CELL MIGRATION AND CHEMOTAXIS

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One of the most damaging aspects of cancer is metastasis, in which cells spread beyond the tumour in which they arose and colonise other organs. In normal organs, and most early solid tumours, cells do not migrate. However, when tumours become metastatic, suppression of cancer cell migration may be lost – cells spread into the blood and lymph systems to form secondary tumours. It is believed that cells cannot spread or move efficiently unless they are steered by something. However, it is not understood what provides the directional steer, or how cells manage to read and respond to it. Our group brings together multiple tools, from mathematical modelling to cell biology and biochemistry, to improve understanding of how cell migration is controlled.

We ask questions of two distinct types. The first 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 particularly subtle type of chemotaxis, in which cells steer themselves, by creating and manipulating gradients of signals in their environments. The second 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. The lab contains mathematicians, 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 most importantly how it is steered.

Mechanisms underlying chemotaxis: Pseudopods and self-generated gradients

Chemotaxis is emerging as 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. Pseudopods – the structures that actually move cells – are not made following a decision, but constantly generated in random directions; steering and migration occur when pseudopods that point in the best directions are selected and maintained. We have shown that this is true in multiple different cultured melanoma lines, and constructed computer models that reproduce it. We also 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. 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 metastatic cancer.

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, donated neutrophils and Dictyostelium.

We are collaborating 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.

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, homogenous complex that couples Rac and lipid signalling to actin polymerisation. However, this view seems very simplistic in view of the size of the complex and its dynamic behaviour.

Our experiments are currently focused on identifying the activators and other proteins that regulate each component of the complex. We are using the Institute's expertise in mass spectrometry to identify proteins that crosslink to SCAR in living cells at different migration rates. We have set up a system that allows us to purify biochemically useful amounts of SCAR complex from living cells. This is a unique facility. We have now found that SCAR is phosphorylated at multiple sites when it is activated; this is an exciting result, because it has never been possible before to identify the active molecule. We are now seeking to understand what regulates this phosphorylation, and how it connects to upstream signalling molecules such as receptors and G-proteins. The behaviour of SCAR's relative WASP is slightly anomalous – there is a high degree of consensus among cell biologists about how it is controlled, but the standard view does a poor job of explaining the observed behaviour. We are therefore mutating and dissecting WASP to see how it works.

Publications listed on page 86