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The Self-ish Cell: Cancer's emerging evolutionary paradigm

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The Self-ish Cell: Cancer's emerging evolutionary paradigm

A report from the First International Biannual Evolution and Cancer Conference

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Abstract

Cancer cells are both self-ish, in that they originate from within us, and selfish, in that they behave in ways that benefit themselves at the expense of other cells. As a result of somatic evolution, cancer cells have stopped cooperating with the other cells of a multicellular body but are similar enough to those cells to make it difficult for the immune system to detect and eliminate them. We recently held the first International Biannual Evolution and Cancer Conference (IBECC) at the University of California San Francisco to bring together and support the community of researchers working on evolution and cancer. Here we highlight a few of the exciting themes from the conference: The importance of measuring variation among cells within neoplasms, the evolution of cancer suppression and susceptibility across species, the use of life history theory at the cellular level to develop novel interventions that select for less aggressive tumors, and the important role of viruses in shaping our genomes and our susceptibility to cancer. Each of these themes are part of the research program of the new Center for Evolution and Cancer at the University of California San Francisco.

Introduction

Our bodies represent a seeming miracle of biological design and coordination. Our cells and tissues execute a dazzling array of complex functions with symphonic timing, from which we, as multicellular beings, emerge. A long history of natural selection on these cells and tissues has given rise to these highly cooperative and well-coordinated systems. As with most highly cooperative systems, this strength is also our body's greatest weakness. We are vulnerable to the exploiters—the selfish cells—similar enough to the other cells in their genetic makeup to evade our immune systems but different in that they turn the cooperative inclinations of the other cells to their own competitive advantage. This is cancer, in its simplest and most abstract form.

In reality, cancer is more complex than we can currently study, even with our most sophisticated technologies. It has puzzled physicians and researchers with its mutability and resilience, leading exasperated physicians to view cancer through the heuristic lenses of “magic” and “intelligence.” Indeed, cancer has been so hard to understand because it adapts dynamically, evolving over the course of progression and in

response to treatment. It changes in response to its environment, not as a single organism does, but rather as a population of genetically heterogeneous individuals evolves in response to environmental pressures. Cells with mutations that enhance their survival or promote proliferation outperform the more restrained cells, slowly shifting the population towards a more exploitative phenotype. These kinds of evolutionary dynamics have made cancer puzzling for the standard approaches, but they also point to an unrealized opportunity for applying evolutionary theory and methods to understanding and treating cancer.

Realizing this opportunity requires interdisciplinary collaborations, and fostering such collaborations was a major goal of the First International Biannual Evolution and Cancer Conference (IBECC), held at UCSF June 3-5, 2011. We invited cancer researchers, clinicians, evolutionary biologists, and social scientists from across the world to address the applications of evolutionary thinking to cancer research and treatment. Presentations addressed a large range of diverse topics relating to cancer's selfish nature and the evolutionary dynamics that result from conflicts among levels of selection.

Here we report a selection of highlights from the first IBECC meeting.¹ We discuss four main themes. We begin by (1) reporting several findings pointing to the importance of measuring variation to understand evolutionary dynamics in cancer, then we discuss several themes relating to cancer's selfish nature, including (2) the conflict among levels of selection in the evolution of mechanisms to suppress selfish cancer cells in multicellular organisms, (3) the evolution of more selfish cells within a tumor, with some cells evolving to use resources more rapidly or evolving fast life history traits and (4) the possibility that somatic cells may literally become infected with selfish predispositions and capacities through the action of retroviruses, which may reprogram cells to promote the fitness of the retrovirus to the neglect of the broader multicellular organism. Finally, we describe a variety of opportunities for involvement with the Center for Evolution and Cancer at UCSF and with the evolution and cancer research community more generally.

1) Variation among cells leads to natural selection

It is a general principle that natural selection occurs in any system where there is (fitness relevant) heritable variation among the units of selection. This is the case with cells within a multicellular body, just as it is with organisms or social groups. The importance of measuring variation at different levels of selection was addressed by a number of presenters at IBECC. Alexander (Sandy) Anderson (Moffitt Cancer Center) presented data from single cells that were tracked *in vitro* so that the variation in cell generation time and cell lineage reproduction rates could be quantified. Jasmine Foo (U. Minnesota) noted the importance of the fitness distributions of mutated cells during the evolution of therapeutic resistance, a point that was echoed in the presentation of Ricard Solé (U. Pompeu Fabra).

These approaches are promising for addressing neoplastic progression because variation among units of selection is not only necessary for natural selection to occur, but it is also a driver of the pace of evolution. Since evolution is driven by the fitness outliers, more variation among them leads to faster evolution. This means that measuring the variation among units of selection (cells in the case of cancer) can be more important than measuring the mean trait, especially if the goal is to understand and predict the future trajectory of an evolving population of cells within a tumor (which may help us predict which tumors are likely to be specially fast-growing and pernicious).

2) Evolving the capacity to suppress selfish cells

Building a complex multicellular body requires a degree of cooperation and coordination that is impossible if cells behave without regard for the interests of the fitness of the germ line. This means that cancer was the central problem that had to be overcome in the transition to multicellularity. Suppressing cancer has remained a major selective force in the evolution of animals, as they grew larger and lived longer. Comparative biology provides a valuable window into understanding how evolution has suppressed cancer,² and this forms one of the five themes of the Center for Evolution and Cancer. The value of comparative biology for cancer research was clear from the work of Andrei Seluanov (U. Rochester) and his collaborator Vera Gorbunova (U. Rochester). They study the comparative biology of rodents, which vary widely in body size (by >2,000X) and life span (by >7X).³ Interestingly, they found evidence that rodents with large bodies suppress cancer in part through limiting the number of times cells can divide by suppressing telomerase (preventing the rebuilding of telomeres which are shortened with every cell division).³ David Haig (Harvard U.) predicted that cancer should be more of a problem for placental mammals than for birds due to the intragenomic conflicts resulting from imprinting in mammals, with paternally inherited genes imprinted to promote cell proliferation and maternal genes imprinted to suppress growth. Haig presented zoo pathology data that suggest that birds and reptiles are indeed less prone to cancer than mammals⁴⁻¹⁰. Building upon such findings, the Center for Evolution and Cancer seeks to explore highly effective mechanisms of cancer suppression in other animals,² and is currently collaborating on the sequencing one of the largest and longest lived mammals, the Humpback Whale.

A number of presenters at IBECC, including Boyd Eaton (Emory U), and Beverly Strassman (U Michigan) discussed cancer susceptibility in humans from an evolutionary perspective, highlighting issues such as the mismatch between our modern environment and the environment in which our ancestors evolved. This is especially clear for the case of breast cancer, where modern populations experience better nutrition, delayed reproduction, and shorter periods of breastfeeding—all of which lead to higher levels of exposure to hormones such as progesterone and estrogen, as well as a delay in the ancestral pattern of breast tissue differentiation. It may also be the case that social features of the modern environment—fewer kin and less social support—plays a role in cancer, as suggested by Karen Wiehs (U Arizona); she reported research showing that social bonding is protective against cancer and that oxytocin inhibits cell proliferation. Randy Nesse (U Michigan) noted that women with visual impairment (and who therefore have less exposure to light) have lower rates of breast cancer and higher melatonin levels, suggesting the possibility that circadian disruption from modern light exposure may be an important risk factor for breast cancer¹¹⁻¹³. Athena Aktipis (UCSF & Arizona State U.) suggested that the environmental mismatch hypothesis is viable for hormone receptor positive breast cancer, but not for hormone negative breast cancer. Hormone negative breast cancer might instead involve within-organism life history tradeoffs between early reproduction and somatic maintenance.

Reproductive cancers such as breast (and prostate) cancer affect a large proportion of the population and an evolutionary perspective on human susceptibility to these cancers is promising. Understanding the evolutionary tradeoffs underlying human reproductive cancers is one

of the main research goals of the Human and Social Evolution themes of the CEC, directed by C. Athena Aktipis.

3) Selecting less aggressive cells

Above we described how the evolutionary dynamics favoring cancer suppression can be understood as a need for multicellular bodies to suppress selfish cells in order to create effective multicellular organisms. Similar evolutionary dynamics are relevant to the evolution of selfish cells *within* tumors as well. Somatic evolution of cells within a body during carcinogenesis is an additional theme of the Center for Evolution and Cancer. Tumors are not homogeneous masses of genetically identical cells, rather they are heterogeneous collections of cells with very different genetics and phenotypes^{14,15}. This means that cancer cells within a tumor will vary in their 'social' traits (traits affecting the fitness of neighbors) as well—with some cells having higher rates of metabolism (allowing them to consume resources more quickly), higher production of growth or angiogenic factors (allowing them to boost their own and their neighbors' growth), and higher rates of proliferation or motility (allowing them to colonize new environments and resource niches). Although all cancer cells are selfish, some are more selfish than others. This diversity of traits means that cells within a tumor can evolve to have more benign or more aggressive traits, depending on the environment and selection pressures they face within and around the tumor. This also suggests a potentially important, and counterintuitive, approach target for cancer prevention and cancer therapy: selecting for less aggressive cancer cells.

This possibility was suggested both by AJ Figuredo (U. Arizona) and Robert Gatenby (Moffitt Cancer Center) in their presentations at IBECC. Figuredo noted that evolutionary life history theory¹⁶ can help us understand the evolution of highly exploitative cancer phenotypes (e.g., those characterized by high rates of resource consumption, high rates of proliferation, and high rates of motility). Figuredo noted that high extrinsic mortality and unpredictable environments (which could be imposed by immune system predation or chemotherapy) should select for cells that proliferate quickly and consume resources rapidly (fast life history cells). This suggests the counterintuitive possibility that *stabilizing* the environment of cancer cells could be beneficial because such an environment would select for cells that proliferate more slowly and exploit their local environments less aggressively (slow life history cells). Along these lines, Gatenby showed that he was able to keep mice possessing an aggressive ovarian cancer cell line (xenotransplants of OVCAR-3 cells) alive indefinitely by treating to maintain the size of the tumor rather than to irradiate it. In other words, it appears that lower levels of chemotherapy actually selected for less aggressive cells, possibly through selecting for cancer cells that have relatively slower life histories. Understanding and shaping the evolution of life history traits could lead to novel approaches to cancer prevention and therapy. Aurora Nedelcu (U. New Brunswick) noted that life history traits at the cancer cell level may be particularly good targets for new therapeutic approaches because of fundamental evolutionary tradeoffs that underlie any biological unit. Specifically, she suggested that the increase in reproduction potential that accompanies cancer is likely to lead to vulnerabilities that could be targeted to reduce the cancer cell fitness.

4) Viruses may infect cells with cancerous tendencies

Perhaps the most intriguing talks and discussions at IBECC were about the potential role of viruses in cancer. Listening to the talks of Paul Ewald (U. Louisville), John Tooby (UCSB) and David Haig one couldn't help but feel stuck in limbo between the world of science fact and science fiction. Might viruses be infecting cells with selfish genes? Do ancient retroviruses sit in our genomes awaiting the opportunity to transform their host cells into machines for replicating themselves? Do viruses sit in the reproductive tract awaiting opportunities to enter the germline? Could it be that the large number of unexplained skin conditions and rashes are methods of transmission for these viruses? These and many other interesting questions were raised in the talks and discussions about retroviruses at IBECC.

When viruses integrate into the host genome, becoming proviruses, their fitness can become aligned with the host cell. By inducing their host cell to proliferate, their genetic material is copied as well. This means that there may be selection on proviruses to cause unchecked cell proliferation, which may ultimately lead to cancer. Ewald pointed out that an effective survival strategy for a provirus is to hide from the immune system within cells and to reproduce through cellular proliferation. Thus, it is in the provirus' interests to suppress apoptosis of its cell, inhibit cell cycle checkpoints, prevent cell senescence and suppress cell adhesion—all of which are necessary steps in carcinogenesis.

Tooby argued that selection on viruses may help to explain the complexity of the phenotypes of cancer. Viruses have longer than a human lifetime to evolve mechanisms for evading the tumor suppressive mechanisms of our bodies (in contrast to somatic cells whose evolution is limited to a single lifetime). Furthermore, as inactivated proviruses leave behind the wreckage of their genes in our genomes, they may well leave behind genes that make us vulnerable to cancer. Tooby suggested that the legacy of the arms race between retroviruses and their hosts may be that hosts are perpetually on the verge of developing cancer and may only need the infection of an intact virus to supply the missing piece.

Conclusion

Cancer involves fundamentally evolutionary processes. Given the explanatory power of evolution and the fact that the evolutionary theory of cancer has survived over 30 years of experimental investigation, one might expect that evolutionary theory and methods would be widely used in cancer research¹⁷. Virginia Kwan reported recent work showing that evolutionary thinking is still notably absent from the cancer literature, with only about 1% of articles on therapeutic resistance using evolution terms in abstracts, and less than 10% of recent articles using evolutionary theory or methods anywhere in the paper¹⁸. This highlights both an unfortunate absence of evolutionary thinking in cancer research, but also the opportunity for increasing the impact of cancer research through education about the ways in which evolutionary principles apply to cancer. The goal of this meeting and of the Center for Evolution and Cancer more generally is to accelerate progress in cancer research through facilitating interdisciplinary research that will help close this gap—bringing evolutionary biologists and cancer researcher together to devise novel approaches to cancer treatment, prevention and risk stratification. Such methodological and theoretical innovations illustrate how valuable evolutionary approaches to medicine can be, and are a (perhaps unique) case in which there has been little resistance to the applications of evolution in medicine.

The excitement about using an evolutionary approach to address problems in cancer was reflected not just in the talks and discussions at IBECC, but also in the involvement of the larger community in this topic. Our conference participants included many cancer researchers at

UCSF for whom evolutionary approaches are novel, a number of science journalists¹, and representatives from organizations that support innovation in science such as the National Evolutionary Synthesis Center (NESCent) and the X-Prize Foundation. The X-prize is designed to harness human creativity and innovation by providing large prizes for reaching scientific or technological goals. Rafe Furst chose this conference as a venue for beginning a discussion about what an X-prize for cancer would look like, eliciting ideas and feedback from the evolution and cancer community.

The first biannual IBECC was not only the first time the evolution and cancer community gathered as a whole to share ideas and results, but it also brought connected this community with some of the most talented and well-regarded theoretical evolutionary biologists. The result was both the sharing of information among researchers asking similar questions, as well as an explosion of questions arising from applying new aspects of evolutionary theory to cancer biology.

If you missed the first IBECC conference but would like to learn more about evolution and cancer or get involved with the CEC, please check out our website (<http://cancer.ucsf.edu/evolution>) where you can learn more about the activities and opportunities at the CEC, download slides from the conference talks, and sign up for the CEC mailing list. If you work on evolution and cancer and would like to join the faculty of the CEC, you can contact Carlo Maley. Faculty participate in monthly seminars, collaborate with other faculty and present at the CEC. You can also learn more about our next IBECC, to be held in 2013, by checking the CEC website or joining the mailing list.

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