Modeling the mechanism of drug transport to solid cancer tumor

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Abstract

Cancer has emerged as one of the leading causes of death in humans in both developed and developing countries [1]. In spite of remarkable advances in cancer research in the past few decades that enabled early diagnoses of various cancers and more effective anti-cancer drugs and novel treatment therapies, a complete understanding of the origin of cancer is yet to be realized due to the complex nature of tumor formation and the unpredictable functionality of the tumor in the human body.

Proliferation of the tumor cells and the tumor vasculature (*blood and nutrient supply vessel system*) differ among different tumors and even among individuals who have same type of tumor [2]. Such differences pose difficulties in generalization of the phenomenological factors and also affect effective transport of these drugs to the tumor [3]. Therefore developing effective drug delivery mechanisms needs to have a thorough understanding of: (i) the formation of the tumor, (ii) the biological structure of the tumor, (iii) the functionality of the tumor at various stages of its proliferation, and (iv) the physiological barriers in the drug delivery mechanism caused by the tumor. Additionally due to the lethal nature of these treatments and the interactions of these drugs with other functional cells in the body, the treatments are required to be implemented in stages and confined to small doses.

The transport of effective doses of anti-cancer tumor drugs to solid tumors is challenging due to the barriers imposed by the tumor vasculature [1]. Furthermore, drug metabolizability, the body's natural removal process, and binding to non-target cells [4] make complete utilization of the drug impossible. In addition, both the physiological configuration (i.e. the size and shape) and the biological structure of the tumor play major roles in drug transport [3], [5], [6], [7]. Thus, permeability, porosity of the diffusion media (i.e. the composition of capillary wall, interstitium and tumor etc.), inter-cellular interactions and bindings, and local pressures also contribute to the transport mechanisms [7],[8]. In order to quantify the effectiveness of the anti-cancer drug, a thorough understanding of the mechanisms of drug transport to the tumor is needed. When, blood-borne molecules or particles enter to the tumor vasculature, they reach the cancer cell via distribution through the vascular compartment, transport across the micro vascular wall and transport through the interstitial compartment. The transport mechanism involves convection, diffusion, or a combination of both mechanisms. The presence of a concentration gradient causes diffusion based transport.

The fluid movement caused by the pressure gradient leads to convective fluid transport where, the solute is carried away by solvent drag.

The objective of this study is to develop a general computational model that describes the mechanisms of drug transport to a solid tumor using solute transport concepts. Accountability of the changing tumor boundary due to the change in cell population is incorporated in the computational model. The computational model also considers drug transport through the vasculature and the interstitium that surround the tumor. The transport mechanisms depend on the diffusivity of the drug within the different media, permeability of the vessel geometry, compartment pressures, the concentration of the anti-cancer drug, and other related factors. The effects of these factors will be analyzed using a parametric sensitivity analysis. It will be shown that computational models that embody the physics of the transport mechanisms can improve our knowledge about the barriers to effective drug therapies, the efficacy of the treatment, and the effectiveness of current and future anti-cancer drugs.

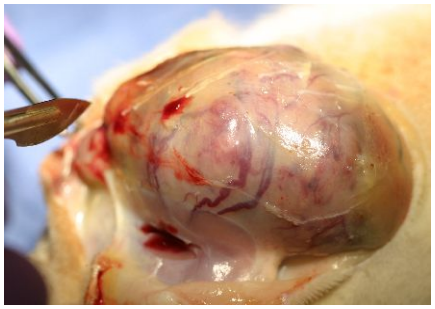

Figure 1:A rat tumor with vasculature.

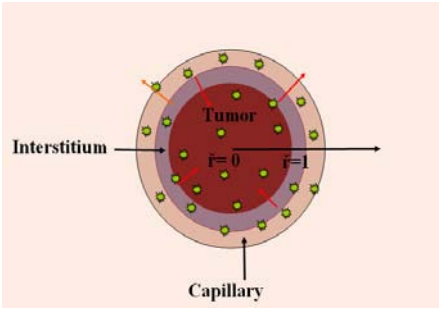

Figure 2: Schematic of the model for drug transport to solid tumor with vasculature

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