A Conversation with Gerard Evan

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Gerard Evan is the Sir William Dunn Professor of Biochemistry at the University of Cambridge.

Richard Sever: You've likened the evolution of a cancer to the Apollo 13 mission. Can you explain what you mean by that?

Dr. Evan: The language we use about cancer is loaded with terms that imply that it's got a plan or a purpose, and it's heading in a direction, which is basically to kill the patient. We use the word "progression" as the disease gets worse. Really though, cancers arise by random mutations, followed by natural selection for the fastest growing or most surviving variant. It's a very random process. There's this wonderful moment in the film *Apollo 13* when the astronauts have got too much carbon dioxide because they don't have scrubbers that can remove it and they don't know what to do. They tell the people at NASA that they've got to sort this out and find a solution. Then a guy comes in with a big garbage bag and empties it on the floor; you see that it's just this pile of debris. He says, "This is what they've got, and we've got to make something that does that out of this." And it's that process of coupling together bits and pieces that might not work particularly well, but that work well enough, that is the hallmark of evolution.

When we look at cancers, we see this chaotic process, yet remarkably, cancers of particular tissues tend to look the same as each other. That means that although they arise by a random process of mutation and selection, something constrains and channels the way that they form. For example, the diagnosis of pancreatic cancer is that it looks like other pancreatic cancers with a lot of connective tissue and stroma. Lung cancers look like other lung cancers with their abundant blood vessels and inflammation. Pancreas tumors look like each other but look different from lung tumors, even when they seem to be caused by the same general types of mutations in the same general types of genes.

Richard Sever: It's not a superficial similarity with different mutations?

Dr. Evan: That's what we don't know. Why is it that through random mutations pancreatic cancers all end up looking like each other, and lung cancers all end up looking like they do, and liver cancers end up looking like they do? It can't just be random. There has to be something that's constraining them.

There are two possible explanations, both of which have some merit. One is that the way cancers can evolve in particular tissues is constrained by the way in which that tissue works. That is, cancers look like they're hijacked, hacked versions of processes that occur normally in tissues when that tissue is damaged. When a tissue is damaged, the program that repairs it needs to be fairly specific for that tissue—this just reflects the fact that different tissues are built in different ways.

Richard Sever: To your "Apollo 13" analogy, this is because the parts available in that rubbish bag are different in different organs.

Dr. Evan: That's correct. The other idea, which I think is also probably true to some extent, is that there's some tissue-specific constraint as to which mutations and which processes can get mutated, and in which ways, to drive a cancer in each tissue type. There's probably some sort of top-down selection, i.e., certain types of mutation that give rise to faster growth in some tissues don't do so in another tissue, perhaps because they just don't have, say, the right blood supply in that tissue. They simply have no way of making it in that tissue. So my guess is that there are constraints from the bottom up, the canalization I referred to first, colliding with some constraints from the top that confer a selective advantage to specific mutations in one tissue versus another.

Richard Sever: Almost like internal as opposed to external constraints?

Dr. Evan: Correct. And we're left trying to sort this out. Of course, what we all want to know is if there are commonalities across cancers, or certain types of cancer. Are there general cancer principles? Yes, everybody's cancer is different from everybody else's cancer because they arise by these spontaneous, random mutations. And even within cancer, there's a huge amount of heterogeneity within the cells. But if cancers are really irreducible, complicated messes, then there's no way of generally describing the process or of identifying general therapies. On the other hand, if—as it seems to be—cancers are quite highly constrained, then we can guess that there must be general principles that would apply to, say, all cancers that arise in a particular tissue type. There could even be general principles that apply to all cancers in all tissues.

Richard Sever: That scenario is almost the opposite of personalized medicine.

Dr. Evan: Yes, I like the idea of impersonalized medicine. It's very easy to get bogged down in the differences between cancers, but just because there are differences doesn't mean to say they are different. All humans have huge differences one from the other, but they share a huge amount of commonality.

Richard Sever: Right. Antibiotics will work if you've got plague.

Dr. Evan: That's a perfect analogy. It doesn't matter who you are—unless you're allergic to the antibiotics! If we could identify these nodes, the shared common elements that go wrong in cancers, then there's no reason why we wouldn't be able to develop therapies that work against many cancers, perhaps all. It sounds like science fiction but to me it's a very real possibility.

Richard Sever: You've recently looked at Myc and Ras in pancreas and lung. What have you been doing there to look at this issue of constraints?

Dr. Evan: We know that these two archetypical oncogenes cooperate. Ras does something that Myc doesn't do, and Myc does something that Ras doesn't do, and you need to put them together to get the full process of tumorigenesis, or at least to provide the platform on which further evolution of tumors can arise. They are two cooperating cancer nodes whose deregulation is implicated in most, perhaps all, cancers. This Ras plus Myc cooperation is a platform on which all tumors depend, and upon which are erected minor secondary embellishments—giving this clone a bit more of an advantage to this, and perhaps a bit less of an advantage to that. The point is that targeting these secondary attributes is not going to knock

out the platform and make the tumor go away. You're just going after the hydra head by head, when actually what you want to do is pour bleach on the thing and wipe it out completely. You want to hit the nodes.

We've built in vivo mouse models where we flick on Myc and Ras in different adult tissues and ask what happens. In all cases, the Myc–Ras combination drives tumorigenesis very effectively, almost instantaneously, but you have to have them both. Ras without Myc arrests cells permanently. Myc without Ras, the cells die. This is the prototypical way that biology solves the problem of how to make something incredibly easy—cell proliferation—when it needs to happen but incredibly difficult when it shouldn't happen. As an analogy, it's the same way that we make it easy to get into our house for us, but difficult for someone else. There's a key that turns a combination. You have to have the combination of Myc and Ras to unlock the proliferative machine and cells “cul-de-sac” if they are each activated separately by mutation. But when mutations activate the two together, then you get the full-blown cancer platform.

Remarkably, these Ras–Myc-codriven cancers look like they are a hacked regenerative program from each tissue. If you activate Myc and Ras in pancreas, you immediately get a pancreatic adenocarcinoma: collapse of blood vessels, lots and lots of connective tissue, all the inflammatory and immune attributes of pancreatic cancer. You switch on the same Myc–Ras pair in lung, and you get a full-blown non–small cell lung cancer: huge numbers of blood vessels, highly inflammatory and devoid of immune cells. The tumors that Ras and Myc together induce in any one tissue look like each other in terms of behavior, dynamics, and appearance and like spontaneous tumors that emerge in that tissue. But they look very different from tumors driven by Ras and Myc in another tissue. So while cancers in differing tissues look very different they still can, and likely are, driven by the same mutated nodes.

It's rather like the way that the same cell cycle gives rise to all the distinct tissue types. If you look at the bewildering variety of tissue shapes and structures you might conclude that they all have different cell cycle machineries. But that's actually not the case. One size cell cycle fits all tissues. Another analogy that I find very useful is that long before people got old enough to ever get cancer, we were being invaded by highly genetically diverse, rapidly proliferating cells called bacteria. If we'd discovered infectious disease in the era of “-omics”, I'm sure many would be saying, “You have to have a different way of targeting each different bacterial infection.” It's not true. If you hit them where they share common dependencies, you can wipe them out. That's why we have antibiotics—we discovered antibiotics long before the “-omics” revolution.

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