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Using Single Cell Technology To Predict The Cell Of Origin Of Aldosterone-producing Adrenal Adenomas

Kate Laycock, MBBS, BMedSci[1], *Claudia Cabrera, PhD*[1], *Eva Wozniak, BSc*[1], *Charles Mein, PhD, BSc*[1], *Elena Azizan, PhD*[2], *Xilin Wu, PhD, BA, MBBS*[1], *Giulia Argentesi, BMBS, MSc*[1], *Emily Goodchild, BMBS, BSc*[3], *William Drake, DM, MRCP*[4], *and Morris Jonathan Brown, MD, FRCP*[5]

[1]Queen Mary University of London, London, United Kingdom; [2]Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; [3]Queen Mary University London, London, United Kingdom; [4]Saint

Bartholomew's Hospital, London, United Kingdom; [5]Queen Mary University of London, Cambridge, United Kingdom

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Background: Aldosterone-producing adrenal adenomas (APAs) are the commonest surgically curable cause of hypertension, but individual prediction of postoperative outcome is challenging. Emerging data suggest that outcomes are influenced by APA genotype; identifying the cell of origin of APAs could facilitate a greater understanding of why certain genotypes are more/less likely to be associated with residual/recurrent autonomous aldosterone production(1, 2). **Aims:** 1. To develop an adult adrenal single cell atlas. 2. To identify the likely cell of origin for APAs with different mutations. **Methodology:** Bulk RNA sequencing from 67 APAs discovered known or novel somatic genotypes in 55, and replicated or discovered distinctive transcriptomes for each genotype. Single nuclei RNA sequencing was performed on 13 adrenals adjacent to the genotyped APAs. After aggregation of all 13 datasets, cluster analysis was undertaken to identify cell types and some of the transitions between these. Similarities were sought between the genotype-enriched transcriptomes of APAs, and the transcriptomes of individual cell clusters in adjacent adrenal. **Results:** A single nuclei atlas of 56,442 nuclei was developed. Clusters included each of the 3 cortical zones, aldosterone-producing micronodules, capsular cells, adrenal medulla, macrophages, T cells, stromal cells, endothelial cells and neurones. Several zona glomerulosa selective transcripts in previous laser-capture studies(3, 4) clustered separately from *CYP11B2*-positive cells (e.g. *LGR5, GABBR2*) or in distinct non-steroidogenic clusters (e.g. *KIAA1210, RSPO3, PTGDS*).A sub-cluster of stromal cells, positive for *KIAA1210, RSPO3, CDH13* and *MFAP5* (each p<10-254 cf other clusters) is likely to represent the distinctive KIAA1210+ capsular/interstitial cells on adrenal immunohistochemistry (www.proteinatlas.org). Bulk RNA sequencing of a rare *CLCN2*-mutant APA showed 13-30-fold higher expression of these and multiple other genes localising to the single nuclei stromal-cell cluster. **Conclusion:** Single nuclei sequencing documents the heterogeneity of adrenal cells, and potential for multiple different cell-types to develop into APAs. Ongoing analysis is underway to replicate the *CLCN2*-mutant transcriptome and identify cells-of-origins for tumours with commoner mutations. 1.Wu X *et al*. 11C metomidate PET-CT versus AVS for diagnosing surgically curable PA: a prospective within-patient trial. Nat Med. In press 2.Zhou J *et al*. Somatic mutations of GNA11 and GNAQ in CTNNB1-mutant APAs presenting in puberty, pregnancy or menopause. Nat Genet. 2021 3.Nishimoto K *et al*. Aldosterone-stimulating somatic gene mutations are common in normal adrenal glands. Proc Natl Acad Sci USA. 2015 4.Shaikh LH *et al*. LGR5 Activates Noncanonical Wnt Signaling and Inhibits Aldosterone Production in the Human Adrenal. J Clin Endocrinol Metab. 2015

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