Karen Vousden: Getting the big picture on p53

Vousden studies the activities and regulation of the tumor suppressor p53.

p53 is famous—or infamous—as a fulcrum in the development of cancer. As a transcription factor, it controls the expression of a bevy of genes that protect cells in times of stress or, when stresses exceed certain thresholds, sends them down the path to cellular suicide. Its mutation or loss is observed in many types of cancer.

Karen Vousden has been studying p53 since the early stages of her career as an independent scientist. Her lab has investigated everything from the processes that regulate p53 stability (1, 2) to the genes whose expression is controlled by p53 (3, 4) and the functions of mutant versions of p53 that accumulate in cancer cells (5). We called her at her lab at Cancer Research UK's Beatson Institute in Glasgow, where she's now the Director, to flesh out the details on p53 and to sketch the larger picture of her career.

BIO SKETCH

Where did you grow up?

I grew up in Gravesend, an industrial town on the banks of the Thames in the southeast of England. Neither of my parents is an academic; my mother was a school dinner lady, and my father was a toolmaker in a factory. They always strongly supported me in my schoolwork but never really had any academic aspirations for me. Nonetheless, they are very happy about the way things worked out.

When I was little, I wanted to be a teacher. Then, when I went to secondary school, I had some outstanding chemistry and biology teachers who encouraged an ambition to become a scientist. But when I was about 14, a career advisor visited the school. She asked me what I wanted to do, so I said, "I want to be a research scientist," and she said, "Oh, that's much too difficult. Have you thought about working in a bank?" [Laughs]

So in spite of this advice—

Yeah, I stuck with it. In the end, I went to the University of London and studied biology. I started off in straight biology courses and then ended up graduating with a degree in microbiology and genetics. But I never really had a long-term plan.

Now I occasionally get invited to talk to graduate students, and they want insights into the right steps and strategy for a career in science. But I always feel I have nothing to offer because I had no strategy—I made most of my career decisions based on what seemed like it would be fun and interesting.

What grabbed your interest first?

As a graduate student, I carried on with an undergraduate project I had been working on, studying transcriptional suppressors in fungi with Lorna Casselton, who really encouraged me to continue in research. When I finished my PhD, I realized I would probably have to think about getting a job. I saw an advertisement in the back of *Nature* for a position with Chris Marshall, a new group leader who had just started at the Institute of Cancer Research. I thought, "Oh, cancer research, that sounds like fun." [Laughs]

> "I made most of my career decisions based on what seemed like it would be fun and interesting."

So I duly sent him a letter, as we did in those days, and applied for the job. Working for Chris at the ICR exposed me to a really exciting and intense research environment. That was back in the days when people were first discovering human oncogenes and the role of Ras in cancer—it was fantastic, from the very start.

FIRST STUDY

When did p53 first start getting your attention?

I went to Doug Lowy's lab at the NIH to do a second postdoc—in part because I thought it would be fun to work in the States. I knew Doug from his excellent work on Ras, but half his group worked on papillomaviruses, which were already suspected to be involved in cervical cancer. When he offered me a choice of area to work in, I chose papillomaviruses. But I hadn't been in Doug's lab for very long when I saw an advertisement looking for group leaders to join a newly established branch of the Ludwig Institute at St. Mary's in London that was focused on viruses and cancer. I applied, and it surprised, I think, both Doug and myself when I got the job.

PHOTO COURTESY OF BEATSON INSTITUTE FOR CANCER RESEARCH

Karen Vousden

I spent another year in Doug's lab and then went back to London to set up my own lab. I remember sitting there on my first day and thinking, "What have I done?" I was really quite lost. I spent the first week making up ethidium bromide. [Laughs] Finally, Paul Farrell—he was the director—came and asked me whether I was ever planning on doing any experiments. So I hired a few people and carried on trying to understand how papillomavirus oncogenes work.

The big break in this area was really the work by Peter Howley, Ed Harlow, Arnie Levine, and others showing that the transforming genes of papillomaviruses work by interacting with the cell

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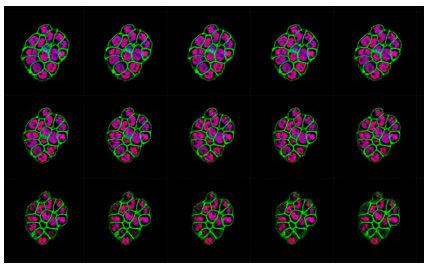

IMAGE COURTESY OF PATRICIA MULLER

Selected images from a Z-stack through a colony of human colon cancer cells showing p53 (red), DNA (blue), and E-cadherin (green).

proteins Rb and p53. So we did some work on the interaction between Rb and the viral protein E7 before starting to look at the E6–p53 interaction. And it just became clear that p53 itself was probably a more interesting problem than E6, so, over the next couple of years, the lab moved to focus just on p53.

You've studied many aspects of p53's function and regulation...

I think sometimes we try to do too much and spread ourselves too thin. But it all comes back to the same issue, that we find it hard to resist investigating the things that we think are exciting. We, along with Moshe Oren and David Lane, were lucky to uncover the fact that Mdm2 targets p53 for degradation. Following up on that work has led us into some really interesting areas.

Your lab also identified the p53 effectors PUMA and TIGAR. Does someone in your lab have a penchant for big cats?

No, not really. [Laughs] After working at the Ludwig, I was recruited back to the States by George Vande Woude. I had many excellent postdocs there, and one—whose name, in a funny twist, is Katz—had done an expression array looking for genes activated by p53. One of his hits was also discovered around the same time in Bert Vogelstein's lab. We both had our own pet names for the gene, but, while our papers were being revised, we agreed to use a completely different name. It was Ken Kinzler, I think, who came up with the name PUMA, for "p53 up-regulated modulator of apoptosis."

Another hit from Katz's screen was TIGAR, but at the time we had no idea what it did. We later realized that TIGAR had some sequence similarity to the bisphosphatase domain of the metabolic enzyme PFKFB. By that time I was here at the Beatson, and we had been lucky enough to recruit Eyal Gottlieb to the Institute. Eyal's a world expert on metabolic pathways, and he helped us figure out how TIGAR works.

THE BIG PICTURE

How do TIGAR and p53 affect cell metabolism?

It's well known that cancer cells tend to rely on glycolysis even under aerobic conditions. We also know from other people's work that p53 can dampen glycolysis—and this may be one way in which p53 impedes tumor development. Although TIGAR can limit glycolysis, we've found that it can also help cells adapt to and survive transient periods of stress. One idea we find really interesting is that TIGAR might actually help tumors develop if its expression is uncoupled from p53. This could be true for other p53-regulated genes as well, and that's an idea we're actively working on right now. So I have a couple people in my lab working on TIGAR, and others are looking at how p53 helps cells cope with various nutrient stresses. The rest of my lab is working on how ubiquitination and ubiquitin-like protein modifications regulate p53 and on the activities of mutant p53.

> "TIGAR might actually help tumors develop if its expression is uncoupled from p53."

What does mutant p53 do in cancer cells?

Many tumors express high levels of point-mutated p53 protein. That gives the impression that maybe there's more to mutant p53 than just loss of wild-type p53 function. In collaboration with Jim Norman here at the Beatson, we've come up with some really interesting observations on how p53 affects trafficking and recycling of cell surface receptors and how that might contribute to the increased metastatic potential that is associated with mutant p53 expression in many cancers.

Can you share your secrets to success?

I wish I could, but I don't think there is any secret formula, really. I've been very fortunate to work for some inspirational scientists who have all helped and supported me along the way. I also have fantastic people in my lab, and I try to make sure that they're working on projects they find interesting. Success only comes after a lot of hard work and disappointment, so it's very important to be working on something that you feel passionate about. From my point of view, it's a privilege to be able to do this job—it's enormously good fun and incredibly satisfying. And in addition to running my own lab, I'm now in the happy position of being the director of the Beatson, which allows me to contribute to the development of others' careers, too. It's just the perfect job.

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The Vousden lab hard at work plundering p53's mysteries.