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A mathematical multiscale model of the role of microRNA-451 in glioblastoma growth

Glioblastoma (GB) is the most aggressive primary brain tumor and even with the most recent therapies median survival is only about 12 months.To aid the better understanding of tumor growth as well as the development and improvement of therapies computational modeling can be employed. In this work we introduce a multiscale model covering the molecular and microscopic scale. The model combines a molecular interaction network representing the influence of glucose and microRNA-451 (miR-451) on the subcellular level with an agent based model (ABM) for the cellular scale.

Many cancer cells utilize glucose to pursue proliferation and under unfavorable glucose conditions they migrate to more beneficial sites to avoid metabolic stress. In [2] it was shown that the level of miR-451 in GB cells is elevated under normal glucose conditions and decreased in a low glucose environment. MicroRNAs are short (22 nucleotides long) non-coding RNAs that regulate the expression of approximately 60% of all human genes at the post-transcriptional level. As one of these genes MO25 is targeted by miR-451. The MO25 protein binds to the protein LKB1 and this complex activates the AMPK and MARK3 signaling pathways, by that either initiating cell migration (low glucose environment) or cell proliferation (high glucose environment).

We translated the above described biological processes that take place within each GB cell into a molecular interaction network that is represented by ordinary differential equations (ODEs). In total 17 molecular species are involved whose concentrations constitute the 17 variables of the system which are governed by 17 ODEs. We then reduced the system to a total number of 12 variables and 12 ODEs by eliminating the five variables and equations that are merely part of a complementary pair, i.e. describing the phosphorylated and non-phosphorylated form of a protein or the active and inactive form of a protein. By following the approach introduced in [1] we coupled this subcellular interaction network with an ABM to also investigate the tumor development on a microscopic scale. The tumor cells represent the agents that are placed on a regular square grid. Initially, a constant glucose concentration is assumed on the whole grid. Over time, glucose is consumed by the cells influencing the molecular interaction network and diffuses through the grid as mathematically described by a partial differential equation. In each time step for each cell first the molecular interaction network will be evaluated. Then, based on the concentrations of phosphorylated MARK3 and active mTORC1 the cell's phenotype is determined as either proliferating, migrating or quiescent. Finally, cell migration and the spatial placement of daughter cells follows the gradient of a chemotactic agent (glucose).

First results show that the above described model is capable of reproducing the results obtained from biological experiments. We simulated the development of the in silico tumor under different glucose conditions chosen to be in accordance to the migration array experiments in [2]. The results demonstrate that under low glucose conditions a tumor tends to migrate faster and further than under medium glucose conditions. This is qualitatively in good agreement with the results of the in vitro experiments in [2]. In particular under low glucose conditions, the simulated tumor exhibits a behavior that is essential for the aggressive character of GB tumors: individual cells separate from the tumor bulk and invade the surrounding (healthy) microenvironment.

References

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