Deciphering the role of the RUNX/CBFβ transcriptional complex in breast cancer

Our lab has a long-standing interest in the RUNX/CBFβ transcriptional complex, an essential regulator of mammalian development which is often found dysregulated in cancer. It is not surprising that this family of genes is altered in cancer considering the pathways regulated by this complex (Figure 1); yet there is often a dichotomy on how these proteins manifest their effects in different cancer settings. Genetic aberrations in the RUNX and CBFβ genes are particularly prevalent in breast cancer, and two PhD students, Hirin Sweeney and Adiba Khan, recently submitted and successfully defended their theses exploring the enigmatic role of these genes.

In collaboration with Prof Ewan Cameron (University of Glasgow) and funded in part by Breast Cancer Now, Adiba Khan’s thesis was titled ‘Investigating the tumour suppressor function of RUNX1 in breast cancer’. Deletion of Runx1 in two independent in vivo models of breast cancer accelerated disease onset and led to emergence of multifocal and multicentric tumours. RNAseq analysis revealed an increased stem-like transcriptional signature in Runx1-deficient tumours, while loss of Runx1 predisposed to increased stem/progenitor-like behaviour in functional mammosphere assays. Adiba’s studies revealed that while loss of Cbfβ did not overly alter normal development of the mammary gland, when combined with oncogenic Wnt signalling it dramatically accelerated onset of mammary tumours, providing the first in vivo evidence that Cbfβ has a tumour suppressor role in a mouse model of breast cancer. Adiba, along with Masters Student Nimrit Kaur, showed however that loss of Cbfβ did not promote tumour susceptibility within the MMTV-PyMT model. Thus, as observed in patients, Cbfβ played a variable role in breast cancer. Profiling of RUNX/CBFβ-deleted mammary tumours has revealed that loss of the complex evoked changes to the tumour microenvironment where an important aspect of RUNX/CBFβ activity might be to orchestrate the immune microenvironment, a hypothesis we are pursuing further.

The MRC/NIH/NHGRI Cancer Cluster

Specific projects in the lab focus on how the RUNX/CBFβ transcriptional complex and the BCL-2 family of apoptotic regulators contribute to tumour progression, metastasis and recurrence in breast, prostate and other cancers.

Gene dependency...