

Ecology, Evolution, and the Cancer Patient

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Incredibly, experimental cancer treatments are no more successful today than they were in the middle of the last century. Patients are better off, of course: childhood cancers and breast cancers are much more curable than they used to be. That is because oncologists rapidly learn from successful clinical trials. But the chance that any particular experimental cancer treatment will work is no higher now than it was in the 1950s. We know this from extensive metaanalyses. Today, just as in the middle of the last century, patients in the control arm of randomized trials are as well off as those in the experimental arm. The average effect size is essentially zero, a sobering number that has not changed over 60 years (Djulbegovic et al., 2008, 2013; Kumar et al., 2005). In one important sense, this is good news: randomized control trials remain an ethically sound way to test the efficacy of new therapeutic interventions. But in another important sense, the observation is something of an affront. How is it that the spectacular achievements of molecular and cellular biology together with terrific advances in cell culture, animal models, and trial design have failed to improve our ability to identify novel treatments that help patients? It is as if something is missing.

Of course everyone in cancer research thinks they know what is missing: it is the thing they are working on. It is an inadequate knowledge of the epigenetic mechanisms, insufficient deep sequencing data, and a poor understanding of mechanisms of cell cycle control. Judging from the grants awarded by the US National Cancer Institute, perhaps the prevailing general view is the one given recently by *The Economist* magazine: “The main reason cancer has been such a hard problem to tackle is a lack of basic understanding of the underlying molecular mechanisms that drive it” (Anon, 2016a). Reading through the chapters in this book, it is clear that ignorance of molecular mechanisms is indeed important. But

every second chapter (almost literally) makes a strong case that ignorance of ecological and evolutionary mechanisms is just as important.

I agree. There has never been a more important time to study the ecology of neoplastic cells, and in particular to study them in what Michael Hochberg (*in press*) calls the disease ecosystem. We now know that the huge array of diseases we call cancer are all the result of evolutionary processes happening in clinically relevant time (Chapters 1, 10). Therapeutic breakthroughs have to involve finding new ways to control that evolution. Molecular mechanisms are the stuff that evolution chews on. But patient health depends on what evolution does with them—and that depends on the ecology. An analogy: if you want to fix traffic congestion, it is important to understand how a combustion engine works and the constraints on its performance. But alone, such knowledge will not produce a fix.

Evolution is one of the most potent life forces known. Whenever humans have tried to deliberately extinguish life, supposedly magic bullets such as antibiotics, antifungals, herbicides, pesticides, and rodenticides eventually lost efficacy in the face of evolution (Greene and Reid, 2012). “Use ‘em and lose ‘em” is the rule. The situation is even more sobering in cancer. Normal and neoplastic cells share a very recent common ancestor, and so there are few potential targets for magic bullets. Worse, cancers become more evolvable as malignancy progresses. This has several implications. Perhaps most importantly: prevention, prevention, prevention (Greaves and Maley, 2012). Second, treatment regimens have to be optimized to slow resistance emergence (Chapters 8, 10, 14). This, as I argue below, is a largely unstudied problem in applied population ecology. Importantly, conventional treatment aims, like minimizing tumor burden at the end of treatment, can exacerbate

the resistance problem (Costa and Boldrini, 1997; Hansen et al., *in press*). And third, given the huge expense of novel therapeutics, investment has to be directed at evolution-proof targets. Note that “evolution-proofing” is like water-proofing. Ideally it is perfect, but substantially delaying water ingress is still a gain.

In other contexts, particularly agriculture and infectious diseases, there is a considerable theory and sometimes compelling evidence that partial or complete evolution-proofing is possible (Greene and Reid 2012; Consortium, 2013). A key message from those fields is that there is simply no understanding evolution without understanding the ecological context in which it is happening. It is tempting to think that with modern sequencing tools, cancer management is a question of reconstructing phylogenies, identifying driver mutations, and coming in hard with drugs targeted at cell lineages specific to an individual patient's tumor. But as with political history, it is easy to see how things could have been changed—after the event. More challenging is to predict and change the future before it happens. For cancer, that requires strategies that slow or prevent the emergence of molecular mechanisms which are not yet detectable.

That is possible. The process of a population evolving itself out of trouble is called evolutionary rescue (Gonzalez et al., 2013). We know that advanced malignancies are fantastically good at that: cancer cells have ferocious capacity to adapt to the insults oncologists throw at them. The rate at which adaptation can save a population from extinction depends primarily on the rate at which heritable variation arises (which can be fearsome in a tumor) and on natural selection and drift acting on that heritable variation. Natural selection and drift (demography) are ecological forces (Gonzalez et al., 2013; Uecker et al., 2014). Understanding the ecology is therefore an essential part of understanding cancer.

This is nowhere clearer than in the context of cancer chemotherapy. Every day, oncologists battle to keep their patients alive. When they lose that battle, as they will almost 600,000 times a year in the US alone (Anon, 2016b), it is largely because they could not tame resistance evolution. The fundamentals of that evolutionary process are essentially the same in all tumors. In the absence of drug treatment, the population size of resistant cells is tiny. Aggressive chemotherapy completely remodels the ecosystem experienced by those resistant cells. For instance, the therapy-sensitive cells are removed, enabling a vast amplification of resistance (Chapters 14, 19). That amplification process, or the ones that follow in subsequent rounds of the arm race between oncologists and tumors, is what kills the patient.

There are just two ways to prevent or delay therapeutic failure (Day and Read, 2016; Read et al., 2011). The first is to prevent resistance arising in the first place. This is what happens in modern HIV therapy; the right combination

of drugs in fully compliant patients prevents resistant mutants. The second is to try to delay or prevent the emergence of resistance when it is present. Given that resistance to many chemotherapeutic agents is already present in a tumor when treatment begins, managing the emergence phase is often the only hope for the patient. This means managing the population dynamics of therapy-resistant cells. To do that rationally involves a more detailed understanding of the relevant ecology than we currently have. For instance, at the heart of the problem is a ‘simple’ trade-off involving therapy-sensitive neoplastic cells (Hansen et al., *in press*). Sensitive cells are a potential source of resistance, since they can acquire (epi)genetic changes that confer therapy-resistance (Chapters 5, 6, 10). But they also suppress populations of resistant cells. This must be one very important reason why resistance is so rare prior to treatment: sensitive cell lineages are keeping them in check. Thus two opposing forces—competitive suppression and resistance acquisition—together determine the fate of the patient. Several ingenious solutions for resistance management revolve around trying to tip these forces in the patients’ favor (Baym et al., 2016; Maley et al., 2004; Willyard, 2016) (Chapters 10, 14, 21). For example, treatment regimens aimed at containing a tumor may prolong patient life longer than regimens which attempt to eliminate a tumor (Chapter 14). Critically, the ecology of cell–cell competition determines when containment can make things better, and when it makes the prognosis worse (Hansen et al., *in press*).

Yet we barely understand the nature of competition occurring within and between cancer cell lineages. It is clear that it can occur (Chapters 1, 4, 8, 10, 14, 19, 21). But is it scramble competition, with cell lineages proliferating in a resource rich environment at the edge of a tumor? Or are resources limiting, so that density dependent effects are important? In many cases, resistance mechanisms come with fitness costs (Chapter 14). Fitness costs are highly dependent on environmental context. Fitness costs can affect growth in an unconstrained environment, or they can affect competitive ability in density-dependent environment. The evolutionary consequences are very different. Quite possibly a variety of different competitive interactions are going on at once, even for the same type of genetic resistance mechanism in the same location. I know of no work looking quantitatively at competition between resistant and sensitive neoplastic cell lineages across resource gradients, the simplest and most fundamental ecological question. What nutrients or resources are involved? How does immunity modify competition? Where is any density-dependence coming from? How does therapy modify that? How best can we modify competition or fitness costs to enhance patient health?

Over recent decades, science has generated rich catalogs of the genetic events that can cause therapeutic resistance (Housman et al., 2014). But once resistance has

arisen, ecological forces determine the fate of those resistance mechanisms and, among other things, how long a patient will live. Mathematical models can do a lot to capture the possible processes and study the potential impact of contrasting therapeutic options (Beerenwinkel et al., 2015; Bozic et al., 2013; Diaz et al., 2012; Foo and Michor, 2014). Indeed mathematical models are essential, not least because it is impossible to empirically investigate the wide variety of possible treatment regimens. But there is a frustrating lack of empirical cancer ecology from which such models can be parameterized. For instance, it is popular to model tumor growth as a Gompertz process (Foo and Michor, 2014). When is it Gompertzian and when is it Logistic, and in either case, what are the ecological mechanisms underlying whatever phenomenological model we do fit?

Solutions to global challenges in conservation biology, control of invasive species, and the management of resistance in agricultural all benefit from a thorough understanding of the ecological context (Alexander et al., 2014; Edward et al., 2009). Those problems are directly analogous to the problem of controlling resistance in the cancer ecosystem. General principles are usually clear; the solutions that flow from them are specific to the particular setting because details matter. One-size-fits-all rules seldom work (Day and Read, 2016; Hansen et al., in press). When we understand particular disease ecosystems in the way that card-carrying ecologists understand more traditional ecosystems, novel solutions to cancer will suggest themselves—and we will be able to make more effective use of the precious chemotherapeutic agents we already have.

In his small but powerful book *Ignorance, How it Drives Science*, Stuart Firestein, a neuroscientist, makes the interesting case that the discovery of voltage spikes in the brain and sensory organs in the early part of the 20th century was a mixed blessing (Firestein, 2012). Spike analysis occupied neuroscience for the better part of a century and generated a vast mountain of data and facts about spikes. But because of the focus on spikes, electrical signals more subtle than spikes and chemical processes that were not electrical were missed for decades. These nonspike processes may turn out to be as important as the spikes. I can't help, wonder if we will look back on this era of molecular oncology and wonder why for so long we missed the ecology.

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