# Exposing cancer's deep evolutionary roots

by Paul Davies

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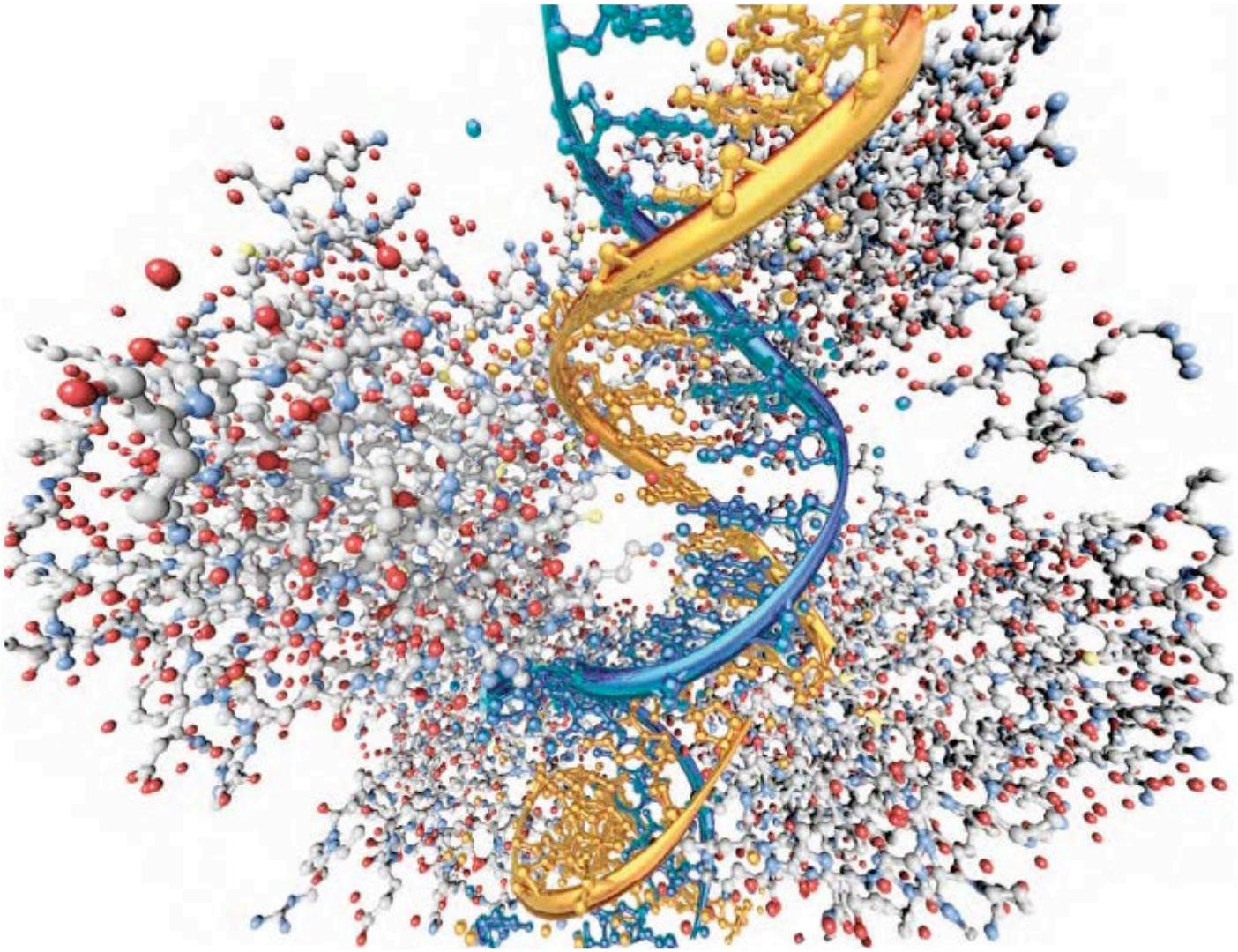

Paul Davies argues that cancer is an ancient genetic program present within us all, with roots in the dawn of multicellularity over a billion years ago.

"The miracle of life." To a physicist, life does seem almost like magic. Faced with the sheer complexity of the living cell, many physicists feel bewildered. Yet some biological processes are remarkably deterministic. The development of the embryo is one. Cancer is another. Although there are inevitable patient-by-patient variations in the progression of cancer, generally speaking, once it is initiated the disease follows a depressingly predictable trajectory.

When a physical process follows a pattern, physicists can bring valuable insights from their discipline. Recognizing this, in 2009 the US National Cancer Institute created 12 centres for physical science and oncology in an effort to identify radically new approaches to cancer

research and treatment.

When I was asked to lead such a centre, I knew almost nothing about cancer. My background in fundamental theoretical physics and cosmology prompted me to start with the basics. First of all I simply wanted to know what cancer is – how it is defined I then pondered what causes its distinctive hallmarks and predictable progression, and what physical parameters control its properties and behaviour. Meanwhile, I began thinking about why cancer exists at all and what its place is in the grand story of life on Earth.

Such questions are rarely asked by oncologists or cancer biologists, who mostly focus on the human disease aspect and are caught up in the frantic and expensive search for an elusive "cure".

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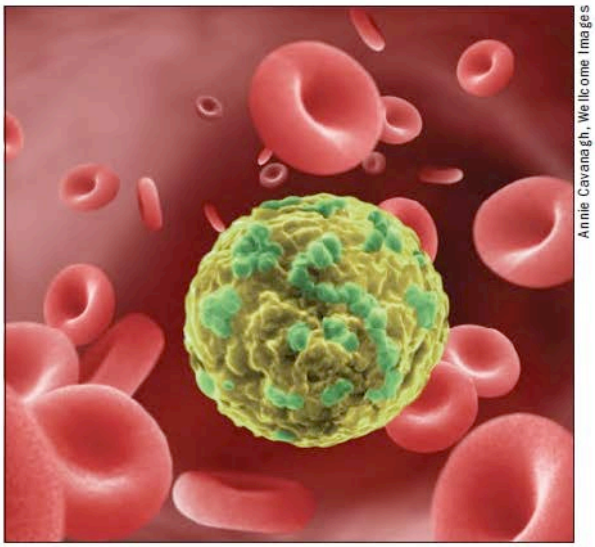
**Selfish cells** Single-celled organisms act to preserve themselves, while cells in multicellular organisms act for the greater good.

Annie Cavanagh, Wellcome Images



**Hitching a ride** Cancer cells can become mobile and travel in the bloodstream to invade other organs.

**A disease of the genes?**

I soon learned that cancer is widespread among mammals, birds, fish and reptiles, suggesting it has deep evolutionary roots stretching back at least hundreds of millions of years. In fact, its prevalence in multi-cellular organisms implies it is deeply embedded in the logic of life. The genomes of nearly all healthy human cells, containing the entirety of an individual's inherited information, evidently come pre-loaded with a "cancer sub-routine" that is normally idle but can be triggered into action by a wide variety of insults, such as chemicals, radiation and inflammation. Once initiated, most cancers follow a pattern. Cells first proliferate uncontrollably in a particular organ (cancers are specific to organ types) forming a tumour or "neoplasm" (new cells). After a time, some neoplastic cells become mobile, leave the tumour and spread around the body, invading and colonizing other organs. This process is called metastasis and accounts for 90% of cancer deaths.

To accomplish their journey, cancer cells mostly hitch a ride in the bloodstream or lymphatic system. In doing so they face formidable challenges – they tunnel through tissues, squeeze through membrane barriers and experience highly varying sheer stresses once inside the vessels. To cope with such trials, cancer cells systematically deploy many specialized properties and functions.

Evidence is mounting that the micro-environment at the cells' destination plays a key role in the success of metastasis. Primary tumours send out chemical cues into the body to "prepare the ground" for the invasion, and metastatic tumours create cancer-friendly niches by recruiting and adapting healthy cells. The disseminated neoplasm can display long-range organized behaviour that suggests a command-and-control, system-wide communication network mediated by various physical and chemical signalling mechanisms. The overall impression is of a carefully orchestrated and pre-programmed strategy – its aim to multiply cancer cells and colonize new sites – which is unleashed when neoplastic cells somehow evade the normal regulatory mechanisms of the organism and embark on their own agenda.

Whenever one encounters highly organized and efficient behaviour in biology, a ready explanation lies at hand: Darwinian evolution. Orthodox explanations suppose that cancer results from an accumulation of random genetic mutations, with the cancer starting from scratch each time it manifests, and over a period of several years evolving survival traits within the host under the pressure of selection by the body's defences. Viewed this way, cancer is a disease of the genes that produces an aberration of normal cellular function – rogue cells running amok and developing their own agenda, which conflicts with that of the host organism. And it is true that many cancer cells are genetic monsters, with deranged and sometimes duplicated chunks of DNA, grotesquely malformed and swollen nuclei and wholesale rearrangements of their chromatin (genetic material).

The standard explanation leaves many puzzling questions, however. If the genetic mutations are random then the cells ought to be highly defective and vulnerable, yet paradoxically they are often fitter than healthy cells. There is no obvious reason why random mutational accidents should just happen to confer a whole series of mutually supportive survival traits in the same neoplasm, conveniently manifesting themselves in a period of just years or months. Cancer dormancy is also perplexing; in most cases, cancer (of the same organ variety) eventually returns, sometimes years or even decades after removal of a primary tumour, having somehow lain harmlessly quiescent somewhere in the body. Just what awakens it is a mystery. Another question is why cancer cells deliberately transplanted into certain tissues, or cancer nuclei into healthy cells, often results in normal behaviour. Conversely, normal nuclei implanted into cancer cells often become cancerous.

From a physics perspective, there are clues pointing to cancer as a phenomenon influenced by forces and fields – not one that is purely ruled by genetic instructions. It is fascinating, for example, that the Young's modulus of cells changes as cancer progresses, sometimes dramatically (they are generally softer), while the stiffness of the tissue that cells touch can affect their gene expression – a process known as mechano-transduction. Even more tantalizing is that electric potentials, across cell and mitochondrial membranes as well as through tissue, serve as an organizing field that affects both healthy and malignant behaviour.

All this adds up to a serious problem for the standard genetic model of cancer. While nobody would deny that genomic changes play some sort of role in driving the cancer phenotype (i.e. the physical tissue that results from expressing the information in the genes), at least as much weight must be given to environmental factors. This subject is collectively known as epigenetics and encompasses the effects of physical properties such as tissue architecture, elasticity and electric potential.

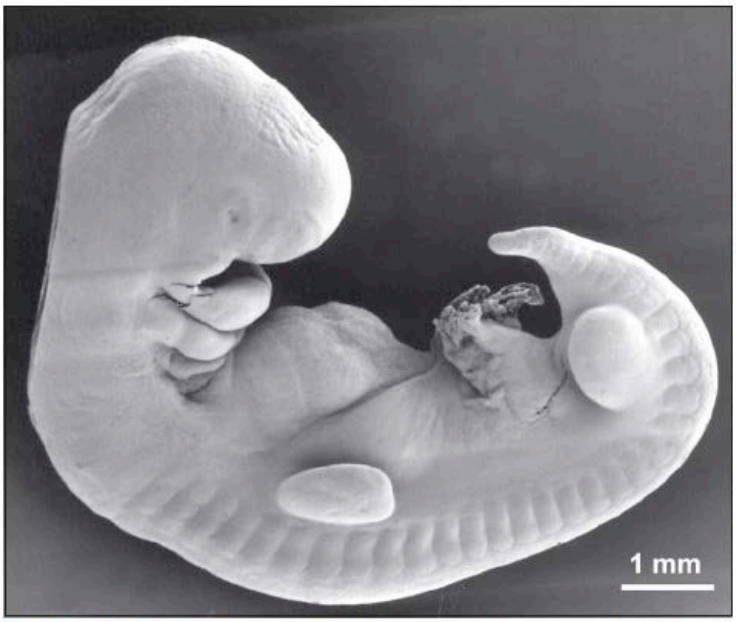
**An ancient subroutine**

To address these puzzles, Charles Lineweaver of the Australian National University and I have proposed a very different theory of cancer. Biologists agree that cancer is a breakdown of the contract between individual cells and the organism. This contract dates back to the dawn of multicellularity, over a billion years ago. Single-celled organisms replicate by division and are in a sense immortal. In multi-cellular organisms, immortality is relinquished and the genetic legacy of the organism is outsourced to specialized sex cells – eggs and sperm – known as the germ line. Although all cells in multicellular organisms have the same DNA, most of them differentiate into specific types – kidney, brain, muscle, etc. These are known as somatic cells, and they eventually die, for the greater good of the organism and its germ line. Somatic cells demonstrate this altruism every day in the phenomenon of apoptosis, or programmed cell death, which occurs after damage to a cell or as a result of ageing. But policing this contract is hard work, and requires complex regulatory mechanisms. If cells start to cheat, abandoning the ancient covenant by refusing to apoptose, then runaway proliferation results and a neoplasm forms.

Lineweaver and I build on this uncontroversial concept, but go much further by bringing insights from evolutionary biology, microbiology and astrobiology. (In this endeavour, we are collaborating with the NASA Astrobiology Institute.) In a nutshell, we agree that cancer is a type of throwback, or atavism, to an ancestral phenotype. Cells are usually regulated by mechanisms that instruct them when to multiply and when to die. What we believe is that when these mechanisms malfunction, the cells revert to the default option, a genetic subroutine programmed into their ancestors long ago, of behaving in a selfish way. To use a

computer analogy, cancer is like Windows defaulting to “safe mode” after suffering an insult of some sort.

Our atavism theory appeals to the fact that the genomes of the organisms we see today retain traces of their evolutionary past. This is sometimes made strikingly apparent when humans are born with a tail or extra nipples, or dolphins with four fins instead of two, expressing ancestral phenotypes.

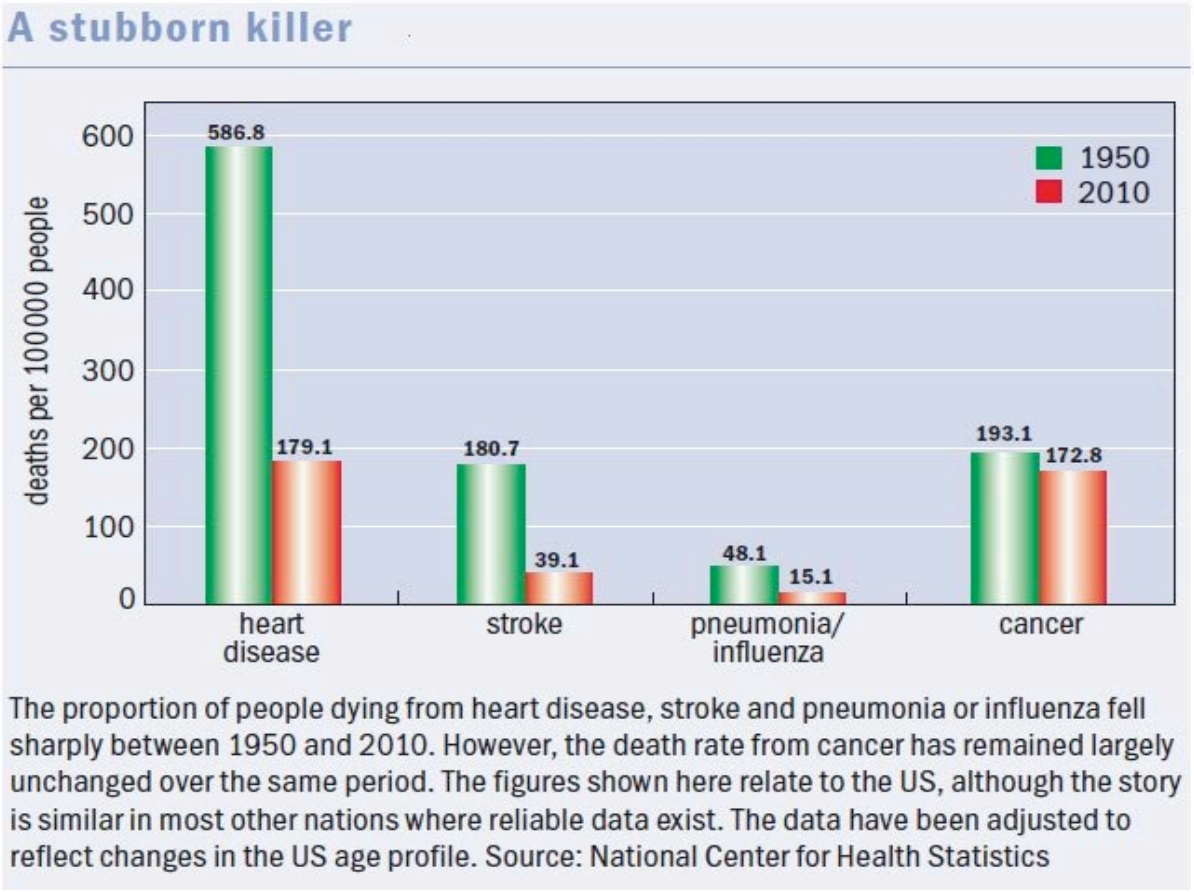



**Building on the past** This typical four-week-old human embryo looks similar to fish embryos, with proto-gills and a tail.

Ancestral genetic pathways will be preserved only if they continue to serve a useful purpose. One such purpose involves embryogenesis. When a fertilized egg develops, much of the basic body plan is laid down in the early stages. Because all animals share an evolutionary past, early-stage embryos bear clear resemblances to each other: even human and fish embryos show obvious similarities such as proto-gills and a tail. This is no surprise. Evolution builds on what has gone before (our remote ancestors were fish), and ancient features that have stood the test of time will likely be recapitulated. Altering or abandoning the ancient foundations of the developmental programme would fatally compromise the embryo’s development. Very roughly, the earlier the embryonic stage, the more basic and ancient will be the genes guiding development, and the more carefully conserved and widely distributed they will be among species.

To use a computer analogy, cancer is like Windows defaulting to “safe mode” after suffering an insult of some sort

Another feature of embryonic cells relevant to our theory is that they start out "pluripotent" – they remain capable of forming cells of any organ. As the embryo develops, so most cells differentiate step by step into their terminal forms (brain, lung, kidney, skin, etc). Although all cells in an organism possess the same genes, as differentiation proceeds, different genes get switched off and silenced, leading to different cell types being manifested. However, so-called stem cells retain a measure of pluripotency, and are present even in the adult form in order to replenish fully differentiated cells that are lost by ablation, damage or simply by ageing and undergoing apoptosis.




The proportion of people dying from heart disease, stroke and pneumonia or influenza fell sharply between 1950 and 2010. However, the death rate from cancer has remained largely unchanged over the same period. The figures shown here relate to the US, although the story is similar in most other nations where reliable data exist. The data have been adjusted to reflect changes in the US age profile. Source: National Center for Health Statistics

Lineweaver and I suggest that genes that are active in early-stage embryogenesis and silenced thereafter – which, by our hypothesis, are generally the ancient and highly conserved genes – may be inappropriately reactivated in the adult form as a result of some sort of insult or damage. This trigger serves to kick-start the cascade of maladaptation events we identify as cancer. So the "cancer subroutine" is really just a re-run of an embryonic developmental program. We envisage a collection of ancient conserved genes driving the cancer phenotype, in which the metastatic mobility of cancer cells and the invasion and colonization of other organs merely reflects the dynamically changing nature of embryonic cells and their ability to transform into different types of tissues.

The big picture is that we attribute cancer's survival traits to deep evolution on a billion-year scale, rather than orthodox explanations that point to evolution from scratch with each case of the disease. In our theory, the latter remains true, but is a small perturbation.

**Mounting evidence**

Evidence for deep links between embryogenesis and tumorigenesis have come from several experimental studies. Isaac Kohane, a paediatrician who specializes in bioinformatics, and his colleagues at Harvard University have identified a pattern of genes that are switched on in most cancers and shown that this same signature is active in early embryo development. John Condeelis, a biophysicist at Albert Einstein College of Medicine in New York, has demonstrated that invasive cancer cells have a gene expression profile resembling that of embryo tissue development.

Further evidence that supports our theory comes from experiments in which the nuclei of egg cells are replaced with cancer-cell nuclei. Astonishingly, embryos start to develop normally. But abnormalities eventually appear, at earlier stages when the cancer is more malignant (advanced). This inverse correlation of cancer stage with embryo stage is consistent with our theory. Cancer is rarely an all-or-nothing affair. Once it is initiated, it tends to follow a well-defined progression of accelerating growth, mobility, spread and colonization. Lineweaver and I envisage cancer progression within a host organism as like running the arrow of biological evolution backward in time at high speed. As the complex regulatory mechanisms of the body break down, the cancer defaults to earlier and earlier phenotypes, with the most malignant cells representing the most ancestral forms.

If we are right, the various distinctive hallmarks of cancer ought to map inversely onto the evolutionary tree of life. For example, cells display surface adhesion molecules called cadherins to help them stick together. As cancer progresses, the cadherin gene expression changes to a more ancient type. There are, in fact, many types of cadherin among multicellular organisms, and we predict that this backwards-in-time function of cancer stage will be seen in some of these too.

There is a quite different additional link between cancer and early forms of life. Cancer cells tend to adopt an ancient mode of metabolism known as fermentation, or glycolysis, which takes place in the cytoplasm of the cell. In contrast, healthy cells mostly use a process known as oxidation-phosphorylation, or ox-phos, which is performed within tiny organelles called mitochondria. The characteristics of fermentation are its ability to flourish in low-oxygen conditions (hypoxia), its high demand for sugar (glucose) and a low-pH environment – all conditions characteristic of tumours. Could it be, we wonder, that cancer's predilection

for a hypoxic environment reflects the prevailing conditions on Earth at the time when multicellularity first evolved, before the second great oxygenation event?

Cancer touches every family on the planet and is a growing health and economic calamity. Attempts to tackle it with toxins, radiation and surgery are often little more than a delaying tactic. Life expectancy for someone with metastatic cancer has hardly changed in five decades, despite all the hype about imminent “cures”. It is clear that some radically new thinking is needed. Like ageing, cancer seems to be a deeply embedded part of the life process. Also like ageing, cancer generally cannot be cured, but its effects can certainly be mitigated – for example, by delaying onset and extending dormancy. But we will learn to do this effectively only when we better understand cancer, including its place in the great sweep of evolutionary history.

Paul Davies is principal investigator at the US National Cancer of Arizona State University’s Center for Convergence of Physical Science and Cancer Biology, US,
e-mail paul.davies@asu.edu

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