Could you summarise some of the headway you have made in studying macrophages?

Macrophages are not particularly easy cells to work with and microscopy methods often need to be altered to observe the unique adhesion and cytoskeletal structures underpinning their motility. Much of my microscopy expertise, therefore, has been in developing and optimising various protocols for these cells. For example, macrophages do not form large adhesions, which are called focal adhesions, but they form thousands of much smaller focal complexes and tiny point contacts to allow powerful but rapidly modified adhesion to the substratum. I found that using an antibody directed to a phosphorylated (and, therefore, ‘activated’) form of paxillin allowed me to observe macrophage adhesion structures with striking clarity because background cytoplasmic paxillin was eliminated.

Why do you think in vitro methods of experimentation are often neglected? What unique advantages can such investigations offer?

In vitro conditions are considered artificial, which indeed they are. However, in vitro experiments allow us to observe and interrogate cells in a manner that is just not possible in vivo. They allow a simplification of complex behaviour in order to tease apart individual cellular contributions to normal or abnormal mechanisms.

How important is mentorship, especially of women, to the broader aims of your work?

Mentorship and leading by example are central to my life and are certainly not restricted to my work in the lab. I have spent a number of years coaching women and younger girls in water polo, from the Great Britain team while living in England in the 1980s to under-16 teams in the US and now back in Perth.

From my own experiences, girls and women often lack confidence in their own abilities and this, when combined with institutionalised bias, is often deadly to careers and feelings of self-worth. Women need to be told that they’re up to the job and that they’re just as good as the guys! People in positions of power will often take on those who look like a good fit, ie. junior copies of themselves, as their trainees and this works against women as there are fewer women in high positions. This bias is often magnified when doctors or lab heads meet junior trainees at conferences and other meetings.

I also find the lack of encouragement and identification of women who don’t stand out from the pack incredibly depressing. Guys who don’t stand out from the pack manage to get noticed and secure good jobs much more readily than women with equivalent credentials.

What are your thoughts on collaboration and competition in your field, and science more generally?

Limited access to funding is likely to restrict my work to largely in vitro studies for some time at least. Thus, collaborations that combine the optimised cell-based and biochemical assays used widely in my lab with in vivo studies in a collaborator’s lab would be most useful for me. As for trying to swing the balance away from the highly competitive, winner-takes-all approach to funding and towards a more collaborative one, that would require more time than I have available. What we really need is for the people who run the show to understand how detrimental this approach can be to the progress of good science.
Researchers at the University of Western Australia have made inroads in studying macrophage cells and their role in cancer progression; now, they seek collaborators to take their work to the next level.

MACROPHAGES ARE SPECIAL cells, set apart from their compatriots by a number of features. Although they are among the most widely recognised cells, and their ability to destroy foreign cells and particles by engulfing and ‘digesting’ them is well-known even amongst lay people, it is far from being their only talent.

In addition to their aggressive powers of phagocytosis, and their abilities to rigorously interrogate and identify other cells by their surface proteins, macrophages also have the capacity to send signals to other cells, inducing or preventing inflammation and modulating the entire immune response to foreign bodies. They even act as a trophic support system for other cells, ‘feeding’ them with growth factors and other cytokines. Although they were named for their defensive capacities, these ‘big eaters’ actually perform diverse roles, the hierarchy of which is still not completely understood.

Another important feature that distinguishes macrophages is that they can be found in all bodily tissues. Unlike other living cells, which cluster together to perform functions in concert, these stewards of the body range freely throughout tissues and organs, destroying intruders wherever they are found and supporting the activities of other cells. As a result of this necessity to travel, macrophages are highly motile cells, able to digest extracellular proteins and effectively ‘burrow’ through tissues; they can quickly move from one region of the body to another and have efficient methods for accomplishing this.

TRAITOR CELLS

It is all very well to rest secure in the knowledge that these powerful cells are indefatigable defenders of human health – but unfortunately, disease states can turn the macrophage army against its commander. When the body is affected with a condition like cancer, macrophages can cease to act normally. This change in behaviour hinders their defensive actions and can even give the advantage to the enemy; cancer cells, for example, are capable of recruiting macrophages for their own purposes, hijacking their ability to tunnel through tissues and achieving metastasis.

By achieving a more detailed understanding of macrophage behaviour, scientists could potentially gain an insight into important diseases and how they subvert the actions of these protective cells.

Associate Professor Fiona Pixley at the University of Western Australia (UWA) leads a laboratory that specialises in examining this topic. Based in the Pharmacology, Pharmacy and Anaesthesiology Unit at UWA’s School of Medicine and Pharmacology, this dedicated group of scientists is conducting cutting-edge research into the behaviour of macrophage cells in vitro – and has already developed and optimised a number of novel tools to facilitate this process. Although their studies focus nominally on breast cancer, the impact of their work could have much broader implications – as Pixley explains: “To be considered fundable in this day and age, we always have to package up what we do into the context of a specific disease – but macrophages play a role in many diseases, since they’re found throughout diseased tissues as well as healthy ones”.

NOVEL METHODS AND INVESTIGATIONS

The methods Pixley and her colleagues employ to capture the behaviour of macrophages include both tried-and-true tools and more innovative approaches. In general, however, they can examine both the motility and invasion of cells in similar ways. Transwell assays, for example, are designed to assess motility, and with the addition of Matrigel, an artificial extracellular barrier, they become tests of...
MACROPHAGE MOTILITY

OBJECTIVES

- To determine how macrophages move within and between tissues to carry out their wide range of functions in virtually every organ system in the body
- To examine the role of macrophage migration in the context of breast cancer

KEY COLLABORATORS

Professor Matthias Ernst, Scientific Director, Olivia Newton John Cancer Research Institute, Australia
Associate Professor Evan Ingleby, Harry Perkins Institute of Medical Research, Australia
Associate Professor Wendy Ingman, University of Adelaide, Australia
Professor E Richard Stanley, Albert Einstein College of Medicine, USA

PARTNERS

The University of Western Australia (UWA)

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FIONA PIXLEY is a medically trained scientist with a Bachelor of Medicine, Bachelor of Surgery [Honours] and a DPhil in Clinical Medicine/ Epidemiology from the University of Oxford. After five years of clinical work in Oxford and London hospitals, she spent a year learning molecular biological techniques at the Weatherall Institute of Molecular Medicine in Oxford and subsequently worked at the Albert Einstein College of Medicine in the US. In 2007, she started up her own laboratory in the School of Medicine and Pharmacology at UWA.

SEEING THE INVISIBLE

The outcomes of this research have been surprisingly diverse, and many of them have centred on the new methods and revised tools that the researchers have developed to carry out their work. For example, Pixley’s collaborative studies with electron microscopist Frank Macaluso at Albert Einstein College of Medicine led to the advent of an osmium tetroxide ‘quick fix’ protocol for preserving the morphology of individual macrophages while they undergo scanning electron microscopy, as well as an adapted actin cytoskeleton fixation protocol suitable for these cells.

These methods, which are now several years old, have allowed Pixley to gain insight of unprecedented clarity into the structure and behaviour of macrophages. “Macrophages form these beautiful button-like ‘feet’ on their ventral surface known as podosomes, which are used for adhesion, motility and probably primarily for digging through the matrix,” she enthuses. Seeing such detailed pictures offers scientific insights as nuanced as the aesthetic qualities of the cells themselves – and this may be part of the reason why Pixley’s published works on this topic have been cited more than 1,000 times collectively.

COLLABORATIVE OPPORTUNITIES

The Australian researchers plan to capitalise on recent advances in imaging to focus in ever-greater detail on their subject – but they are also actively searching for potential collaborators specialising in in vivo studies. “The results obtained from in vitro experiments complement in vivo findings and enable us to gain a more complete picture of cell behaviour,” Pixley observes – and similarly, a partner with experience in this area would complement her research portfolio perfectly.

INFLUENTIAL FROM THE START

Although Professor Fiona Pixley’s attention has been focused on macrophages for a number of years, her earlier work in other areas was also influential. During her PhD studies at the University of Oxford, for example, Pixley conducted her first sustained work on the epidemiology of gallstones in female patients. She found that vegetarians were half as likely to develop gallstones when compared with women following regular diets, a discovery that is still being cited 30 years on.

Following her training and entry to the Royal Colleges of Physicians, she began education again with a different objective: to achieve qualifications in molecular biology. During this period, Pixley contributed to the development of novel rapid and sensitive methods for diagnosing pneumonia in HIV patients. The publications from that work have accrued over 600 citations collectively.