ICR The Institute of Cancer Research

UKRI Medical Research Council

PhD Project Proposal

Funder details

Studentship funded by: MRC DTP

Project details

Project title: Exploiting intercellular interactions to overcome prostate cancer cell states cooperation and plasticity

Supervisory team

Primary Supervisor: Marco Bezzi

Associate Supervisor(s): Adam Sharp

Secondary Supervisor: Anguraj Sadanandam

Divisional affiliation

Primary Division: Molecular Pathology

Primary Team: Tumour Functional Heterogeneity

Site: Sutton

Project background

Cancers emerge as a result of somatic evolution, often leading to genetic and phenotypic heterogeneity that culminates in metastatic dissemination of therapy-resistant, lethal tumoural clones(1). The characterization of such diversity is crucial to our understanding of the dynamics that govern the cancer ecosystem. Our Team (Tumour Functional Heterogeneity Lab) is part of Centre for Evolution and Cancer and of the CRUK Convergence Science Centre. We combine preclinical modelling, functional genomics approaches and multi-parameter single cell analysis to investigate both genetic and nongenetic tumour heterogeneity. Our goal is to identify and target trajectories of convergent evolution in response to therapy and mechanisms of cooperation between cancer clones within their microenvironmental context.

This project focuses on the functionalization of cancer cell states, defined as differentially expressed transcriptional programs that underpin phenotypic properties(2). The heterogeneity of cell states provides a vital source of diversity for tumour evolution and is influenced by multiple factors, such as genetic aberrations, epigenetic history, lineage determinants and environmental cues. Transcriptional modules that delineate cell states can recur across cancer types (e.g., 'hypoxia', 'cell cycle', 'epithelial-mesenchymal transition', etc…) or be lineage-specific(3). Exacerbating such complexity is increasing evidence of cancer cell state plasticity and cooperation within a tumour niche(4,5), highlighting the pressing need for a deeper understanding of cancer cell states and their interactions to prevent drug resistance and metastatic spread.

The development of metastatic castration resistant prostate cancer (mCRPC) perfectly exemplifies this urgency due to a high level of phenotypic heterogeneity that cannot be explained by tumour genotype. Additionally, mCRPC is directly associated with therapies that target a specific pathway (the androgen receptor (AR) pathway) and induce the emergence of both recurrent and lineage-restricted cancer-cell states that drive resistance(6). In this context, mCRPC is an ideal system to study cells states plasticity and interactions in drug resistance.

Project aims

- Aim 1: Establishment of a traceable in-vivo model of the prostate cancer metastatic cascade
- Aim 2: Mapping cellular states and dynamics within tumour cellular neighbourhoods at single cell resolution
- Aim 3: Clonal recovery and functionalization of cooperative interactions between cellular states in 3D co-culture systems
- Aim 4: Identification of novel therapeutic strategies exploiting intercellular interactions
- Aim 5: Validation of novel therapeutic strategies in-vivo

Research proposal

Prostate cancer (PCa) is a multifocal disease with a high degree of intratumoural heterogeneity(7). Androgen deprivation therapies (ADTs) are currently the first-line treatment for patients with advanced prostate cancer. Nearly all patients eventually experience recurrence and progression to metastatic castration resistant prostate cancer (mCRPC), a stage of the malignancy where therapeutic options are limited and ineffective. Next generation therapies for mCRPC are AR Pathway Inhibitors (ARPI). Whilst these treatments can offer an extension to life, they are not curative, and as such the identification of novel targets for mCRPC is critical. Notably, inhibition of the AR pathway applies a strong selective pressure which drives the evolution of CRPC toward a phenotypic shift from a luminal, AR driven cell state to a variety of AR negative/independent prostate cancer cell states (e.g., ‘neuroendocrine’, ‘stem cell-like’, ‘partial epithelial-mesenchymal transition’, etc…) which exhibit a vast spectrum of disease behaviour, making mCRPC resilient to molecular classification(6). In this context, identification and characterization of mechanisms of cell states plasticity and interactions is of vital importance for the development of novel therapies to prevent this lethal disease.

Aim 1: Establishment of a traceable in-vivo model of the prostate cancer metastatic cascade

To establish a relevant model for the analysis of prostate cancer cell states and interactions during the evolution of mCRPC, the student will utilise mouse allograft models that grow in immunocompetent mice and can be cultured as ex-vivo organoids(8). To achieve the resolution of data required for the analysis of both the clonal dynamics and the tumour microenvironment (TME), a labelling approach using multifunctional clonal barcoding(9) and niche labelling(10) will be implemented. This will enable the profiling of tumour cells from different regions at different stages of the disease, and of the associated microenvironment unique to these regions (Aim 2). The effect of androgen deprivation therapy will be modelled and compared to the lack of intervention. The use of a multifunctional clonal barcoding system will allow for the recovery of specific cell populations providing a relevant system for ex-vivo exploration in Aim 3. Similarly, the niche labelling will provide a key insight into the TME cell populations required for further co-culture assays.

Aim 2: Mapping cellular states and dynamics within tumour cellular neighbourhoods at single cell resolution

Mouse tumours form primary and metastatic sites. will be isolated at different time points. These will be processed to separate tumour cells, TME cells and non-tumour associated microenvironment cells. Through the use of single-cell RNA sequencing (scRNAseq) the clonal dynamics, transcriptome, as well as distinct microenvironment populations (such as specific immune cells), will be profiled. This analysis will provide a comprehensive, longitudinal analysis of cell states frequencies, plasticity, and association with TME cell populations. The insights from this stage will guide the further aims by determining the exact clones and microenvironmental factors to be modelled in Aim 3. These will be assessed by their association with resistance to therapy and metastasis.

Aim 3: Clonal recovery and functionalization of cooperative interactions between cellular states in 3D co-culture systems

Following the characterisation of the tumour ecology using scRNAseq in Aim 2, clones showing specific cellular states and TME cells of interest will be isolated using cell sorting. The student will recreate pre- and post- castration heterocellular ecosystems ex-vivo to investigate the emergence of clones that adopt a ‘persiter cell state’ (a dormant state that exhibits tolerance to castration), and pre-metastatic clones potentially involved in the emergence of plastic and invasive cell states. The student will use complex 3D co-culture methodologies developed in our lab to implement a coupled imaging and in-vitro modelling strategy to evaluate survival, plasticity and invasiveness of heterocellular systems. These systems will be used to unravel functional cooperation and competition between clones that show different cell states and the role of specific cell types of the TME.

Aim 4: Identification of novel therapeutic strategies exploiting intercellular interactions

By using scRNAseq data collected in Aim2 and co-culture system established in Aim 3, novel therapeutic strategies will be designed to disrupt cooperative interactions between cell states and the TME observed in Aim 3. The student will test the efficacy of molecules targeting specific paracrine signaling pathways or cell types, with the aim to inhibit the emergence of resistance to castration, cell plasticity and invasiveness.

Aim 5: Validation of novel therapeutic strategies in-vivo

Here the student will set out to validate therapeutic strategies determined in Aim 4. Treatments will be chosen based on the greatest impact on resistance to castration and on the metastatic potential. Using the models from Aim 1, the primary and metastatic sites will be collected to understand the impact of these therapies on tumour progression and on the ecological dynamics of tumours.

Literature references

[1] McGranahan N, Swanton C. Clonal Heterogeneity and Tumor Evolution: Past, Present, and the Future. Cell. 2017;168(4):613–28.
[2] Barkley D, Rao A, Pour M, França GS, Yanai I. Cancer cell states and emergent properties of the dynamic tumor system. Genome Res. 2021;31(10):1719–27.
[3] Barkley D, Moncada R, Pour M, Liberman DA, Dryg I, Werba G, et al. Cancer cell states recur across tumor types and form specific interactions with the tumor microenvironment. Nat Genet. 2022;54(8):1192–201.
[4] Marusyk A, Tabassum DP, Altrock PM, Almendro V, Michor F, Polyak K. Non-cell-autonomous driving of tumour growth supports sub-clonal heterogeneity. Nature. 2014;514(7520):54–8.
[5] Campbell NR, Rao A, Hunter MV, Sznurkowska MK, Briker L, Zhang M, et al. Cooperation between melanoma cell states promotes metastasis through heterotypic cluster formation. Dev Cell. 2021;
[6] Beltran H, Hruszkewycz A, Scher HI, Hildesheim J, Isaacs J, Yu EY, et al. The role of lineage plasticity in prostate cancer therapy resistance. Clin Cancer Res. 2019;25(23):clincanres.1423.2019.
[7] Gundem G, Loo PV, Kremeyer B, Alexandrov LB, Tubio JMC, Papaemmanuil E, et al. The evolutionary history of lethal metastatic prostate cancer. Nature. 2015;520(7547):353–7.
[8] Simons BW, Kothari V, Benzon B, Ghabili K, Hughes R, Zarif JC, et al. A mouse model of prostate cancer bone metastasis in a syngeneic immunocompetent host. Oncotarget. 2019;10(64):6845–54.
[9] Gutierrez C, Al'Khafaji AM, Brenner E, Johnson KE, Gohil SH, Lin Z, et al. Multifunctional barcoding with ClonMapper enables high-resolution study of clonal dynamics during tumor evolution and treatment. Nat Cancer. 2021;1–15.

Candidate profile

Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1).

Pre-requisite qualifications of applicants:

First class or upper second class honours BA or BSc Honours/MSc or equivalent in biological sciences or computational biology.

Preliminary experience in in vivo tumour models and single-cell analysis approaches desirable.

Intended learning outcomes:

- Advanced skills in mammalian cell engineering
- Organoid culture and genetic manipulation
- Single cell RNA sequencing experimental design and data analysis
- Experience in drug screening approaches
- Generation and characterization of prostate cancer mouse models

Advertising details

Project suitable for a student with a background in: ☒ Biological Sciences

- [ ] Physics or Engineering
- [ ] Chemistry
- [ ] Maths, Statistics or Epidemiology
- [ ] Computer Science