Genetics of Adrenocortical Development and Tumors

Maya Lodish, MD, MHSc

KEYWORDS

• Adrenal development • Adrenocortical carcinoma • Ontogenesis • Zonation • Signaling • Pathway • Genetic • Driver mutation

KEY POINTS

- Current understanding of normal adrenocortical development sheds light on the molecular pathways that, when altered, may stimulate abnormal proliferation and drive adrenocortical tumor formation.
- Knowledge obtained from inherited syndromes that are characterized by adrenocortical tumors and next-generation sequencing of adrenocortical tumors have helped find causative mutations for these lesions.
- Recent studies have identified cyclic AMP-dependent protein kinase A (PKA) signaling as a key mediator of cortisol secretion by the normal adrenal cortex. It therefore follows that mutations in genes that involve dysregulated cAMP/PKA pathway components are implicated in adrenocortical pathology.
- ARMC5 is a recently discovered gene that is associated with bilateral macronodular adrenocortical hyperplasia.

INTRODUCTION

This article links the understanding of the developmental physiology of the adrenal cortex to adrenocortical tumor formation. Many molecular mechanisms that lead to the formation of adrenocortical tumors have been discovered via next-generation sequencing approaches. The most frequently mutated genes in adrenocortical tumors are also factors in normal adrenal development and homeostasis, including those that alter the p53 and Wnt/β-catenin pathways. In addition, dysregulated protein kinase A (PKA) signaling and *ARMC5* mutations have been identified as key mediators of

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Pediatric Endocrinology Fellowship, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Building 10, Room 9D42, 10 Center Drive, MSC 1830, Bethesda, MD 20892-1830, USA
E-mail address: lodishma@mail.nih.gov

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adrenocortical tumorigenesis. The growing understanding of the genetic changes that orchestrate adrenocortical development and disease pave the way for potential targeted treatment strategies.

Adrenocortical carcinoma (ACC) has a bimodal age distribution with a peak in early childhood with a mean age of diagnosis at 3.2 years, and a peak in adulthood in the fourth and fifth decades.[1,2] ACC has an annual incidence of 0.7 to 2 per million.[3,4] The understanding of the pathophysiology of ACC is limited, and the disease carries a poor prognosis.[5] Recent identification of genetic characteristics of ACC may lead to the development of novel therapeutic interventions. Several genes have been implicated as tumor drivers in sporadic ACC, including mutations in insulin-like growth factor 2 (*IGF2*), β-catenin (*CTNNB1* or *ZNRF3*), and *TP53*.[6,7] Importantly, germline variants of some of the same genes identified to be drivers of sporadic ACC are also associated with familial tumor syndromes characterized by ACC, including Beckwith-Wiedemann syndrome (BWS), familial adenomatous polyposis (FAP), and Li-Fraumeni syndrome.

Elevated cAMP signaling is related to most benign cortisol-producing tumors of the adrenal gland. The first human disease that directly linked cAMP signaling to cortisol-producing lesions was with the discovery more than 25 years ago that activating mutations in GNAS1 caused adrenocortical tumors in infants with McCune-Albright syndrome (MAS). Mutations in the regulatory subunit type 1 α (R1α) of the cAMP-dependent protein kinase or PKA were then identified as the cause of another form of cortisol-producing hyperplasia, primary pigmented nodular adrenocortical disease (PPNAD). Inactivating mutations in inhibitors of the cAMP-signaling pathway (phosphodiesterases [PDEs]) were later identified as another cause of adrenocortical hyperplasia. Most recently, somatic activating mutations in the main catalytic subunit of PKA have been discovered in cortisol-producing adenomas. Put together, these findings provide convincing proof that increased cAMP signaling is key to adrenal tumor development. The implications of this finding lead to the search for targeted treatment strategies for adrenal tumors and hypercortisolism that act on the cAMP/PKA cascade.

A novel gene was recently identified that provides evidence that bilateral macronodular adrenal hyperplasia is frequently a genetic disorder. Germline mutations in the tumor suppressor gene *ARMC-5* lead to the development of an autosomal dominantly inherited form of Cushing syndrome (CS). Because this type of CS may present in a cyclical manner that may take many years to diagnose, the potential to identify individuals at risk for the development of CS based on genetic findings has the potential to lead to more timely diagnosis of CS. Recent advances in the understanding of adrenocortical signaling have taught that cortisol secretion within the adrenal gland is more complex than previously thought. It is now known that paracrine signaling via intra-adrenal secretion of corticotrophin is a factor in adrenal hyperplasia.

OVERVIEW OF ADRENOCORTICAL DEVELOPMENT

The adrenal cortex derives from components of the urogenital ridge, sharing a common origin with the kidney and gonads.[8] The human adult adrenal cortex is separated into three distinct zones that may be characterized by their functionality and histology. The outermost layer, the zona glomerulosa, secretes aldosterone; the middle zona fasiculata secretes glucocorticoids; and the innermost zona reticularis produces sex steroid hormone precursors androstenedione and dehydroepiandrosterone (**Fig. 1**).

Adrenocortical cell precursors originate from the coelomic epithelium that, together with the gonadal cell precursors, forms the adrenogonadal primordium. The