

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 attachment to organ surfaces in the abdominal cavity, followed by 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

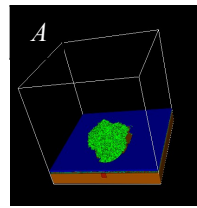
IN ovarian cancer, the majority of patients are not diagnosed until surgery is needed to remove large tumor masses. Following surgical debulking and chemotherapy, there is significant risk of relapse due to chemoresistant tumor cells remaining in the peritoneal cavity [2]. In our xenograft model, human 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 mesoscopic cellular Potts models (using CompuCell3d [3]) of micro-tumor morphologies on mesothelium overlying muscle or attached to the mesentery (a dual mesothelial membrane containing vascular bundles surrounded by fat). We incorporate tumor cell growth, cell division, chemotaxis,

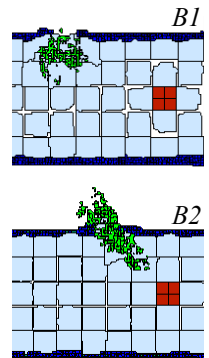
invasion, and O_2 and glucose consumption. When possible, we included experimental values directly in the simulation, such as adipocyte secretion of the chemotactic factor IL-8 [4], concentrations of O_2 , glucose, and IL-8 in blood and peritoneal fluid, and normal cell volumes (such as of adipocytes) in our mice. 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 our mouse model of ovarian cancer peritoneal metastasis.

III. RESULTS & CONCLUSIONS

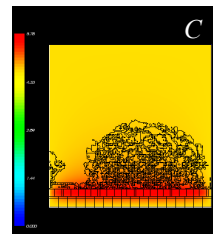


A. Models of spheroids attached to the mesothelium where the underlying tissue is characterized by “tight” cellular junctions with no space between cells (such as at the surface of the small intestine (image A)) generate a non-invasive semi-spheroidal morphology in small tumors, both *in silico* and *in vivo*.

B. A chemotactic chemical gradient originating from adipocytes generates a tumor growth pattern (B1) different from that created when dual signals from adipocytes and vessels are included (B2; images are 2-D sections of 3-D simulations.). Similarities to the dual-signal model are seen in GFP tumors in the mesentery of the xenografted mice. We will continue to explore this hypothesis using our mouse xenograft model.



C. Simulations show that tumors ~30 cells wide, comparable to those excised from mice at 1 week, are small enough that all cells are sufficiently oxygenated (image C: cell consumption of O_2 does not create a hypoxic area at the center of the spheroid; red = max O_2). Nevertheless, tumors 1 and 3 weeks old are fully vascularized. Our microarray data also shows that these cells constitutively express the angiogenic factor VEGF, and upregulate another, Ang2, in tumors. We are building simulations of hypoxia-independent tumor angiogenesis and will perform morphometric analysis on simulated tumor vasculature patterns for comparison to the uniform vasculature seen *in vivo*.



These models lay the foundation for modeling tumor cell death after the delivery of different classes of drugs via either intravascular or intraperitoneal injection. Results of

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these models will guide the design of preclinical trials in mice engrafted with ovarian tumor cells.

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