Adaptive Therapy and the Cost of Drug-Resistant Mutants

Dominik Wodarz

The concept of adaptive cancer therapy proposes that the use of drugs at less than maximum tolerated dose can provide clinical benefits by allowing persisting drug-sensitive cells to competitively suppress drug-resistant cells; this can delay the outgrowth of these cell clones. The adaptive therapy concept has been developed with mathematical models and has subsequently been explored in clinical trials with promising results. In studies performed so far, a fitness cost of drug-resistant cells has been invoked for this treatment approach to be beneficial. In new work, it is shown that a clinical benefit can be achieved even in the absence of a fitness cost for resistant cells, which broadens the applicability of adaptive therapy.

See related article by Strobl et al., p. 1135

Recent years have seen tremendous advances in the way in which several cancers are treated, driven by the development of new targeted inhibitors. At the same time, however, the development of drug resistance is an almost universal long-term problem, which leads to a relapse of disease and loss of control. Drug resistance can arise through various mechanisms (both nongenetic and genetic), but much emphasis has been placed on the evolution of drug-resistant mutant cells and its prevention. Especially if drug-resistant mutants preexist before therapy initiation, the use of multiple drugs, either sequentially (1) or in combination (2), has been predicted to be able to significantly delay the emergence of resistance and relapse. However, mutations giving rise to simultaneous resistance against multiple drugs, and issues arising from increased toxicities, remain problematic in this respect.

In addition to these approaches, there is an urgent need for new ideas and new treatment paradigms in the fight against this deadly set of diseases. One such avenue of research that has been recently developed is based on viewing the cells and tissues within humans as complex ecosystems, where populations of cells with varying genetic makeup and characteristics interact (3). Thus, ecological interactions—such as competition among different cell types within the tumor, as well as evolutionary processes—drive the disease and contribute to treatment outcomes. Manipulations of these ecological and evolutionary processes by therapies can in principle change this ecosystem in a way that prevents certain types of tumor cells, such as drug-resistant mutants, from dominating. One example of this approach is the concept of adaptive therapy (4), which has been initially defined through mathematical models, for example, ref. 5, and has subsequently been studied both experimentally (6) and in clinical trials (7) with encouraging results. Traditional treatment approaches aim to hit the cancer with the MTD, that is, with the highest drug dose that a patient can withstand. The rationale behind this is that a rapid destruction of the susceptible cancer cells is a desired outcome for the patient and limits any further evolution of the cancer cells during the treatment phase. If, however, drug-resistant mutants already exist in the tumor at the time of treatment initiation, the elimination of drug-sensitive cells by therapy can "release" the existing drug-resistant cells from natural suppression (4). Sensitive and resistant tumor cells are thought to compete for space and resources within the tumor, and this competition can keep the resistant strains at bay while the sensitive cells are dominant. If the drug-sensitive cells have largely been eliminated, however, this competitive suppression of resistant cells ceases, which can result in the rapid outgrowth of drug-resistant mutants. Treating the tumor with a lower drug dose, and thereby only partially suppressing the drug-sensitive cell population, may represent an alternative approach that circumvents the release of drug-resistant cells. This method enables the sensitive cells to persist at a certain level during treatment and to continue to suppress the drug-resistant mutants through competitive interactions. Both lower dose drug applications and specific dosing schedules can contribute toward this goal.

In the context of this work, an underlying assumption has often been that drug-resistant mutants suffer a fitness cost compared with the drug-sensitive tumor cells in the absence of therapy. This makes intuitive sense because the mutations that confer drug resistance can render the cells less efficient at replicating, and resistant mutants have been shown to have a fitness cost in the absence of treatment in bacterial and viral infections (8). There are also data that support this notion for cancer cells (5). The estimation of the relative fitness of drug-resistant cancer cell mutants, however, is very difficult *in vivo*. These estimates typically rely on experiments in cell cultures, which are characterized by different microenvironmental conditions that can have an impact on their fitness. Indeed, it is possible that some drug-resistant mutants are competitively neutral compared with sensitive cells (i.e., have the same fitness) *in vivo*, or are actually advantageous (9). Therefore, over the years, a very important question for the concept of adaptive therapy has emerged. Does the success of adaptive therapy rely solely on the assumption that resistant mutants suffer a basic fitness cost, or can patients benefit even if the fitness cost is low or absent?

Strobl and colleagues (9) address this question with mathematical models and present the important finding that, under some circumstances, adaptive therapy can be beneficial even if drug-resistant mutants are not characterized by a fitness cost. This is a very important development because it broadens the clinical applicability of this therapy concept. Their insights are based on classic mathematical Lotka-Volterra competition models that have been adapted to describe the dynamics of cancer growth and therapy. The intensity of competition between drug-resistant and -sensitive cells during these dynamics is of central importance in deciding whether adaptive therapy

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provides significant benefits compared to standard therapies. One important determinant in this respect is how close the tumor cell population size is to what is called its "carrying capacity." In ecological terms, this is the maximum population size that the environment can sustain. If the tumor grows significantly below the carrying capacity, the model suggests that a fitness cost is required for adaptive therapy to provide benefits to patients. A fitness cost, however, is not required if the tumor grows closer to its carrying capacity, because the extent of competition is intensified in this situation. Given these results, it is important to better understand the concept of carrying capacities in cancers and how they can be influenced by treatments to increase the degree of competition during adaptive therapies. Toward the end stages of the disease, the carrying capacity of the tumor is large and is determined by the amount of tissue space the tumor can occupy without killing the patient. Tumor progression, however, is a multistage process, and growth can be stepwise: initial fast tumor growth can slow down and temporarily converge toward a steady state, that is, a temporary carrying capacity. This reduced growth is brought about by constraints that the tumor cells cannot currently overcome. Emergence of mutant cells that can overcome this initial growth barrier can subsequently lead to another tumor expansion phase and convergence toward a larger carrying capacity. This process can repeat until the tumor has sufficiently evolved toward higher virulence and the ability to metastasize. When considering adaptive therapy for a particular cancer, it would thus be important to better understand the natural history and the detailed growth dynamics of the cell population as the disease progresses. This will indicate how intense the competition dynamics are at the start of treatment and could offer insights that might allow the carrying capacity to be lowered during adaptive therapy, for example, by oxygen or nutrient depravation (9). This would increase the degree of competition during the treatment phase, resulting in a larger benefit from adaptive therapy.

The turnover of tumor cells is another important parameter that was shown to determine the intensity of competition (9). A population of cells is said to have a low turnover if the death rate is small relative to the division rate. A high turnover means that cells die faster such that their death rate is closer to the division rate. Strobl and colleagues (9) demonstrated that adaptive therapy is unlikely to improve outcome for low-turnover tumors, even if resistant mutants have a relatively large fitness cost. For high-turnover tumors, however, adaptive therapy was shown to provide substantial benefits if the cost of resistance was low or even nonexistent. Hence, the natural turnover rate of a tumor could be an important determinant of response to adaptive therapy. Furthermore, this suggests that the benefits of adaptive therapy could be improved by additional interventions that increase the turnover rate of cells, such as low-dose chemotherapy (9).

On the basis of the principles elucidated by Strobl and colleagues (9), it is possible that other dynamical processes are at play during adaptive therapy that could determine the intensity of competition and hence the benefit of adaptive therapy. For example, during uncontrolled tumor growth, immune responses against tumor cells are thought to be suppressed through various mechanisms. If cell numbers are reduced to low numbers due to therapy with the MTD of a drug, insufficient antigenic stimulation might remain to induce immunity. Lower dose, adaptive therapy, however, can result in a situation where reduced tumor burden leads to lower levels of immune suppression, while simultaneously maintaining enough tumor antigen to boost immune responses. A boosted immune response could help adaptive therapy not only by limiting overall tumor growth, but by further adding another type of ecological interaction to this system: indirect or "apparent" competition (10). When two populations (drug-resistant and sensitive cells) share a natural enemy (the immune response), dynamics occur with properties that are very similar to those of direct competition interactions: one cell population can inhibit the other through a shared immune response. This might further enhance the benefits of adaptive therapy even for low or absent fitness costs of resistant mutants, which might be interesting to explore both mathematically and experimentally.

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