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Cancer and Evolution

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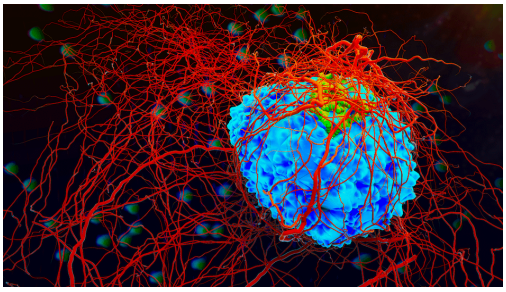

Theodosius Dobzhansky, an Eastern Orthodox Christian and scientist, famously wrote in 1973 that "nothing in biology makes sense except in the light of evolution." He was talking specifically about fossils, the diversity and geography of life, and the sequence similarities between proteins. We now know he could also add cancer to his list. Our understanding of both cancer and evolution are intertwined.

Evolutionary theory "makes sense" of cancer, giving us critical insight into how it works.

This has become particularly clear in recent years. Now, we can sequence all the genes in a patient's cancer, and see how they change over time as cancer evolves. Cancer evolves with the same evolutionary mechanisms[1] that drive the evolution of new species.

This important article was written after my first Nature Genetics paper. It was original published at elsewhere in January 2017, where it had become one of the most viewed forum topics on their website.

In response to this article, ID proponents now highlight cancer as one of the Icons of Evolution, and it certainly is. Cancer is only possible because life evolves. Cancer biology showcases in observable timelines the most important mechanisms of evolution, including the origin of species and neutral theory.

Of note, "Darwinism" is not modern evolutionary science. In many ways, positive selection on beneficial mutations (Darwinism as it is often understood), was falsified as the dominant mechanism of evolution in the 1960's. This, of course, raises questions about why so much effort is invested in arguing against a long falsified theory, instead of engaging modern evolutionary science. Moreover, this is the same scientific theory that we've used to understand the limits of evidence against a single couple bottleneck. The same mathematical theory is used to understand the evolution of cancer, the evolution of species, and the size of human populations in the past.

Peaceful Science aims to be a trusted resource for people wanting an accurate account of science. With this in mind, I decided to republish this article here.

Like breadcrumbs marking a path through a forest, cancer evolution leaves information in cellular genomes that evolutionary theory can decode.

Going the other direction, cancer makes sense of evolution too. Cancer itself is not evolution at the species level. However, it validates the mathematical framework underlying modern evolutionary theory. Cancer cells evolve multiple new functions in an evolutionary process, creating precise genetic signatures of common descent. At both a genetic and functional level, cancer follows patterns explained by evolutionary theory.

Skeptics of evolution often doubt we know enough about how genomes change over time, or how new functions arise, to correctly infer common ancestry from patterns in genetic data. They sometimes argue that "historical science" cannot be trusted, since it is making claims about the distant past. In cancer, however, we can directly verify that evolutionary theory correctly reconstructs a cancer's history, including its ancestry. We see all the same patterns in cancer evolution that we do in the evolution of species: neutral drift, nested clades, novel functions, and positive selection. The same math, software, and theory that is used to study the evolution of species works for cancer too.

If evolutionary theory is wrong about the origin of species, why does it work so well for cancer?

What is Cancer?

On a human level, we are all affected by cancer. Many of us will die from it. Almost of all of us will be close to someone who dies from it. Cancer is a tragedy. Scientists want to understand how cancer works so we can intervene and reduce human suffering.

From a biological point of view, it is now clear that cancer is an evolutionary disease. Cancer biologists use evolutionary theory because it is useful and accurate, not because they are pushing an "evolutionary agenda." In cancer, cells evolve a set of new functions. These functions are beneficial to the cancer cell, but ultimately lethal to their host. And cancer must do much more than just grow quickly. It must also...

1. ignore signals to die,
2. evade immune defenses,
3. grow blood vessels to obtain nutrients,
4. invade surrounding tissue,

1. We see both Darwinian and non-Darwinian mechanisms in cancer. The "Darwinian" mechanism is the most commonly understood mechanism of evolution: positive selection acting on random mutations. While this mechanism of evolution is important, is not the only mechanism of evolution. Evolution also works by several "non-Darwinian" mechanisms in addition to strict Darwinism. For example, neutral drift and negative selection (sometimes called purifying selection) are also necessary to understand evolution at a genetic level. This fact makes *A Scientific Dissent From Darwinism* very strange. Biologist do not think "random mutation and natural selection" can fully "account for the complexity of life;" for example, we need non-Darwinian mechanisms too. Moreover, the precise mechanisms of evolution are an active area of continued "examination" in science.

5. survive in the bloodstream,
6. establish new colonies throughout the body,
7. and even resist treatment.

Not every cancer acquires all these functions. Nonetheless, in all cases, more than just rapid growth is required for cancer to develop. Several new functions are required. Ultimately, many cancers will acquire more than ten beneficial (to the cancer cell) mutations that enable these new functions.

One incorrect metaphor for cancer (and a misguided way of dismissing evolution) is that cancer is just cells "breaking down" or "gunk in the machine." Superficially, the "breaking down" metaphor explains some changes in cancer. For example, some cells acquire the ability to divide uncontrollably by truncating, or "breaking," specific proteins that normally control cell division.

The "breaking down" metaphor, however, is not adequate. When our technology breaks down, it never produces anything resembling cancer. Old cars, laptops, and watches do not grow tumors as they break down. In this way, cancer reminds us that biology is unlike any human design. Cancer is unique to biological systems, and we are afflicted with it because we are intrinsically capable of evolving.

Evolution, it turns out, is a much more useful framework for understanding cancer. From the cell's point of view, cancer is evolving new functions in the environment of the host's body. It evolves these functions in an evolutionary process. Cancer exists only because biological systems, including humans, have the intrinsic ability to evolve.

Does Cancer Evolve New Species?

Of course, cancer does not evolve new species. At least not usually...

In biology, there are exceptions to almost every rule, including this one. As it turns out, cancer occasionally produces new species. The two most interesting examples of this are a parasite that infects dogs, and another that infects Tasmanian devils. In these cases, a cancer evolved specific new functions: genetic stability and infectivity. Then, because of its location and the behavior of its host, it spread to others. A new species of parasite is born.

New species arise from cancer only very rarely; this isn't the rule. Still, sometimes, they do. The evolution of new species from cancer is an important reminder that biology is surprising. It does not work according to our intuitions. In biology, there are always exceptions to the rules, and the improbable flukes are important.

Moreover, cancer still demonstrates how evolution works at a genetic level. Instead of millions of years, the time scale of cancer's evolution is just years. So, cancer enables us to repeatedly study evolution in a system that matches our own biology. We see several important patterns: signatures of evolution. Evolution leaves information in our genomes from which we can reconstruct the past.

"Neutral" Processes Dominate Evolution

A common misconception about evolution is that it is dominated by natural selection acting on beneficial mutations (this is often what is meant by "Darwinian" mechanism). However, brilliant mathematical work and genetic experiments in the 1960s and 1970s by scientists like Haldane and Kimura demonstrated that evolution, at the genetic level, is usually dominated, instead, by the drift of neutral or near-neutral mutations. So most of the genetic differences between different lineages were either non-functional or not beneficial enough for natural selection. Only a few of the differences were fixed by natural selection. This is one reason biologists say that Darwinian evolution[2] is quantitatively less important than non-Darwinian evolution (e.g. neutral drift, neutral draft,[3] and other mechanisms) in explaining the complexity in genetic differences between species.

Cancer evolution independently confirms that neutral theory is correct. We see the same patterns here, but the terminology is different.

In place of beneficial and neutral mutations, Cancer biologists often talk about "driver" and "passenger" mutations. The driver mutations are the ones that cause cancer, by conferring new abilities on the cancer cells. The passengers have no strongly selectable function: they are neutral. Rather than by natural selection, these neutral mutations are fixed by other mechanisms, like neutral drift. Any individual cancer cell will have tens, hundreds, or even thousands of mutations. But only a few[4] of the mutations are drivers that are selected by natural selection. We know this fact from direct experimentation; only a small handful of mutations (of the thousands we observe) can actually induce cancer.

This is exactly what we expect from neutral evolutionary theory: drivers are vastly outnumbered by passengers. This is true for cancer, and it is also true for the evolution of new species. For example, the vast majority of genetic differences between humans and chimpanzees are *neutral*, and were fixed by neutral mechanisms like drift and draft. Over the last 6 million years, our ancestors explored hundreds of billions of mutations,[5] tens of millions of these mutations

2. In this sentence, Darwinism does not refer to the modern understanding of evolution, but the definition of Darwinism in *A Scientific Dissent From Darwinism*: exclusively random mutation and natural selection.
3. Genetic "draft" is subtly different than neutral drift, but also a mechanism by which neutral mutations are fixed. In this case, they are fixed because they are nearby beneficial mutations in the genome. They "hitchhike" on the selective force generated by the drivers. In principle, "passenger" mutations can be fixed by either drift or draft, though sometimes the distinction is not clarified when "passengers" are referred to as "hitchiker" mutations. Either way, these mutations are selectively neutral, are the most common mutations in cancer, and are not fixed by positive selection acting on their beneficial.
4. Estimates range from three to about seven rate limiting mutations, and perhaps ten or so more likely mutations too. The seminal work by Armitage-Doll in 1954 is a brilliant study of this point, well ahead of its time.
5. A low estimate of the number of mutations explored by our ancestors over the last 6 million years is 400 billion mutations. The human genome is only 3 billion bases long, so every possible point mutation could have been explored more than one hundred times.his estimate is computed assuming 10,000 individuals, 100 new mutations per individual, and a generation time of 15 years (10,000 x 100 x 6 million / 15). Remember, this is a very low estimate that ignores the upward contributions of population growth, individuals that die before reproducing, and variations in mutation rate. In this simplified model, we expect about 40 million mutations to be fixed by neutral drift (100 x 6 million / 15) and for there to be about 80 million point differences between chimps and humans (or 1.3% difference). This very rough calculation is reasonably close to the observed differences human and chimpanzee genomes (about 2% different). These are very rough estimates with simplified formulas and imprecise data, so some discrepancy is expected. As we improve the models and the data, the discrepancies reduce and neutral drift still accounts for the vast majority of genetic differences between us and our common ancestors with apes. Only a

were neutral and drifted into our genomes, and perhaps just a few thousand mutations were functionally important enough to be selected by natural selection.

Genetic Information and Common Descent

Most of the information in cancer genomes is a record of history. Genomes record the origins and evolution of every cancer cell, and their relationships to one another. Using evolutionary theory, we can read this history out of genetic data.

The specific part of evolutionary theory that reads history from genetic data is " phylogenetics." Phylogenetics is foundational to modern evolutionary theory, with deep roots in information theory, population genetics, and neutral theory. It bears repeating, the exact same math, software, and theory that so accurately reconstructs a cancer's history, is also used to reconstruct the evolutionary history of species.

Phylogenetics is powerful because there is so much historical information in genetic data. This information traces the ancestry of cancer cells. For example, one study used phylogenetics to map the ancestry of cells in a colon with a large tumor.[6] This analysis showed that the cancer arose from a mutated original cell that also gave rise to neighboring regions of the colon and nearby polyps. The genetic mutations in the colon are in a " nested clade" pattern, exactly as evolution predicts.

Phylogenetics can identify exceptions to the normal rules of biology; it can reconstruct surprising and unexpected events. For example, we usually assume that cancer descends from a single cell in the host patient, but this is not always the case. Evolutionary analysis of genetic data (based on neutral theory), is how scientists demonstrated that the parasitic cancer in dogs is not a normal cancer, but an infectious parasite. Phylogenetically, parasitic tumors from different dogs shared most recent common ancestry with each other, rather than with the cells of the dogs. In the distant past, a single dog's cancer evolved into an infectious parasite. This cancer is the common ancestor of all the parasitic cancer tumors we see today in dogs. As surprising as this is, we see the story recorded in the genetic information.

Phylogenetics also detects exceptions to common descent from a single Tree of Life, an overly simplified model of evolution. For example, many cancers are partly caused by "horizontal gene transfer." In these cases, viruses transfer new genes into normal cells. Famously, the human papilloma (HPV) virus causes cervical cancer in this way. It transfers genes into the cells it infects. The newly transferred HPV genes give our cells some of the new functions needed for cancer.

In the same way, phylogenetics detects horizontal transfer of genes in the evolution of species. For example, an important protein in human placentas looks and functions like a viral protein that transferred to our ancestors in the same way HPV transfers its genes to enable cancer evolution.

Convergence and Multiple Solutions

What about the drivers? What patterns do we see in how cancer evolves new functions? Two key patterns emerge. On one hand, we see cancer evolution "converge" to the same solutions. On the other hand, cancers are incredibly diverse, demonstrating that there are multiple ways to evolve the same function.

Cancer demonstrates "convergent evolution." We see this at both a genetic and a functional level. For example, specific driver mutations are often "recurrent": they appear independently in different patients. In other common cases, different mutations in the same genes have very similar overall effects. Similarly, proteins in the specific pathways are often independently mutated in different patients. Functionally, cancers usually evolve new functions in a predictable sequence. So, cancer demonstrates convergent evolution in multiple ways.

We see convergent evolution of species too. At a functional level, bat and bird wings are a type of structural and functional convergence. So are the wide variety of eyes we find in nature, where we frequently observe structural and functional convergence. Evolution sometimes shows convergence on a molecular level as well. In these cases, the same mechanisms, pathways, and mutations occur independently in multiple lineages. For example, different mammals evolved similar placentas by horizontal gene transfers from different viruses (a convergent mechanism and genetic change). Then, as placentas became more effective at nourishing embryos, egg yolk became obsolete. Then, each line of mammals began to independently lose their yolk genes (a convergent genetic change).

On the other hand, cancer demonstrates there are thousands of possible mutations that could evolve the same functions. There are a very large number of ways to solve the problem. This makes evolution more likely, because no single specific set of mutations is required to generate a new function. Instead, evolution has only to find one of the many solutions. This makes it much easier for new functions to arise.

We see multiple solutions in the evolution of species too. A large number of mutations can all have the same functional effect. There are multiple ways to solve the same functional problem. In fact, convergence at one level is usually accomplished with totally different solutions at other levels.

For example, there are multiple ways to lose a gene, so there is divergence in the specific inactivation histories of yolk genes in each mammalian line. A similar example: bats and birds both have wings (convergence), but their wings are also different and make use of many different genes and structures (divergence). Evolution makes coherent sense of these patterns of convergence and divergence. And this feature of biology, that there are multiple ways of solving the same problem, makes the evolution of new functions much more likely.

small number of differences, perhaps just a few thousand mutations, were beneficial enough to be fixed by natural selection. The rest were fixed by neutral processes (like drift and draft). Moreover, the rough formula is often a good approximation: mutation rate multiplied by divergence time approximately equals the observed divergence divided by two.

6. In the linked figure (warning: graphic image of internal organ), because of the low mobility of colon cells, we also see the clades in a geographical distribution that matches their ancestry. The spatial pattern of biogeography was one of the earliest clues to the evolution of species, and we see it in cancer too. We also see convergence, as multiple polyps (a convergent function) develop independently in different lineages. Moreover, phylogenetics has become a critical tool in studying colon cancer specifically, other cancers too, and also cancer metastasis.

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Some see convergence as evidence against evolution. Cancer, however, empirically demonstrates that evolutionary processes do converge to similar solutions. Likewise, most mathematical arguments against evolution assume that specific mutations are required to evolve new functions. Cancer, however, empirically demonstrates that the same function can evolve from a very large number of different mutations.

Cancer's Testimony of Evolution

We have some understanding of cancer evolution, but we are learning more all the time. Currently, we have the genomes of over 10,000 tumors, covering dozens of different types of cancer, and this number is going to exponentially grow in coming years. Repeated observations of the same evolutionary process gives us unprecedented understanding of how life evolves.

In the end, cancer does not (usually) demonstrate evolution of new species. It does not demonstrate that humans arose from a common ancestor with the great apes. It does not demonstrate the full story of evolution. To tell that story, we need information from the genomes from multiple species and the fossil record. Encouragingly, the same evolutionary theory that reconstructs cancer's history works here too.

Even before engaging the larger story, a detailed look at cancer leaves us with some important conclusions; without doubt, evolution makes sense of cancer. Whether or not we agree with the full evolutionary story, cancer demonstrates that evolutionary theory itself is useful. Going a small step farther, understanding evolution is centrally important in medical research. Fundamentally, cancer is an evolutionary disease. It only arises because life evolves.

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