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The Role of Metabolic Heterogeneity and Microenvironmental Selection in Tumor Growth and Treatment

Heterogeneity of the tumor and its microenvironment is now widely accepted fact in cancer biology. Here we specifically focus on heterogeneity of the metabolic cellular phenotype and within the environmental factors that influence it. Using a hybrid multi-scale mathematical model of tumor growth in a vascularized tissue, we investigate the selection pressures exerted by the tumor microenvironment as the cancer progresses. A key feature of the model is the focus on both normal and tumor metabolism. The metabolic phenotype of tumor cells is allowed to drift, and selection due to the microenvironment leads to increased glycolysis and decreased pH. Once this aggressive phenotype emerges, the tumor dramatically changes its behavior due to acid-mediated invasion, an effect that depends on both phenotypic and spatial arrangement of the tumor. In early stages of growth, the tumor is stratified, with the most aggressive cells developing and residing within the interior of the tumor. Eventually, these aggressive cells can grow out to the edge of the tumor and invade into the normal tissue by causing acidosis. The model is supported by experimental results from both murine and clinical data.

Results from the model suggest that diffusible cytotoxic treatments such as chemotherapy may increase the metabolic aggressiveness of a tumor post-treatment due to the altered selection pressure caused by the drug. Chemotherapy removes the metabolic stratification of the tumor and allows more aggressive cells to grow towards blood vessels and normal tissue. In contrast, a second type of therapy that buffers the extracellular pH significantly slows down the development of aggressive tumors if the treatment is given early enough. However, if the tumor reaches critical mass and begins to invade, the buffering treatment has little effect, suggesting that this approach is preventative but not curative. A third treatment we consider is the use of anti-angiogenic therapy, which foments the development of aggressive phenotypes due to degradation of the tumor microenvironment.

All of these simulated treatments highlight the importance of the dialogue between tumor and environment and critically how this dialogue modulates heterogeneity driving the tumor down very different evolutionary paths.