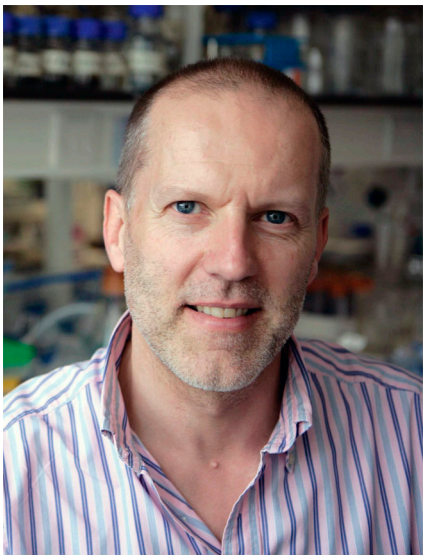
Martin Humphries: Attached to adhesion

Humphries studies how interactions with the extracellular matrix influence cell phenotype.

Interactions with extracellular matrix proteins such as fibronectin influence cell locomotion, survival, and even growth. At the crux of all these activities sit integrins, transmembrane receptors that pass environmental information into the cell and also modulate the cell's interactions with the exterior milieu. Appreciation and understanding of integrins' importance continues to grow, but both the identity and nature of these receptors were once complete mysteries.

Martin Humphries made important contributions toward early efforts at characterizing cell interactions with fibronectin (1, 2). Later, he found himself at the center of efforts to characterize the mechanisms regulating β1 integrin affinity and ligand binding (3, 4). Now, he's mapping out how integrin signaling modulates a multitude of cellular processes (5), as he explained when we reached him at his office at The University of Manchester in the UK.



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Martin Humphries

EARLY SERENDIPITY

What set you on the path to becoming a scientist?

There are a number of pivotal moments in anybody's career where, through serendipity, you end up undergoing a transformational change in your life. For me, the first of these moments was an examination I took at age 11 in the UK, which determined what kind of high school I went to. I was lucky that I did so well on that exam that I got a scholarship to Nottingham High School. It turned out that the ethos of that school was perfect for me, and it set me on an academic path. My best subject in high school was art, but it was the enthusiasm of a young biology teacher that really inspired me to apply to universities to study for a biochemistry degree.

Did you have any other role models in the sciences while growing up?

Not really. Neither of my parents had been to university, and they didn't try to force my brother and me into anything. Actually, my wife, who is a science teacher, and I have tried to do the same thing with our kids. I also do this with the faculty and students I advise. I believe it is best to create a supportive environment that allows an individual's wishes and ambitions to develop, rather than trying to shape them too closely.

I hope my wife and I have been successful at that. Our elder daughter is now an architect, which I think is great because architecture represents a combination of science and art that I think I would have found attractive as a career. Our younger daughter is in the final year of her PhD, working on the actin cytoskeleton—which of course is not far from what I do. I think she'll soon be looking for a postdoc position in the US, in case anyone over there is looking for a postdoc. [Laughs]

> "A good scientist can get excited about any unanswered question."

Did you ever have doubts about pursuing a PhD?

I've been on the academic ladder since day one, but I never really knew at any stage whether I would be able to take the next step. I was very flattered when I was offered a PhD position in the final year of my undergraduate course—so much so that I didn't seek any alternative offers.

While I was an undergraduate at Manchester, I had to do a short, two- or three-month research project during my final year. And my project, which was randomly allocated, was on fibronectin. That's how I first started working on it and why I was offered a PhD position in a fibronectin lab.

STAY THE COURSE

Obviously you stuck with studying fibronectin as a postdoc…

This was another pivotal moment in my career, when I got a letter from Ken Yamada at the US National Institutes of Health. I'd had several offers of postdoc positions, but Ken's letter was phrased very carefully and persuasively. He wanted me to work with him, but he didn't have room in his lab at the time, so he suggested that I take a position instead with Ken Olden, who was Director of the nearby Howard University Cancer Center. Then I could be a guest researcher at NIH.

I'd heard of Ken Olden, but I'd never heard of Howard Cancer Center. So, of course, when I arrived at Howard and found out it was a historically black university, it was quite a surprise. It was interesting to be working at an institution that viewed me as a minority and to be regularly driving from Howard—which was located in what was then a dangerous area of DC—to Bethesda, the land of plenty. It was really a rather schizophrenic postdoc period, but it worked. My two bosses, Yamada and Olden, were just fantastic—very different personalities but the best of friends. What I learned from them really set me up for the rest of my career.

How did you manage having two bosses?

I'm obsessed with knowing where everything is, and I'm a compulsive list maker. I used to run several projects at once with Yamada and Olden, and Yamada couldn't believe it when he saw my jobs list. I used to have four or five projects running simultaneously, with a series of experiments

Text and Interview by Caitlin Sedwick
csedwick@gmail.com

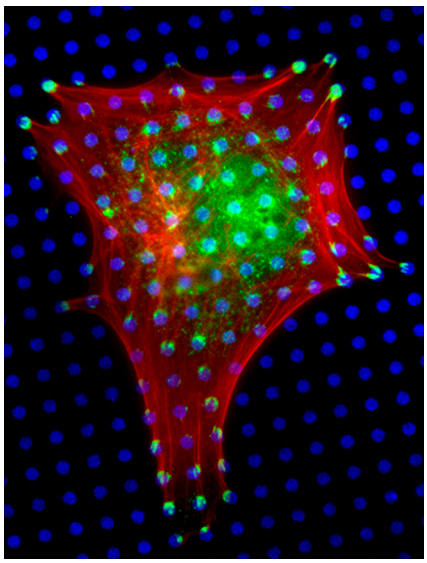

IMAGE COURTESY OF JANET ASKARI

A human fibroblast (actin shown in red, vinculin in green) adhering to a nanopatterned fibronectin surface (blue).

planned in each and several levels of priority for the experiments so I did the right one first.

RIGHT CONTEXT

Did you ever consider working on something other than adhesion?

I'm a firm believer in the idea that a good scientist can get excited about any unanswered question. Certainly, as an undergraduate, I never gave much thought to the importance of the questions I was trying to answer, but of course my work has evolved over the years. At the start of my postdoc, integrins were identified as the cellular receptors that bind to the arginine-glycine-aspartate amino acid motif in fibronectin. And the first thing I did as an independent researcher was to identify the receptor for the IIICS region of fibronectin. These discoveries opened up the field. I then spent 10 years trying to work out—obviously, with many other people in the world—how integrins work as receptors. We now know that integrins undergo dramatic shape changes that determine the affinity of ligand binding, but that took a long while to figure out.

The next step down the chain was to study integrin signaling. And all of a sudden, we're no longer following a linear chain, because integrin signaling impinges on many pathway inside of the cell. So now we're working on what I think is a really important issue, which is how adhesion has evolved to control global cell functions—not just adhesion and migration but also growth control, gene expression, differentiation, and maybe even cell metabolism. My main focus at the moment is on understanding how the signaling from integrin receptors links into these different processes. To do that, we're taking a proteomic approach by isolating adhesion signaling complexes and looking at how they change under different circumstances to try to get a clue as to how they integrate cell functions together.

What contextual changes take place?

The ligands that adhesion receptors stick to are not evenly distributed outside the cell; they're present in fibers, in networks, and in gels that are not homogenous. The central hypothesis is that cells can interpret this spatial pattern and its mechanical and chemical properties and respond accordingly. But how do they do this?

> "Spatial control of signaling tells the cell about its environment."

Adhesion signaling complexes assemble on the cytoplasmic face of adhesion receptors, along the membrane and cytoskeletal fibers, and the location of these complexes maps directly onto the topology of the matrix proteins outside the cell. We speculate that this spatial control of signaling tells the cell about its environment and then is integrated into the control of cell function.

Another way adhesion complex signaling can be modified is through receptor cross talk. There are other adhesion receptors besides integrins, including immunoglobulin superfamily members, cadherins, selectins, syndecans, and growth factor receptors. Integration of receptor signaling is a common mechanism used by cells as a way of sensing multiple extracellular ligands simultaneously. We've done a lot of work on integrin/syndecan cross talk, and I think syndecans are underappreciated receptors that are probably more important than most people perceive at the moment.

How's the research environment at Manchester?

I think Manchester is one of the very best places in Europe for biomedical research. I first returned here because I got funding from the Wellcome Trust, which offered great research support. I had fellowship support from the Wellcome Trust for 20 years and only recently gave it up when I became Dean of the faculty here.

This hybrid job of running my lab and being Dean has made good communication very important. I've actually started using Twitter as a means of communicating with our more than 250 faculty. Twitter's the best way I know of finding out what's going on in the world and to get my own information out there. I'm careful tweeting about personal views, though. I don't want to say anything that would restrict discussion by others because I think universities need to tolerate any view in order to support debate. Then again, if you never say anything, will anyone listen to you? So I've started to loosen up a little bit!

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3. Mould, A.P., S.K. Akiyama, and M.J. Humphries. 1995. *J. Biol. Chem.* 270:26270–26277.
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PHOTO COURTESY OF TONY BENTLEY

Humphries' lab wants to understand integrin signaling inside-out and outside-in.