Medical Xpress

Hacking into normality: Gerard Evan

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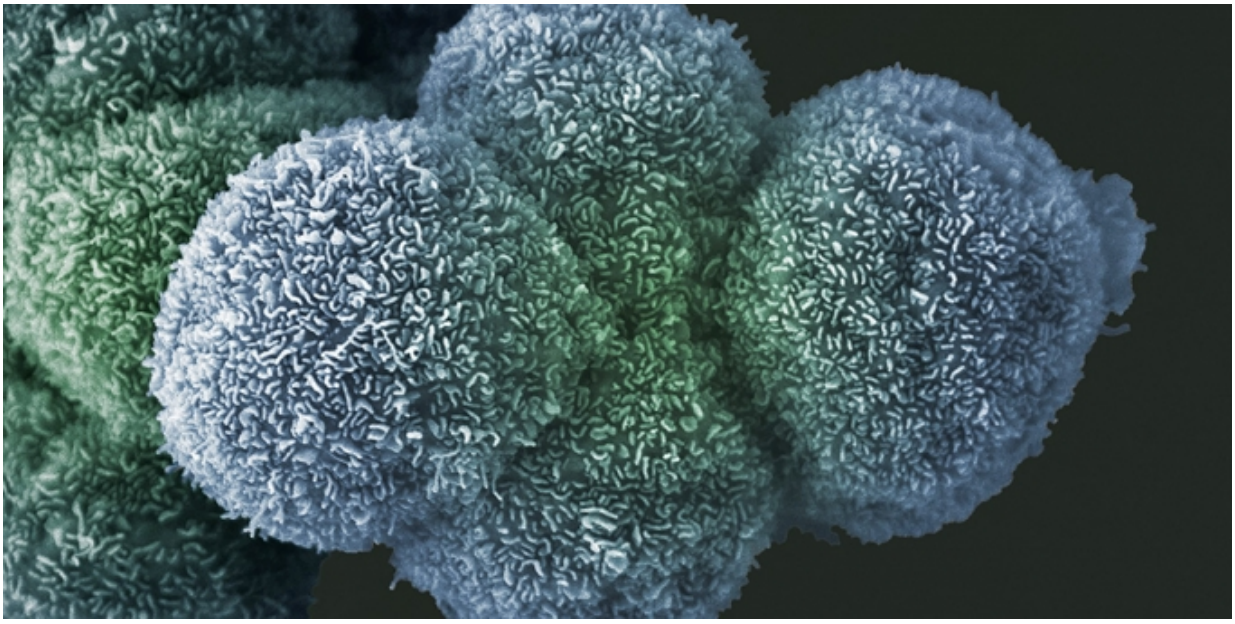

Pancreatic cancer cells. Credit: LRI EM Unit

Currently Sir William Dunn Professor at the University of Cambridge, Gerard Evan has focused his research the MYC oncogene. His lab has recently started working on pancreatic and lung cancer, drawn in part by the excellent mouse models available. Here, Gerard discusses a new way of viewing cancer that has major implications for our understanding of the disease, and how to treat it.

"There are two questions in biology – how and why? Both are important: the 'how' addresses how the nuts and bolts of a biological process are

hooked up with each other. The 'why' question is the one that British science has always been very good at addressing – why are things the way they are and why do they work the way they do? As a cancer biologist, my version of this question is simple: why is it that cancers of a particular tissue or cell type share a remarkably consistent histological phenotype – so consistent, in fact, that we use it as a primary diagnostic tool?

I always tried to understand biology for what it is: a set of evolved processes rather than a purposefully constructed machine. Thinking this way sheds a very different light on cancer because cancer is generally a late-life, post-reproductive disease. Hence, its impact on our reproductive 'fitness' is negligible. We therefore have to view the properties and behaviour of cancers, and of our bodies' responses to it, as a subversion of a process that is important for survival and reproduction – namely, our amazing ability to repair our bodies when they get damaged.

Viewed through this lens, it makes perfect sense that cancers of a particular tissue all look similar to each other. Although the oncogenic mutations that drive cancers are very diverse, they all do basically the same thing: they hack into the resident regenerative engine of each tissue type. Many drivers but only one car. These regenerative engines differ from tissue to tissue because each tissue type has its own unique structure and function, and so requires its own distinct programme to rebuild it when damaged. Take pancreatic cancer, for instance. A major function of the normal pancreas is to make digestive enzymes. When the normal pancreas is damaged, the body has to deal with a leaky bag full of digestive enzymes, able to wreak havoc on any nearby cells and tissues. To counter this threat, areas of injury are rapidly walled off by dense connective tissue, termed desmoplasia. Now, desmoplasia is not only a hallmark of a regenerating pancreas but also of pancreatic adenocarcinoma. So, we think pancreatic cancers look the way they do

because they are hacked versions of the normal pancreatic regenerative programme.

Damage to other types of tissue is repaired in other ways. For example, lungs are exposed to the outside world so lung damage is most commonly associated with infection. To combat infection, an enhanced blood supply is needed to be pump the damaged region with lymphocytes and other protective cells. After the damage has been contained, the lung tissue needs to be rebuilt, but in a different way to the pancreas as its structure and functions are totally different. Hence, if we postulate that lung cancers are driven by a corrupted version of the regenerative process specific to lungs, we end up with a coherent explanation for why lung and pancreatic cancers look so different, despite sharing many oncogenic driver mutations.

Using transgenic mouse models in which we can reversibly switch on and off the pivotal RAS and MYC oncogenes in either lung or pancreas, we've shown two really important things that support our hypothesis. First, as soon as you switch on RAS and MYC in each tissue, you see tumours arise immediately that, from the outset, have the signature characteristics of each cancer type. In the lung, the tumours explode with blood vessels but little desmoplasia. In the pancreas, the tumours immediately resemble highly pancreatic adenocarcinomas in which 90% of the mass is not even tumour cells but desmoplasia. The same drivers but different engines.

Second, and most encouragingly, because we build off-switches in our driving cancer genes, we have been able to address what happens to lung and pancreas tumours when we switch off MYC. The answer is that both kinds of tumour rapidly regress. This is intriguing since a similar thing happens in the regeneration of normal tissues. The idea we're working on now is that shutting down oncogenic signalling is essentially a trigger for a dominant wound resolution programme, which prunes the excess and

aberrant tissue in the cancer and remodels it back to where it was originally. Cancer therapies essentially work by invoking a normal physiological process involved in wound repair.

Why does this matter to our eventual aim of curing cancer? The current dogma is that each cancer in each patient is different and, even within an individual patient's cancer, there is huge heterogeneity amongst the component cells. Hence, treatment will require expensive personalised therapy tailored to each patient. By contrast, if we start from the observation that cancers are actually pretty similar in terms of the way they look and behave, then perhaps this implies the existence of shared vulnerabilities common to all patients with a particular type of cancer. We're really fired up by the possibilities this idea – of 'impersonalised therapy', if you like – offers for the future. The payoff is potentially colossal and my intuition tells me we're on the verge of some really exciting insights."

How did you get interested in biology?

From a B movie called Fantastic Voyage, when I was about 10. A submarine gets miniaturised and injected into someone's bloodstream, and I suddenly realised that was cooler than dinosaurs, my previous passion.

What was the high point of your career?

I'm still most proud of making the strange discovery that the MYC oncogene can drive cell death. But I actually think what I'm working on now will be of greater importance, if it's true.

Do you believe in hunches?

I'm a great believer in the notion that if you find an explanation that covers not just the problems you're facing, but also gives you collateral insights into other things, you're onto something.

What does cancer research need today?

More people skiing off-piste! There are fundamental questions that have been bypassed for ages, like how does p53 suppress cancer? There are 87,000 publications on p53 and we still don't know why or how it suppresses cancer in all tissues.

Do you have a mentor?

I owe a great debt to Rod Porter, who was Professor of Biochemistry at Oxford when I was an undergraduate. I worked for him as a Part II student and he took me under his wing. I would go back to Oxford when I was struggling with my PhD and he would tell me to hang in there.

Do you have any advice?

Go where the best science is and be passionate about it. If you lose the passion, stop doing it.

Tell us a secret...

You can have three! I got to the end of my degree in Oxford not really understanding the difference between transcription and translation. I have no sense of smell. And I only recently found out that Montmorency in Three Men in a Boat was a dog.

Provided by Cancer Research UK