ICR The Institute of Cancer Research

PhD Project Proposal

Funder details

Studentship funded by:
Breast Cancer Now

Project details

Project title:
Harnessing the principle of cell competition to treat breast cancer

Supervisory team

Primary Supervisor:
Prof. Pascal Meier

Associate Supervisor(s):

Secondary Supervisor:
Prof. George Poulogiannis

Divisional affiliation

Primary Division:
Breast Cancer Research

Primary Team:
Cell Death and Immunity

Site:
Chelsea

Project background

The majority of metastatic cancers remain incurable. Treatment with standard approaches may extend survival, but ultimately fails due to the emergence of resistant clones. This is the natural consequence of a process of clonal evolution fuelled by competitive interactions and intra-tumour heterogeneity. The ability of clones to compete and evolve under selective pressure of drug treatment poses a significant challenge for anti-tumour therapies. A deeper understanding of the mechanism of cell competition may ultimately lead to new treatment approaches that target the fitness landscape of supercompetitive cancer clones. Ultimately, we aim to understand how we can **restrain** cancer evolution by **manipulating cell competition mechanisms**.

Cell competition is an active cell selection process that promotes elimination of viable but suboptimal cells for the benefit of more competitive neighbours. Cell competition plays an important role for the maintenance of tissue health during development and adulthood[1-5]. However, the process of cell

competition can also be hijacked by cancer cells to subdue their wild-type neighbours. The signalling pathways and how relative fitness is measured across tissues have only recently emerged.

Many genes shown to generate supercompetitors are known tumour suppressors or oncogenes: Myc, Jak-Stat, Notch, Yap/Taz, Ras, Apc and p53. We and others have shown that Myc and Ras tumour cells behave as supercompetitors due to their ability to hijack the NMDAR signalling circuit[6, 7]. We find that differential levels of Glutamate and its receptor N-methyl-D-aspartate receptor (NMDAR) in winners and losers is crucial for cell competition[6]. Further we find that differential NMDAR signalling reprogrammes metabolism in losers and winners, driving losers to produce and transfer lactate to winners. Preventing transfer of lactate from losers to winners abrogates Myc-mediated supercompetition and prevents their overgrowth. Here we propose to build on our preliminary data and gain a deep understanding how glutamate-mediated NMDAR signalling contributes to the supercompetitor status of cancer cells.

The ultimate goal of this proposal is to identify the molecular mechanisms through which we can 'steer' the competitive behaviour of cancer clones to prevent clonal evolution and the appearance of drug resistance.

Project aims

- To elucidate how the NMDA receptor (NMDAR) is activated during cell competition, and delineate the signalling pathways downstream of NMDAR that control metabolism, proliferation and survival/death.
- To identify genes involved in defining fitness fingerprints of adjacent competing winners and losers.
- To develop novel treatment protocols for cancer that are based on the principle of cell competitive behaviour. The aim is to target the competitiveness of tumour cells, thereby converting supercompetitive tumour cells into 'superlosers' that are killed by their wild-type neighbours.

Research proposal

The goal of this proposal is to gain a better understanding of how to manipulate the 'mechanisms of cell competition' so that we can restrain the evolution of fitter cancer cells, thereby preventing the appearance of lethal clones.

We have previously laid the foundation for this approach, demonstrating that targeting the fitness landscape of supercompetitor cancer cells can indeed trigger their murder by neighbouring wild-type cells. Here, we will build on our expertise in cell death and immunity[6, 9-18] to delineate the signalling routes through which glutamate and its receptor NMDAR influences life versus death decisions in competing populations. To achieve this, we will study how the NMDA receptor is activated and how it influences signalling pathways that regulate metabolism, growth, survival and death of competing cells **(1).** Further, we will identify fitness fingerprints of adjacent winners and losers **(2)**. Finally, using mammalian 3D co-culture assays and a cancer models, we will translate our findings from *Drosophila* to the mammalian setting and develop novel anti-cancer treatment protocols that target the competitiveness of tumours, thereby converting supercompetitive tumour cells into 'superlosers' **(3)**.

Since cell competition is not easily studied, except in genetic mosaics that specifically contain cells with distinct fitness, we will initially use *Drosophila* as an entry point due to its reduced complexity and the availability of cell competition-related reagents. This will provide us with the necessary blueprint from which to explore similar mechanisms in mammals. Ultimately, we will investigate cell competition mechanisms using murine organoids as well as murine tumours.

Experimental plan

Overview: Although differential metabolic states at the interface between winners and loser act as direct drivers of cell competition, how relative metabolic states are measured across tissues, is not understood. Here, we will build on our discovery that the NMDA receptor signalling axis underpins Myc-driven metabolic cell competition[6] and pursue the following aims:

Objective 1: Elucidate how NMDAR is activated during cell competition, and delineate the signalling pathways downstream of NMDAR that control metabolism, proliferation and survival/death.

Objective 2: Identify genes involved in defining fitness fingerprints of adjacent winners and losers.

Objective 3: Learn more about cell competition in mammals and develop novel anti-cancer treatment protocols for cancer. The aim is to target the competitiveness of tumour cells, thereby converting supercompetitive tumour cells into 'superlosers' that are killed by their wild-type neighbours.

Literature references

1. Johnston LA. Socializing with MYC: cell competition in development and as a model for premalignant cancer. *Cold Spring Harbor perspectives in medicine* **4**, a014274 (2014).

2. Claveria C, Torres M. Cell Competition: Mechanisms and Physiological Roles. *Annu Rev Cell Dev Biol* **32**, 411-439 (2016).

3. de la Cova C*, et al.* Supercompetitor status of Drosophila Myc cells requires p53 as a fitness sensor to reprogram metabolism and promote viability. *Cell metabolism* **19**, 470-483 (2014).

4. Traynelis SF*, et al.* Glutamate receptor ion channels: structure, regulation, and function. *Pharmacol Rev* **62**, 405-496 (2010).

5. Rhiner C*, et al.* Flower forms an extracellular code that reveals the fitness of a cell to its neighbors in *Drosophila*. *Dev Cell* **18**, 985-998 (2010).

6. Merino Marisa M, Rhiner C, Portela M, Moreno E. "Fitness gingerprints" mediate physiological culling of unwanted neurons in *Drosophila*. *Curr Biol* **23**, 1300-1309 (2013).

7. Merino Marisa M, Rhiner C, Lopez-Gay Jesus M, Buechel D, Hauert B, Moreno E. Elimination of unfit cells maintains tissue health and prolongs lifespan. *Cell* **160**, 461-476 (2015).

8. Portela M*, et al. Drosophila* SPARC is a self-protective signal expressed by loser cells during cell competition. *Dev Cell* **19**, 562-573 (2010).

9. Meyer SN*, et al.* An ancient defense system eliminates unfit cells from developing tissues during cell competition. *Science* **346**, (2014).

10. Dijkers PF, O'Farrell PH. *Drosophila* Calcineurin promotes Induction of innate immune responses. *Curr Biol* **17**, 2087-2093 (2007).

11. Li Y-X, Dijkers PF. Specific calcineurin isoforms are involved in *Drosophila* Toll immune signaling. *J Immunol* **194**, 168-176 (2015).

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:

- MSc in an appropriate scientific discipline [essential].
- Preliminary technical experience [essential].
- Experience in cell biology, biochemistry or molecular biology [essential].
- Ability to design and implement experiments using state-of-the-art techniques [essential].
- Good communication and presentation skills [essential].

Intended learning outcomes:

- To work independently on a defined project and to consult when appropriate.
- To take an interest in the relevant scientific literature.
- To present work at conferences and participate regularly in group meetings.
- To publish work in the scientific press.
- To generate insight and leads to further our understanding of cell death regulation, which may have significant impact on the development of new therapeutic strategies for the treatment of cancer.
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Advertising details

Project suitable for a student with a background in:

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