Incorporating Cellular Metabolism into Growth Models of Multicellular Tumor Spheroids

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Many chemotherapeutic strategies have failed due to pronounced diffusion limitations in tumors induced by poor vasculaturization. Diffusion limitations, present in three-dimensional tissue, produce nutrient deficient regions that eventually become necrotic in tumors *in vivo*. Multicellular spheroids are better models of *in vivo* tumors than monolayer cultures because they mimic the heterogeneous microenvironments present in tumors (Sutherland, 1988). Because the growth progression of spheroids in the presence of diffusion limitation is not fully understood, the development of predictive models for the growth of *in vitro* spheroids has received considerable attention. Such predictive models can be used to guide the design of better chemotherapeutic strategies.

A wide variety of mathematical models have been developed to predict avascular tumor growth dynamics. Multicellular spheroids possess desirable mathematical properties such as radial symmetry which has facilitated the derivation of tumor growth models. A common modeling objective is to predict the formation of the three cell types commonly observed in fully developed spheroids: (1) proliferating cells located near the perimeter of the spheroid where good nutritional conditions lead to cell growth and division; (2) quiescent cells located further inside the spheroid where the local nutritional environment is not sufficient for proliferation but is adequate to ensure cell survival; and (3) necrotic cells located near the interior of the spheroid which have died due to prolonged exposure to poor nutritional conditions.

Several mathematical models which describe the diffusion of various nutrients and growth factors from the surrounding environment to the tumor spheroid interior have been developed. Typically, these models are based on the assumption of a single growth limiting nutrient. Growth models that combine diffusion equations with reaction-convection equations for the expanding spheroid also have been proposed (Casciari et.al., 1992; Sherratt and Chaplain, 2001; Ward and King, 1997). While they provide useful insights into tumor growth dynamics, these models are based on highly simplified descriptions of cellular metabolism, which effectively precludes the development of predictive models.

Tumor cells in monolayer cultures have been shown to oxidize some glucose and convert some glucose to lactate. Analysis of tumor interstitial fluid suggests that the TCA cycle is saturated, which could explain the high rate of lactate production. Furthermore, lactate can be reabsorbed in the absence of glucose. The existence of hypoxic and glucose deficient regions within the tumor spheroid might lead to either cell death or a switch in the cellular metabolism from using glucose to using lactate for respiration. Therefore,

different nutrients can be consumed by cells in different tumor microenvironments, thereby invalidating the concept of a single growth limiting nutrient.

In this paper we present a spheroid growth model that includes the diffusion of multiple nutrients and their effects on cellular metabolism in different microenvironments. The nutrients considered are glucose, oxygen and lactate. Cell metabolism is described by a minimal model that accounts for nutrient uptake, glycolysis, the TCA cycle and lactate production and reabsorption. Pseudo-steady state conditions are assumed for cellular metabolism since the spheroid growth dynamics are significantly slower than the intracellular kinetics. As a result, local metabolism is dependent only on the extracellular concentrations of glucose, oxygen and lactate. The spheroid growth model is comprised of reaction-convection equations for living and necrotic cell populations as well as steady-state diffusion equations for the three nutrients.

The partial differential model equations are solved subject to moving boundary conditions that represent nutrient concentrations at the surface of the spheroid. Representative parameter values are obtained from previous experimental and modeling studies. Numerical solution of the moving boundary problem yields predictions of: (1) the nutrient concentrations and cell population densities as functions of time and the radial position in the spheroid; and (2) the spheroid diameter as a function of time. Simulations are performed to investigate nutrient concentrations in different microenvironments, the formation of a necrotic zone and tumor growth saturation. We discuss future development of the spheroid model that will allow the evaluation of chemotherapeutic strategies.

References

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