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Review

Genetics and epigenetics of adrenocortical tumors

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ABSTRACT

Adrenocortical tumors are common neoplasms. Most are benign, nonfunctional and clinically irrelevant. However, adrenocortical carcinoma is a rare disease with a dismal prognosis and no effective treatment apart from surgical resection. The molecular genetics of adrenocortical tumors remain poorly understood. For decades, molecular studies relied on a small number of samples and were directed to candidate-genes. This approach, based on the elucidation of the genetics of rare genetic syndromes in which adrenocortical tumors are a manifestation, has led to the discovery of major dysfunctional molecular pathways in adrenocortical tumors, such as the IGF pathway, the Wnt pathway and *TP53*. However, with the advent of high-throughput methodologies and the organization of international consortiums to obtain a larger number of samples and high-quality clinical data, this paradigm is rapidly changing. In the last decade, genome-wide expression profile studies, microRNA profiling and methylation profiling allowed the identification of subgroups of tumors with distinct genetic markers, molecular pathways activation patterns and clinical behavior. As a consequence, molecular classification of tumors has proven to be superior to traditional histological and clinical methods in prognosis prediction. In addition, this knowledge has also allowed the proposal of molecular-targeted approaches to provide better treatment options for advanced disease. This review aims to summarize the most relevant data on the rapidly evolving field of genetics of adrenal disorders.

Contents

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1. Introduction

Adrenocortical tumors (ACT) are common neoplasms, the prevalence of which increases with age, reaching a peak of 6% after 60 years. Most are benign cortical adenomas (ACA) and some are associated with endocrine syndromes (hypercortisolism in Cushing's syndrome, hyperandrogenism in virilizing syndrome or mineralocorticoid excess in Conn's syndrome) (Grumbach et al., 2003; Arnaldi and Boscaro, 2012). On the other hand, their malignant counterparts, adrenocortical carcinomas (ACC), are rare neoplasms with an incidence of 0.5–2/million per year (Fassnacht and Allolio, 2009). ACC is usually a very aggressive disease, with a dismal prognosis, with a 5-year survival rate of 16–44% (Fassnacht and Allolio, 2009). Surgical resection is the treatment of choice and the only therapeutic approach that significantly increases survival. Once ACC is not completely resectable, the available therapeutic options (which include the adrenolytic drug mitotane, systemic chemotherapy, radiation therapy, and, more recently, molecular-targeted therapies) have a small impact on survival (Fassnacht and Allolio, 2009). The differential diagnosis between ACA and localized ACC can be challenging, considering that clinical, laboratory, radiological, and pathological features can overlap to some extent. The accurate distinction between ACA and ACC is very important, since treatment is radically different (Fassnacht and Allolio, 2009). In recent years, considerable advances toward understanding the pathogenesis of ACT have been made. Different strategies have enabled these achievements:

1. Identification of genetic alterations in rare familial syndromes and evaluation of whether the same defects are present in sporadic tumors.
2. Investigation of signaling pathways that were proved important in other tumors types.
3. Employment of high-throughput techniques such as genome wide expression profiling, methylation profiling and microRNA profiling to interrogate novel signaling pathways.
4. Studies with animal models with one or more genetic defects in known signaling pathways.

Here we discuss the most relevant genetic aspects of ACTs. This review summarizes our current understanding of molecular pathogenesis of ACTs.

2. Genetics of adrenocortical tumors

2.1. Lessons from rare genetic syndromes

ACTs, both benign (ACA) and malignant (ACC), may occur sporadically or in the setting of a heritable genetic syndrome. ACTs and adrenocortical hyperplasias are commonly a feature of multiple neoplasia syndromes (Table 1). The elucidation of the genetic basis of these syndromes has contributed to the identification of key signaling pathways that are dysregulated in sporadic ACTs. Clinical and molecular aspects of these genetic syndromes and their relationship to sporadic ACTs will be briefly discussed below.

2.2. Genetic aspects of benign adrenocortical disease

The incidence of adrenal incidentalomas has been increasing and now approaches the 8.7% in autopsy series and 4% in radiology series (Bovio et al., 2006; Singh and Buch, 2008; Arnaldi and Boscaro, 2012). Approximately 80% of the adrenocortical tumors are non functional, the remaining 20% are cortisol producing tumors and aldosteronomas (Arnaldi and Boscaro, 2012). Cortisol-producing adrenocortical adenomas (CPAs) are usually sporadic, constituting the most frequent cause of endogenous ACTH-independent Cushing's syndrome. Rarely, ACTH-independent cortisol overproduction is observed in the setting of a rare genetic syndrome, such as McCune–Albright syndrome (MAS), primary pigmented nodular adrenocortical disease (PPNAD), which may be isolated or associated with Carney complex, isolated micronodular adrenocortical disease (i-MAD) and ACTH-independent macronodular adrenal hyperplasia (AIMAH) (Stratakis, 2008). Considerable advances toward understanding the pathogenesis of such lesions have been made in the last two decades. A common feature of all these syndromes is the abnormal activation of protein kinase A (PKA) signaling pathway (Fig. 1). PKA is a serine/threonine kinase which is the main mediator of cAMP signaling in mammals (de Joussineau et al., 2012). Various physiological ligands can activate PKA-induced phosphorylation, which affects cell metabolism, proliferation, differentiation and apoptosis. In the adrenal cortex, the PKA pathway is activated when ACTH binds to the MC2R receptor, a G protein-coupled receptor, causing activation of the Gs-alpha subunit, which generates cyclic AMP (cAMP) from ATP (de Joussineau et al., 2012). The PKA holoenzyme is a tetramer composed by four distinct elements: two catalytic and two regulatory subunits. In the inactivated state, the regulatory subunits inhibit the kinase activity of the catalytic subunits. Upon activation of the pathway, cAMP binds to specific domains at the regulatory subunits, dissociating the tetramer and releasing the catalytic subunits, which will phosphorylate different intracellular targets, including the transcription factor CREB, which is translocated to the nucleus, activating the transcription of cAMP-responsive element-containing genes (Pearce et al., 2010). After the stimulus finishes, cAMP is inactivated by phosphodiesterases and the PKA tetramer is assembled again, returning to its original, inactivated state (de Joussineau et al., 2012). Abnormal activation of PKA pathway may be caused by mutations in different genes of the signaling cascade, as will be discussed below. In addition to PKA, MC2R signaling also activates ERK-MAPK pathway, which induces cell proliferation at the *zona fasciculata* (Gallo-Payet and Payet, 2003; Roy et al., 2011). The role of abnormal ERK-MAPK pathway activation in adrenocortical disease, however, is not clearly understood.