Ovarian cancer relapse: micro-carcinomas vary in form with peritoneal niche

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***Short Abstract* — In ovarian cancer, the morphology of microscopic tumors depends on local characteristics of tissues to which cells initially attach in the peritoneal cavity. We use an integrated experimental and modeling approach to study tumor growth during cancer relapse, incorporating data from a mouse xenograft model into a cellular Potts model. Simulations include tumor spheroid chemotactic invasion where permitted by the features underlying the mesothelial layer at different sites [1]. The *in silico* model also includes the essential features of angiogenesis; oxygen gradient fields indicate that new blood vessel formation is not dependent on the tumor mass reaching a hypoxic state.**

***Keywords* — ovarian cancer relapse, cellular Potts, SKOV3-IP1, Compucell3d, *in silico* model, cellular automaton**

I. Purpose

In ovarian cancer, the majority of patients are not diagnosed until surgery is needed to remove large tumor masses. Following surgical debulking and chemotherapy, there is significant risk of relapse due to chemoresistant tumor cells remaining in the peritoneal cavity [2]. In our xenograft model, human ovarian tumor cells (SKOV3.ip-GFP) are injected into the peritoneum of immunocompromised mice. Tumors develop within a few weeks. We note that the morphology and angiogenesis potential of new micro-tumors is highly dependent on local physical and chemical characteristics of tissues to which they attach in the peritoneal cavity. We postulate that these features have the potential to determine the local efficacy of specific classes of cancer therapeutics (*i.e.* small molecules vs. protein-based therapies such as monoclonal antibodies). These hypotheses will be explored using mathematical models that consider local penetrance as well as route of delivery.

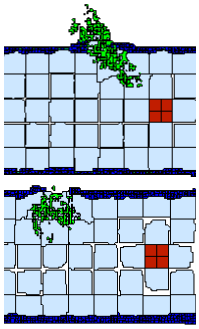
II. Methods

Data from the mouse model was used to parameterize cellular Potts models (using Compucell3d [3]) of micro-tumor morphologies on mesothelium overlying muscle, and on the mesentery (a dual mesothelial membrane containing vascular bundles surrounded by fat). We incorporate tumor development processes of cell growth, division, chemotaxis, invasion, and O_2 and glucose consumption. When possible, we entered experimental values such as adipocyte secretion of the chemotatic factor IL-8 [4], concentrations of O_2, glucose, and IL-8 in blood and peritoneal fluid, and volume of cells in our mice directly into the code. Otherwise, model parameters were systematically tuned to re-create experimental values, such as rate of invasion/chemotaxis of ovarian cancer cells into mesothelium [5]. We compared simulation results to images from our mouse model.

III. Results & Conclusions

A. Models of spheroids on tissue with "tight" cellular junctions in underlying tissue and no space for invasion between cells (such as muscle) generate semi-spheroidal morphology in young tumors, both *in silico* and *in vivo*.

B. A chemotactic chemical gradient in a layer of adipocytes generates a tumor growth pattern different from dual signals from adipocytes and vessels (image: 2-D sections of 3-D sims.). Similarities to the dual-signal model are seen in GFP tumors in the mesentery of our xenograft mice. We may continue to explore this hypothesis using our mouse xenograft model.



C. Simulations show that tumors 33 cells wide, comparable to those excised from mice at 1 week, are small enough that all cells will be sufficiently oxygenated. Nevertheless, tumors 1 and 3 weeks old are fully vascularized. Our microarray data also shows that these cells constitutively express angiogenic factors (Ang2, VEGF). Our simulations of hypoxia-independent tumor angiogenesis produce tumor vasculature patterns that are comparable to those in 2-week-old tumors.

These models lay the foundation for modeling tumor apoptotic cell death after *in silico* delivery of several different classes of drugs via either vascular or peritoneal injection. Results of these models will guide the design of preclinical trials in mice engrafted with ovarian tumor cells.

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