GROWTH OF TUMOR MICROTUBE NETWORKS IN A GLIOBLASTOMA

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Glioblastoma (GBM) is the most frequent and most aggressive primary brain tumor with a dismal prognosis and a median survival of 15 months after diagnosis [1]. Astrocytic brain tumors, the most common type of gliomas, originate in a specific kind of glial cells called astrocytes. These are incurable neoplasms characterized by a diffusely infiltrative growth. During GBM progression, the malignant astrocytic cells extend ultra-long membrane protrusions, called tumor microtubes, and use them as routes for brain invasion, proliferation and to establish a large pathological network or connectome. This structure not only intermingles with the vasculature, but it is also highly resistant to radiotherapy administration [2]. Therefore, the disruption of the astrocytoma network by targeting the tumor microtubes is extremely relevant, and it emerges as a new principle to reduce the resistance of this disease to conventional treatments. In this work we present a phase-field model that describes the dynamics of the GBM connectome by capturing the interplay between the tumor microtubes, astrocyte irrigation and angiogenesis. The dynamics of the interface between the capillaries, the cells and the stroma, is treated with the phase-field formalism, using two order parameters. The activation of the tip cell phenotype in endothelial cells is implemented in the model through an agent-based component. The same approach is used for the tip of the tumor microtubes in the tumor cells. The vessels follow the gradient of an effective factor, in this case VEGF, and the tumor microtubes of the glioma cells follow the gradient of another effective factor, presumably TGF. Our numerical simulations elucidate the role of irrigation in regulating the interconnectivity of malignant astrocytes in vivo.

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References


SPACE-TIME MODEL FOR THE UNDERSTANDING OF ABERRANT CRYPT FOCI MORPHOGENESIS

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Colon cancer is one of the most common and aggressive cancers. However, if it is diagnosed at an early stage, it proves to be much less aggressive. The understanding of the phenomena that are at the origin of this disease is therefore fundamental. The surface of the human colon is densely punctured by tiny tubular cavities called crypts. The process of cellular renewal of the colon epithelium takes place in these crypts. It is believed that one of the first manifestations of colon cancer, observable in vivo by conventional colonoscopy, is the appearance of aberrant crypt foci. These are clusters of crypts that have a behavior different from the normal ones, namely the abnormal shape of their top orifices and the abnormal proliferative capacity of their cells. We propose a space-time model that correlates an abnormal cell proliferation in the colonic crypts with aberrant shapes of these crypt’s top orifices. The model is formulated in a two-dimensional domain, representing a single crypt and its surrounding region in the colon (see [1, 2] for related articles). The cell renewal process within the crypt is represented by a continuous cell dynamics model. The cellular proliferation causes a pressure that is responsible for the convective movement of the colonic cells, and which, in the normal case leads to a stable solution. An increase in the cells’ proliferative capacity causes an increase in pressure and consequently a change in the normal colonic cellular mechanism. In this proposed model, the colonic crypt is considered to be an elastic material, while the surrounding colonic material is assumed to be visco-elastic. The internal forces acting in the colonic tissue are originated by the variation of the pressure generated by the abnormal alteration of the cellular proliferation. The numerical simulations show that it is possible to relate the various abnormal shapes of the colonic crypt’s orifices, found in vivo in colonoscopy exams, with changes in the proliferative capacities of the cells.

References

CELL DENSITY INFLUENCES CLUSTERING AND MIGRATORY BEHAVIOUR OF TRIPLE-NEGATIVE BREAST CANCER CELLS

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The ability of cancer cells to invade neighbouring tissue from primary tumours is an important determinant of metastatic behaviour. Quantification of cell migration characteristics such as migration speed and persistence helps to understand the requirements for such invasiveness. One factor that may play a role here is how local tumour cell density shapes the migration characteristics, which we here investigate with a combined experimental and modelling approach. As a first step, we analysed time-lapse imaging data on three aggressive Triple-Negative Breast Cancer (TNBC) cell lines (MDA-MB-231, Hs578T, and HCC38) during 2D migration assays at different cell densities. HCC38 cells exhibited a counter-intuitive increase in speed and persistence with increasing density, whereas the other cell lines did not exhibit such an increase. Moreover, HCC38 cells could be distinguished from the other cell lines because they exhibited cluster formation, and the clusters were more stable at low than at high cell densities. This suggests that the cluster formation is related to the changes in migration characteristics.

In order to integrate these experimental data and obtain a mechanistic understanding of the density-dependent cell migration characteristics and cluster formation, as a second step we developed realistic spatial simulations using the Cellular Potts Model (CPM). Because all three cell lines exhibit high pseudopod activity, we included a description of pseudopod dynamics in our model. Analysis of the model suggests that pseudopod-driven motion is the source of directional persistence in these cells. We are currently investigating whether inclusion of different adhesion properties in the in silico cells can explain the experimentally observed density-dependent migration characteristics and presence or absence of cluster formation. Furthermore, experimental work is ongoing to investigate whether inhibition of cellular adhesion in HCC38 cells will prevent cluster formation and at the same time alter the density dependence of migratory behaviour. Our project shows how combined computational and experimental approaches can accelerate scientific progress in a synergistic fashion, hopefully leading to an increased discovery rate of novel treatment options.
PITFALLS IN CLUSTERING METABOLIC LANDSCAPES

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Nowadays, substantial majority of high-throughput technologies undergo a constant developmental progress, which results in higher precision of experimental measurements, lower cost of conducting these experiments, but also an easier access to huge biomedical databases. Thanks to this availability of a vast palette of types of data describing various biological phenomena we are able to infer more insightful and accurate observations as well as mechanisms driving these observations. Additionally, using sophisticated statistical and mathematical tools (e.g. Markov Random Fields, Flux Balance Analysis, Petri Nets, etc.) can lead to construction of integrative models that are supposed to discover novel descriptions of studied phenomena.

In our case study we use the transcriptomic data from the Cancer Genome Atlas and the RECON2 description of human metabolic network [1] along with the integrative model described by Shlomi et al. [2] which is a widely used tool for describing the tissue-specific metabolic activity in human. It turned out that determined metabolic-landscapes perfectly cluster our data into two well-separable groups. These groups are characterized by specific reactions, which can be well described as probable cancer progression level. Nonetheless, we show that the differential gene expression analysis performed on purely transcriptomic data provides the same result and clustering. Moreover, a further investigation confirmed that discriminating genes are related to the previously selected discriminating enzymatic reactions. As a consequence we prove that we do not gain any additional information from the model that cannot be independently deduced from the transcriptom statistical analysis.

Summarizing, in this work we present how mathematical modeling that is focused on data integration may lead to misconceptions, and thus how important in the scientific world is the interdisciplinary communication. Especially, when the goal is to understand and describe the biological reality.

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References
