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A Cell Based Model of Tumor Induced Angiogenesis

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Tumor-induced angiogenesis is the formation of new blood vessels from existing vasculature in response to chemical signals from a tumor. This process marks the pivotal transition from avascular to vascular tumor growth, a progressive stage of cancer beyond which cancer becomes extremely difficult to treat and survival rates decrease.

The result of this research is the first cell-based model of tumor-induced angiogenesis. Existing models of tumor associated angiogenesis are at best able to reproduce realistic vascular patterns on a macroscopic scale, but because they describe cell densities, they are unable to capture the fine scales of capillary development and morphology. Our model is structured in terms of the dynamics occurring at the extracellular and intercellular levels. At the extracellular level, a partial differential equation describes diffusion, uptake, and half-life decay of tumor-secreted pro-angiogenic factor (VEGF). At the cellular level, the cellular Potts model is used to describe cell migration, growth, proliferation or cell division, cellular adhesion, and the evolving structure of the tissue. A complete description of the model and our results is available in [1]. This model provides a quantitative framework to test hypotheses on the biochemical and biomechanical mechanisms that cause tumor-induced angiogenesis.

Results

The composition and structure of the tissue through which the new capillaries must grow in order to reach the tumor can vary greatly depending on where in the body the tumor is located. We examined the role of tissue inhomogeneities on cell migration and capillary formation by explicitly modeling the interactions between endothelial cells, which line our blood vessels, and the tissue, which is composed of matrix fibers (collagen), resident tissue cells and interstitial fluid. Our studies revealed that local heterogeneities in the tissue, such as matrix fiber density and structure and the presence of other tissue cells, influence sprout migration and capillary morphology during angiogenesis and may be mechanisms for sprout branching (vessel bifurcation) and anastomosis (loop formation). Figure 1 shows the model's ability to capture realistic vascular structures and more complex events

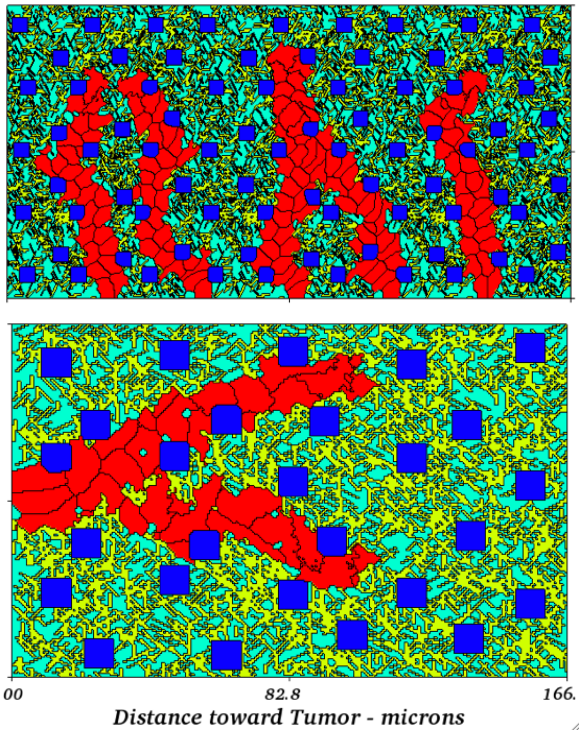

Figure 1. *Numerical simulations showing the tumor-induced growth and migration of endothelial cells (red) through the extracellular matrix (yellow collagen fibers and light blue interstitial fluid). The model is the first to capture anastomosis (top) and branching (bottom) without needing to predefine rules for these events.*

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such as branching and anastomosis. From known cellular and molecular level dynamics, capillary sprout branches and vessel loops are structures that emerged naturally as a collective result of single cell behaviors. This is the first model to simulate branching and anastomosis without needing to predefine rules for these events.

Experimental models have reported conflicting results regarding the precise region of proliferating cells during angiogenesis. We used our model to investigate the effects of various proliferating regions on how quickly the sprout progresses towards the tumor. We looked at capillaries that developed when proliferation occurred (i) only at the tip of the growing sprout, (ii) immediately behind the sprout tip, (iii) three cell lengths behind the advancing tip, and (iv) at the base of the sprout.

Figure 2 shows the relationship between the proximity of the proliferating region to the tip and sprout extension speeds toward the tumor. The data indicate that as the proliferating region moves further away from the migrating tip, the average rate of extension toward the tumor increases. These results suggest some interplay or competition between the mechanical forces exerted by the migrating tip and the proliferating cells. When a proliferating cell is adherent to a migrating cell, each phenotype has to overcome the forces exerted by the other. However, the forces exerted by each phenotype have only short range effects so that once the proliferating region is far enough away, there is no statistically significant change in sprout extension speed. To investigate the validity of this explanation, a numerical experiment was performed that was identical to (i) except that migration and proliferation were no longer independent and exclusive cellular events. When proliferating cells also moved chemotactically, the average rate of sprout extension was 7.7 μm/day, representing a significant increase over the fastest average speed observed (i-iv) (see Figure 2). This finding supports the view that proliferating and migrating cells exert competing forces on each other and further suggests

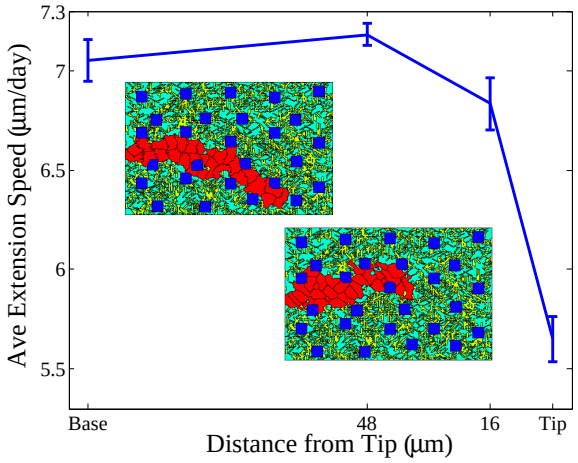

Figure 2. *The relationship between the the location of the proliferating cells and how quickly the sprout advanced toward the tumor. The further the proliferating region was from the migrating tip, the faster the average rate of sprout extension, suggesting that the mechanical forces exerted by the migrating tip and the proliferating cells are in competition with each other.*

that coordination of these cellular functions could have a significant effect on the rate of capillary extension.

Our initial results underscore the importance of modeling cell-matrix and cell-cell dynamics and demonstrate that a cell-based physical model can help provide insight into the processes controlling angiogenesis.

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References

[1] Bauer, A.L., Jackson, T.L., Jiang, Y., A physical cell-based model exhibiting branching and anastomosis during tumor-induced angiogenesis. Submitted for publication to *Biophysical J.*, 2006.