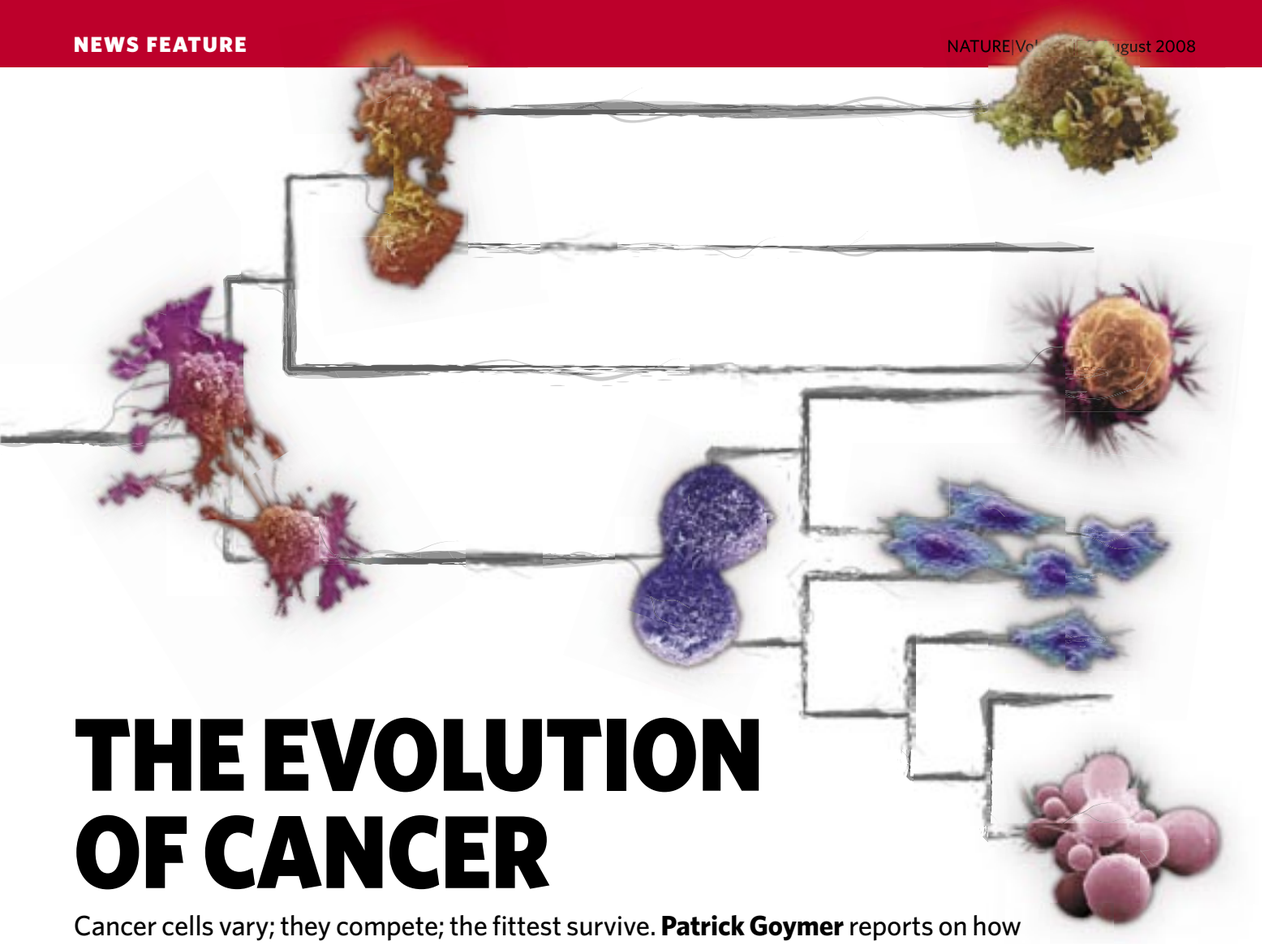

THE EVOLUTION OF CANCER

Cancer cells vary; they compete; the fittest survive. **Patrick Goymer** reports on how evolutionary biology can be applied to cancer — and what good it might do.

The oncology clinic isn't a field site where one might expect to find an evolutionary biologist. But within the complex ecosystem that is the human body, tumours grow, mutate and face diverse selective pressures as they change and react to their environment. Over hundreds of generations, cells can acquire mutations that promote their errant growth and survival. This makes for diversity both between cancer types and within an individual tumour. But just as species have evolved convergent similarities, cancers too have common themes and steps along their developmental paths. If properly directed with evolutionary theory in mind, treatments might become more effective (see 'Targeting what isn't there').

Tony Green of the University of Cambridge, UK, and his colleagues have looked at evolutionary processes in myeloproliferative disorders — overgrowths of blood-producing bone-marrow cells that can become cancerous. Changes to the *JAK2* gene play an initiating role in these disorders, allowing the cells to bypass their growth-control mechanisms. Green and his colleagues began to study these mutations as the disorders progressed, in some cases, towards a cancer of the white blood cells called acute myeloid leukaemia, or AML. As expected, the *JAK2* mutation arises often and early in myeloproliferative disorders because of the growth advantage it confers on cells. But three of four individuals who went on to develop AML no longer had the mutation[1]. "This was a surprise," says Green. "An initiating mutation was not present in the more evolved state."

Did cancer cells that had acquired *JAK2* mutations lose them over time as other mutations and physiological changes took over the controls of the disease? Or were the *JAK2* mutants outcompeted by other cells taking advantage of the changing environment within the cancer-afflicted individuals?

Green stumbled across this evolutionary parallel, but some scientists specialize in comparing the similarities between changes to a cell in the body and the evolution of organisms within an ecosystem. As more information about cancer genetics accrues, the importance and usefulness of this evolutionary analogy is becoming clear.

Science has been looking for commonalities in cancer, and several large-scale projects aimed at sequencing the genetic changes in different cancers have in their earliest stages revealed what many feared. The main feature of cancer, says Bert Vogelstein of Johns Hopkins University in Baltimore, Maryland, is its complexity and heterogeneity. Most mutations found in cancer are rare. "There are a few genes that are commonly mutated — we call these the mountains — but the landscape is dominated by hills," says Vogelstein. Evolutionary theory, in conjunction with the sequencing of cancer genomes, could help map that countryside more quickly.

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Diversity breeds success

Peter Nowell of the University of Pennsylvania in Philadelphia first developed the idea of cancer as a Darwinian process in 1976 (ref. 2). Cancer is known to occur because of the stepwise accumulation of mutations in certain cells of the body. Nowell added to this the population-genetics idea of clonal expansion, in which cells that have a mutation to make them grow faster or survive better produce more offspring than surrounding cells without the mutation.

Carlo Maley of the Wistar Institute in Philadelphia sees the diversity of cancer cells as key to understanding their resistance to drug treatment. "One thing that is surprising is that the multidrug therapies in cancer haven't worked nearly as well as they have in HIV," he says. "That seems to me to be a basic evolutionary question that should be addressed and is at the heart of why we haven't been able to cure cancer."

Maley has been applying evolutionary theory to a condition called Barrett's oesophagus, which can progress to become cancer. As surgical treatment for Barrett's oesophagus is extremely risky, standard medical practice is to monitor cells in the oesophagus for signs that they have started to progress towards cancer. Maley uses biopsy samples to track the evolution of the disorder, testing each biopsy for changes in specific genes such as *CDKN2A* and *p53*. His group has found that in the early stage of the disorder, individuals with diverse populations of cells harbouring different mutations are more likely to develop cancer[3]. This might be because the body is struggling to defend itself against more kinds of attacks. Maley uses methods borrowed from ecology to measure the diversity and make predictions about progression.

Quick and easy

Perhaps the most important advance in cancer biology has been cheap and fast DNA sequencing. The technology that allows researchers to sequence the genomes of hundreds of species, and of individual humans, is now being applied to the genomes of tumours. Knowing the genome sequence of a cancer cell allows scientists to look in detail at how a tumour has evolved from the normal cells of the body — which genes have mutated, how much of the original genome has been lost or duplicated, and whether the evolutionary process has unfolded similarly in each individual case.

Several large-scale projects are taking this approach, including the Cancer Genome Project, which is sequencing protein-coding genes in cancer cells to look for mutations; the Cancer Genome Anatomy Project, which is looking at levels of gene expression in cancer cells; and the Cancer Genome Atlas, which is looking at various types of genomic alteration in specific cancer samples.

But cancer genome sequences aren't by themselves going to explain the evolutionary process of tumour development. In fact, Maley and Green point out that the sequences provide only 'snapshots' of the evolutionary process, so further work is needed to fill in the gaps, such as the order in which the mutations appear. And current technology means that

Targeting what isn't there

Drug developers have long had cancer-causing mutations in their sights. But cancer cells invariably evolve ways to become resistant to drugs and ensure survival. Alexander Varshavsky at the California Institute of Technology in Pasadena suggests that drugs should be targeted at something that arises in the cell's evolution that is not so easily side-stepped — deletions of DNA segments[6].

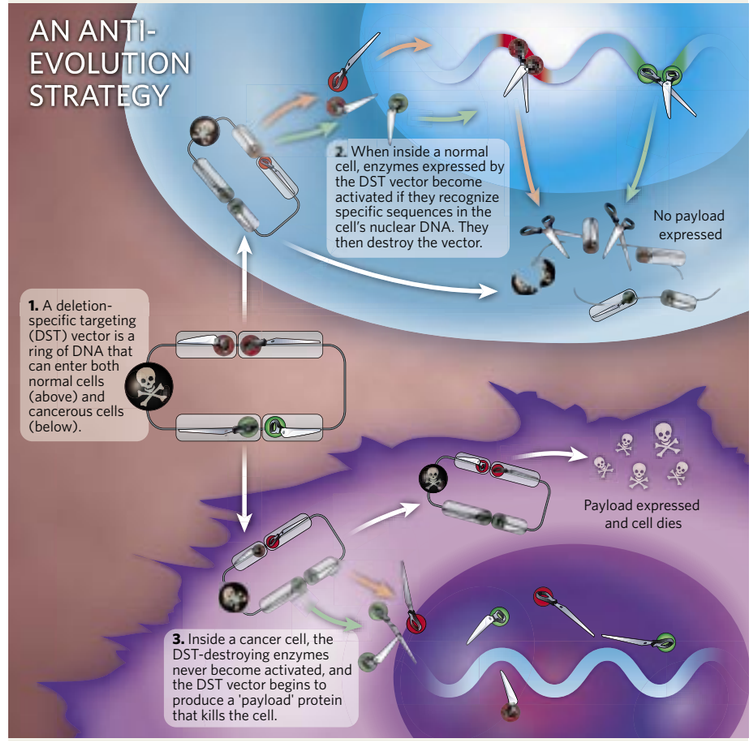
A fundamental principle of evolutionary genetics is that once a gene is lost it is very unlikely to be regained — a phenomenon known as Muller's ratchet. Varshavsky thinks that chance deletions occurring early in a tumour's development could be a hallmark of that tumour whatever course its subsequent evolution takes.

Varshavsky envisages a deletion-specific targeting (DST) vector — a ring of DNA that encodes a cell-killing 'payload' protein and fail-safe enzymes that will destroy the vector when they recognize specific sequences of DNA within the cell. In normal cells, the fail-safe enzymes become activated and destroy the vector before it has a chance to release its payload. Because the specific DNA sequences are missing in cancer cells, the enzymes never become activated and the vector begins to express its deadly payload (see graphic).

Caveats abound. The diverse and shape-shifting nature of cancer means that identifying effective deletion sequences will be difficult. Carlo Maley of the Wistar Institute in Philadelphia, Pennsylvania, cautions that cancer has a knack for overcoming obstacles, including deadly payload proteins. Moreover, the strategy is predicated on gene-delivery techniques that have not yet been proved in cancer.

Still, experts are excited. "It's a brilliant idea," says Bert Vogelstein of Johns Hopkins University in Baltimore, Maryland, "because it exploits the Achilles heel of cancers. Deletions are likely to be present in every cancer."

Varshavsky hopes that the US$1-million Gotham Prize, which was awarded to him last year, will allow him to develop his blueprint into a clinical reality. "I'm committed to implementing the deletion-specific therapy strategy and/or its descendants, taking them as far as they can go. All the way to patients, I hope." **P.G.**



the genome sequences are actually an 'average' sequence taken from a heterogeneous collection of tumour cells, whereas much of the interesting detail is in the differences between individual cells within a tumour — after all, variation is the basic stuff on which natural selection acts.

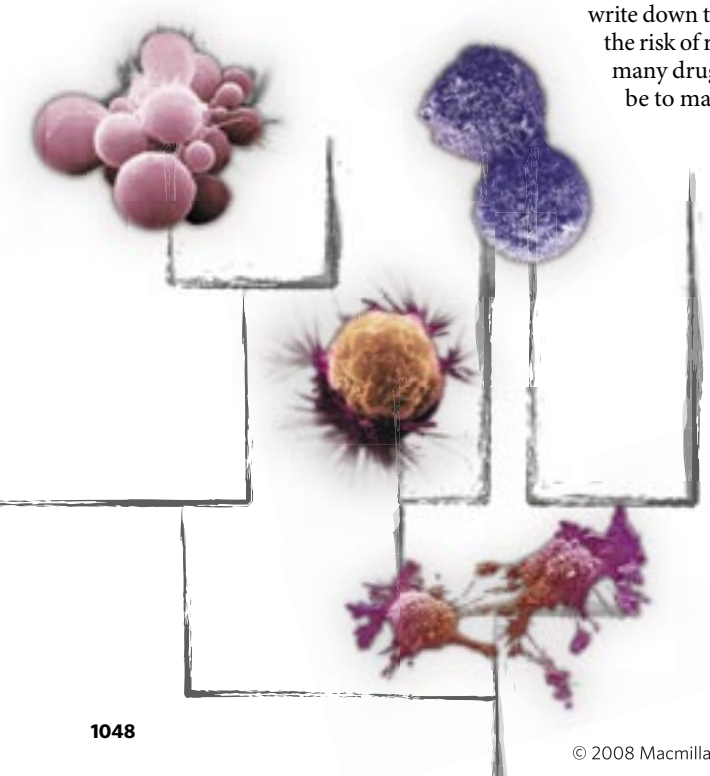
The need for a sophisticated evolutionary understanding of cancer led Vogelstein to team up with biologist and mathematician Martin Nowak from Harvard University in Cambridge, Massachusetts. Nowak has applied his modelling ideas to problems as diverse as the evolution of HIV, altruism and the politics of climate change. Cancer, he says, "is just like any other evolutionary process, but it's even simpler. Because of this we can ask much more complicated questions."

Sequencing the genomes of cancer cells, says Nowak, can "help us get quantitative data to calibrate our evolutionary models". From Vogelstein's data on sequence variation between individual colorectal cancers, Nowak could predict when malignant tumours would arise from benign ones and when they would metastasize, or spread to other parts of the body[4]. He found that malignant tumours do not mutate more frequently than normal cells, as is often thought. Instead, it is the evolutionary context in which these mutations occur that matters.

Nowak's former student, Franziska Michor, now at the Memorial Sloan-Kettering Cancer Center in New York, is interested in developing her mentor's approach of modelling the process of cancer evolution. The roots of this approach go back half a century. In the 1950s, Richard Doll at the University of Oxford, UK, found that solving equations containing terms for growth and mutation rates allowed him to predict the number of mutations that are required for a tumour to evolve[5]. Doll developed a model in which the time taken for cancer to arise depends on the probabilities of each of the mutations needed to cause the cancer actually occurring, and he fitted the model to real incidence statistics. But Michor says that this approach fails to take into account population-genetics theory. Doll's models look at single cells, ignoring the fact that if the first mutation increases the evolutionary fitness of that cell, then the mutation will expand into many cells, increasing the probability that subsequent mutations will occur.

Understanding this population effect will be hugely important in overcoming evolved drug resistance. One way to deal with this is to use combinations of treatments that tackle different aspects of the disease. "We can try to come up with treatment strategies if we understand how many mutations are needed for resistance," says Michor. "We can actually write down the equations that predict what the risk of resistance is depending on how many drugs you use." A crucial goal will be to make these models predict what is going on in systems with complicated evolutionary trajectories, such as AML.

> **"Cancer genomes help us get quantitative data to calibrate our evolutionary models."**
> — Martin Nowak



Pushing the parallels

So how far can the evolutionary idea be extended? The small number of cell divisions within a cancer compared with that in the evolution of species is an obvious limitation. But there are still plenty of evolutionary ideas to be explored in cancer, several of which come from thinking about the whole ecosystem of the disease. As with 'real' ecosystems, these involve not just the species in question, but also its competitors, predators and symbionts.

The evolving cancer cell not only needs to outcompete the normal body cells, it must also evade attack by the immune system and, if it is to reach the advanced stages of cancer, it needs to cooperate with other cells and then migrate and colonize other parts of the body. For example, once a tumour reaches a certain critical mass its cells require a blood supply to keep them oxygenated. This means that it needs to co-opt the body's system for creating blood vessels.

How these processes take place is ripe ground for evolutionary biologists and ecologists to investigate, something that Maley and his colleague John Pepper, of the University of Arizona in Tucson, were keen to encourage when they organized a recent workshop on the topic at the Santa Fe Institute in New Mexico. The fact that a similar workshop was organized by the National Cancer Institute, a major funding body, suggests that the money might follow. Maley certainly hopes so. "I see my role," he says, "as attempting to bring evolutionary biologists into cancer biology and advocating the need for evolutionary biologists as part of our interdisciplinary teams." Whether such interdisciplinary research will entice evolutionary biologists to shift their field study to the clinic is yet to be seen, but for investigations of variation and selection, cancers unfortunately continue to produce ample material for study. ■

Patrick Goymer is associate editor of *Nature Reviews Genetics*.

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