Biosketch

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Cynthia Andoniadou is a Reader in Stem Cell Biology at the Centre for Craniofacial and Regenerative Biology, King's College London and affiliated with the Centre for Internal Medicine, Technical University of Dresden as a Group Leader. She is a basic scientist focusing on the regulation of stem cells of endocrine tissues. Her team consists of basic and clinical researchers.

Dr Andoniadou's research is funded by the Medical Research Council (MRC), Deutsche Forschungsgemeinschaft (DFG), and charities Paradifference Foundation and AMEND. Cynthia is the recipient of a Lister Institute Research Prize (2016), SfE Young Endocrinologists' Basic Prize Lecture (2014) and the SfE Starling Medal (2022).

Research Summary

The Andoniadou lab focus on understanding the function of endocrine stem cells in normal physiology and disease with emphasis on the pituitary gland and more recently the adrenals. The team have used genetic tools to demonstrate that SOX2+ cells are pituitary stem cells (PSCs) during normal physiology and have carried out in-depth characterisations of these cells in mouse and humans using multi-omic approaches together with the Sealfon lab (Mount Sinai). They have revealed that this long-lived population contributes to all endocrine pituitary cell lineages throughout life. Additionally, they have shown that PSC act as signalling hubs, secreting instructive paracrine factors that promote proliferation among neighbouring endocrine progenitors, ensuring physiological turnover. This is relevant to multiple organ-specific stem cells throughout the body and of importance to regenerative medicine approaches.

The team have shown that PSC can be involved in the formation of tumours and have identified two separate mechanisms for their pathogenic contribution: (i) a direct contribution where the stem cell is the tumour cell of origin (i.e. cancer stem cell), and (ii) an indirect paracrine instigation of tumourigenesis:

(i) The group identified that the Hippo kinase signalling cascade, a readily druggable pathway implicated in growth and cancer, is active in the human and mouse pituitary. They demonstrated that a subset of human pituitary tumours display elevated levels of the Hippo pathway effectors YAP/TAZ, rendering these candidate targets to inhibit tumour growth. Genetic manipulations in mouse confirmed that regulation of YAP/TAZ is essential for normal pituitary development, whilst aberrant expression leads to disease states ranging from Rathke's cleft cyst to pituitary carcinoma, depending on mutation timing and the levels of pathway elevation. The research revealed a dose-dependent function for YAP, where overexpression controls the switch between re-activating the normal proliferative potential of PSCs and their transformation into cancer stem cells, which generate aggressive non-functioning pituitary tumours.

(ii) Over-activating the WNT signalling pathway only in PSCs, the team, together with the Martinez-Barbera lab (UCL), have shown these instigate the generation of tumours resembling adamantinomatous craniopharygioma (ACP). Genetic lineage tracing revealed a non-classical contribution to tumour formation, where PSCs prompt tumourigenesis through a paracrine secretory mechanism. This is relevant to multiple additional cancers, such as hepatocellular carcinoma and acute myeloid leukemia.

These studies have led to the generation of several mouse models of disease and have been instrumental in our understanding of physiological pituitary stem cell function and pathological involvement. The insights gained into tumour initiation/progression are applicable to tumours and cancers of multiple organs. The lab is highly collaborative and have active projects with several groups worldwide.

The lab has a range of current ongoing projects, on both the pituitary and adrenal glands: e.g. using computational approaches to identify key stem cell and lineage commitment genes *in silico*; addressing the function of newly identified stem cell markers through genetic approaches; using *in vitro* and *in vivo* tools to characterise pathogenic variants and their mechanisms of action; analysis of newly generated mouse models of tumour formation; establishing the function of key signalling pathways in human pituitary tumourigenesis.

Commonly used techniques include: *in vitro* culture of primary and established cell lines (rodent and human), lentiviral transduction, dissection of mouse endocrine organs, tissue

processing (paraffin and cryo-embedding and sectioning), histology, immunofluorescence, immunohistochemistry, RNAscope mRNA in situ hybridisation, microscopy (brightfield, confocal), computational analyses using R and Python.

Selected Publications
Full record: https://www.ncbi.nlm.nih.gov/myncbi/c.andoniadou.1/bibliography/public/

1. Zhang Z, Zamojski M, Smith GR, Willis TL, Yianni V, Mendelev N, Pincas H, Seenarine N, Amper MAS, Vasoya M, Nair VD, Turgeon JL, Bernard DJ, Troyanskaya OG, **Andoniadou CL***, Sealfon SC*, Ruf-Zamojski F*. Single nucleus pituitary transcriptomic and epigenetic landscape reveals human stem cell heterogeneity with diverse regulatory mechanisms *bioRxiv* 2021.06.18.449034 *Corresponding Authors
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7. Lodge EJ, Santambrogio A, Russell JP, Xekouki P, Jacques TS, Johnson RL, Thavaraj S, Bornstein SR, **Andoniadou CL**. Homeostatic and tumourigenic activity of SOX2+ pituitary stem cells is controlled by the LATS/YAP/TAZ cascade. ***Elife.*** (2019) Mar 26;8. pii: e43996. doi: 10.7554/eLife.43996.
8. Steenblock C, Rubin de Celis MF, Delgadillo Silva LF, Pawolski V, Brennand A, Werdermann M, Berger I, Santambrogio A, Peitzsch M, **Andoniadou CL**, Schally AV, Bornstein SR. Isolation and characterization of adrenocortical progenitors

involved in the adaptation to stress. ***Proc Natl Acad Sci U S A.*** (2018) Dec 18;115(51):12997-13002. doi: 10.1073/pnas.1814072115.

9. Xekouki P, Lodge EJ, Matschke J, Santambrogio A, Apps JR, Sharif A, Jacques TS, Aylwin S, Prevot V, Li R, Flitsch J, Bornstein SR, Theodoropoulou M, **Andoniadou CL**. Non-secreting pituitary tumours characterised by enhanced expression of YAP/TAZ. ***Endocr Relat Cancer.*** (2019) Jan 1;26(1):215-225. doi: 10.1530/ERC-18-0330.

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