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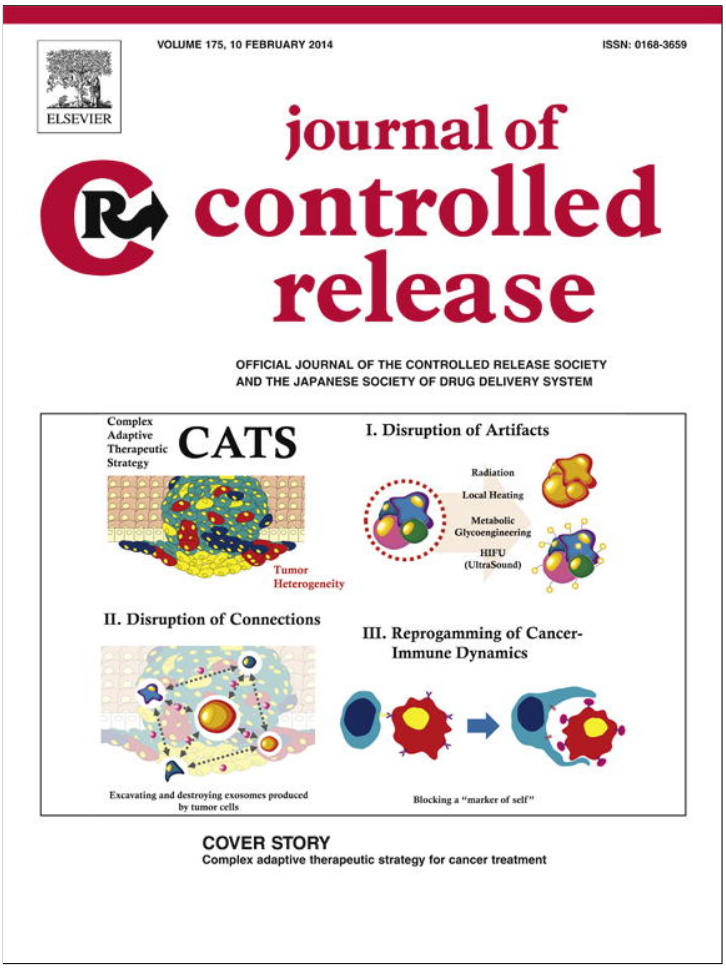

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Cover Story

Complex adaptive therapeutic strategy for cancer treatment

Traditional chemotherapeutic agents have focused on "killing" cancer cells, however, they exert high toxicity on normal cells leading to serious side effects. Anticancer drugs target those cells that divide rapidly, one of the important characteristics of most cancer cells. This implies that chemotherapy can also be highly effective to cells rapidly dividing under ordinary circumstances, such as cells in the bone marrow, the lining of the digestive tract, reproductive organs, and hair follicles. This leads to extensive side effects, including myelosuppression, immunosuppression, gastrointestinal distress, nausea, vomiting, infertility, and hair loss. In attempts to attack cancer cells while sparing normal cells, numerous nanoparticle-based systems have been designed and tested. Although nanoparticle systems have always shown better efficacy than the solution formulation in small animal xenograft models, the results have not been translated into human clinical studies. Cancer is a very complex disease, and no cancer has been cured by introducing a cancer drug once or twice, as commonly done in the small animal xenograft models. It is time to ask what made the drug delivery scientists rely on nanoparticle systems so heavily in the first place. It is also time to ask whether there are better ways to treat tumors.

The targeted drug delivery systems, usually based on nanoparticles, are hoped to be discriminatory solely against cancer cells, sparing normal cells. This approach is based on the concept of "overexpression" of target proteins on fast dividing cancer cells. This approach may work, if the majority of the administered drugs go to the target cells. The reality is that only a very small fraction (i.e., <5%) of the total dose reaches the target tumor [1]. Furthermore, the mere presence of the delivery vehicle around the tumor does not mean the free drug is available for killing tumor cells. More importantly, there are high degrees of intra- and inter-tumoral heterogeneity [2]. Such heterogeneity inherently limits targeted drug delivery, because the majority of human tumors display astounding phenotypic heterogeneity including the expression of cell surface receptors and growth factors. This important factor has to be considered, if clinically effective targeted drug delivery systems are to be developed.

In this issue, Professor In-San Kim and his coworkers discuss targeted therapeutics with a view of tumors as a complex adaptive system [3]. In their view, tumor development is regarded as an evolutionary process in which tumors are a collection of clones that are in competition to survive, just like various species in a local ecosystem. The cancer cells that survive in this competition are the most adaptive, and acquire the ability of evasion from antitumor immunity as well as the high capability of proliferation and metastasis. Thus, the tumor should be handled as an evolutionary complex organization involving different kinds of tumor cells, tumor-associated cells, normal cells, and immune cells, rather than as a simple mass of malignant cells. This new approach is named a "complex adaptive therapeutic strategy" (CATS).

The CATS consists of three intermediate concepts. The first concept is the disruption of artifacts, i.e., phenotypic features developed by the evolutionary adaptive nature of tumors. The most apparent feature is the enormous heterogeneity in tumors. Induced phenotype targeted therapy (IPTT) is a representative strategy for disrupting artifacts in tumors. A specific phenotype is artificially induced, and the induced phenotype is targeted and amplified by the phenotype-specific, activatable drug delivery system. This may be a good example to overcome the phenotypic heterogeneity in tumors. The second concept is the disruption of connections in intricate tumor networks. Indeed, tumor cells interact continuously with normal cells and immune cells as well as with their surrounding environments. The CATS aims at the entire complex tumor network, not individual tumor cells. Professor Kim and his colleagues particularly address exosomes produced by tumors, because they play extensive roles in many pathological features of cancer development, growth, metastasis, and therapeutic resistance. The CATS is focused on not only destroying exosomes but also educating exosomes to attack tumors by reprogramming cancer-immune dynamics (the third concept). The tumor cells that survive in an immune-competent host already have mechanisms to evade the immune system. The authors discussed a representative strategy for improving anti-tumor immunity by blocking a "marker of self".

In retrospect, it is clear that treating the tumor requires much more than simply delivering anticancer drugs using nanoparticles, but it took a decade of testing to realize that. For diseases as complex as tumors, a single strategy may not be able to overcome the complex adaptive nature of tumors. The perspective on the CATS, as far as I can tell, is the first article in the drug delivery field explaining why it is not that easy to treat cancer, and a better approach is necessary through a better understanding of the tumor. The drug delivery field has accumulated vast knowledge on making smart nanocarriers which can be effectively used in carrying out the concepts of the CATS. There is no doubt that the cancer treatment will be enhanced, step by step, by merging the CATS with the existing and future drug delivery technologies.

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