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Review

Genetics and genomics of childhood adrenocortical tumors

Abeer El Wakil[a,b], Mabrouka Doghman[a,b], Perle Latre De Late[a,b], Gerard P. Zambetti[c], Bonald C. Figueiredo[d], Enzo Lalli[a,b,*]

[a] Institut de Pharmacologie Moléculaire et Cellulaire, CNRS UMR 6097, France
[b] Université de Nice - Sophia Antipolis, Valbonne, France
[c] Department of Biochemistry, St. Jude Children's Research Hospital, Memphis, TN, USA
[d] Instituto de Pesquisa Pelé Pequeno Principe and Faculdades Pequeno Principe, Curitiba PR, Brazil

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ABSTRACT

Adrenocortical tumors in children are usually diagnosed because of signs of virilization and their prognosis is poor. They possess several distinct pathological features compared to adrenocortical tumors in adults and have an exceptional prevalence in southern Brazil, where they are nearly invariably linked to the presence of a germline specific *TP53* (R337H) mutation. Other important factors in childhood adrenocortical tumor pathogenesis are overexpression of the Steroidogenic Factor-1 transcription factor and imprinting defects in the 11p15 genomic region, causing overexpression of Insulin-like Growth Factor-2. Genomic studies have revealed the prognostic relevance of the expression of some Major Histocompatibility Complex genes and the deregulation of the Insulin-like Growth Factor/mammalian Target Of Rapamycin pathway by microRNAs in these tumors. Our hope is that these findings will constitute the basis for the development of novel therapies that will be more active against these tumors and less toxic for the patients.

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Contents

1. Introduction

Starting just after birth, a profound remodeling process pervades the human fetal adrenal. Cells of the outer definitive zone proliferate and differentiate to form the glomerulosa, fasciculata and reticularis zones of the adult cortex, while the inner androgenic steroid-secreting fetal zone regresses progressively by apoptosis (Mesiano and Jaffe, 1997). Childhood adrenocortical tumors (ACT) are thought to be originated by abnormal persistence and/or defective apoptosis of the fetal adrenal because of their early postnatal age distribution, their pattern of hormone secretion and their molecular phenotype (Wilkin et al., 2000; Michalkiewicz et al., 2004). According to the published studies taking into analysis the highest numbers of patients (Liou and Kay, 2000; Wieneke et al., 2003; Michalkiewicz et al., 2004), the median age at diagnosis is around 3 years or earlier (considering the usual diagnosis delay reported by these and other authors), with a predominance of

Abbreviations: ACT, adrenocortical tumors; IGF2, Insulin-like Growth Factor-2; LFS, Li-Fraumeni syndrome; mTOR, mammalian Target Of Rapamycin; NOV/CCN3, Nephroblastoma OVerexpressed/CYR61-CTGF-NOV family member 3; SF1, Steroidogenic Factor-1; TP53, tumor protein 53.

* Corresponding author at: Institut de Pharmacologie Moléculaire et Cellulaire, 660 route des Lucioles, 06560 Valbonne, France. Tel.: +33 4 93 95 77 55; fax: +33 4 93 95 77 08.
E-mail address: ninino@ipmc.cnrs.fr (E. Lalli).

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Table 1
Distinctive features of ACT in children and adults.

	Childhood ACT	Adult ACT
Peak age at diagnosis	3–4 years	40–50 years
Clinical presentation	Most often virilization; may be associated with Cushing syndrome	Most often clinically silent (incidentalomas); sometimes hypertension or Cushing
Prevalence	Worldwide: 0.3–0.4 annual cases/million children <15 years Southern Brazil: 3.4–4.2 cases/million children <15 years	>4% for incidentalomas; 0.7–2/million for ACC
Most common cytogenetic alterations	11p15 LOH; 9q34 gain	Complex pattern
Prognostic relevance of pathological score	Low	High
Prognostic relevance of:		
TP53 mutations	No	Yes
IGF2 overexpression	No	Yes
NOV/CCN3 downregulation	No	Yes
SF1 overexpression	No	Yes

girls. Signs of virilization are present at time of diagnosis in more than 90% of patients and may be associated with other signs of endocrine dysfunction, especially Cushing's syndrome. Long-term survival is approximately 50% overall, but when stratified by age, it approaches 80% for the group of patients with younger age (0–3 years), while it is very poor (20%) for the group of older children (13–20 years) (Michalkiewicz et al., 2004). In the same study, favorable prognostic factors were reported to be stage I at diagnosis, tumor weight $\leq$200 g, volume <200 cm^3, age younger than 4 years and presence of virilization alone. Remarkably, histological grading, which has a key role in assessing malignancy of adult ACT, does not have prognostic value for childhood ACT (Wieneke et al., 2003; Lau and Weiss, 2009). Table 1 compares the main clinical, biological and pathological differences between ACT in children and in adults.

2. An exceptional prevalence of *TP53* mutations in southern Brazil and its impact on ACT pathogenesis

Important clues about the genetic causes of childhood ACT came from the study of the peculiar epidemiological situation in the state of Paraná, Brazil, where mortality due to ACT in children is 12–18 times higher than in the rest of the world (Pianovski et al., 2006a). Increased ACT incidence in children can be found across all ethnic groups in the population of Paraná. Since ACT can be found in the context of the Li-Fraumeni syndrome (LFS), a multiple cancer syndrome due to germline mutations of the *TP53* tumor suppressor gene (Malkin et al., 1990), Ribeiro and colleagues investigated the presence of *TP53* mutations in a cohort of 36 children with ACT from southern Brazil. Remarkably, 35 out of the 36 patients studied were found to be carriers of a specific *TP53* mutation (R337H) (Ribeiro et al., 2001), with loss of heterozygosity in the tumor. Further studies confirmed these findings in a group of patients from the neighboring state of São Paulo (Latronico et al., 2001) and showed that penetrance of ACT is low (about 10%) in the families carrying the R337H *TP53* mutation (Figueiredo et al., 2006). This mutation lies in the C-terminal TP53 tetramerization domain, which is essential for its function. Intriguingly, this specific *TP53* mutation appeared to associate more frequently with only ACT in the patients' families, and not to the larger spectrum of tumors typical of LFS, but in 7 out of 31 families the coexistence of ACT with other tumor types could be characterized as LFS-like (Figueiredo et al., 2006). However, surprisingly, the R337H TP53 mutant behaved like the wild-type protein in a battery of assays for the study of TP53 activity, indicating that its function is not deficient, at least when it is expressed at supraphysiological levels (Ribeiro et al., 2001). On the other hand, it would be premature to generalize this described normal function before it is confirmed within the natural environment of different cell types. Further structural studies showed that the mutant R337H TP53 tetramer is unstable when pH and temperature are elevated (DiGiammarino et al., 2002), but the real presence of these conditions in the adrenal cortex during development and their impact on tumorigenesis are still a matter of debate. The final assessment of whether the mutant R337H TP53 has a deficient activity will only come from the production of mutant knock-in mice or from the possible identification of R337H *TP53* homozygous patients.

3. Other genetic alterations in childhood ACT: role of an increased SF1 dosage and of imprinting defects in the 11p15 region

The data summarized before show a high incidence of *TP53* mutations in childhood ACT from southern Brazil. *TP53* mutations are also frequently found in familial and sporadic childhood ACT diagnosed in other parts of the world (Varley et al., 1999), but what additional genetic alterations are present in these tumors and how are they related to their pathogenesis? A couple of studies published in 1999 identified a characteristic pattern of chromosomal alterations in these tumors (Figueiredo et al., 1999; James et al., 1999), which are in great part distinct from those found in ACT from adults. One of the most consistent chromosomal alterations found in almost all cases of childhood ACT investigated is the gain/amplification of 9q34. Interestingly, 9q34 gains were also found in one study of chromosomal alterations in adult ACT (Dohna et al., 2000). This finding is intriguing, since nearby this chromosomal region lies the gene encoding the transcription factor Steroidogenic Factor-1 (SF1/Ad4BP; NR5A1 in the standard nomenclature), which plays a pivotal role in the development and function of adrenal glands and gonads (reviewed in Schimmer and White, 2010). Further studies showed that indeed the *SF1* gene is amplified and overexpressed in most cases of childhood ACT from southern Brazil (Figueiredo et al., 2005; Pianovski et al., 2006b; Almeida et al., 2010). The relevance of SF1 overexpression in the pathogenesis of ACT is supported by studies demonstrating that an increased *SF1* dosage increases the proliferation of H295R human adrenocortical cancer cells in a fashion dependent on its transcriptional activity and that *Sf1* overexpressing mice develop adrenal tumors (Doghman et al., 2007a). Remarkably, adrenocortical tumors present in *Sf1* transgenic mice express gonadal markers (Gata4, Amh) and activated Stat3. These tumors are most probably derived from bipotential adrenogonadal precursor cells lying in a subcapsular position in the mouse adrenal gland (Looyenga and Hammer, 2006). Further studies have shown that, consistently with the hypothesis of an important role for SF1 in driving proliferation of adrenocortical cancer cells, SF1 inverse agonists of the isoquinolinone family (Madoux et al., 2008) inhibit proliferation elicited by SF1 overexpression (Doghman

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