Primary pigmented nodular adrenocortical disease (PPNAD) is a rare form of bilateral hyperplasia leading to high morbidity due to pituitary-independent hypercortisolism and Cushing’s syndrome. PPNAD may be either sporadic or regarded as the most frequent endocrine manifestation of Carney’s complex (CNC), an autosomic dominant multiple neoplasia syndrome characterized by cardiac myxomas, spotty skin pigmentation and endocrine overactivity [1]. Both isolated PPNAD and CNC have been associated with null mutations in PRKAR1A, a gene encoding the type 1a regulatory subunit (R1a) of the cAMP-dependent protein kinase (PKA) [2,3]. Tumor-specific loss of heterozygosity within the chromosomal region harboring PRKAR1A is observed in CNC patients and isolated PPNAD suggesting that PRKAR1A is a potential tumor suppressor gene [4]. Because general homozygous loss of Prkar1a is lethal in early mouse embryos [5], adrenal-specific knockout was required to demonstrate tumor suppressor activity. Therefore, we produced mice with Prkar1a gene inactivation in adrenocortical cells by mating Prkar1a floxed mice with the Akr1b7-Cre mouse line, a novel Cre expressing line we developed to allow specific gene ablation in the steroidogenic lineage of the adrenals without affecting the gonads [6]. Adrenal cortex-specific Prkar1a knockout mice (AdKO) develop pituitary-independent Cushing’s syndrome and evident signs of deregulated adrenocortical cells differentiation and proliferation. These defects lead to improper maintenance and expansion of foetal adrenal cells in adult adrenals and establishment of pretumoral conditions. Our data provide the first in vivo evidence that the absence of R1a subunit of PKA is sufficient to explain autonomous adrenal hyperactivity and bilateral hyperplasia observed in PPNAD. They also strongly suggest that deregulated PKA activity positively affects the maintenance of foetal characters in adult glands.

References


© 2009 Elsevier Masson SAS. All rights reserved. - Document downloaded on 23/02/2019 It is forbidden and illegal to distribute this document.