The impact of age, parity and germline mutations on mammary gland development at the single cell level

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Principal supervisor's CRUK CC theme: Precision Breast Cancer Institute

Department for student registration: Pharmacology-CSCI
Department or institute where research will take place: CSCI and Pharmacology

Postgraduate scheme:

- **MRes + PhD (1 + 3-year non-clinical applicants)**
- **Part-time MRes + PhD (2 + 3-year clinical applicants)**

MRes project outline:

Understanding the molecular and cellular mechanisms of how epithelial tissue maintain a homeostatic state throughout the lifespan of mammals is a major challenge for developmental and stem cell biology. From a developmental perspective, the epithelium of the mammary gland is unique as it undergoes most of its development during adulthood. Despite recent efforts of characterising the tissue homeostasis at a cellular level little is known about how this is affected by various developmental processes such as pregnancy or aging and how this might ultimately disrupt epithelial homeostasis resulting in malignant outgrowth.

In this study we wish to further our understanding of the changing nature of the differentiation dynamics of the mammary gland by using single-cell RNA-sequencing. To fully understand how tissue homeostasis is affected by parity and other events it is mandatory to characterise the differentiation dynamics in an age-dependent manner. This becomes evident when looking at epidemiological data. Age is the greatest risk factor for breast carcinomas, and it has been suggested that this is not only due to accumulation of mutations but also due to decreased clonality and selection of clones with proliferative advantage. More importantly, the age-dependent risk of tumorigenesis is modulated by for example parity, which attenuates the risk or predisposing germline mutations which increase the age-associated risk (6). However, the exact mechanisms and effects of the interaction of these risk factors on tissue homeostasis of the mammary gland still remain to be elucidated. We here propose to map the effects of parity, aging and germline mutation (BRCA1/2) on the homeostasis of the mammary gland. This will be done using single-cell RNA-sequencing, which will allow us to identify transcriptional programs that govern changes in the differentiation dynamics as well as changes in phenotypes and proportions of the various cells in the mammary gland.

MRes experimental plan:

For this project the student will be analysing a large dataset of mouse and human scRNAseq which has been collected over several years. This project will suit someone with some experience in using R and/or Python. There might be an opportunity to validate some of the scRNAseq using orthogonal techniques such as IHC.

PhD project outline:
To be decided based on rotation

PhD experimental plan:
To be decided based on rotation

Main techniques:
To be decided based on rotation

Key references:
Reed A, Pensa S, Steif A, Stenning J, Kunz D, He P, Twigger AJ, Kania K, Barrow-McGee R, Goulding I, Gomm J, Jones L, Marioni JC, Khaled WT. . A Human Breast Cell Atlas Mapping the Homeostatic Cellular Shifts in the Adult Breast. BioRxiv. (2023)

Twigger AJ, Engelbrecht LK, Bach K, Schultz-Pernice I, Pensa S, Stenning J, Petricca S, Scheel CH, Khaled WT. Transcriptional changes in the mammary gland during lactation revealed by single cell sequencing of cells from human milk. Nature Communications (2022)

Twigger A-J and Khaled WT. Mammary gland development from a single cell ‘omics view. Seminars in Cell & Developmental Biology (2021)

Bach K*., Pensa S.*, Zarocsinceva M., Katarzyna K., Stockis J., Pinaud S., Lazarus K., Shehata M., Simões B., Greenhalgh A., Howell S., Clarke R., Caldas C., Halim T., Marioni J. #, Khaled WT. #.Time-resolved single-cell analysis of Brca1 associated mammary tumorigenesis reveals aberrant differentiation of luminal progenitors. Nature Communications (2021)

Watson C.J. and Khaled W.T. Mammary development in the embryo and adult: new insights into the journey of morphogenesis and commitment. Development (2020)

Bach, K., Pensa, S., Grzelak, M., Hadfield, J., Adams, D.J., Marioni, J.C., Khaled, WT. Differentiation dynamics of mammary epithelial cells revealed by single-cell RNA-sequencing. Nature Communications (2017)