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A Generalized Continuum Model of Tumor Acidity and Invasion

We model the metabolism and behavior of a developing cancer tumor in the context of its microenvironment, with the aim of elucidating the drivers and consequences of altered metabolism—a possible hallmark of malignancy [1] and avenue for novel treatment strategies. Of particular interest is the glycolytic phenotype, a constitutive switch in tumor metabolism of glucose from oxidative phosphorylation to a glycolysis pathway normally reserved for anaerobic conditions [2]. Widely observed across many types of cancer and seemingly paradoxical due to a resulting build-up of toxic acid by-product in the tissue, this phenotype is highly complex and remains incompletely understood.

A potential explanation for the prevalence of the glycolytic phenotype in tumors is the acid-mediated invasion hypothesis [3], which suggests that by acquiring resistance to acidification of the microenvironment, tumor cells expressing the glycolytic phenotype may gain a selective advantage over neighboring healthy cells, functioning similarly to an invasive species in an ecosystem. Many open questions remain concerning the details of this hypothesis and how it fits into the larger features of tumor pH and metabolism, and hence into the somatic evolution of cancer in general. Here, we discuss our efforts to determine how the acid-mediated invasion hypothesis manifests at the tissue level.

We have generalized a canonical non-linear reaction-diffusion model of acid-mediated invasion [4] to consider additional, potentially important, biological features. Numerical methods reveal that our model attains clinically relevant tumor behaviors not captured previously, such as benign growths which lack the ability to invade; and a non-standard asymptotic analysis of the system in a traveling wave framework, inspired by [5], provides an explicit understanding of how fundamental parameters govern the speed and shape of an invading wave of tumor cells. Additionally, comparison with conclusions drawn under the original system—a special case of our generalized system—allows us to comment on the structural stability and predictive power of the modeling framework.

Further study will link this work to a finer-scale consideration of the intricate biochemistry underlying pH regulation in tumors, with the hope of building up a comprehensive picture of tumor acidity and thereby advancing our understanding of cancer metabolism.

References

[1] Hanahan, D., Weinberg, R.A. (2011). Hallmarks of cancer: the next generation. *Cell*, 144: 646-674.

[2] Warburg, O. (1930). *The Metabolism of Tumors*. Arnold Constable, London.

[3] Gatenby, R.A., Gillies, R.J. (2004). Why do cancers have high aerobic glycolysis? *Nature Reviews Cancer*, 4(11): 891-899.

[4] Gatenby, R.A., Gawlinski, E.T. (1996). A reaction-diffusion model of cancer invasion. *Cancer Research*, 56(24): 5745-5753.

[5] Fasano, A., Herrero, M.A., Rodrigo, M.R. (2009). Slow and fast invasion waves in a model of acid-mediated tumor growth. *Mathematical Biosciences*, 220(1): 45-56.