CELL MIGRATION AND CHEMOTAXIS

Group Leader
Robert Insall FRSE

Research Scientists
Simona Buracco
Hannah Donnelly[1]
Abhimanyu Kiran[1]
Peggy Paschke
Luke Tweedy[1]

Graduate Students
Sophie Claydon
Adam Dowdell
Lucas Farndale[2]
Elena Mandrou[2]
Joshua Roche[3]
Chris Walsh[4]

[1]Wellcome Investigator Grant
[2]MRC Precision Medicine Studentship
[3]PREDICT-Meso Studentship
[4]CRUK Glasgow Centre

University of Glasgow

The cell migration and chemotaxis lab studies how & why cells move, using a wide range of multidisciplinary tools, including cell biology, computer modelling and artificial intelligence techniques such as deep learning.

Metastasis, when cells spread from the tumour in which they arose and colonise other organs, is responsible for most of the damage cancer causes. In normal organs, and most benign tumours, cells do not migrate. However, when tumours become metastatic, cancer cells may start to migrate – spreading into neighbouring tissues, the blood and lymph systems to form secondary tumours. We are working to understand why cells move, and what steers them.

We ask several different questions, all aimed at the same general problem. One question is how cells are steered by external signals, a process known as chemotaxis, which is increasingly seen as a fundamental cause of cancer metastasis. We are particularly interested in a complex type of chemotaxis, in which cells steer themselves. The Insall lab are world leaders in the field of "self-generated gradients" and were recently awarded Wellcome funding to develop this area.

Another is the mechanics by which cells drive their migration. We focus on the structures that cells use to migrate, known as 'pseudopods'. Pseudopods are made by assembling fibres of a protein called actin; we try and understand what controls how actin is built, and how this leads to formation of pseudopods.

A third, and particularly relevant to cancer at the moment, is to use artificial intelligence (AI) techniques – in particular deep learning – to predict from pathology images whether tumours are metastatic. The lab contains mathematicians, computer scientists, biochemists, microscopists and geneticists. We see one of our chief jobs as spreading true multidisciplinarity – mathematicians do cell biology experiments, and biochemists use mathematical models and computational tools. However, our strategy is always based around cell migration – what drives it, and why?

Mechanisms underlying chemotaxis: Self-generated gradients

Chemotaxis is a major driver of tumour metastasis. We have found that it does not work the way we used to think it does, on many different levels. We design and build chemotaxis chambers to make experiments more informative. We can use these to show that many different types of cancer cells are exquisitely chemotactically sensitive (much more so than was previously thought), including melanoma, pancreatic ductal adenocarcinoma, glioblastoma, and of course blood cancers like lymphoma. The changes that occur as cells become malignant are more to do with speed than steering – early melanomas, for example, are slower but still highly chemotactic. We have shown that this is because the pseudopods grow and develop in a different way as cancers become more malignant.

The most interesting part of melanoma cells' response is that we find they make their own chemotactic gradients. Lysophosphatidic acid (LPA) – which appears to be present at substantial levels in the tissue surrounding tumours – is a strong attractant for all the melanoma cells we have observed. But melanoma cells also break down LPA. This leads to a self-generated gradient, in which cells move out of tumours in response to gradients they are themselves creating. Thus, tumours appear to need no external drivers to steer metastasis – they do it themselves. This appears to be a fundamental feature of many metastatic cancers.

We are now studying the details of self-generated gradients, using mathematical models to identify the range of possible behaviours, and doing experiments with a wide range of different cell types, including melanoma, glioma, pancreatic ductal adenocarcinoma, lymphoma, immune cells such as dendritic cells, cultured neutrophils and Dictyostelium. We have shown that cancer cells and Dictyostelium can use self-generated gradients to solve mazes of remarkable complexity.

We have also shown how cells can use self-generated gradients to repel one another, making cells move away from a source. This is obviously important in metastasis, where cells being driven away from a tumour results in cancer spread.

We collaborate with the Mathematics departments of the Universities of Strathclyde and Glasgow to make different computational models representing moving cells. We are now using these models to test our predictions about self-generated chemotactic gradients and the underlying mechanisms of chemotaxis. We have shown that even single cells can create their own gradients. We have also found that chemotaxis is most likely mediated by several dissimilar mechanisms acting in parallel, including regulated pseudopod growth, pseudopod retraction and the control of adhesion.

We also collaborate with the Physics and Engineering departments in Glasgow to build microscopes that will allow us to test what real cells in tissues and organs are perceiving, live and in real time. This will allow us to test which cells are responding to self-generated gradients, under realistic conditions. The microscope will combine high-resolution CMOS sensors with time-resolved SPAD sensors that allow us to measure the times when individual photons are released. This allows us to interrogate a family of intracellular probes called FRET probes, which give excellent detail about the states of living cells in 3D.

Regulators of actin and the Arp2/3 complex

Most mammalian cells use pseudopods made of polymerised actin to power migration. Our current research focuses on the proteins and pathways that control these pseudopods. We use three approaches. For genetic studies, we use Dictyostelium, taking advantage of its ease of manipulation, and prominent cell movement and chemotaxis. To apply our knowledge to cancer, we use melanoma cells cultured from tumours with different degrees of metastasis, and actual tumours from mouse models and, when possible, from fresh patient tissue.
Actin drives nearly all cell movement, and the principal driver of actin is an assembly called the Arp2/3 complex. We are particularly interested in the family of proteins that turns on the Arp2/3 complex. One such regulator is SCAR/WAVE, which is a fundamentally important regulator of cell movement. Mutants in a variety of species show that it is required whenever cells need to make large actin-based structures such as lamellipods; without SCAR/WAVE such structures are either small and malformed, or completely absent. It is found as part of a five-membered complex with the Rac-binding protein PIR121, Nap1, Abi and HSPC300. The prevailing view in the field is that all these proteins act simultaneously as a huge, homogeneous complex that couples Rac and lipid signalling to actin polymerisation. However, this view seems very simplistic considering the size of the complex and its dynamic behaviour. We were recently awarded an MRC programme grant to follow this line of research.

Deep learning from pathology images

Recently, we and others have found that deep learning can usually distinguish metastatic from nonmetastatic solid tumours, from H&E stained pathology slides alone. We are developing this technology for many reasons. It offers the prospect of faster, more accurate diagnosis for patients, but it also promises to give us new information about why cells become metastatic, how to understand it, and potentially how to stop it. Our most recent work concerns self-supervised learning, where the AI seeks to classify different regions of a tumour without training by pathologists. This offers the hope of a complementary view that bolsters what pathologists already see, rather than reproducing it.

Publications listed on page 105