The aim of our research is to understand how ageing influences stem cell behaviour and cancer outgrowth. We aim to use this knowledge for early detection of cancers before the cancer occurs and to identify and test new clinical therapies to prevent or treat cancer at an early stage. We also consider the influence of the ageing tumour microenvironment and effects of senescence on the tumour niche. We then examine cross talk of stem cells with their surroundings. In the majority of our studies, we use mouse models and primary patient samples.

Age is the single biggest factor underlying the onset of many haematological malignancies, with myeloid disease being especially prominent. The onset of myeloid bias in the haematopoietic stem cell (HSC) compartment with increasing age is well documented and leads to malfunction of the immune system but might also be a factor for predisposition to myeloid cancers. Myeloid cancers often originate from defects in the haematopoietic stem and progenitor cell (HSPC) compartment in which a single mutation can often account for disease. For instance, the JAK2V617F mutation is sufficient for the development of myeloproliferative disease (Baxter et al., 2016). Therefore, studying HSC ageing is essential for gaining insights into mechanisms underlying the transformation of aged HSPCs into cancer stem cells. Upon the accumulation of DNA damage, the hyperproliferation of an oncogene or other events compromising a cell’s integrity, senescence is a tumour suppressor pathway where the p53 and p63/Rb pathways are engaged to permanently force exit from the cell cycle. A prominent feature of primary senescence is the senescence-associated secretory phenotype (SASP) (Acosta et al., 2008). Through the secretion of factors like extracellular matrix proteases and signalling proteins such as interleukins and chemokines, senescent cells modulate the tissue organisation and recruit immune cells, mediating their own clearance. In addition, SASP factors can act in a paracrine fashion to induce secondary senescence in surrounding cells and tissues (Nielson et al., 2012). Secondary senescence is thought to act as a sentinel mechanism enhancing immune surveillance and to act as a fail-safe programme minimising the retention of damaged cells in the vicinity of primary senescent cells. Our work has shown that senescent cells also spread by inducing senescence more directly, through cell-cell contact (juxtacrine) (Teo et al., 2019). However, whether secondary senescence is indeed part of a fail-safe mechanism or has other implications remains unknown (reviewed in Kirschner et al., 2020).

Single cell approaches to investigate primary and secondary senescence

The role of secondary senescence in vitro and in vivo remains elusive since its discovery in 2012. Thus far, it was assumed that primary and secondary senescence phenotypes are identical. A recent publication from the lab showed, for the first time, that both senescence types differ transcriptomically. We found that Notch blunted the SASP in secondary senescence with a simultaneous accumulation of collagens. The lab aims to understand the roles different senescence phenotypes play in cancer. We combine single cell omic approaches with advanced mouse models to assess consequences of secondary senescence in genetic model systems.

Elucidating senescence heterogeneity is an important concept in the context of senology, a novel group of drugs, specifically targeting senescent cells. These drugs have shown great promise in rejuvenation approaches in a wide variety of organs but have not been exploited in pre-neoplastic disease setting and tumour prevention.

Longitudinal profiling of clonal haemopoiesis mutations

Clonal haemopoiesis of indeterminate potential (CHIP) is defined as the clonal expansion of HSPCs in healthy aged individuals with a myeloid bias. CHIP is associated with an increased risk for haematological cancer and all-cause mortality, whereby age is a major risk factor. In addition, patients who are carrying CHIP mutations and are undergoing chemo- or radiation therapy for solid tumours, are at an increased risk of developing secondary leukaemia. We have previously shown an association between an increase in biological age acceleration and the presence of CHIP, as well as finding transcriptional differences between young and old HSCs carrying the JAK2V617F mutation (Robinson et al., 2019; Kirschner et al., 2017).

CHIP is characterised by mutations in leukaemia driver genes in healthy aged individuals. Several groups reported that CHIP is driven by somatic mutations in DNMT3A, TET2, and JAK2 genes, mutations previously described as drivers of myeloid malignancies. Such mutations can increase stem cell fitness, leading to growth advantages over neighbouring cells and eventually disease. We hypothesise that identifying the distinct stem cell fitness conferred by individual CHIP mutations will enable us to predict clonal dynamics, and hence estimate risk of progression towards age-related disease.

Several studies have predicted fitness effects of CHIP in cross-sectional cohorts. As these use single-time point data, inferring fitness had to rely on assumptions about when in life mutations occurred. This introduced uncertainty and made mutation-specific estimates challenging. Current estimates showed a wide uncertainty in mutational fitness and strong dependence on an accurate, yet difficult, estimated time of mutation. Longitudinal data offer a direct and accurate way to infer fitness effects of individual variants.

The Lothian Birth Cohort (LBC) of 1921 (n=550) and 1936 (n=1091) are two independent, longitudinal studies of ageing. Participants have been followed up every ~3 years, for five waves, from the age of 70 (LBC1936) and 79 (LBC1921) years. They provide one of the most comprehensive assessments of later-life ageing anywhere in the world. We set out to quantify the fitness effects of CHIP drivers over a 12-year lifespan in older age, using longitudinal error-corrected sequencing data from the LBCs. We developed a new filtering method to extract fitness effects from longitudinal data, and thus quantified the growth potential of variants within each individual, while taking into account individual mutational context. We showed that gene-specific fitness differences could outweigh inter-individual variation and therefore could form the basis for personalised clinical management.

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