1999, 1998). DNMT3L does not possess enzyme activity, but functions as a co-factor to stimulate activities of DNMT3A and DNMT3B (Suetake et al., 2004). DNMT1 is universally expressed and responsible for methylation maintenance during DNA replication and repair (Leonhardt et al., 1992; Mortusewicz et al., 2005). Among the three enzymatically active DNMTs, only DNMT3B has been shown to be up regulated in human pituitary tumors by a histone modification mechanism (Zhu et al., 2008). Although DNMT3B was suggested as a putative mediator of epigenetic control in pituitary adenomas (Zhu et al., 2008), it remains to be determined whether it is responsible for gene silencing in these tumors. Over the years, a number of genes have been found to be inactivated in pituitary tumors by genetic or epigenetic mechanisms (Table 1). They are functionally linked to the two most important tumor suppressors, RB and p53. In this review we will discuss recent progress on these tumor suppressive genes involved in the development of human pituitary adenomas.

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