Tumor Progression associated with microenvironmental independence: results from a joint experimental-mathematical study

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***Short Abstract* — Tumor progression is known to be influenced by the microenvironment, but the mechanism is unclear. We carried out a joint experimental-computational study to model the role of microenvironmental conditions on tumor population dynamics and progression toward a more aggressive tumor. In simulated tumors, individual cells were represented as collections of experimentally parameterized phenotypic traits in a hybrid discrete-continuum model, and allowed to grow and compete for resources. We find that biologically aggressive cells only achieve clonal dominance under conditions of microenvironmental resource constraints. These results suggest that the process of tumor progression involves strong selection for microenvironmentally-resistant cells.**

***Keywords* — Tumor microenvironment, mathematical modeling, tumor progression.**

I. Purpose

THE goal of our study was to gather an experimental dataset for the explicit purpose of parameterization of a mathematical model of tumor growth [1, 2]. Frequently, mathematical models are parameterized with data gathered from the literature or from fitting. However, a problem with this approach is that most experimental values are highly dependent on the culture conditions, making comparisons across platforms difficult without standardization. Furthermore, theoretical values depend on assumptions about what represent "aggressive" or "nonaggressive" trait values. We therefore gathered experimental phenotypic trait values from a panel of breast cell lines that ranged in biological aggressiveness from normal to highly tumorigenic and invasive. Simulations were run in a hybrid discrete-continuum model under diverse microenvironmental conditions.

II. Results

We find that in a resource-rich microenvironment, with few limitations on proliferation or migration, transformed but not tumorigenic cells were most successful and outcompeted other cell types in heterogeneous tumor simulations. Conversely, constrained microenvironments with limitations on space and/or growth factors gave a selective advantage to phenotypes derived from tumorigenic cell lines. Analysis of the relative performance of each phenotype in constrained versus unconstrained microenvironments revealed that, although all cell types grew more slowly in resource-constrained microenvironments, the most aggressive cells were least affected by microenvironmental constraints. A game theory model testing the relationship between microenvironment resource availability and competitive cellular dynamics supports the concept that microenvironmental independence is an advantageous cellular trait in resource-limited microenvironments.

III. Conclusion

These results suggest that a critical feature of the process of tumor progression is selection of cells that can escape from resource limitations by achieving a relative micro-environmental independence.

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