DOI 10.18699/SBB-2022-114

Tumor mechanobiology and related prospects for targeted therapies *in silico* simulations and analysis

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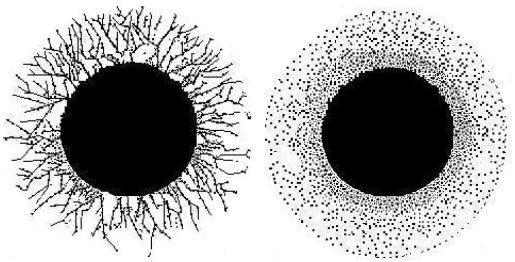
Key words: Glioblastoma multiform, Multicellular Tumor Spheroids, targeted therapy

Glioblastoma multiform (GBM) is one of the most lethal types of human cancers with a median survival time slightly above a year. The current work is focused on mechanics of glioma cells in Multicellular Tumor Spheroids (MTS) in order to determine Mechanical Modulators of glioma – possible alterations in mechanical properties or structure of tumor that may have a critical effect on glioma progression. Unlike typical targeting therapies designed to ultimately destroy or damage cancer cells, the mechanical modulation may affect tumor growth on the structural level, slowing down its progress. The work presents analysis based on in- silico MTS simulations of glioma growth and also available *in vitro* results.

Mechanical factors of tumor growth represent rheological properties of Cell- ECM system and also combination of the hydraulic mobility and motility of glioma cells can be seen as Mechanical Modulators of glioma progression. The difference between the last two cell characteristics is that the first one- mobility characterizes purely passive cell motion under intercellular pressure resulting from excessive cell proliferation, while cell motility relates to their individual activity providing their motion through ECM. The effect of glioma suppression, where these modulators were ultimately targeted has been demonstrated experimentally [1], as well as on computer models [2]. The pathways of these *modulatory* effects have been studied in the current work.



a *b*

Fig. 1. Stylized schemes of the two typical forms of invasive patterns: Radial (*a*) and Disperse (*b*). Patterns of 'Radial' glioma invasion typically obtained in in vitro tests demonstrated 'moderate' cell activity. Aggressive cell lines often exhibit dispersal invasion [3, 4]

It was demonstrated in number of studies that different glima cell lines exhibit different invasive strategies. This difference is especially noticeable between highly malignant glioma cell lines and less aggressive cells [3, 4] and can be observed optically on invasive patterns. An example of the two characteristic types of glioma invasive patterns is shown on Fig. 1. As shown earlier [2] the transition from 'Radial' to 'Dispersal' type of invasion may be related to formation of subtumors, where distant cell clusters are

being formed in the invasive zone. The current study demonstrates that subtumor appearance results from radial instability in tumor core (Fig. 2) and is conditioned by the ratio of K_{C0}/K_{ECM}, where K_{ECM} and K_{C0} bulk moduli of ECM and glioma cells correspondingly. The Fig. 2 shows formation of a single cluster in the periphery of invasive zone and its growth. This cluster suppresses radial invasion, but initiates formation of 'star burst' pattern (see Fig. 1, *b*) typical for aggressive gliomas. Stiff cells may form more than one distant cluster (Fig. 3). Therefore, the model demonstrates a transition from relatively moderate radial strategy of invasion to the aggressive dispersed structure. The diagram on Fig. 3 covers the range of moduli values much wider than the one typical for *in vitro* and *in vivo* gliomas. This range is shown to demonstrate the principal diagram shape with most occurrences of dispersed invasive pattern at $K_{C0}/K_{ECM}\sim 1$.

The model assumptions are to be outlined briefly to demonstrate the capabilities of the toolkit used. It considers three cell phenotypes: proliferative cells with low or zero motility, highly motile hypoxic cells with low or zero proliferation rate and necrotic cells, which do not exhibit any proliferation or motility, while show the same hydroulic mobility as all other cells do, being under interstitial pressure. The local oxygen content determines all transitions between cell phenotypes within predetermined transition times. Viscoelastic compressible cell continuum moves through elastic compressible extracellular scaffold driven by individual cell motility and stress distribution in the composite system. The model is based on continuum approximation with the following assumptions. Extracellular Matrix (ECM) is isotropic, compressible, linear elastic, porous material. The cells exert attractive and repulsive forces on each other depending on intercellular distances. The lower limit of cell concentration in the colony is determined by the critical distance between them. Beyond this threshold cells cannot sense or forcibly affect each other. The model has been described in details in [2], including mathematical problem statement, initial and boundary conditions and model validation based on exprimental data.

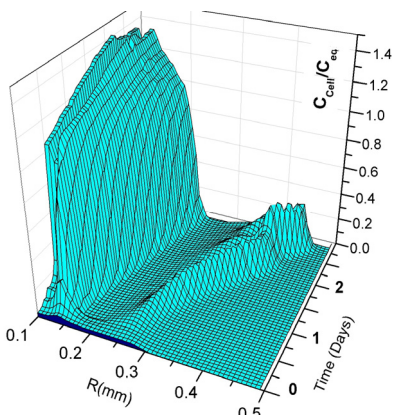


Fig. 2. Calculated radial distribution of glioma cell density C_{Cell} as function of time in MTS growth; $C_{eq}= 3.5 \times 10^8$ cells/cm^3. This dynamics demonstrates the formation of subtomor in front of MTS

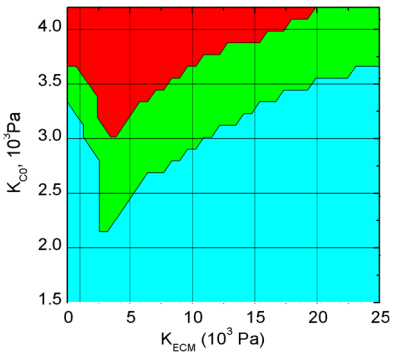


Fig. 3. Calculated zones of subtumor formation, as they depend on ECM and cell colony bulk moduli, based on the current model of glioma invasion. Blue zone- radial invasive strategy; Green- formation of a single sublayer around MTS; Red- two or more sublayers lead to dispersed structure of invasive pattern

Modulation of tumor growth through variation of cell-ECM system rheology has been demonstrated experimentally [5, 6]. The model also allows us to observe alterations of tumor agressiveness induced by modulations of cell-ECM dynimics. This collective cell dynamics of 3D tumor growth is not being replicated in typical invasion/migration assays. Though the assays produce valuble data for further *in silico* simulations of glioma growth. Cell motility and hydraulic mobility, as their key invasive characteristics, are individual mechanical attributes of each cell line and can be extracted from the assay results. The results of transwell assays obtained in [1] for A172, U87-MG, SW1088 and H4 glioma cells have been used for *in silico* simulations of glioma MTS growth in the current work. The simulation results are in line with the available data on aggressiveness of tumors formed by these glioma cells. The cell modifications carried out in [1] resulted in their new mechanical characteristics were also used for glioma MTS simulations. The simulations confirmed glioma suppression for most aggressive lines A172 and U87-MG assumed by authors of [1], showing for the first case even a transformation of the invasive structure from dispersal type to radial one, as illustrated on Fig. 1. At the same time, the model does not confirm the expected promotion of tumor activity for modified SW1088 and H4 cells. This result illustrates one more time that invasion assays do not replicate 3D tumor growth. It's important to note that the modulatory effect on dynamic cell characteristics depends dramatically on cell-ECM rheological conditions, as shown on Fig. 3. An immediate consequence of this effect is that 3D *in vitro* test results of tumor growth may differ completely from *in vivo* tumor dynamics, as the rheological properties of typical gels used for *in vitro* tests, matrigel in particular, differ substantially from *in vivo* rheology. However, *in silico* simulations were shown as an efficient complementary toolkit capable of predicting the modulatory effects on 3D tumor growth. It can be potentially a part of computer aided mechanobiological targeting strategy for potential anticancer therapy.

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