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Effects of vascularization on cancer nanochemotherapy outcomes

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HIGHLIGHTS

- A 3D model for chemotherapy based on anticancer nanoparticles is investigated.
- Therapeutic success is mainly determined by the nanoparticle endocytic rate.
- The eradication of highly vascularized tumors demands more aggressive therapies.
- Our results discourage the use of therapies that normalize the tumor vasculature.

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ABSTRACT

Cancer therapy requires anticancer agents capable of efficient and uniform systemic delivery. One promising route to their development is nanotechnology. Here, a previous model for cancer chemotherapy based on a nanosized drug carrier (Paiva et al., 2011) is extended by including tissue vasculature and a three-dimensional growth. We study through computer simulations the therapy against tumors demanding either large or small nutrient supplies growing under different levels of tissue vascularization. Our results indicate that highly vascularized tumors demand more aggressive therapies (larger injected doses administrated at short intervals) than poorly vascularized ones. Furthermore, nanoparticle endocytic rate by tumor cells, not its selectivity, is the major factor that determines the therapeutic success. Finally, our finds indicate that therapies combining cytotoxic agents with antiangiogenic drugs that reduce the abnormal tumor vasculature, instead of angiogenic drugs that normalize it, can lead to successful treatments using feasible endocytic rates and administration intervals.

1. Introduction

Cancer, owing to its metastatic spreading through the organism, requires therapies based on medicines capable of efficient and uniform systemic delivery. Conventional chemotherapeutic agents exhibit several limitations such as nonspecific biodistribution and targeting, toxicity and low therapeutic indices [1]. Packaging clinically approved drugs into nanoscale delivery vehicles is a promising strategy for developing safe and efficacious anticancer treatments [2].

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Nanoparticles, in order to achieve passive targeting to tumors via the enhanced permeability and retention effects, should be large enough in size to prevent their rapid leakage from normal capillaries but functionalized and small enough to avoid opsonization in the blood and rapid clearing by the reticulo-endothelial system in liver, lungs, spleen, and bone marrow. Consequently, the size of nanoparticles should be up to 100 nm to reach tumor affected tissues [3]. According to Perrault et al. [4], studying the effect of nanoparticle size on tumor accumulation in a murine cancer model, the optimal nanoparticle size is approximately 60–80 nm. In addition to size, nanoparticles should ideally have a hydrophilic surface to escape macrophage capture [3]. Also, as positive-charged nanoparticles lead to significant immune reactions, neutral and negatively charged ones are preferable for clinical application [1].

Simultaneously to the quest for therapeutic agents with optimal physicochemical properties, other strategies to overcome drug delivery barriers exploring the repair of the tumor abnormal physiology are in progress [5]. These alternatives include as a target the tumor vasculature. If the abnormal structure and function of the tumor vascular network can be transiently normalized by some angiogenic drugs, more efficient oxygen and drug delivery is provided, alleviating hypoxia and increasing therapeutic efficacy [6–8]. Improving blood flow in tumors also means enhancing the nutrient supply to cancer cells. Thus, although remaining in the proof-of-principle stage, this approach apparently underestimates the latter effect, antagonic to the former one. At the theoretical level, mathematical models can provide valuable insights about the efficacy of combined therapies based on antiangiogenic agents that normalize the abnormal tumor vasculature and cytotoxic drugs.

Angiogenesis, vascular remodeling, tumor blood perfusion, drug accumulation in cancerous vasculature, interstitial flow, and cellular drug response are major features in cancer chemotherapy. From the recent literature we can highlight several mathematical models focused on the understanding of each one of these features (for instance, Refs. [9,10] for angiogenesis and vascular adaptation; [11–13] for blood perfusion and interstitial flow; [14–16] for drug delivery and [17] for cellular response). In particular, regarding vascularization and interstitial flow, these models reveal that (i) the collapse and regression of vessels accelerates perfusion and all portions of the remodeled tumor vasculature are reached by a tracer substance flowing through the network [11]. Consequently, (ii) the interstitial flow emerges as the key component of the drug delivery barrier [12]. Indeed, the interstitial pressure inside the tumor is uniformly high and abruptly decreases at the periphery, generating a very slow interstitial flow within the tumor and a rapidly rising convective flow outwards the tumor. In addition, an elevated interstitial hydraulic conductivity together with poor lymphatic drainage causes the plateau profile of the interstitial fluid pressure and contributes to a broad-based collapse of the tumor lymphatics [13]. Naturally, these and other models inspired or evolved to multiscale approaches integrating most of those major features involved in cancer chemotherapy [18,19].

Here, we address the *in silico* cancer therapy based on chimeric polypeptides (CP) that self-assemble into nanoparticles on doxorubicin (Dox) attachment [20]. These drug-loaded nanoparticles display good pharmacokinectics and tumor accumulation, low toxicity and high antitumoral efficacy. Specifically, we investigate via computer simulations the effects of pre-existent tissue vasculature, CP–Dox nanoparticle endocytic rate and selectivity for cancer cells, therapeutic doses and administration intervals on the treatment outcomes. The model assumes a 3D vasculature network which supplies nutrients and nanomedicines to the tumor affected tissue. After extravasating the capillaries, these chemicals are transported through the interstitium mainly by diffusion and uptake by cells. Inside the cells, doxorubicin released from the CP–Dox nanoparticles disassemble impaired cell viability, eventually eliciting cell death. The pharmacokinetics of CP–Dox nanoparticles is accounted in an effective, empirical manner, thus neglecting detailed molecular interaction mechanisms. Similarly, cell responses to their microenvironment are translated into stochastic actions (proliferation and death) regulated by local concentrations of nutrients and drugs supplied by the tissue vasculature. Finally, the spatio-temporal concentration distributions of nutrients and drugs are determined by the vasculature geometry. Besides more realistic, a 3D geometry for the vasculature and its surrounding tissue enables a richer set of reaction–diffusion growth patterns than in 2D systems [21–23]. A paramount biological illustration of this precept is heart arrhythmias. Ventricular fibrillation is a three-dimensional phenomena, i.e., that only occurs in sufficiently thick heart muscle [24].

The outline of this paper is as follows. In Section 2, the model is described. It extends our previous models introduced in Refs. [21,23] by introducing a three-dimensional tissue fed through a vascular network. As before, the model considers cells as individual agents whereas nutrients, CP–Dox nanoparticles and free Dox are continuous fields. The simulation results are reported in Section 3 and discussed in Section 4. Finally, our conclusions are drawn in Section 5. Appendices A and B present complementary details of the model.

2. The model

The model consists of a cubic lattice (the tissue) fed by a capillary vessel network established before the emergence of the first cancer cell and that does not evolve in time. Their capillaries branch throughout the normal tissue according to correlated random walks starting from randomly chosen sites on either the bottom or lateral lattice borders. Specifically, each vessel proceeds in a randomly chosen direction (defined by the axial and azimuthal angles ϕ and θ) with fixed perturbations $\delta\phi$, $\delta\theta$. Further details about the capillary network model are presented in Appendix A.

Sites associated to the capillary network cannot be occupied by either normal or cancer cells. Any site that does not belong to the capillary network can be occupied by normal or cancer cells. These cells are individual agents and their populations