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The molecular genetics of adrenocortical carcinoma

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1 Introduction

Adrenocortical carcinoma (ACC) is a rare endocrine malignancy defined by a heterogeneous clinical presentation, dismal prognosis, and lack of effective therapeutic regimens. The incidence of ACC ranges from 0.5 to 2 cases per million people per year, accounting for 0.02% of all reported cancers [1]. Unfortunately, most patients present with metastatic disease which reduces the 5 year survival rate to less than 10% [2]. The resultant limited clinical experience has hampered significant research interest, public awareness and overall support from a limited pool of funding agencies. This review aims to summarize emerging genetic and molecular events implicated in the pathogenesis of ACC that can serve to energize current and future efforts to provide effective diagnostic and therapeutic approaches to this deadly cancer.

2 Epidemiology and clinical management

Adrenal neoplasms are routinely uncovered during medical imaging studies (e.g. abdominal CT scans) performed for other health concerns. Post-mortem studies reveal that approximately 3–9% of autopsy cases of patients over 50 years old [3, 4] harbor adrenocortical neoplasms. In the vast majority of cases, these 'incidentalomas' are benign adenomas rather than the rare and deadly ACC. Physicians encountering such tumors in patients must always be wary of the potential but unlikely scenario of ACC, particularly when confronting a necrotic or hemorrhagic lesion or a mass with irregular borders or signs of invasion. While size is considered a reliable predictor of malignancy (greater than 5–6 cm^3 considered an high risk of malignancy), even small lesions presumed benign are routinely followed by CT or MRI, as adrenocortical carcinomas less than 5 cm^3 have already metastasized in ~14% of cases [5].

ACC has been characterized as having a bimodal age distribution with an increased incidence in the first and fifth decades of life [6]. In addition, ACC is slightly more common in women [7]. The vast majority of pediatric ACCs are uncovered by signs and symptoms of hormone excess stemming from the steroidogenic activity of the tumor—the most common symptom being virilization secondary to androgen hypersecretion [7]. Although ACC in children may manifest in the context of a familial cancer syndrome (such as Li-Fraumeni or Beckwith-Wiedemann syndromes discussed below), the majority of pediatric ACCs, and nearly all adult cases, arise sporadically [8].

The prognosis for ACC is largely dependent on the grade of tumor and stage of diagnosis, with the most dismal scenario held for those presenting with distant metastases. Pediatric patients generally have a favorable prognosis due to the early detection because of symptoms associated with the functional status of their tumors. Unfortunately, the majority of adult ACCs are hormonally silent [7], making early diagnosis extremely uncommon. Most adult ACC patients present incidentally or with constitutional symptoms secondary to abdominal mass effects [9].

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Surgical resection is the treatment of choice for patients with resectable primary and even metastatic lesions. Additionally, adjuvant mitotane [1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl) ethane] treatment, following radical ACC resection, may prolong recurrence-free survival by 17 to 32 months [10]. Although only a limited number of small therapeutic trials have been initiated for ACC, the International Consensus Conference on Adrenal Cancer, held at the University of Michigan in 2003 formally endorsed two "best practice" regimens for advanced disease [11]. The EDP schedule, etoposide, doxorubicin, cisplatin plus mitotane boasts a response rate of approximately 50% with a median survival time of 2 years [12]. Alternatively, a regimen of streptozotocin plus mitotane has induced response rates of approximately 35% with a median survival of 16 months [13]. Current efforts include an evaluation of these regimens head-to-head in an international randomized control trial (FIRM-ACT.ORG) and investigations by a number of groups into the molecular genetics of the disease in search of unique signaling defects that can be exploited in a targeted therapeutic approach.

3 Genes implicated in ACC pathogenesis

In comparison to other more prevalent cancers, very little is known about the genetic defects contributing to sporadic ACC. While many investigators hypothesize that benign adrenal tumors rarely, if ever, progress to ACC, no rigorous studies have examined whether a dysplasia–adenoma–carcinoma sequence (first shown in colorectal cancer and confirmed in several of other cancers) [14, 15] occurs in the adrenal cortex. However, insights into the pathogenesis of sporadic ACC have been gained from studying inherited cancer syndromes that include ACC—as both diseases appear to manifest similar molecular profiles (see Table 1) [16, 17]. Although not discussed in this review, a growing body of work has also characterized several genes implicated in the adrenocortical hyperplasias and adenomas including *CYP21* (Congenital adrenal hyperplasia), *PRKAR1A* (Carney complex and primary pigmented nodular adrenal dysplasia), *Menin* (Multiple endocrine neoplasia type 1), and *GNAS1* (McCune-Albright syndrome) [8, 18, 19].

3.1 p53 and Li-Fraumeni syndrome

The *p53* gene, located on the 17p13.1 chromosomal segment, encodes the 393 amino acid tumor suppressor protein situated in the center of a network of signaling pathways that are essential for cell growth regulation and apoptosis induced by a diverse array of cellular stresses. In normal unstressed cells, the level of p53 protein is tightly regulated through binding of proteins such as MDM2 that promote p53 degradation via the ubiquitin/proteasome pathway. After sensing genotoxic or non-genotoxic stress, p53 protein levels increase by inhibition of its interactions with negative regulators and concomitant p53 activation by several kinases and acetylases. This results in p53-dependent transactivation of a large series of genes that

Table 1 Molecular and clinical aspects of genetic syndromes associated with adrenocortical neoplasms

Familial syndrome	Adrenal adenoma (ACA) or carcinoma (ACC)	Gene and chromosomal location	Protein name	Major clinical features	Mendelian inheritance of man (number)
Li-Fraumeni	ACC	*TP53* (17q13.1)	p53	Soft tissue sarcoma, breast cancer, brain tumors, osteosarcoma, leukemia	151623
Beckwith-Wiedemann	ACC	Epigenetic dysfunction of locus (11p15.5)	Associated with IGF-II, $P57^{kip2}$, H19 mRNA	Macrosomia, macroglossia, abdominal wall defects, ear anomalies, renal abnormalities, cleft palate	130650
Gardner	ACA (rare ACC)	*APC* (5q21–22)	APC	Colorectal cancer and extracolonic tumors	175100
Carney Complex	ACA	*PRKAR1A* (17q23–24) Others? (2p16)	PRKAR1A	Cardiac and cutanous myxomas, testicular and pituitary tumors, PPNAD (primary pigmented nodular hyperplasia)	160980 605244
Multiple Endocrine Neoplasia Type 1	ACA (rare ACC)	*MEN1* (11q13)	Menin	Parathyroid, pituitary, pancreatic, and adrenal adenomas	131100
McCune-Albright	ACA	*GNAS 1* (20q13)	G_s alpha subunit	Precocious puberty, café-au-lait spots, polyostotic fibrous dysplasia	174800

trigger DNA repair mechanisms, sustain cell cycle arrest in G1/S phase, and initiate growth arrest or apoptosis if DNA damage is not repaired [20].

It is no surprise that p53's guardian function, which protects against unbridled proliferation, is bypassed in the vast majority of human cancers by direct and indirect inactivating mutations. Individuals carrying germline *p53* mutations develop cancers early in life, with carriers afflicted with tumors originating from multiple tissues in an autosomal dominant fashion. Tumor suppressor genes, such as *p53*, generally must have alterations in both alleles to cause a loss of function. Loss of heterozygosity (LOH), where a deletion or other mutational event within the remaining normal allele renders the cell homozygous for the deleterious allele, has been demonstrated in ACC at the 17p13.1 locus [21, 22]. In fact, LOH at this locus has been reported to occur in 85% of carcinomas and 0% of adenomas, suggesting a possible marker for malignancy [22]. Referred to as Li-Fraumeni syndrome (LFS), tumors resulting from germ-line loss of p53 include breast cancer, soft tissue sarcomas, brain tumors, osteosarcoma, leukemia, and adrenocortical carcinoma [23]. The LFS mutations in *p53* are most commonly located in exons 5 to 8 containing the highly conserved DNA binding domain of *p53* [24]. It is not surprising therefore that the most frequently inherited p53 mutations associated with LFS are also found in sporadic cases of ACC [25].

Two mutations in *p53* that are implicated in LFS and result in an increased incidence of ACC are noteworthy. One of the most common p53 point mutants, Arg 175 to His, fails to bind DNA and therefore results in complete loss of p53 transcriptional activity. While this mutation manifests with a classic LFS cancer spectrum including ACC, it actually accounts for 6% of the missense mutations identified in all human cancers [26]. On the contrary, in the southern region of Brazil where the rate of pediatric ACC is 10–15 times greater than worldwide incidence [27], virtually all patients have an identical germ-line point mutation of p53 encoding an Arg 337 to His amino acid substitution in exon 10 [28]. This particular mutation led to ACC development with a paucity of the other tumor types seen in LFS. This R337H polymorphism leads to a destabilization of p53 tetramerization in a pH-dependent manner, providing a mechanism for loss of p53 transcriptional activity and adrenocortical-specific tumor formation [29]. From a therapeutic standpoint, *in vivo* restoration of a lost tumor suppressor such as p53 has been a long sought after goal. Recent research has shown restoration of endogenous p53 expression led to a prompt and impressive tumor regression of established *in situ* mouse tumors [30–32]. Thus, renewing efforts to use pharmacological reactivation of p53 must be explored further as a potential therapeutic target for human cancers like ACC.

3.2 IGF-II and Beckwith-Wiedemann syndrome

The insulin-like growth factor (IGF) system is well characterized for its contribution to normal and pathological adrenocortical growth. The IGF pathway is comprised of two receptors (IGF1R and IGF2R) with their respective ligands (IGF-I and IGF-II) and six IGF binding proteins (IGFBP1-6). Following binding of either ligand, the IGF1R efficiently engages the cell to proliferate, differentiate, and survive. IGF1R is a receptor tyrosine kinase composed of two heterodimeric chains with intrinsic tyrosine kinase activity that is responsible for mediating IGF ligand (both IGF-I and IGF-II) dependent intracellular action. Transduction of signals through IGF1R leads to multiple intracellular phosphorylation events and the activation of several signaling pathways. The two predominant effectors for this are the PI3K/Akt and MAPK pathways [33]. Several cancer models have validated IGF1R significance in cancer progression and recent value as a therapeutic target [34]. IGF2R is a single pass membrane protein, lacking intrinsic signaling activity, which acts as a negative regulator of IGF activity by sequestration, endocytosis and degradation of only the IGF-II ligand [35]. The liver produces IGF-I primarily as an anabolic endocrine hormone in response to growth hormone stimulation. IGF-II acts predominantly during fetal life, as gene expression profiling demonstrates a >25-fold higher expression of IGF-II in human fetal adrenal in comparison to in adult adrenal tissue [36]. In addition, serum IGF-II levels have been shown to significantly decline after human birth and is a poor stimulant of whole body growth in mice [37].

Beckwith-Wiedemann syndrome (BWS) is a familial syndrome resulting in macrosomia, macroglossia, abdominal wall defects, ear anomalies, renal abnormalities, cleft palate and an increased incidence of childhood tumors including ACC [38, 39]. This disease is the result of a defect in genomic imprinting of the 11p15.5 chromosomal region which contains several genes including *IGF-II*, *CDKN1C* (cyclin-dependent kinase inhibitor $p57^{kip2}$) and *H19* (an untranslated mRNA). $p57^{kip2}$ is an embryonic cyclin-dependant kinase inhibitor that acts to negatively regulate cell proliferation and actively direct differentiation. *H19* gene encodes a 2.3-kb non-coding mRNA which is also strongly expressed during embryogenesis at levels comparable to β-actin. Genomic imprinting is a normal embryonic/fetal process which involves methylation of DNA regions leading to stable patterns of transcriptional gene activation or silencing. Within this locus, *IGF-II* is normally expressed from the paternal allele due to imprinting of the maternal copy, while *CDKN1C* and *H19* are paternally imprinted and maternally expressed [18]. Individuals with BWS often have uniparental paternal isodisomy (a form of LOH)—loss of the maternal locus

with an accompanying gain of the paternal allele. Less frequently, there is a loss of imprinting (LOI) phenomenon leading to excessive transcriptional activation of the paternal allele [40]. Regardless of mechanism, the overall result is marked overexpression of IGF2 with concomitant decrease in $p57^{kip2}$ and H19 expression.

Sporatic ACCs also have striking overexpression of the *IGF-II* gene, with several studies showing >100-fold higher expression levels in 60–90% of carcinomas in comparison to adenomas and normal adrenal tissue [16, 22, 41]. Interestingly, 11p15 LOH has a higher prognostic value than IGF-II overexpression in this cohort suggesting the *CDKN1C* and *H19* genes are important contributors to sporadic ACC pathogenesis [22]. Transgenic mouse studies support these observations. Postnatal overexpression of IGF-II in mice results in significant adrenocortical hyperplasia but not ACC suggesting that it alone is not sufficient for tumorigenesis [42]. Mice with targeted deletion of $p57^{kip2}$ exhibit a BWS-like overgrowth phenotype adrenocortical hyperplasia, while overexpression results in embryonic lethality, indicating its role as a tumor suppressor and a potent regulator of embryonic growth [43, 44]. Targeted *H19* deletion in mice led to an increase in IGF-II levels and an overgrowth phenotype consistent with a role in regulating IGF-II expression [45]. Collectively, these studies support a major role of increased IGF-II in the etiology of ACC but also suggest that concomitant changes in expression of the other imprinted genes of the 11p15.5 locus (decrease in $p57^{kip2}$ and H19) are likely key contributors to ACC development.

4 Future prospects

The recent arrival of high throughput gene expression profiling utilizing DNA microarrays has revolutionized the cataloging of the human genome. Initial microarray studies commencing just 5 years ago have already assigned distinct molecular signatures to subgroups of adrenal adenomas versus carcinomas [16, 17, 46–48]. All of these studies confirmed that subsets of genes, whether over- or underexpressed in adrenocortical tumors, can discriminate between benign and malignant tumors, with IGF-II displaying the highest expression level in the vast majority of carcinomas. In a recent study, de Fraipont and colleagues studied a larger cohort of tumor samples that allowed for a correlation of gene expression with patient outcome. This powerful report demonstrated a cluster of 22 genes (including IGF-II, other growth factors and coordinate receptors) can predict a higher probability of metastatic recurrence over a period of 24 months [46]. To utilize these data sets and/or generate larger ACC cohorts with diagnostic or prognostic utility requires national and international collaboration. Cooperative efforts such as the European Network for the Study of Adrenal Tumors (http://www.ensat.org) and the International Adrenal Cancer Symposium: Clinical and Basic Science (http://www.med.umich.edu/intmed/endocrinology/acs.htm) are predicted to make major strides in these areas and facilitate rational drug design for this disease.

For example, a growing body of evidence indicates that a distinct subpopulation of cells within a tumor causes disease relapse and metastasis. These cells, termed ‘cancer stem cells’ are uniquely endowed with the ability to self-renew and differentiate into multiple different cells types, akin to normal tissue stem cells. The cancer stem cell hypothesis has already been validated in blood, breast, brain, colon, pancreatic cancers and the list is expanding. While cancer stem cells are predicted to be the only cells within the bulk tumor that can give rise to new tumor cells, they are also predicted to be the only cells that are not responsive to standard chemotherapeutic protocols. This paradigm challenges current dogma on cancer therapeutics that all tumor cells possess equal malignant potential. Instead, drug discovery is challenged to shift towards targeting this tumorigenic subpopulation of cancer stem cells for potential cure [49]. A myriad of questions arise from applying this new perspective of oncology to adrenocortical carcinoma. Are there adrenal cancer stem cells? Can they be isolated from human ACC samples like other cancers? Can therapeutics target these cells and lead to relapse-free survival?

Numerous studies in several model organisms indicate the presence of undifferentiated multipotent adrenocortical cells [50]. Further characterization and isolation of these adult adrenocortical stem cells will be necessary to implicate a stem cell origin of ACC and to determine whether ACC stem cells share similar characteristics and regulatory mechanisms that control stem cell properties such as pluripotency and self-renewal. Interestingly, a few molecular and genetic studies have implicated Wnt signaling pathway activation in ACCs [51, 52]. The canonical Wnt pathway describes a conserved signaling mechanism critical in stem cell biology, embryogenesis, and cancer. Secreted Wnt glycoproteins bind to cell-surface Frizzled receptors, ultimately resulting in nuclear translocation of β-catenin and target gene transcription. Regulation of β-catenin is akin to p53. Unstimulated conditions result in continual degradation via the APC destruction complex [53]. Gardner’s syndrome is a genetic disorder characterized by the presence of multiple polyps in the colon and ACC in rare instances [54]. Gardner’s syndrome is caused by inactivating mutations in the *APC* gene located in chromosome 5q21, suggesting increased β-catenin levels may play a role in ACC formation. We and others have demonstrated β-catenin potently activates adrenal specific

transcription of genes critical in tissue development and homeostasis [55, 56]. Further investigations are necessary to elucidate the contributions of developmental signaling pathways like Wnt (and others including Notch and Sonic hedgehog) may play in the normal adrenocortical growth and adrenal tumorigenesis.

5 Conclusions

ACC remains a difficult disease to treat despite recent advances elucidating several mutations that contribute to the dysregulated adrenocortical growth in the disease. Transgenic mouse models that validate the importance of these molecular defects are active areas of investigation that will facilitate preclinical testing of novel therapeutic strategies and targeted chemotherapeutics. The need for larger multi-institutional registries and international clinical trials is paramount and will assure a more rapid and unified pursuit of these goals.

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