



Feedback, Lineages and Vascular Tumor Growth



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ABSTRACT:

Cancer arises when the carefully regulated balance of cell proliferation and programmed cell death (apoptosis) that ordinarily exists in normal homeostatic tissues is disrupted. Cancer cells are assumed to acquire a common set of traits. However, not all the cells in a tumor seem to matter equally and tumor cells progress through lineage stages regulated by feedback pathways. It is known that the microenvironment plays an important role in this regulation. Secreted factors by vascular endothelial cells (ECs) have been found to support and maintain cancer stem cells (CSCs) and it has even been observed that CSCs can transdifferentiate into ECs. It has been hypothesized that transdifferentiated ECs may contribute to tumor vascularization via vasculogenesis. However, these processes are not well understood and mathematical modeling can provide insight on the underlying biology. We use a hybrid continuum-discrete multispecies mathematical model to simulate numerically the three-dimensional spatiotemporal dynamics of hierarchically-structured, vascularized solid tumors. Tumor cells and substrate species are treated as continuum, while vessels are treated as discrete quantities. We account for protein factors secreted by tumor cells and ECs that affect angiogenesis, tumor cell self-renewal, differentiation and transdifferentiation, and proliferation pathways. By testing different combinations, our models reveal the effects of feedback regulation on tumor size, invasiveness as well as on the heterogeneous distribution of cells within the tumor and the structure of the vascular network. Consistent with experimental observations, positive feedback from the ECs to the CSCs creates perivascular niches and increases the CSC fractions in the tumor as well as the tumor sizes and the amount of functional vasculature. Intratumoral vasculogenesis is found to result from transdifferentiation of CSCs into ECs, thereby increasing tumor sizes further. Negative regulation by ECs on CSCs transdifferentiation is paradoxically found to increase tumor sizes, CSC fractions and vasculogenesis. The close interactions between tumor cells and the vascular network present opportunities and challenges for therapeutic intervention.

Host: Mary Sehl, M.D.

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