Lessons from Applied Ecology: Cancer Control Using an Evolutionary Double Bind

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Abstract

Because the metastatic cascade is largely governed by the ability of malignant cells to adapt and proliferate at the distant tissue site, we propose that disseminated cancers are analogous in many important ways to the evolutionary and ecological dynamics of exotic species. Although pests can be decimated through the application of chemical toxins, this strategy virtually never achieves robust control as evolution of resistant phenotypes typically permits population recovery to pretreatment levels. In general, biological strategies that introduce predators, parasitoids, or pathogens have achieved more durable control of pest populations even after emergence of resistant phenotypes. From this we propose that long term outcome from any treatment strategy for invasive pests, including cancer, is not limited by evolution of resistance, but rather by the phenotypic cost of that resistance. If a cancerous cell's adaptation to therapy is achieved by upregulating xenobiotic metabolism or a redundant signaling pathway, the required investment in resources is small, and the original malignant phenotype remains essentially intact. As a result, the cancer cells' initial high level of fitness is little changed and unconstrained proliferation will resume once resistance evolves. Robust population control is possible if resistance to therapy requires a substantial and costly phenotypic adaptation that also significantly reduces the organism's fitness in its original niche: an evolutionary double bind. [Cancer Res 2009;69(19):7499–502]

Report

Systemic dissemination of tumor cells carries a grim prognosis and is estimated to be the cause of death in up to 90% of cancer patients (1). Although modern chemotherapy can successfully cure some patients with metastases, most common metastatic cancers remain fatal.

The metastatic cascade (2) consists of a sequence that includes tumor cell invasion into the lymphatic or vascular systems at the primary site, circulation, arrest in a distant organ, extension into the adjacent tissue, and colony formation through invasion and proliferation. Fortunately, this is an inefficient process (3) with less than 1% of circulating cancer cells producing clinically evident metastases (4–6). Multiple studies have shown that most circulating tumor cells survive vascular transit, and the inefficiency of the metastatic cascade results largely from the tumor cells' failure to proliferate in a distant organ. For example, in one study 87% (4) of injected cells survived to invade into the extravascular tissue space of a distant organ where they remained viable for prolonged periods of time, often several years. Only 0.02% (4) of these surviving cells grew into clinically evident metastases. Although some of the impacted cells formed clinically insignificant micrometastases, the vast majority did not survive.

These results indicate that development of metastases is largely dependent on the complex, dynamic interactions between the phenotypic properties of the circulating tumor cell and microenvironmental conditions in the tissue at the metastatic site. Only tumor cells that are pre-adapted to or able to adapt to the local "ecological" conditions of the "foreign" landscape within the distant organ can form a metastasis. This finding is consistent with the long-held "seed and soil" concept (7, 8) and indicates that Darwinian dynamics at the distant site play a fundamentally important role in the metastatic cascade. A feedback likely occurs between the tumor cell's new environment and the ecological and evolutionary responses of the tumor cell's phenotype to its novel circumstance.

In the past 200 years, foreign species have been introduced into a wide range of habitats by human activities as well as random natural processes (9). Clearly, metastatic cancers and invasive pests are both complex and highly diverse processes, and there are many obvious and subtle differences. However, we propose that there are sufficient similarities that general principles from the evolutionary ecology of invasive pest species may provide insights into treatment strategies for metastatic cancers (10). For example, invasion ecology involves the pest's dispersal, establishment, spread, and evolution; processes analogous to the steps in the metastatic cascade (11). Like the circulating tumor cells, most species introductions fail to establish (12). Furthermore, invasive populations are more likely to be successful when there are multiple introductions and if the originating population is genetically and phenotypically diverse (13, 14). Many invasives never spread beyond the introduction site or do so only after a prolonged lag phase during which there is typically significant phenotypic evolution (15). Populations that do invade may pass through a genetic bottleneck in which the population is initially genetically homogeneous (16). Following such a bottleneck, successful invasives typically undergo rapid evolution (17). This evolution results in increasing diversity of phenotypes and subpopulations with adaptations to exploit the opportunities and avoid the hazards of their novel environments (18, 19).

Growth of invasive species often leads to significant damage to native ecosystems and important crops. As a result, humans have an extensive and checkered experience with attempting to eradicate those species that damage crops and native ecosystems. These control methods can be divided into chemical, mechanical (i.e., trapping or weed pulling), and biological (introduction of predators, parasitoids, and pathogens) strategies. Although a

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complete review of the experience in treatment of invasives is beyond the scope of this article (see, for example, ref. 20), we would like to emphasize the following general observations as potentially applicable to the treatment of metastatic cancer.

1. The invasive population originates from one or a very small number of individuals and, therefore, is genetically more homogeneous (initially) than the population of origin (genetic bottleneck, St. John's wort case study in Box 1). However, progressive growth and spread of an invasive species typically results in increasing genetic variation that allows for the evolution of more successful phenotypes (14). Regional variations in environmental conditions (such as those that may be found in a tumor) can select for maintenance of population-wide genetic heterogeneity. For example, substantial genetic differences have been reported in urban frog populations separated by less than 3 km (21).
2. Largely because of phenotypic and environmental heterogeneity, complete eradication of invasives is achieved primarily when the population is small (and relatively homogeneous) or geographically isolated such as on an island. Eradication of established, heterogeneous, disseminated invasives is virtually never successful (22, 23).
3. Chemical control of pests, although often initially quite effective, consistently leads to the emergence of resistant phenotypes and almost never achieves long term eradication or control (see Diamondback moth case study, Box 1; refs. 24, 25).
4. Biological strategies, unlike chemical pesticides, may yield enduring control (see Rhinceros beetle case study, Box 1; ref. 23), often enforcing a stable pest population even after development of resistant phenotypes. However, multiple predators, parasitoids, and pathogens are often required to achieve durable population control.

Two general lessons potentially relevant to cancer therapy emerge from this experience: (1) Complete eradication of a disseminated invasive population is all but impossible because of their ability to evolve adaptive strategies. (2) Long-term control of invasives can be achieved, even with evolution of resistance, if the control strategy imposes a high phenotypic cost on the adaptation(s) that confer resistance.

The potential value of incorporating the cost of resistance into therapeutic strategies is new to oncology but the frequent subject of investigation in applied ecology. For example, invasive pests can negate the cytotoxic effects of chemicals by upregulating one of many xenobiotic metabolic pathways. This upregulation, often through a single protein, allows pests to become resistant with minimal change in the initial phenotype. Thus, the pest's initial high level of fitness essentially remains intact, and the population can readily continue unconstrained proliferation once therapeutic resistance is achieved. When the phenotypic cost of adaptation to a treatment is small, unless it can eradicate every member of the target population, it will have only a short term effect and never achieve robust control.

On the other hand, introduction of predators, parasitoids, or pathogens generally requires significant changes in phenotype that may result in a greater loss of fitness than that necessary to adapt to chemicals. For example, in response to introduction of a predatory hawk, mice may restrict their foraging patterns leading to less food intake and fewer offspring per mating pair. Avoidance of such a predator, although possible, always comes at an unavoidable cost in terms of other fitness-enhancing activities. In fact, the nonlethal effects of predators on their prey can be as great or greater than the lethal effects (31). This cost of resistance has been shown in the pea aphid (*Acrythosiphon pisum*), which can be controlled through introduction of the endoparasitic wasp *Aphidius ervi*. Gwynn and colleagues (32) found that aphids that were resistant (using a symbiotic bacteria that induces death of the parasitoid eggs) were significantly larger than sensitive phenotypes and that there was a positive relationship between fecundity and susceptibility to parasitoid attack. They conclude that "aphids can either invest in defence or reproduction." This trade off between adaptation and fecundity represents an evolutionary double bind.

Thus, although adaptation to any treatment is inevitable, control of an invasive species can be maintained if the adaptation causes significant reductions in other components of fitness. With an evolutionary double bind, the resistant phenotype can only achieve limited proliferation in the face of the control agent.

Invasive Case Studies

- St. John's Wort (*Hypericum canariense*; ref. 26) is a perennial plant that is native to the Canary Islands and produces hundreds of large yellow flowers. It is prized by collectors as a rare ornamental garden plant resulting in world-wide introductions. However, it has escaped cultivation and spread aggressively in only three locations (Kula on Maui, and Point Loma and San Mateo in California), all of which have mild wet winters and hot dry summers similar to the native habitat. Extensive studies have shown that each of the three invasive populations have lost about 45% of the expected heterozygosity found in the native population in Tenerife (26). However, all invasive populations show evidence of significant local adaptations including increased survival and reproduction rates. There is also divergence of the invasive populations from each other as seen by a latitudinal cline in flowering time. Flowering day for each population differs appropriately depending on its latitude, and this seems to be an evolved shift rather than a phenotypically plastic response.
- Diamondback moth (*Plutella xylostella*) is probably of European origin and was first observed in the United States around 1854 in Illinois. The moth has been treated with a wide range of chemicals with transient success. It has now spread throughout North America causing serious damage to cabbage crops. In 1988 the moth was reported to be resistant to all available insecticides (27).
- Rhinoceros beetle (*Oryctes rhinoceros*) is a significant pest of the coconut palm in islands in the south Pacific. A baculovirus that attacks both the larval and adult stages was discovered in Malaysia. Introduction of the baculovirus has resulted in successful control of the beetle population for more than 20 years despite the fact that a number of beetle phenotypes with resistance to infection have been reported (28).
- Red squirrel (*Tamiascirus hudsonicus*) was introduced into several regions in North America to serve as prey for the pine marten (*Martes Americana*; ref. 29). However, the red squirrel exerted selection pressures on the cone characteristics of the conifer trees, reducing seed abundance available for native birds, and acted as predators of bird nests, changing nesting habits and life histories (30).

We propose the following conclusions from experiences with invasive pests as relevant to cancer:

1. Because of the genetic bottleneck that results from the founder effect, small populations (such as micrometastases) are relatively homogeneous and, therefore, more likely to be uniformly sensitive to some cytotoxic therapy. This sensitivity provides a window of opportunity in which the population is susceptible to eradication, consistent with the clinical benefits observed in adjuvant therapy. However, as the metastatic populations become larger, the resulting phenotypic and environmental heterogeneities make emergence of resistant subpopulations increasingly likely. As a result, eradication of disseminated, clinically apparent metastases by any therapeutic strategy is extremely unlikely.
2. Control of established, phenotypically diverse, metastatic colonies will not typically be achieved by any therapy drug that aims to kill the maximum numbers of tumor cells. Similar to eradicating invasive pests with chemicals, this approach provides strong selection pressure for adaptive strategies and the evolution of chemo-resistance. Resistance to chemicals or targeted agents can usually be achieved through a relatively simple addition to the existing phenotype (i.e., upregulation of the *MDR* gene or upregulation of a redundant signaling pathway). This action is ecologically and evolutionarily "inexpensive" and only minimally compromises the underlying malignant phenotype. Proliferation can resume once resistance is established, so that long term control is unlikely.
3. Robust control of diverse cancer populations requires more "evolutionarily enlightened" strategies such as treatment that places malignant cells in an "evolutionary double bind."

Experience in applied ecology suggests that a double bind in cancer can be achieved using "biological methods" that, for example, use the predatory effects of the immune system. Interestingly, despite this theoretical advantage, immunotherapy and oncolytic viruses, which mimic in many ways the dynamics of predators and parasitoids, have not proved clinically effective.

If the theoretical analysis is correct, we must conclude that, thus far, the biological methods of cancer therapy have not truly achieved an evolutionary double bind. There are several possible reasons suggesting additional avenues of research.

First, the immune response may be directed at tumor antigens that are not essential for proliferation. That is, if tumor cells can down-regulate surface antigens without loss of proliferations, then they adapt to the immune attack with little cost, and a double bind is not achieved. Interestingly, Khong and colleagues (33) showed that the recurrent tumors in a patient who had initially responded to immunotherapy exhibited either loss of tumor-associated antigens or HLA class 1 expression. Thus, the reduction in fitness that resulted from adapting to immunotherapy did little to prevent tumor regrowth. This suggests the need to develop strategies for immunotherapy that are directed toward gene products that are both uniquely expressed in a cancer and critical to its ability to proliferate and invade (e.g., hawks are particularly effective when they exert the most threat in the habitats where mice must seek food). An example of this might be the *TMPRSS2-ERG* gene fusion in prostate cancer (34). Tumor cells that reduce expression of TMPRSS2-ERG will evade the immune response, but its loss has been reported to decrease proliferation and invasion (35). However, it is difficult to predict *a priori* the phenotypic cost of down-regulation of any immune target on the cell surface so that implementation of this theoretical strategy will require explicit measurement of proliferation of the adapted phenotype *in vivo*.

Second, any single cell surface protein may not be sufficiently critical such that its down-regulation will cause significant loss of cellular fitness. Thus, a single biological agent may not be sufficient owing to the phenotypic and environmental heterogeneity of most cancers. In fact, this is observed in pest management where often a number of predators, pathogens, and parasitoids are needed to control a single exotic species. The alfalfa weevil, for example, is a significant crop pest that is now well controlled, but this has required the introduction of at least nine parasitoids and predators. Thus, loss of fitness in the adapted phenotype may occur only with simultaneous attack at multiple components of the cancer cell phenotype (36). Thus, "predator facilitation" can be a particularly effective means for producing an evolutionary double bind. For instance, in response to owl predation, desert rodents simply shift their activity toward the safety of shrubs. But, if there are also snakes, these predators will wait in shrubs to ambush the gerbils. Owls facilitate the hunting success of snakes and vice versa (37).

Finally, biological and chemical therapies could be combined using strategic multistep approaches that focus on both the immediate cytotoxic effects of the treatment and on the subsequent adaptation, with a goal of exploiting or overcoming the adaptive responses of the tumor cells. For example, Antonia and colleagues (38) treated 29 patients with small cell lung cancer (SCLC) using a cancer vaccine directed against p53. Although p53-specific T-cell response was observed in 57% of the patients, tumor progression following vaccination was observed in all but one. Interestingly, however, the patients that exhibited a T-cell response were highly sensitive to subsequent chemotherapy, with a partial remission or complete remission of 62%, which is much greater than the historic norm of less than 8%. The results suggest that the tumor cells were able to successfully adapt to the immune attack but that this adaptation (1) could be overcome by the effects of chemotherapy or (2) rendered the cells more sensitive to the cytotoxic effects of chemotherapy, a strategy previously described by Maley and colleagues (39) as a "sucker's gambit."

In summary, more than 200 years of experience in combating invasives in a wide range of ecological circumstances provides novel insights that seem relevant to treatments of disseminated cancers. A specific lesson from applied ecology is that cancer therapeutic strategies must be evolutionarily enlightened by extending the typical treatment time horizon. Thus, each therapy must be evaluated both in terms of its immediate effects on the cancer population and on its long term effects in producing specific phenotypic adaptations. In general, we propose that robust cancer therapies should aim to control tumor growth by placing the cancer cells in an "evolutionary double bind" so that it can evade the cytotoxic effects of treatment only with a strategy that compromises its other fitness attributes, thus preventing the resistant phenotype from proliferating or evolving complete resistance.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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