New study describes cancer's cheating ways

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Patterns of abnormal growth in some flowers and plants result in rare features known as fasciations. Pictured here, a crested saguaro cactus, displaying fanlike irregularities thought to be the result of somatic mutations in their stem cells. Credit: By Alan Vernon, Wikipedia, Creative Commons Attribution 2.0 Generic

Cancer cells share certain traits with anti-social members of human society. They shirk community responsibilities and engage in behavior

aimed at fulfilling their selfish needs at the expense of the greater good.

In a new study, Athena Aktipis, a researcher at Arizona State University's Biodesign Institute, along with her international colleagues, explore the ways in which cancers bypass the protective mechanisms used by multicellular forms to ensure their survival and wellbeing.

The paper identifies five foundations of multicellularity; maintenance factors present in all multicellular organisms across the tree of life. Cancer is shown to be highly adept at eluding all five foundations described, effectively "cheating" the multicellular regime for the cancer 's own benefit. While such cheating pays dividends to the cancer cells, the results are often disastrous for the organism.

The study was conceived and largely written at the Institute for Advanced Study, Wissenschaftskolleg, in Berlin. The collaborative work was carried out over the course of a year by a diverse collective of evolutionary biologists and cancer biologists, wrestling with foundational issues in multicellularity and their relevance for cancer research.

The group's findings appear in a special comparative oncology issue of *Philosophical Transactions of the Royal Society of London B*.

"The idea of the five foundations really builds on decades of work in the field of multicellularity evolution," Aktipis says, referring to a subfield of evolutionary biology concerned with such questions as: how do cells come together to form higher level entities that have functions of their own; why have these entities evolved and what kinds of mechanisms enable the transition from unicellular to multicellular life?

The current examination of cancer and cancer-like phenomena across the spectrum of multicellular life is the first of its kind, providing researchers with a picture of cancer incidence across life as well as clues

about how multicellular controls are cheated by aberrant cells. Insights gleaned through such research may point to better methods of diagnosing and treating cancer, a disease whose capacity for rapid evolution continues to thwart the best clinical efforts to control it.

Endless forms most beautiful

Multicellular life arose independently on multiple occasions over the course of earth's history, ultimately giving rise to an astonishing diversity of forms. To ensure essential cooperation and coordination of multicellular components, all such organisms have evolved sophisticated cancer suppression mechanisms to keep cells in check and ensure they are acting in concert.

The five foundations of multicellularity pinpointed in the study are: inhibiting cell proliferation, regulation of cell death, division of labor, resource transport and creation and maintenance of the extracellular environment. Without these mechanisms, multicellular organisms could not have evolved into the endless forms we see today. Such cooperative mechanisms are essential for the proper function and survival of many multicellular forms —from fungi to humans.

Cancer cells however have the capacity to break free of this multicellular tyranny over their behavior. As the authors note, research and clinical practice to date have focused primarily on the first two violations of the multicellular framework, namely limits to cell proliferation and regulation of cell death. In both cases, cancer appears capable of short-circuiting the built-in multicellular constraints, exhibiting the unchecked proliferation and growth characteristic of cancerous tumors.

Factors affecting the sheer number of cells, including cell proliferation and cell death may be thought of as demographic foundations of multicellularity. By contrast, the remaining three foundations of

multicellularity can be considered economic factors: a division of labor involving specialized cell types, the transport of vital resources to places where they are needed and maintenance of the extracellular environment.

Aktipis and colleagues found that both demographic and economic cheating were found in all cases of cancer-like phenomena across the tree of life, pointing to the importance of these economic forms of cheating that involve resources, labor and the environment. The importance of these economic forms of cheating speak to the many parallels between multicellularity and cooperation in other forms of complex sociality including bee hives, ant colonies and even human groups.

Nature vs cancer

Evolution has strongly selected for the five foundational mechanisms underpinning successful multicellularity especially in large and long-lived organisms, and a number of specific examples have been the focus of intensive study. These include the presence of specialized genes like p53, which regulate the cell cycle and prevent cell proliferation unless precise conditions have been met. Misbehaving cells are targeted for destruction to help ensure the viability of multicellular systems.

The study compares the five foundations of multicellularity with so-called hallmarks of cancer, a set of underlying principles governing cancer behavior, proposed by researchers in 2000. According to the cancer hallmarks framework, cancer cells supply their own growth signals, resist inhibitory signals limiting their growth, resist programmed cell death (known as apoptosis), multiply indefinitely, stimulate blood vessels to supply tumors with nutrients (angiogenesis) and activate invasion of local tissues and the spread of cancer cells to distant sites (invasion and metastasis).

"For us, putting together the hallmarks of cancer with the foundations of multicellularity suggested that maybe these more economic forms of cheating have been neglected as components of cancer and contributors to cancer progression," Aktipis says. "Potentially we may be able to do better by creating diagnostics and measures of those types of economic cheating."

Unlike demographic cheating leading to unchecked cell proliferation and the development of tumor masses, economic cheating can present diverse manifestations, including lack of cell differentiation due to labor cheating, invasion of blood vessels due to resource cheating or a breakdown of the extracellular matrix due to environmental cheating.

The study notes that cheating in division of labor activities may be of particular relevance as it appears across the spectrum of multicellular life . Here, differentiation of cells into specialized types is deregulated—a central feature seen in tumor development, though not currently identified as a cancer hallmark.

There is also emerging evidence that processes of cancer cell cheating that involve monopolizing resources and exploiting the local environment may lead to selection pressure for cancer cells that are more mobile, thereby contributing to invasion and metastasis, another topic of Aktipis's research.

While the study found evidence of the five foundations of multicellularity across the tree of life, it is clear that mechanisms for suppressing cheating are not equally divided among all life forms. Animals appear to be more susceptible to cancers than plants and other multicellular organisms. This may be due to higher metabolic rates that leave animals more vulnerable to cheating in resource allocation and division of labor, while animal circulatory systems may enhance an organism's risk of metastasis.

More generally, this study found that cancer and cancer-like phenomena were more common in more complex forms of multicellularity compared to less complex forms and unicellular forms, suggesting that more complex forms of life might be more susceptible to cancer. The present study proposes that organizational complexity of multicellular bodies might enable more opportunities for cheating in complex cooperation - just as breaking rules or shirking labor might be easier in more complex organizations where there may be many more ways to cheat and it may be harder to detect.

Larger animals with greater longevity should theoretically display high cancer rates, due to increased numbers of cells that can potentially become cancerous as well as an increased number of cell divisions. Intriguingly, a number of such animals—including elephants and whales—have lower than expected cancer rates (a phenomenon known as Peto's Paradox), suggesting enhanced cancer-suppression capabilities.

An evolving discipline

"I think of it as the economics of multicellularity," Aktipis says. "How do the resources get where they need to go, how does the labor get done that needs to get done to make the body work, how does the shared environment get taken care of and maintained? These things are important and perhaps underappreciated aspects of maintaining an effective multicellular body and suppressing cancer that would otherwise evolve."

A greater focus on cancer's subversion of the economic foundations of multicellularity may give rise to innovative new strategies for identifying cancer, charting its trajectory and fashioning effective treatments.

To date, most cancer research has been carried out on humans, model systems like mice and rats, pets and some agricultural animals. Aktipis

emphasizes that much more work in comparative oncology needs to be done to explore the rates of cancer across different forms of life and the details of the mechanisms used to suppress cheating.

"This paper is a call to action for the evolutionary biology, comparative genomic and evolution of multicellularity communities to really come together and to collect data that will allow us to answer some of these big, outstanding questions about cancer suppression," Aktipis says. "Together we can look to cancer across life for answers about the nature of cancer and new tools that can be used for cancer prevention in humans."

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