Using the principles of evolution to defeat cancer

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November 24 marked 164 years since the publication of Charles Darwin's revolutionary "On the Origin of Species," one of the most influential scientific books ever written. In acknowledgement, 24 November is known as "Evolution Day" or the quirkier titled "All Our Uncles are Monkeys Day." The Institute of Cancer Research feels bound to commemorate this important work that challenged, and eventually transformed, our understanding of the natural world.

When thinking about evolution—the process by which the heritable characteristics of living things change over successive generations—our years of being glued to David Attenborough shows mean that we tend to focus on the visible formation of new structures and species.

We like to understand and explain the process by considering well-known examples, such as how humans evolved from apes, how finches on the Galápagos islands developed different shaped beaks to suit their food sources, and how insects, birds, and bats have separately evolved the ability to fly.

The darker side of survival

This means that we typically see evolution purely in a positive light. And no other species is likely to argue. After all, without its elongated, bony middle finger, the aye-aye would be unable to forage for grubs in trees, and it would have to compete with other animals for more accessible foods. The axolotl has increased its chance of survival by being able to regenerate parts of its body following injury and by adapting to live in water as an adult.

In possibly the most extreme example, in an absence of water, the tardigrade adopts a dried-out form called a "tun," which can survive being stored in a freezer for years, being sent into space, and being subjected to extremely high pressures. As soon as water returns, it will "reactivate" to its usual state.

The immense power of evolution to support survival in the animal kingdom is clear.

But evolution hasn't only given the giraffe its long neck, the armadillo its shield and the frogfish its specialized lure. It hasn't only benefitted the organisms we want to thrive. After all, anything with a

genome—whether it contains DNA or RNA—can evolve in time.

We have long been aware that the ability of bacteria and fungi to evolve can lead to antimicrobial resistance, and it has been almost impossible to escape talk of the SARS-CoV-2 virus evolving. Conversely, evolution in cancer has stayed under the radar outside of the scientific and medical world. However, it's not something we can ignore. Given that evolution has granted animals with "superpowers," we need to respect its role in disease.

Evolution leads to drug resistance

At the Center for Evolution and Cancer at The Institute of Cancer Research, scientists from across multiple disciplines are working together to determine why humans are vulnerable to cancer, what determines how cancer develops over time and what we need to do to overcome drug resistance.

Drug resistance is arguably the most significant challenge in cancer treatment. There are various mechanisms by which cancer cells can become resistant to drugs, but the outcome is the same—the treatment will stop working, and the patient will need to switch to a different treatment, if there is one available.

In some cases, cancer cells change their phenotype—meaning their appearance or behavior—because of a genetic mutation, and this ends up giving them a survival advantage. As the surviving cells go on to divide and form new cells, the advantage is present in an increasing percentage of the cells in a tumor.

In other cases, beneficial changes occur through alternative mechanisms. Non-genetic evolution, often known as phenotypic plasticity, typically refers to changes in an organism's form in response to an environmental

stimulus. For instance, a cancer cell could switch to a resistant state in response to chemotherapy, without acquiring a genetic mutation.

Using cancer's evolutionary ability against it

Professor Trevor Graham, Director of the Center for Evolution and Cancer, and Dr. Freddie Whiting, a member of Trevor's team, recently wrote an opinion piece discussing the various approaches for studying non-genetic evolution in cancer. They stress that clarity around this process "is essential to enable development of therapies that prevent cancer adaptation to treatment or tumor progression."

As the authors highlight in the paper, which has been published in *Trends in Cell Biology*, cancer cells can also display non-genetic phenotypic changes that are not directly induced by the environment but may still confer a selective advantage. The authors propose that this alternative scenario (where phenotypes can change randomly), which they have coined "phenotypic noise," be clearly distinguished from phenotypic plasticity. As noise and plasticity change a cell's phenotype through different mechanisms, the authors believe that distinguishing between them "will ultimately accelerate efforts to control or prevent phenotype changes that enable cancer cells to resist therapies."

As an example, they touch on "evolutionary steering." This treatment strategy exploits the principles of evolution, but it can only be effective in cases where the environmental changes induced by this treatment are responsible for creating the resistant cancer phenotypes. To make use of this approach, researchers need to be able to confirm that phenotypic plasticity rather than phenotypic noise is at play.

The options might then include adaptive therapy, which is a dynamic approach that aims to prevent cancer progression instead of trying to kill as many cancer cells as possible. The idea is that by stopping and

adjusting chemotherapy, clinicians leave some treatment-responsive cancer cells alive. This stops treatment-resistant cells from taking over and growing out of control. Although patients must live with some tumor burden, they receive lower doses of toxic cancer-killing medications, shielding them from the worst of the side effects. Adaptive therapy with abiraterone, a prostate cancer drug discovered at the ICR, has already proven successful in a clinical trial.

Another option is to use a first treatment to evolve a cancer cell population in a certain way before administering a second drug that is likely to be effective against these changed cells. This can be described as "directing the evolution of the tumor population using Darwinian adaptation to a drug."

The importance of tumor-immune system coevolution

Although many scientists agree that it's essential to factor in evolutionary principles when treating cancer, the theory alone is insufficient. For each type, and even subtype, of cancer, scientists need to determine what causes cancer to develop phenotypes that make it less sensitive to treatment, how to recognize this and how to treat it.

At the same time, they need to consider the patient's immune response. Humans have a powerful immune system comprising a network of cells, proteins and organs. Although the overall system has evolved over hundreds of generations, an individual's immunity can evolve throughout their lifetime.

Researchers have demonstrated that cancer populations and the immune system can coevolve, meaning that they "may persist in an equilibrium state for long periods." This occurs in part due to immunoediting, the process by which the immune system restricts or promotes tumor development. The latter can occur if an attack by the immune system

fails to eradicate the tumor, leaving resistant cells in place. This, in effect, selects for immune-evasive cells, making the cancer more aggressive.

In a recent study that was led by Dr. Luis Zapata Ortiz, now Group Leader of the Evolutionary Immunogenomics group at the ICR, and published in the journal *Nature Genetics*, scientists found a way to distinguish between two types of cancer cells that have been selected in this way.

The first type, which the authors labeled "immune-edited," lack neoantigens (foreign proteins that generate an immune response) while the second type, described as "immune-escaped," have developed the ability to evade the immune system despite accumulating neoantigens—either through mutations or the expression of certain proteins that help them "hide." The team found that immune-escaped tumors responded well to immunotherapy, whereas this treatment proved ineffective for immune-edited tumors.

Dr. Luis Zapata Ortiz said, "This is a strong example of using evolution as a biomarker for treatment response. We need to be taking into account the role of the immune system in sculpting the cancer genome so that we can make sure we are only giving immunotherapies to patients who will respond."

How the human body can influence cancer evolution

In complementary research, currently available as a preprint on *bioRxiv*, a team of researchers led by Professor Graham and Dr. Annie Baker, a member of his team, has developed and validated a sequencing methodology that makes it possible to analyze how the immune system responds to cancer cells using just a small sample. This can reveal how white blood cells called T-cells react when faced with cancer cells with

different mutations and how they behave once the cancer becomes invasive. As it requires no specialist equipment, this methodology is accessible to most genomic and molecular biology laboratories, so scientists worldwide can use it to develop a better understanding of tumor-immune coevolution.

The immune system is not the only part of the human body that can affect cancer evolution. The microbiome—the collection of all the bacteria, fungi and other microbes that live in the body—also has a part to play.

Additional recent research led by Professor Andrea Sottoriva, Group Leader of the Evolutionary Genomics and Modeling group in the Center for Evolution and Cancer at the ICR, has identified that people with colon cancer have a significantly higher presence of Escherichia coli (E. coli) with a certain gene, known as pks+ E. Coli. This gene encodes a chemical called colibactin that can cause damage to DNA, potentially resulting in a mutation that leads to cancer. This finding is important because the development of colorectal cancer is still not well-understood, and the known mutations do not fully explain it.

Although further research is needed to confirm the involvement of pks+ E. Coli in colon cancer development, this member of the intestinal microbiome has the potential to serve as a biomarker of colon cancer risk. The paper is due to be published in the journal *Nature Communications*.

Celebrating progress in research

Although the evolution of cancer is responsible for many of the difficulties surrounding treatment, we are continually taking steps forward in our understanding of how it works and how we might be able to counter or exploit it.

Professor Trevor Graham, Director of the Center for Evolution and Cancer at the ICR, said, "In many ways, the process by which cancer develops within the body is akin to species evolution. Subpopulations of cancer cells with mutations that give them a survival advantage will expand, whereas those with unhelpful alterations will not. Further mutations follow, often in response to environmental factors, such as the microbiome and cancer-killing treatments. And, over time, the cancer becomes increasingly adapted to the environment of its host, making it harder to eliminate.

"If we don't learn how to work with or overcome this evolution, we will continue to be limited by treatment resistance. At the ICR, we are working hard to apply the principles of evolution to our research so that we can improve the diagnosis, treatment and prevention of cancer.

"If we can understand cancer's evolution—how it develops, spreads and becomes resistant to treatment—we can start to predict its behavior. This will give us a huge advantage when it comes to preventing and treating the disease. Cancer continues to surprise and confound us, but thanks to our understanding of evolution, we are expanding our knowledge more rapidly than ever. Darwin would be proud."

On Evolution Day, we celebrate not only the weird and wacky animals that share our planet but also the highly evolved human brain capable of carrying out the incredible scientific research that saves and improves lives.

More information: Frederick J.H. Whiting et al, Phenotypic noise and plasticity in cancer evolution, *Trends in Cell Biology* (2023). DOI: 10.1016/j.tcb.2023.10.002

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