

# Special Collection on Ecological and Evolutionary Approaches to Cancer Control: Cancer Finds a Conceptual Home

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## Abstract

Despite a century of intense investigation, cancer biology and treatment remain plagued by unanswered questions. Even basic questions regarding the fundamental forces driving the formation of cancer remain controversial. Recent approaches view cancer in the context of a complex web of interactions among cancer cells of the tumor, together with their interactions with the many cells and constituents of the complex and highly dynamic tumor microenvironment. As seen in this special collection, we believe that viewing cancer as a process of evolution driven by ongoing ecological processes playing out within a dynamic environment offers many insights and potential new pathways for cancer control.

## Keywords

ecology, evolution, information, coexistence, storage effect, mathematical modeling, landscape ecology, ecosystem engineering, metastatic management

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## Introduction

Despite a century of intense investigation, cancer biology and treatment remain plagued by unanswered questions. Even basic questions regarding the fundamental forces driving the formation of cancer remain controversial. The current favorite is that cancer is “a disease of the genes,” driven by oncogenic mutations and genomic instability.<sup>1</sup> However, several anomalies in this paradigm have led to its question.<sup>2</sup> Some continue to advocate a hypothesis advanced by Warburg more than a century ago that cancer is a metabolic disease,<sup>3,4</sup> driven by dysregulation of “normal” metabolic pathways in the cancer cell’s never-ending quest for raw materials and energy. Oncogenic and other random mutations are clearly important. Dysregulated—or, as we prefer—reprogrammed metabolism is also a common cancer “hallmark.”<sup>5</sup>

These competing perspectives on the underlying causal basis of cancer initiation and progression fall short because they both fail to incorporate and integrate the complex web of interactions among cancer cells making up the tumor, along with their interactions with the many cells and constituents of

the complex and highly dynamic tumor microenvironment. Bissell et al, for instance, focused attention on the critical role of the microenvironment that can make a normal cell behave like a cancer cell, and a cancer cell behave like it is normal.<sup>6-9</sup> As seen in this special collection, we believe that viewing cancer as a process of evolution driven by ongoing ecological

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Let us view cancer as the evolution of an invasive species within the biome of the human body<sup>2,10</sup> (but see Adler and Gordon<sup>11</sup>). This invasive species, unlike the normal cell from which it evolved, has its own “fitness function” so that its survival, proliferation, and death are determined by their ability to adapt to the local environment compared to other cancer cells with which they compete. A cancer population, in other words, can evolve and thus must constantly optimize its proliferation, often at the expense of its host. Cancer cells interact with cancer-associated fibroblasts, various immune cells, and the associated vasculature, among many other components of the tumor microenvironment. Cancer cells, through their reprogrammed metabolism, secrete acid and, by doing so, reengineer the microenvironment in a way that benefits them by allowing them to invade adjacent host tissue and diminish the predator-like activity of the immune system. Evolutionary biologists and ecologists have grappled with invasive species in natural ecosystems for decades, beginning with the classic volume, *The Ecology of Invasions by Animals and Plants*.<sup>12</sup> Here, we have assembled teams of cancer biologists, together with ecologists, evolutionary biologists, and mathematicians to harness ecological and evolutionary insights for the control of cancer.

Cancer is widely viewed to be many manifestations of complex, dynamic processes. Given the complexity, mathematical modeling provides powerful tools. Robert Beckman, Irina Kareva, Frederick R. Adler address the application of mathematical models to comprehend the complex dynamics of cancer.<sup>13</sup> Key to the successful application of mathematical modeling is choosing the right level of complexity to capture in the models (a point that echoes Levins’ 1966 paper on “The strategy of model building in population biology”<sup>14</sup>). They highlight, compare, and contrast models of “predator-prey, evolutionary game theory, and dynamic precision medicine in the face of uncertainty about mechanisms and parameter values.” Beckman, Kareva and Adler point out that no single modeling approach can encompass the complex dynamics of cancer. They conclude that “broad and flexible thinking about cancer, based on combined modeling approaches, will play a key role in finding creative and improved treatments.”

One of the great problems in evolutionary ecology, well recognized by Darwin,<sup>15</sup> is simply counting the number species that coexist on our planet due to the great diversity of habitats and phenotypes. This is echoed in the great clonal diversity found within tumors: How many cancer cell species and tumor-related habitats exist within a malignant population and how do they interact? One profound solution to this perplexing problem of ecological diversity recognizes the importance of variable environments, together with species-specific responses to that variability, and an ability to subsist through periods of scarcity in a buffered or dormant state. The applicability of this mechanism, known as the storage effect,<sup>16</sup> to cancer is explored by Anna Miller, Nancy Huntly, Joel Brown, and David Basanta<sup>17</sup>. In this contribution, the authors discuss the ecological conditions that promote the operation of the

storage effect, and they assess whether these conditions pertain in cancer. The coexistence of species promoted by the storage effect may have implications for the suitability of cancer therapies, like adaptive therapy,<sup>18</sup> which rely on competition of coexisting cancer “species” that differ in chemosensitivity.

The dynamic and heterogeneous nature of cancer populations, along with the associated microenvironment, is a common theme in each of the contributions. Burt Kotler and Joel Brown address this heterogeneity from the perspective of tumors as ecological communities.<sup>19</sup> In these cancer communities, the cancer cell subpopulations, viewed as different species, compete for limited resources while trying to evade their predators, the immune system of the host. This “ecological theater”<sup>20</sup> plays out within an environment that is often dependent on normal host cells. Brown and Kotler review ecological mechanisms of species coexistence most relevant to the promotion of diversity among cancer cells comprising the tumor, and they consider the implications for cancer therapy. As with the contribution of Miller, Huntly, Brown, and Basanta, insights from ecological coexistence theory may aid in the management of cancer as a chronic disease when cure is not feasible,<sup>18</sup> and design of extinction therapies when cure is within reach.<sup>21</sup>

Many species actively modify their habitats in a process referred to as ecosystem engineering.<sup>22</sup> Autogenic engineers operate simply by existing—for instance, a tree casts shade, which modifies the micro-environment around the tree, altering temperature, humidity, soil moisture, and insolation. Allogenic engineers, like humans, woodpeckers, and beavers, actively modify and create entirely new habitats. These modified or newly created habitats provide ecological opportunities for many additional species—from the agricultural pests that prey upon our gardens and crops, to aquatic organisms that live within beaver ponds. Kayla Myers, Kenneth Pienta, and Sarah Amend apply this useful concept to cancer.<sup>23</sup> As they illustrate, cancer cells engineer the tumor microenvironment by excreting cytokines that recruit monocytes to the tumor. Those monocytes, in the tumor environment, are then polarized to M2-like macrophages. These M2-like macrophages are themselves ecosystem engineers that support cancer cell survival and proliferation by physically altering the tumor microenvironment and through secretion of pro-tumorigenic factors like vascular endothelial growth factor. Myers et al. discuss the targeting of specific aspects of the primary ecosystem engineering of cancer cells and the secondary engineering of the M2-like macrophage cells. As they state, “This strategy has the potential to redirect cooperative pro-tumor ecosystem engineering towards an anti-tumor ecosystem engineering strategy.”

In an approach, they refer to as “Histo-Ecology,” Chandler Gatenbee, Emily Minor, Robert Slebos, Christine Chung, and Sandy Anderson draw parallels between the landscapes of natural ecosystems and the landscapes of the tumor in its micro-environment.<sup>24</sup> They illustrate the use of conceptual and analytic approaches developed over the previous 30 years in landscape ecology for the purpose of modeling species-habitat relationships. These approaches, called species distribution modeling (SDM), habitat suitability modeling, and niche

modeling, have great potential for application to cancer. Of these modeling approaches, Gatenby et al. identify SDMs as potentially most useful for application to cancer. Species distribution modeling may help cancer biologists discover new risk factors through the association of specific biomarkers, cellular constituents, environmental factors (like hypoxia or pH), and disease progression. Species abundance models (SAMs), which are similar to SDMs except that they model abundance rather than distribution, may be particularly appropriate tools to identify and study tumor habitats, given that cell segmentation and phenotyping are often performed using histology. Adopting landscape ecology methods developed to describe scaling relationships, spatial landscape patterns, and species–environment relationships will provide cancer researchers a more complete and holistic view of the tumor ecosystem. This new perspective may in turn suggest methods for cancer control.

Despite decades of seeking a magic bullet to defeat cancer, and many false beliefs that one had been found, cancer inevitably evolves defenses against all known treatment therapies. Jessica Cunningham and Chris Whelan argue that the field of cancer biology, together with the pharmaceutical industry that develops new drugs, can benefit from studying the response of the agricultural industry to essentially the same problem: inevitably, it seems, pest organisms evolve resistance to pesticides.<sup>25</sup> Despite the obvious differences between cancer cells within the tumor ecosystem and pests within agricultural ecosystems, similar resistance mechanisms are found in both. Integrated pest management (IPM), an important response to the evolution of resistance in pests, is the combined use of multiple, complementary methods of pest management. Scouting to determine pest densities, informed by thresholds of economic damage, guides the use of more environmentally harmful methods, like chemical pesticides. Some IPM principles of already been adopted in clinical oncology, adoption of others should follow. Cunningham and Whelan end with a call for the development of an Integrated Cancer/Metastatic Management paradigm modeled on the successful IPM of agriculture.<sup>26</sup>

Chris Whelan, Stan Avdieiev, and Robert Gatenby explore the ways that information acquisition and use by organisms in ecosystems may inspire strategies to exploit the importance of information acquisition by cancer cells and how to disrupt their ability to obtain and use that information.<sup>27</sup> They build upon a simple mathematical modeling framework developed to predict how disruption of information resulting from human-caused habitat fragmentation decreases the probability of population persistence. Because many chemotherapies fragment tumors into isolated, small cancer cell populations, Whelan et al. identify parallels between these 2 systems, and they develop ideas for cancer cure based on lessons gleaned from Anthropocene extinctions.<sup>21</sup> In many Anthropocene extinctions, such as the North American heath hen (*Tympanuchus cupido cupido*), a large and widespread population was initially reduced and fragmented owing to overexploitation by humans (a “first strike”). After this, the species was then vulnerable to extinction from environmental or demographic stochastic disturbances (a

“second strike”). Following this analogy, after a tumor is fragmented into small populations of isolated cancer cells by the initial therapy, additional therapy (or therapies) can be applied with the intent of extinction (cure). Disrupting a cancer cell’s ability to acquire, and use, information may be an effective second strike. As illustrated in this contribution, information, from the scale of cells within tumors to that of species within ecosystems, can be used to identify vulnerabilities to extinction and thus opportunities for control.

The principal message of this special collection is that cancer is a disease that transcends mutations and metabolism. Cancer is a disease that arises by speciation and progresses through an evolutionary succession driven by ecological processes. Cancer biology has progressed tremendously in the last 2 decades by the realization that cancer cells and host cells engage in “crosstalk.” What cancer biology needs now is “crosstalk” between disciplines. Research guided by a crosstalk between cancer biology and evolutionary ecology will, as this special collection illustrates, lead to new insights into basic cancer biology. It is our aim that fostering crosstalk between cancer biology and evolutionary ecology will ultimately shepherd basic research to translation into clinical practice.

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