PERSPECTIVE

Finding cancer's first principles

Genomic analysis of cancer has yielded vast quantities of data. But **Robert Gatenby** would rather try to find the basic tenets of the disease.

Dazzling technological advances in molecular biology have transformed the biology of cancer and generated thousands of articles in the burgeoning fields of cancer genomics, proteomics, metabolomics and others. Yet researchers have revealed significant heterogeneity even between cancer cells in the same tumour, leading some to question the clinical value of this vast enterprise. Evolution can cause the genetic profiles in one region to be substantially different to those in distant or even adjacent sites — the conventional solution to this problem is greater investment in molecular technology so that entire cancer populations can be analysed cell by cell.

Now consider a different timeline. Suppose these technological developments had not occurred and we lacked the ability to obtain molecular data on any cancer population. Clearly, we would know less about cancer genetics, but would we also know less about cancer biology? I believe that the answer is "not necessarily", and that we might actually know more.

Many would vigorously disagree. Most cancer biologists and oncologists take for granted that the first principles of cancer biology are genetic. Indeed, many a cancer-related publication opens with the sentence: "Cancer is a disease of the genes." Medical students memorize the mutations found in each malignancy with the implicit assumption that this represents a full understanding. Perhaps the time has come to question these assumptions.

UNDERSTANDING THE PRINCIPLES GOVERNING LIVING COMMUNITIES DOES NOT NECESSARILY REQUIRE — AND MAY EVEN BE OBSCURED BY — GENETICS

We hold the optimistic belief that ever more detailed molecular analysis will lead to marvellous new cancer therapies. Yet there is clear clinical evidence that existing targeted therapies generally produce mere transient responses that are ultimately defeated by the relentless evolution of cellular adaptations. So we should stop to ask: will better treatments emerge if we apply ever more sophisticated molecular technologies to smaller and smaller populations?

PRINCIPLES, NOT OBSERVATIONS

This edition of *Nature Outlook* features efforts to connect cancer biology to the physical sciences. One important lesson physicists can teach us is the explicit separation of experimental observations and system principles. Whether analysing planetary motion, atomic spectra or subatomic particles, physicists do not define a system by empirical data. Rather, they use data to support or refute a postulated theoretical framework that defines the system's governing principles. In building a framework for cancer biology, I propose that — to paraphrase evolutionary biologist Theodosius Dobzhansky — cancer, like all biology, only makes sense in the light of evolution.

In this spirit, I wonder whether genetic data are sufficient, or even necessary, to understand the evolutionary and ecological dynamics of cancer and its therapy. Darwin knew nothing of molecular genetics — his conceptual model of evolution required only an unspecified "mechanism of inheritance". For nearly 100 years, evolutionary biologists and ecologists observed living systems at various scales and developed the fundamental principles governing complex biological communities with no working knowledge of the underlying genetics. This was possible because the dynamics of both individual organisms and their communities are governed by phenotypic, not genotypic, interactions with environmental selection forces. In other words, understanding the principles governing living communities does not necessarily require — and may even be obscured by — genetics.

Consider cave fish. Across the world, underwater caves are populated by different species of fish, all of which have adapted to eternal darkness by developing exaggerated tactile organs and losing their eyes and skin pigment. These cave-dwelling creatures have evolved from more than 80 different species — a striking example of convergent evolution. Genetic analysis of the world's cavefish populations would produce a huge and highly heterogeneous data set. The data would reflect not only differences between species, but also variable genetic pathways in the same species. Such data might yield interesting insights, but the animal's fundamental biology is readily and instantly obvious simply by looking at the fish.

DATA ARE NOT ENOUGH

Like the proverbial man who looks for his car keys under the streetlight because that's where he can see best, we are drawn to intellectual places that promise high levels of information. But this does not necessarily guarantee success. Dobzhansky once wrote: "Scientists often have a naive faith that if only they could discover enough facts about a problem, these facts would somehow arrange themselves in a compelling and true solution."

The huge and complex data sets we have obtained under the strong light of molecular technology, although unquestionably useful, have caused us to neglect avenues of investigation that might ultimately allow us to arrange the data into a "true solution". In the absence of a true understanding of cancer's evolution and ecology, we have failed to recognize the limits of these data. Without first principles, our continued confidence and unlimited investment in these technologies create an illusion of progress but may be doing more harm than good.

Ultimately, real progress in understanding cancer biology will require a formal intellectual framework. Like gravity or quantum field theory in the physical sciences, we must define the underlying principles governing the nonlinear dynamics that give rise to the vast and complex data sets being generated by the creative minds of molecular biologists. These principles will not be found until we begin to search in the right place. ■

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