Effect of somatic CTNNB1 mutations on adrenocortical cell de-differentiation in adenoma presenting in early pregnancy or menopause

Klotz Communications: Adrenal and Pregnancy

Effect des mutations somatiques CTNNB1 sur la dé-differentiation des cellules cortico-surrénaliennes dans les adénomes révélés en début de grossesse ou à la ménopause

Effect of somatic CTNNB1 mutations on adrenocortical cell de-differentiation in adenoma presenting in early pregnancy or menopause


* University of Cambridge, Cambridge, UK
b MRC Laboratory of Molecular Biology, Cambridge, UK
c National University of Malaysia, UKM Medical Centre, Kuala Lumpur, Malaysia
d William Harvey Research Institute, Barts and the London Medical School, London, UK

E-mail address: morris.brown@qmul.ac.uk (M.J. Brown)

Background Primary aldosteronism is a curable cause of hypertension if the hypertension is due to an aldosterone-producing adenoma (APA) [1,2]. The discovery of somatic mutations defining pathogenetic subtypes of this adenoma has increased recognition of common but small zona glomerulosa-like APAs [3–6]. In this subtype, we have sought APAs with distinctive presentation or outcome, in which analysis of genotype–phenotype associations could help explain the low success rate and variability of adrenalectomy for curing hypertension.

Methods Ten zona glomerulosa-like APAs from three women with primary aldosteronism were analysed by exome sequencing and microarray analysis. Nine had a mutation of ATP1A1 or CACNA1D, and one had a distinctive genotype and transcriptome. Targeted sequencing of further zona glomerulosa-like APAs led to the finding of two with a similar genotype, and to the recognition that all three women presented in early pregnancy or menopause. Quantitative PCR and immunohistochemistry were performed for genes upregulated in the index case. Similar analyses and a TCF–LEF assay for Wnt signalling were performed on immunohistochemistry (LHCGR) in all three APAs. Increased GATA4 expression was further evidence of adrenocortical cell de-differentiation towards their common gonad-adenal precursor cell-type. Transfection of LHCGR-negative APA cells with GFP-mutant-CTNNB1 switched on LHCGR expression in GFP-positive cells.

Interpretation The role of the Wnt system in adrenal physiology and tumour development is well recognised [7,8], De-differentiation of zona glomerulosa-cells after Wnt activation by the CTNNB1 mutation seems to cause aberrant gonadal receptor expression, which is also previously described [9,10]. Our findings connect these observations, and explain the unmasking of small APAs by increases in luteinising hormone and human chorionic gonadotropin hormone in early pregnancy or menopause. Strikingly, all three women, including the treatment-resistant older woman, were clinically cured by adrenalectomy. This contrasts with the failure of adrenalectomy to completely cure hypertension in the majority of patients. This failure is attributable to decades of exposure to aldosterone excess, and the secondary consequences of fibrosis and remodelling in the cardiovascular system [11,12]. CTNNB1 mutations have now been reported in 10% of APAs without a previously reported mutation [13]. Elucidation of APA subtypes could, with preoperative genotyping, permit recognition of patients in whom recent onset of primary aldosteronism is likely to be completely resolved by surgery.

Funding NIHR Cambridge Biomedical Research Centre (Cardiovascular and Metabolic); Wellcome Trust; Agency for Science, Technology and Research (A*STAR) Singapore; British Heart Foundation; Cambridge Overseas Trust Scholarship; NIHR Senior Investigator; Medical Research Council; Tunku Abdul Rahman Centenary Fund (Cambridge); Austin Doyle Award (Servier Australia).

Contributors A.E.D.T., E.A.B.A. and M.J.B. designed the study, with the help of M.B. A.E.D.T. performed functional analyses of the mutant gene and ex-vivo studies of the adenomas (including qPCR, immunohistochemistry, and immunofluorescence), with the help of S.G. S.G. carried out sequencing and provided the constructs for transfection. L.H.S. performed the TCF–LEF assay. M.J.B., E.A.B.A., and J.Z. designed the microarray. E.A.B.A. carried out exome sequencing. F.E.K.F. and M.G. provided clinical data and were involved in patient care. L.H. and A.M. conducted the histological analyses and facilitated tissue collection. A.E.D.T. and M.J.B. analysed and interpreted the data. All authors approved the final submitted version.

Disclosure of interest The authors declare that they have no competing interest.

0003-4266/$ – see front matter
http://dx.doi.org/10.1016/j.ando.2016.04.003
References


http://dx.doi.org/10.1016/j.ando.2016.04.022

© 2018 Elsevier Masson SAS. Tous droits réservés. - Document téléchargé le 10/12/2018 Il est interdit et illégal de diffuser ce document.