P53-gene Mediated Inter-Tumor Cell Competition

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Cancer can be classified as a genetic disease; genetic mutations give a cancerous cell a proliferative advantage over non-mutated cells and are what encode the many different diseases that have been classified as cancers. In this project, we consider one such mutation: the P53 gene inactivation mutation. We model the competitive effect due to the presence of malignant cells with the P53 mutation in an avascular tumor and in a monolayer culture. The P53 gene is known to regulate programmed cell death, or apoptosis. When the P53 gene is inactivated by a mutation, the protein that it encodes is not created properly, and consequently that protein cannot function in the proliferation check points of the cell cycle. The ability to survive under hypoxic conditions is one of the fundamental physiological differences between malignant cells and normal cells. Here, we suppose that the P53 gene mutation alters a cell's ability to proceed to the execution phase of apoptosis under low oxygen, or hypoxic, conditions. Tumor cells, like all cells, require nutrients and chemical signals to grow. When a tumor cell population grows the diffusion nutrients and necessary chemical signals becomes limited; cells in the interior of the spheroid will have less nutrients and chemical signals and will be forced into different non-proliferative metabolic states.

It was hypothesized by Graeber et al that the low nutrient conditions inside a tumor, in particular the low oxygen conditions, gave tumor cells with inactivated P53 genes a proliferative advantage over their unaltered counterparts. They found in a in vitro monolayer model that after 7 rounds of depriving the tumor cells of oxygen and then reoxygenating them, that tumor cells with the P53 mutation would outlive their P53-unaltered counterparts starting with a 1:1000 population ratio [1]. Graeber observed that P53-mutant cells are able to survive better in hypoxic areas in tumors than do P53-unmutated cells. It is this hypothesis that we test in our investigation, namely that the low oxygen conditions created by the tumor spheroid formation itself creates an upregulation mechanism for P53 mutated cells.

We first model the in vitro monolayer experiment of Graeber et al using a 2 dimensional mathematical model with a constant oxygen environment, then model avascular tumor using a 3 dimensional model with diffusion equations to model the environmental oxygen level. In the 3 dimensional model, we utilize a multiscale model of tumor growth: A lattice Monte Carlo Potts model of cellular growth and adhesion, and reaction-diffusion equations describing the oxygen and lactate levels. The description of the cellular scale modeling can be found in Jiang et al [2]. In the 2 dimensional model, the reaction-diffusion equations are replaced by a constant oxygen environment. The oxygen level in the 2 dimensional model is modulated 9 times between a 2 percent and .02 percent with periods of 5 days and 3 days, respectively. We use the cell viability data obtained in Graeber et al to couple the cell proliferation to the oxygen environment.

In the 2 dimensional model, we find that the lattice Monte Carlo model is robust with respect to the observed biological data [1]. It takes approximately 6-7 rounds of hypoxia and reoxygenation for the P53-mutated cell line to dominate when introduced at a 1:1000 ratio with the P53-unmutated cell line (Figures 1,2).

In the 3 dimensional model, we find that the P53-mutated cells do have a proliferative advantage in a tumor spheroid due to the oxygen limitation created by the tumor aggregation itself. The existence of P53-mutated cells in the tumor population increases the maximal growth rate of the tumor and increases the final tumor spheroid saturation size, although it only does so by approximately 10 percent. We first modeled the growth of the tumor in a .28 mM oxygen environ-

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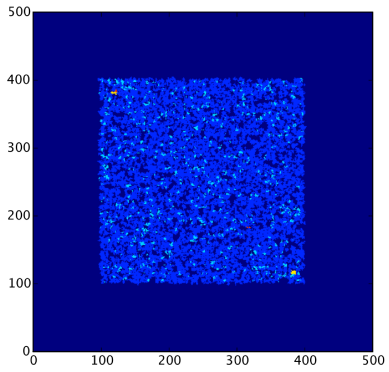

Figure 1: A monolayer simulation of malignant cells. P53 mutated proliferating cells:yellow; P53 unmutated proliferating cells:blue; P53 unmutated quiescent cells:light blue. Cells turn quiescent due to the competition for space.

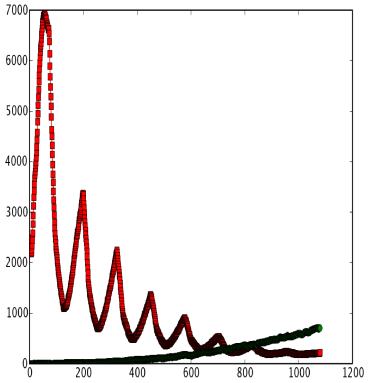

Figure 2: A monolayer simulation of malignant cells, the environment is modulated 9 times between a 2 percent and .02 percent oxygen level for 5 days and 3 days, respectively.

ment, we then lowered the oxygen concentration to .08 mM. We found that lowering the oxygen concentration severely altered P53-mutated cell population level. The model predicts that the P53-mutated cell population is able to dominate the P53-unmutated cell population in a .08 mM oxygen environment but not in a .28 mM oxygen environment (Figures 3, 4).

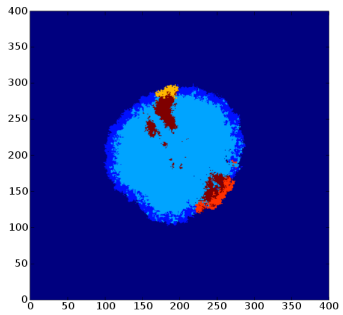

Figure 3: A 3 dimensional simulation of avascular tumor growth in .28 mM oxygen. P53 unmutated proliferating cells:Dark blue; P53 unmutated quiescent cells:Light blue; P53 mutated proliferating cells:Red,Orange; P53 mutated quiescent cells:brown.

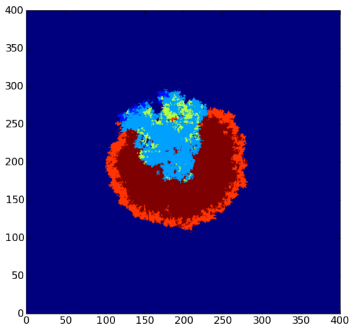

Figure 4: A 3 dimensional simulation of Avascular tumor growth in .08 mM oxygen.

References

[1] Graeber T.G. et al. Nature 379: 88-91, 1996.
[2] Jiang, Y. et al. Biophysical Journal 89:3884-3894, 2005.

Acknowledgements

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