CANCER PHARMACOLOGY

# Eco-evolution of cancer resistance

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**For the past 60 years, the goal of conventional cancer therapies has been the eradication of every cancer cell. To this end, patients are subjected to the highest possible doses of radiation and chemotherapy as well as radical surgeries. In the rare case in which eradication was possible, clinicians achieved long-term control of the disease. For the most part, however, upfront eradication is not possible, and despite intensive and very toxic therapies, the patient dies of the disease or of complications of therapy. As our understanding about the role of tumor microenvironment in tumor progression and drug resistance improves, we are realizing that the paradigm of killing all cancer cells may be flawed.**

In this issue of *Science Translational Medicine*, Enriquez-Navas and colleagues present new evidence that supports the heretofore untested theoretical model of cancer as an evolutionary and ecological process, and ultimately indicates that low-dose, frequent chemotherapy may be better than high-dose cytotoxic therapies (*1*, *2*). The aim of low-dose chemotherapy is a gradual, sustained antitumor effect that prevents disease progression, rather than an instant impact on tumor size. This concept has been explored several times in the past, with different names reflecting the many facets of its action. "Metronomic chemotherapy" was coined to reflect the ability of low-dose, frequent chemotherapy to inhibit angiogenesis, circumvent drug resistance, and enhance native immunity (*3*, *4*). "Dose-dense therapy" explored the effect of elimination of rest periods, and "adaptive therapy" conceptualized evolutionary pressures by responding to the spatiotemporal variability of tumor microenvironment and cellular phenotypes (*5*, *6*). Yet despite an increasing number of clinical trials supporting its efficacy, the mechanism of action explaining continuous low dose chemotherapy has remained unclear.

## ECOLOGICAL AND EVOLUTIONARY DYNAMICS

The so-called "eco-evolutional model" of cancer suggests that in the presence of cytotoxic agents, populations of drug-resistant cells normally kept under control by the high metabolic demands of their resistance machineries become the fitter population because they are able to withstand the environmental change better than can their wild-type competitors (*1*). As resistant cells proliferate unopposed, they become the predominant population, and high-dose chemotherapy fails to prevent tumor growth (Fig. 1). Enriquez-Navas *et al.* (*1*) show how the use of low-dose, frequent chemotherapy preserves a stable population of drug-sensitive cells, exploiting the high metabolic cost of resistance to keep the drug-resistant population under control.

The authors used two well-established orthotopic models of breast cancer—triple-negative MDA-MB-231 and estrogen receptor $(ER)^+$ MCF7—to show that after an initial cytoreduction, decreasing doses of paclitaxel can halt exponential tumor growth, encouraging it to plateau initially then regress (*1*). They demonstrated that such adaptive therapy (continuous, low-dose) was superior not only to standard therapy (interrupted high dosing) but also to adaptive therapy with dose skipping (interrupted low dosing), with tumor burden stagnating at a non-lethal limit (Fig. 1). The animals were followed for a sufficient length of time to see a full divergence of the growth curves between standard and adaptive therapies, which is uncommon in preclinical studies. For ~60% of animals, therapy could be withdrawn altogether with no further breast cancer progression.

This study further validates the theory of Gatenby *et al.*, which states that disseminated cancers are analogous in many ways to the evolutionary and ecological dynamics of exotic species (*2*). Enriquez-Navas *et al.* found that tumor-bearing mice treated with a high dose of paclitaxel will experience initial tumor regression, but the emergence of the new "exotic" chemoresistant species causes the tumor to subsequently progress; administering another high dose after progression produced no effect on tumor growth in these animals (Fig. 1) (*1*). The upshot of this phenomenon—of resistant cells being free to proliferate in the face of chemotherapy, unchecked by drug-sensitive and healthy cells, which is known as "competitive release" in eco-evolutionary dynamics—is that maintenance of equilibrium within the tumor ecosystem can limit the ability of therapy-resistant clones to gain evolutionary advantage. This conceptually simple idea is not only novel, it is also wide-ranging in its application. It suggests that by changing the existing paradigm of cancer as a foreign tissue needing eradication by high-dose chemotherapy to that of a model of cancer as an eco-evolutionary system, in which sustained suppression of tumor growth is a more appropriate therapeutic path—and one with much less toxicity. Even in cases in which some degree of initial cytoreduction is necessary because of acute symptoms, subsequent low-dose metronomic chemotherapy would ensure stability of this initial response.

## DISTURBING THE EQUILIBRIUM

The acceptance of this eco-evolutionary model of cancer is informed by a better understanding of the complexities of the tumor microenvironment (*1*, *2*). Most oncologists have by now recanted the notion that cancer is the mutational emergence of a single highly proliferative clone and accepted the notion that cancer is a heterogeneous disease capable of co-opting otherwise normal physiological processes. This new ecological view supported by the experimental evidence from Enriquez-Navas *et al.* also explains poorly understood clinical observations, such as tumor dormancy or patterns of tumor dissemination, which are affected by the ability of different population of tumor cells to induce inflammation, angiogenesis, and immune evasion (*1*).

Dormancy—the ability of our bodies to harbor malignant clones throughout our lives without developing disease—can be explained with evolutionary dynamics. Autopsies of young and middle-aged women dying for reasons other than cancer have revealed a very high frequency of clinically occult in situ breast cancers; yet, the frequency of breast cancer disease remains relatively low because of an ecologically stable equilibrium. In the same vein, physicians managing patients with prostate cancer often recommend "watchful waiting" before prescribing treatment. More than 40% of men with normal rectal examinations in their 60s have histological evidence of malignant disease, the prevalence of clinically apparent prostate cancer is only 1%. Thus, as continued improvements in medical imaging and biomarkers lead to frequent overestimation of cancer disease, enthusiasm for early interventions should be tempered because it can

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disturb the equilibrium, causing inflammation, escape from dormancy, and more aggressive disease.

This Darwinian setting involves more than therapy-resistant and -sensitive populations. Because maximum tolerated doses (MTD) of chemotherapy and radiation are defined by the dose-limiting toxicities to the normal cells of the bone marrow, intestinal mucosa, and/or hepatic cells, all nonmalignant cells in the tumor microenvironment are "chemotherapy-sensitive." Cytotoxic therapy thus eliminates, along with the chemotherapy-sensitive cancer cells, most of the native anticancer immune effectors and stromal supportive cells (Fig. 1). In fact, because these normal cells are terminally differentiated, evolutionary principles do not apply to their renewal, and myeloid and lymphoid cells are not only eliminated with each round of MTD chemotherapy, they are gradually exhausted. In contrast, low-dose, metronomic chemotherapy, by preventing repeated cycles of myelosuppression, preserves the immune system, enhances immune surveillance, and decreases inflammation and angiogenesis (*3*). Metronomic chemotherapy has been shown to selectively deplete proinflammatory immune cells, such as regulatory T cells, and restore immune T-effector and natural killer (NK) tumor surveillance (*7*). Most importantly, because metronomic chemotherapy is not aimed at the resistant tumor cell but rather at the stroma and its prosurvival machineries, it retains its effectiveness even in pretreated patients (*8*) and in drug-resistant tumors (*9*).

## DESIGNING EFFECTIVE STRATEGIES

Our failure to successfully treat solid tumors and adult leukemias using high-dose chemotherapy may be due to many different factors, but chiefly among those is the lack of appreciation of the degree of genomic complexity and heterogeneity of these entities. With increasing recognition that cancer is not a disease of a single aberrant malignant clone but rather of an ecosystem involving multiple molecularly and metabolically distinct populations and a wide range of tumor-induced environmental and host adaptations, the likelihood that a "magic bullet" against cancer is going to be found is nil. If we have learned anything from the eco-evolutionary model it is that unless we respect these eco-evolutionary laws, we will continue to play a cat and mouse game with cancer (*1*, *2*).

As shown by Enriquez-Navas *et al.*, preserving the a priori balance between the genomically and phenotypically distinct subpopulations can prevent new evolutionary adaptations, and allow initial therapies to work (*1*). The evolutionary fitness of therapy-resistant cancer populations can be due to many events: a genetic mutation, environmentally induced reactivation of a developmentally silenced embryonic signaling pathway already encoded in the genome, multicellular resistance, or stroma-derived growth factors supporting self-renewal and proliferation. With improved understanding about the intricacies of individual cell-cell and cell-stroma interactions, and about the eco-evolutionary pressures embedded in this new cancer model, we are able to rethink our present therapeutic strategies. The ever-increasing availability of new angiogenesis and immune system–regulating agents provide the means for simultaneous regulation of tumor cells as well as tumor stroma, and it may be possible to engage each of the evolutionary pressures to arrive at effective strategies capable of maintaining dynamic equilibrium (*2*).

The new goal, however, needs to be prevention of cancer disease rather than eradication of cancer. We need to stabilize tumor growth and enable gradual, controlled regression over time. A good example of this kind of current

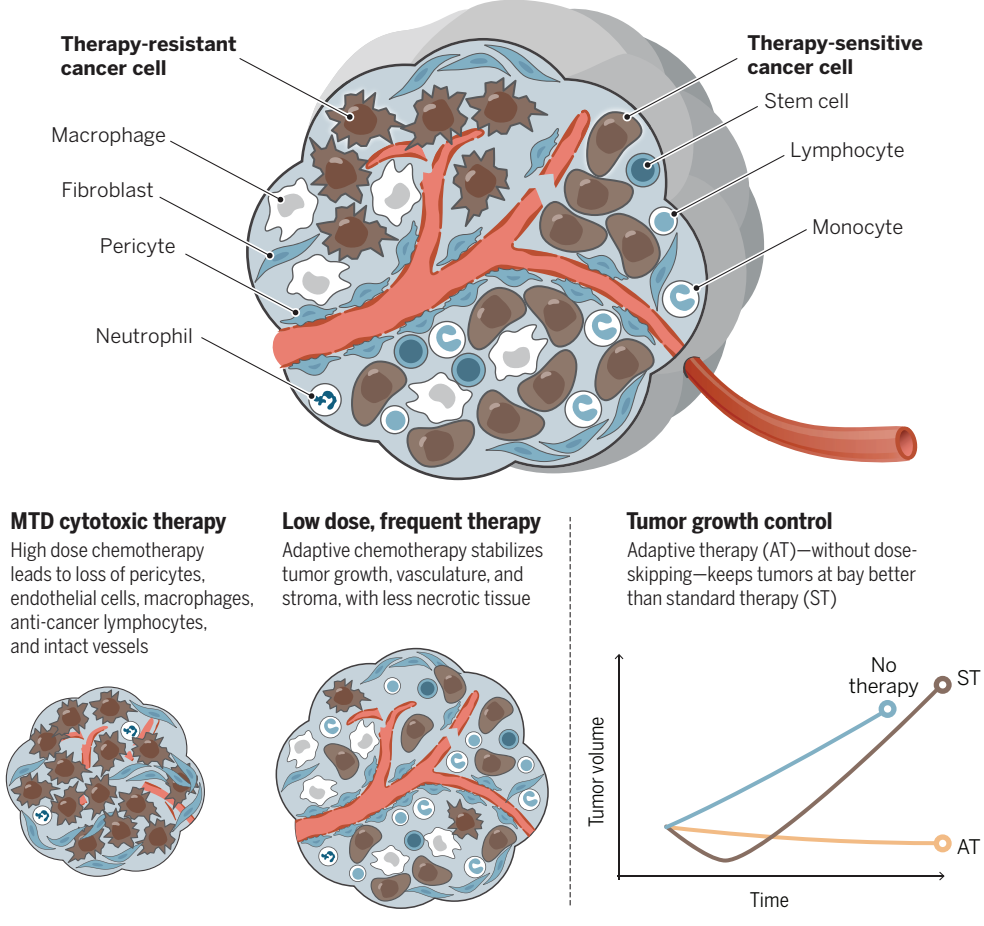


**Fig. 1. Healthy competition.** Standard chemotherapeutic approaches rely on MTD of chemotherapy, invariably selecting for the drug-resistant population by killing off not only drug-sensitive cancer cells but also healthy blood vessels and stromal cells, including native immune responders. The eco-evolutionary model proposed by Enriquez-Navas *et al.* is aimed at controlling tumor growth by maintaining an equilibrium between sensitive and resistant populations by means of low-dose frequent chemotherapy (*1*). The study demonstrated, in two different mouse xenograft models of breast carcinoma, that low-dose adaptive therapy (AT) is more effective than the standard (MTD) therapy (ST), as well as adaptive therapy with dose-skipping. The graph is a representative plot of data from (*1*).

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therapy is the treatment of pediatric acute lymphoblastic leukemias. It consists of remission induction, consolidation (intensification), and 18 months of low-dose daily chemotherapy. The long-term survival rates for this type of leukemia are 93 to 95%. The realization that no single agent can bring about effective tumor suppression is consistent with the present clinical experience. Monotherapy with even the most promising of biological agents, a *BRAF* inhibitor for melanoma, has had either no discernable effect on cancer growth—or, at best, produced a transient tumor suppression followed by relapse. In contrast, the combination of immune checkpoint inhibitors and direct *BRAF*/*MEK* inhibitors can lead to a more sustained tumor suppression (*10*).

The ecological balance within the tumor microenvironment and within the larger human host depends on stable evolutionary forces of a quorum of competing cancer cell populations. Therapeutic strategies should therefore minimize injury to healthy surrounding cells and enable native immune defenses. The new experimental evidence in mouse models by Enriquez-Navas *et al.* shows that a very good possibility for future therapies may be disabling the emergence of a treatment-resistant population by low-dose frequent chemotherapy (*1*) and combining this therapy with angiogenesis inhibitors and immune modulators. Although some may still harbor the hope for the magic bullet, the benefits of the synergistic activity of low-dose chemotherapy and biologic agents are being appreciated, and more and more oncologists are engaging some version of this approach. It is quite likely that in a not-too-distant future, oncologists will keep their patients at home by prescribing low-dose metronomic chemotherapy, an immune checkpoint inhibitor, a multikinase angiogenesis inhibitor, and personalizing it with an agent (or agents) targeting the specific gene alteration (or alterations) or gene activation (or activations) found in the patient's tumor.

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