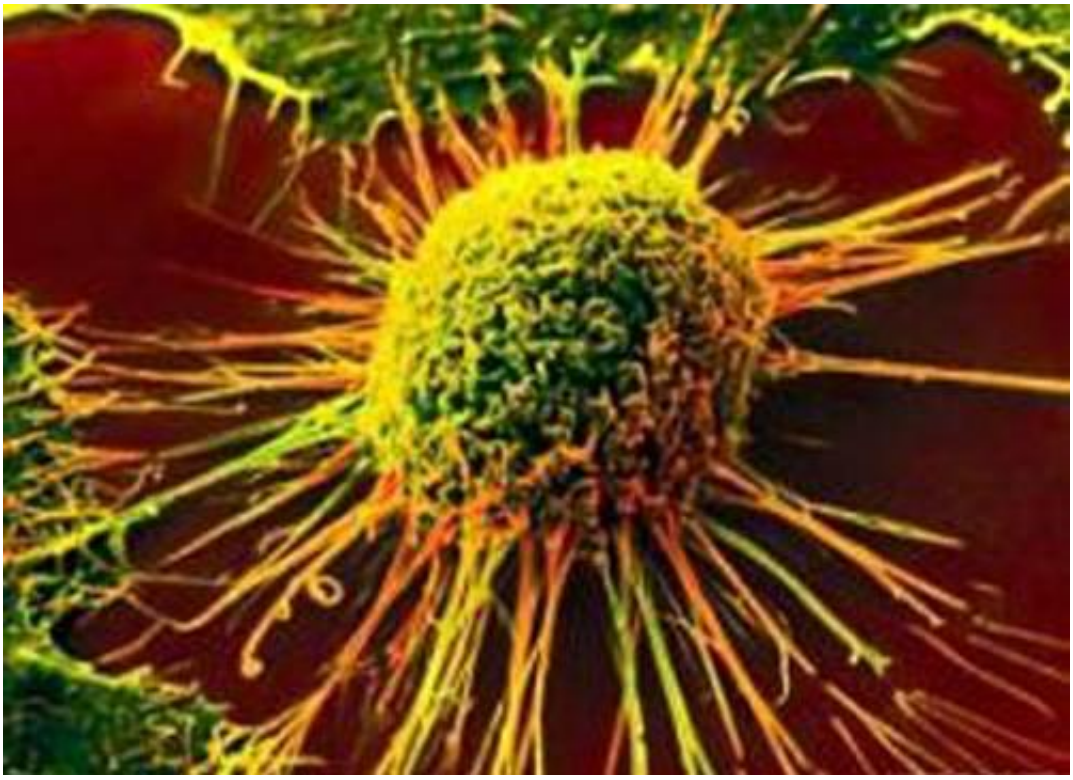
Learning from extinction: New insights on controlling cancer

February 18 2015



The earth is in the throes of a sixth mass extinction of species. Unlike those that preceded it, the current die-off is largely driven by human activity—the destruction of diverse habitats; the pollution of air, earth, and water; the disruption of the planet's climate.

According to a new study however, humankind's ability to understand (and often drive) species extinction may be harnessed in the battle against cancer.

Carlo Maley, Ph.D., a researcher at Arizona State University's Biodesign Institute and School of Life Sciences brings a paleontological view of species extinction to bear on the challenges involved in driving populations of cancer cells to annihilation, (or at least improving patient prognosis through disease-limiting efforts).

In collaboration with international colleagues, Maley reports his findings in the current issue of the journal *Nature Reviews Clinical Oncology*.

"The two themes of this paper are how to drive cancer extinct and how to do better prognosis," Maley says. In both cases, paleontological studies of species extinction can provide valuable insights.

Interminable threat

The enigma of cancer has engaged many of the world's best researchers, while each year claiming millions of lives and costing humankind many hundreds of billions of dollars. In some areas, significant strides have been made and certain once-lethal cancers have been brought under control. Nevertheless, cancer's tenacious resistance to eradication remains one of the great challenges for modern medicine. A fresh perspective on this leading killer is desperately needed.

Many suggest that studies in seemingly far-flung areas of science may help break the deadlock and inspire new techniques for cancer diagnosis and treatment. Researchers like Maley are bringing the tools of evolutionary biology and ecology to bear on the discipline of oncology. The basic idea draws on an intriguing analogy between species and cancers—each involve genetically diverse populations mutating and

evolving under selective pressures in an effort to proliferate and survive extinction.

Over 99.9 percent of species once inhabiting the earth have gone extinct, though the process often occurs over many millions of years. Driving populations of cancer cells extinct in time to save a patient's life is plainly far more difficult to achieve, but the authors of the current study suggest we have much to learn by examining the factors responsible for driving species extinct as well as the traits that may make a given species extinction-resistant.

Although cancer's stubborn resistance to therapy has long been recognized as an evolutionary and ecological adaptation, researchers have yet to fully embrace the central importance of ecology and evolutionary biology in the struggle to eradicate the disease.

The new study highlights a number of key ingredients governing so-called background extinctions, involving individual species. Background extinction is a constant, ongoing process, distinct from mass extinction events, which can lay waste to large numbers of species. From the standpoint of oncology, background extinctions are more relevant, as the aim of cancer treatment is to drive cancer cells extinct while leaving other cell types healthy and intact.

Background extinctions, which account for roughly 95 percent of species loss over the history of the earth, can be driven by environmental alterations and habitat loss, (common in the case of microbial extinction), or long-term losses in reproductive fitness caused by genetic factors, as is often the fate of multicellular species.

Extinction is generally the result of multiple factors acting in concert. Further, extinctions typically do not kill species outright but instead render the environment they rely on uninhabitable.

Some species however are more resilient to extinction. The characteristics associated with greater durability in the face of stress may have important correlates among some types of cancer cells. The study identifies two principle factors governing species resistance to extinction: evolveability (referring to a species' capacity for adaptive evolution) and robustness to perturbations.

A species' evolveability is governed by several considerations. The more genetically diverse a species is, the greater its ability to adapt to environmental change, compared with more homogeneous populations. Large population size also confers benefit, increasing genetic diversity and improving survival likelihood through sheer numbers.

Those species producing many offspring over short generation times may likewise have an advantage, recovering more rapidly from environmental perturbations. In contrast, slow-growing species tend to be more vulnerable to environmental variation and may fail to recover sufficient population size after suffering prolonged stress, succumbing to extinction.

The second critical characteristic for resisting extinction—robustness to perturbations—is similarly dependent on a variety of factors, including species geographic dispersal and the ease with which species are able to move, should changing environmental conditions require it. A species may also beat the odds depending on its degree of generalism. Highly specialized species dependent on a single resource are at greater extinction risk.

From extinction to oncology

The authors note that two principle strategies exist for driving cancer cells extinct: altering their microenvironment and killing them directly. Most cancer therapy to date has relied heavily on the latter strategy. As

Maley notes however, many researchers and clinicians have begun rethinking this approach, noting that highly aggressive efforts to exterminate rather than manage diseased cells may prove counterproductive by exerting selective pressure and enriching cancer cells resistant to a given treatment.

Indeed, destroying those cells responsive to treatment may actually act to clear geographic space and provide resistant cells with additional environmental nutrients, essentially super-charging aggressive cancer in an effort to destroy it. As in the case of species resistant to extinction, genetic diversity provides a key survival mechanism for cancer cells and may be a valuable indicator determining a particular cancer's amenability to successful treatment.

Although humans have driven many species extinct through overhunting, overfishing, and destruction of pests and predators, this often occurs because low numbers of surviving species face insurmountable challenges in finding a mate. Cancer cells have no such requirement however, a fact which may render the overkill model of cancer destruction ineffective. A tiny number of resistant cancer cells is often sufficient to re-ignite tumor growth and eventual metastasis.

Cancer cells are also capable of entering temporary states of quiescence, waiting out cancer therapy regimes, which tend to target aggressively proliferating cells. Like hibernating animals, quiescent cancer cells can reemerge when environmental conditions are more advantageous.

Press-pulse

Many complex factors contribute to a given species going extinct. In broad outline however, the process often occurs when a prolonged period of unrelieved stress weakens the species over time. This is followed by an abrupt event that renders the species unable to recover.

The continuous stress is referred to as the press and the coup de grace leading to extinction is known as the pulse.

Again, cancer treatment generally fails to mimic this natural course of extinction. Radiation and chemotherapy are not applied in a press-pulse regimen that would place cancer cells under relentless, diverse and sustained pressure.

The study emphasizes that a species extinction approach to cancer has important implications for disease prognosis. Cancer forms mirroring characteristics of species resistant to extinction, including rapid population growth, dispersed geographic range, high genetic diversity and ease of motility pose the most serious challenges to successful treatment under currently available therapies. (Such examples include squamous-cell cancers of the cervix, and head and neck.)

Save lives: destroy the environment!

Cancer cells resemble species in another critical respect: they act to modify their environmental surroundings to suit their needs. One means of applying the lessons of species extinction to cancer therapy would involve a shift from targeting cancer cells to targeting the microenvironment surrounding and supporting them.

Such efforts might focus on the extracellular matrix and collagen surrounding cancer cells, but could also target the host cells that produce these features, (known as fibroblasts) or they might target host immune cells. "There's good evidence that cancer cells influence and change fibroblasts and co-opt immune cells—first shutting them down from clearing the cancer and then sending angiogenic signals, instructing them to grow blood vessels and help the cancer survive," Maley says. "There's a whole ecology of different cell types evolving and manipulating the microenvironment."

Some of these insights are already being clinically tested, for example, anti-angiogenic therapy, which attempts to target non-cancer cells playing a supportive role by furnishing cancerous cells with their blood supply. Altering temperature (hyperthermic therapy) or pH levels or disrupting growth and survival signals transmitted by normal cells during carcinogenesis likewise offer new techniques under active investigation.

The problem, according to researchers like Maley, is that such approaches are often used in isolation. If the model of species extinction advanced by paleontologists is indeed applicable to oncology, one key will be to apply many forms of stress to cancer cells continuously, in hopes of short-circuiting their recovery efforts and their successful development of treatment resistance.

More information: *Nature Reviews Clinical Oncology*, doi: 10.1038:nrclinonc.2015.12

Provided by Arizona State University