BCHM 421/422 Project – 2023-24

Background: Cancer cells develop when normal cell maintenance mechanisms are perturbed resulting in uncontrolled growth. This drives the formation of a heterogeneous population of tumour cells that differ in cell surface marker expression, presence of genetic lesions, epigenetic profiles, proliferation kinetics, responses to therapy and ability to initiate tumour growth.

Tumour heterogeneity is thought to be driven by genetic mutations, epigenetic modifications and micro-environmental variations, that permit cell state transitions. These modifications can lead to both irreversible and reversible modifications that affect the trajectory of the precursor somatic cell expressing the original malignant lesion. The ability of cells to adopt different cellular states along a phenotypic spectrum is known as cellular plasticity. The resulting pliability in cell state can facilitate multiple aspects of tumour progression, but importantly may augment or catalyze pre-leukaemic events at very early stages of tumorigenesis.

Somatic mutations accumulate in normal tissue as humans age. When mutations occur in hematopoietic stem cells and give rise to an increased portion of blood cells, this is referred to as clonal hematopoiesis (CH). The most commonly mutated CH genes include DNMT3A, TET2. Both genes are responsible for altering the DNA methylome, and loss of function leads to increased self-renewal in HSCs. Both genes have been well supported in the literature to be linked to CH, conferring a higher probability for individuals to develop cancer, cardiovascular and pulmonary pathologies, however mechanisms behind how this happens, have yet to be fully determined.

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Project Objective: To determine if clonal hematopoiesis mutations that develop during aging, increase the cellular plasticity state of hematopoietic cells

Project Title: Investigating cellular plasticity as the first step in haematological transformation

Keywords: Cancer, TET2, DNMT3A, clonal hematopoiesis

Project Aims:

Aim 1: Profile Hematopoietic Stem and Progenitor Stem Populations in normal and CH mice

Aim 2: Analyze if progenitors are able to de-differentiate to HSCs through flow cytometric sorting in normal and CH mice

Aim 3: Perform Functional analysis of normal and TET2/DNMT3A knockdown mice

Experimental Approaches: murine handling, enrichment of stem cells, flow cytometry

Literature:

1) Hallmarks of Cancer: https://doi.org/10.1016/j.cell.2011.02.013
2) Stem Cell, Cancer and Cancer Stem Cells: https://pubmed.ncbi.nlm.nih.gov/11689955/
3) CH and Evolution to Hematologic Malignancies: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5804896/
4) CH with and without candidate driver mutations is common in elderly: https://ashpublications.org/blood/article/130/6/742/36791/Clonal-hematopoiesis-with-and-without-candidate
5) CH in human aging and disease: https://www.science.org/doi/10.1126/science.aan4673
6) CH harbouring AML-associated mutations is ubiquitous in healthy adults: https://www.nature.com/articles/ncomms12484
7) Human AML is organized as a hierarchy that originates from a primitive hematopoietic cell: https://pubmed.ncbi.nlm.nih.gov/9212098/
8) Emerging role of tumour cell plasticity in modifying therapeutic response: https://www.nature.com/articles/s41392-020-00313-5
9) Mechanisms of Leukemia stem cell plasticity revealed by single cell analysis: https://ashpublications.org/blood/article/136/Supplement%201/32/471759/Mechanisms-of-Leukemia-Stem-Cell-Plasticity
10) TET2 mutations are associated with hypermethylation at key regulatory enhancers in normal and malignant hematopoiesis: https://doi.org/10.1038/s41467-021-26093-2
11) Loss of TET2 affects proliferation and drug sensitivity through altered dynamics of cell-state transitions: 10.1016/j.cels.2020.06.003