Androgen receptor signaling in the normal breast epithelium and in estrogen receptor α positive breast cancer

PhD project

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More than 70% of breast cancers are classified as estrogen receptor α positive (ER+) breast cancers and the estrogen receptor (ER) is targeted in therapy. However, primary and secondary endocrine resistance are a frequent clinical problem and alternative therapeutic approaches are needed. The importance of the finding that ER+ breast cancers frequently co-express other nuclear receptors, in particular the androgen receptor (AR), is poorly understood and whether or not this might by exploited therapeutically is unclear.

Research in this area of hormone-sensitive breast cancer was hampered by the lack of physiologically and clinically relevant models. My laboratory recently overcame this hurdle and demonstrated that both normal human breast epithelial cells and patient-derived ER+ tumor cells, when xenografted intraductally, establish themselves and retain hormone response (Fiche et al., 2018; Sflomos et al., 2016).

Using such intraductal patient-derived xenograft (PDX) models, I will examine the role of AR signaling in the normal breast epithelium and ER+ breast cancers in physiologically relevant endocrine settings, to explore the possibility that AR inhibition may be a therapeutic avenue. I will first establish AR target genes by RNA-seq and ChIP-Seq and will determine, by means of ATAC-seq, how chromatin accessibility is controlled by androgen receptor signaling, both in normal breast epithelial cells and in tumor cells from at least 10 different individuals per group. The bioinformatic analysis will be performed in collaboration with bioinformaticians G. Ambrosini and P. Bucher, EPFL.

The comparison of AR-mediated transcriptional control in normal versus tumor cells will provide insights into mechanisms involved in tumor development. I will then analyze the effects of AR inhibition, induced both pharmacologically and by shRNA-mediated downmodulation of receptor expression *in vivo*. With regard to normal human breast epithelial cells, I will investigate the effects on *in vivo* proliferation and the transcriptional profile. Concerning ER+ tumor cells, I will assess the effects of AR signaling inhibition on cell proliferation, tumor cell invasion as well as metastasis and will characterize the underlying transcriptional changes.

This work will yield insights into androgenic action in the normal breast epithelium and the changes that occur during ER+ breast carcinogenesis. The effects of AR signaling inhibition *in vivo* and the transcriptional mechanisms underlying them will be determined. These insights will help us understand whether AR signaling can be exploited therapeutically and ultimately help identify predictive biomarkers for tumor response.

References

Fiche, M., Scabia, V., Aouad, P., Battista, L., Treboux, A., Stravodimou, A., Zaman, K., RLS, Dormoy, V., Ayyanan, A., *et al*. (2019). Intraductal patient-derived xenografts of estrogen receptor α-positive breast cancer recapitulate the histopathological spectrum and metastatic potential of human lesions. J. Pathol. 247(3):287-292.

Sflomos, G., Dormoy, V., Metsalu, T., Jeitziner, R., Battista, L., Scabia, V., Raffoul, W., Delaloye, J.F., Treboux, A., Fiche, M., *et al*. (2016). A preclinical model for ER alpha-positive breast cancer points to the epithelial microenvironment as determinant of luminal phenotype and hormone response. Cancer Cell *29*, 407–422.